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Practical Pharmaceutics

An International Guideline for the Preparation, Care and Use of Medicinal Products

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ISBN 978-3-319-15813-6 ISBN 978-3-319-15814-3 (eBook)
DOI 10.1007/978-3-319-15814-3

Library of Congress Control Number: 2015933496

Springer Cham Heidelberg New York Dordrecht London
Translation and revision based on the Dutch language edition: Recepteerkunde: Productzorg en bereiding van geneesmiddelen, 5th Ed, edited by Yvonne Bouwman-Boer, Paul Le Brun, Christien Oussoren, Ria Tel and Herman Woerdenbag Copyright © 2009 KNMP. All Rights Reserved

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

The core role of a pharmacist is and has always been to supply the patient with the most appropriate medicines according to their needs. Patients have differing needs. Not all patients fit the 'normal profile' upon which the efficiencies of scale allow the pharmaceutical industry to mass produce medicines. A significant proportion of patients require medicines to be specifically made to suit their needs.[1]

The pharmaceutical art of preparing medicines should be seen in the social context of guaranteeing the availability of necessary medicines to patients. The Council of Europe Resolution on pharmacy preparation[2] considered the preparation of medicinal products in pharmacies as indispensable for accommodating the special needs of individual patients in Europe.

Another reason for preparing in pharmacies is the fact that the pharmaceutical industry has become so international and many of the smaller national industries have been swallowed up in the process that any small effect on the supply chain leads to the observed shortages now felt in all countries around the world.

For several years pharmacists in many European countries have felt the need for knowledge, information and guidelines on the practice of preparation in the pharmacy. This was clearly put forward by experts from many European countries at the EDQM symposium on European Cooperation and Synergy and at the BEAM compounding course.[3] During this course it was agreed that the knowledge for the preparative pharmacist were contained in the Dutch book *Recepteerkunde* and that this book could be used as a base for a European wide textbook on preparation in pharmacies.

The aim of Practical Pharmaceutics is to offer:

- Basic knowledge for undergraduate and graduate pharmacy students.
- Practical knowledge on the design and preparation of medicines for the pharmacists responsible for preparations in community and hospital pharmacies.
- Basic knowledge for the Qualified Person (QP) in industry and all pharmacists involved in quality assurance.
- Product knowledge for all pharmacists working directly with patients, to enable them to make the appropriate medicine available, to store medicines properly, to adapt medicines if necessary and to dispense medicines with the appropriate information to inform patients and caregivers about product care and how to maintain their quality. This basic knowledge will also be of help to industrial pharmacist to remind and focus them on the application of the medicines manufactured.

[1] Fenton May V. Preparation in the hospital pharmacy: from the past to the present and, hopefully, beyond. Eur J Hosp Pharm 2012;19:465–6.

[2] Resolution CM/ResAP (2011) 1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. Available from: https://wcd.coe.int/ViewDoc.jsp?id=1734101&

[3] EAHP Academy third BEAM summit on Aspects of Compounding. 2010.

The first principal was that *Recepteerkunde* would form the basis of the book. Secondly we agreed to retain the principal of using experienced practising pharmacists from hospital and academia as authors to the chapters. In order to ensure that the book reflected the practice from across Europe, experts in the specific fields were chosen from all quarters of Europe.

Practical Pharmaceutics covers such a vast area that the production of the book would have taken many more years to complete if the Dutch starting reference work had not been there as a basis. Its first edition, edited by Harry Cox, Gerad Bolhuis and Jan Zuidema, was published in 1992 as a gift of the Dutch Pharmacists' Association KNMP to their members on the occasion of the 150th anniversary. It has been used since at both universities in the Netherlands offering the Pharmacy curriculum. The fifth edition from 2009 forms the basis of Practical Pharmaceutics.

The book is generally written in GB English but liberties have been taken where it has been considered that an adaption would make the sense easier to understand across Europe. Some of those changes are explained in the Introduction.

We owe a debt of thanks to the authors and translators who were given extremely short deadlines for their tasks, most of whom are practicing pharmacists with full time and often stressful jobs. An editorial advisory group has dutifully answered many questions about the actual situation in their countries.

The financing of such an enterprise is never easy, and we thank EAHP and both the Dutch pharmacists associations KNMP and NVZA for the foresight to invest in the book without which it would not have been produced.

Comments for improvement could be forwarded to PracticalPharmaceutics@eahp.eu

The Hague, The Netherlands — Yvonne Bouwman-Boer
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Contents

Abbreviations

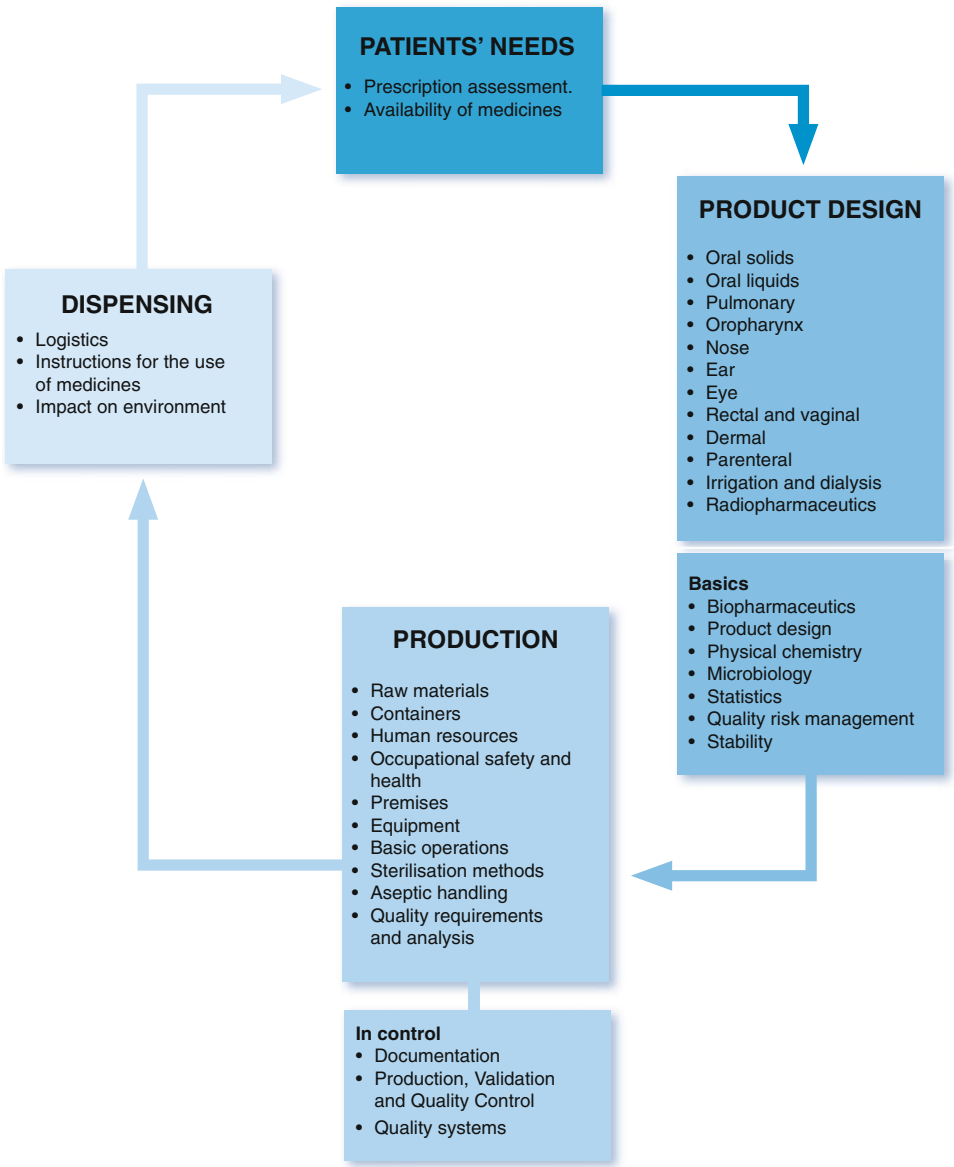
AAD	Adaptive Aerosol Delivery
ACD	Automated Compounding Devices
ADI	Acceptable Daily Intake
ADS	Automated Dispensing Systems
AIO	All In One
ALARA	As Low As Reasonably Achievable
APV	Arbeitsgemeinschaft für pharmazeutische Verfahrenstechnik (Association for Pharmaceutical Technology)
AQL	Acceptable Quality Level
ART	Advanced REACH Tool
AUC	Area Under The Curve
AV	Analytical Validation
BCS	Biopharmaceutical Classification System
BPI	Batch Preparation Instruction
BPR	Batch Preparation Record
BSC	Biological Safety Cabinet
CAN	Critical Aggregation Number
CAPA	Corrective And Preventive Action system
CAPD	Continuous Ambulant Peritoneal Dialysis
CDC	(U.S.) Centers for Disease Control and Prevention
CEDI	Continuous Electro-deionisation
CFC	ChloroFluoroCarbons
CFU	Colony Forming Unit
c-GMP	current Good Manufacturing Practice
CHMP	Committee for Medicinal Products for Human Use
CIVAS	Central Intra Venous Additives Service
CLP	Classification, Labelling and Packaging Regulation
CMC	Critical Micelle Concentration
CMR	Carcinogenic, Mutagenic and Reprotoxic
COC	Cyclic Olefin Copolymer
COMP	Committee for Orphan Medicinal Products
COSHH	Control of Substances Hazardous to Health (UK)
CPD	Continuous Professional Development
CPMP	Committee for Proprietary Medicinal Products
CT	Computed Tomography
CTD	Common Technical Document
CVC	Central Venous Catheter
DEHP	Di-2-EthylHexyl Phthalate
DHPC	Direct Healthcare Professional Communication
DLVO-theory	Deryagin-Landau-Verwey-Overbeek theory
DMEL	Derived Minimal Effect Level
DNEL	Derived No-Effect Level

DOP	Dioctylphthalate
DPI	Dry Powder Inhalers
DQ	Design Qualification
DS	Detail Specification
D-value	Decimal reduction value
ECHA	European Chemicals Agency
EDI	Electro-deionisation
EDQM	European Directorate for the Quality of Medicines
EFQM	European Foundation for Quality Management
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPI	Extemporaneous Preparation Instruction
EPR	Extemporaneous Preparation Record
ERA	Environmental Risk Assessment
EU-OSHA	European Agency for Safety and Health at Work
Eu-US PFI	European – United States Paediatric Formulation Initiative
FAT	Factory Acceptance Test
FMEA	Failure Mode Effect Analysis
FNA	Formularium der Nederlandse Apothekers (Dutch Pharmacist's Formulary)
FRC	Functional Residual Capacity (pulmonary medicines)
FRCs	Functionality-Related Characteristics
FRS	Functional Requirements Specifications
FTU	Finger Tip Unit
GAMP	Good Automated Manufacturing Practice (Guides)
GDP	Good Distribution Practices
GHS	Global Harmonised Classification and Labelling System
GMP	Good Manufacturing Practice
GPP	Good Preparation Practices
GUM	Guide to the Expression of Uncertainty in Measurement
HCP	Health Care Professional
HDF	Haemodiafiltration
HDPE	High Density Polyethylene
HEPA	High Efficiency Particulate Air
HFA	Hydrofluoroalkanes
HLB	Hydrophilic-Lipophilic Balance
HVAC	Heating, Venting and Air Conditioning
IARC	International Agency for Research on Cancer
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IED	Industrial Emissions Directive
IMP	Investigational Medicinal Products
IMPD	Investigational Medicinal Product Dossier
IQ	Installation Qualification
ISO	International Standards Organisation
ISPE	International Society of Pharmaceutical Engineering
LDPE	Low Density Polyethylene
LEL	Lower Explosion Level
LQL	Limiting Quality Level
LTC	Long Term Care
LVP	Large Volume Parenterals
MAH	Marketing Authorisation Holder
MDI	Metered Dose Inhaler

MEC	Minimal Effective Concentration
MICC	Midline Inserted Central Catheters
MKT	Mean Kinetic Temperature
MMAD	Mass Median Aerodynamic Diameter
MPN	Most Probable Number
MRI	Magnetic Resonance Imaging
MSHG	Manufacturers' Safe Handling Guidance
MTC	Maximal Tolerable Concentration
NIOSH	National Institute of Occupational Safety and Health (US)
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NRF	Neues Rezeptur-Formularium (German Formulary)
NSI	Needlestick and Sharp Injuries
OEL	Occupational Exposure Limit
OMCL	Official Medicines Control Laboratories
OOS	Out of Specification
OOT	Out of Trend
OQ	Operational Qualification
OSH	Occupational Safety and Health
OSHA	Occupational Safety and Health Administration (US)
P&IDs	Piping & Instrumentation Diagrams
PAH	Polycyclic Aromatic Hydrocarbons
PAT	Process Analytical Technology
PCA	Patient Controlled Analgesia
PDA	Parenteral Drug Association
PDA	Permitted Daily Exposure
PDCA	Plan, Do, Check, Act
PEC	Predicted Environmental Concentration
PEG	Percutaneous Endoscopic Gastrostomic
PET	Polyethylene Terephthalate
PET	Positron Emission Tomography
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PICC	Peripheral Inserted Central Catheter
PIL	Package Information Leaflet
PK/PD	Pharmacokinetics and Pharmacodynamics
PLC	Programmable Logic Controller
PNEC	Predicted No-Effect Concentration
PP	Polypropylene
PPE	Personal Protective Equipment
PQ	Performance Qualification
PQS	Pharmaceutical Quality System
PTFE	Polytetrafluorethene
PUR	Polyurethane
PVC	Polyvinylchloride
PVDC	Polyvinylidene Chloride
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
QbD	Quality by Design
QC	Quality Control
QMR	Quality Management Review
QMS	Quality Management System
QP	Qualified Person

QPPV	Qualified Person for PharmacoVigilance
QRM	Quality Risk Management
RCA	Root Cause Analysis
RDA	Recommended Dietary Allowance
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RI&E	Risk Inventory and Evaluation
RMM	Rapid Microbiological Methods
RO	Reverse Osmosis
RODAC	Replicate Organism Duplicate Agar Contact
RPN	Risk Priority Number
rsd	Relative standard deviation
RTA	Ready To Administer
SAL	Sterility Assurance Level
SAT	Site Acceptance Test
SED	Safety-Engineered Sharp Device
SLA	Service Level Agreement
SMART	Specific, Measurable, Acceptable, Realistic and Time bound
SmPC	Summary of Product Characteristics
SOP	Standard Operation Procedure
STEP	Safety and Toxicity of Excipients for Paediatrics
SVP	Small Volume Parenterals
TAMC	Total Aerobic Microbial Count
TDM	Therapeutic Drug Monitoring
TFBUT	Tear Film Break Up Time
TGV	Threshold Guidance Values
TLC	Thin Layer Chromatography
TLC	Total Lung Capacity
TPN	Total Parenteral Nutrition
TRS	Technical Requirement Specification
TTC	Threshold of Toxicological Concern
TYMC	Total combined Yeast and Mould Count
URS	User Requirement Specification
VAD	Vascular Access Device, Venous Access Device
VHC	Valved Holding Chamber
VMAD	Volume Median Aerodynamic Diameter
WFI	Water For Injections
WHO	World Health Organisation
WHPA	World Health Professions Alliance
WI	Work Instruction

The Structure of Practical Pharmaceutics



Introduction

1

Yvonne Bouwman-Boer, V'lain Fenton-May, and Paul Le Brun

Contents

Abstract

This chapter explains some of the principles that have been followed during the production of this textbook. The basic principal is that the structure follows the needs of the patient. Concepts such as preparation, manufacturing, reconstitution, aseptic handling, hazardous substances are defined in order to avoid any ambiguity. Specific terminology on the technological operation of dispersing is defined, which covers particle size reduction, mixing and de-agglomeration. Any spelling and notations used in the European Pharmacopoeia have been followed in this book, in the absence of such guidance they are defined herein.

Keywords

Terminology • Definitions • Spelling • Notation • Formulations

1.1 Structure of the Book

The focus of Practical Pharmaceutics is the medicine as a product for the care of patients. The book focuses on its preparation, control, logistics, dispensing and use.

Although the existence of medicines is almost taken for granted, the design, description and control of this whole process of availability is so wide-ranging that this book easily became as large as it is.

Despite of the focus on the medicinal product, the structure of the book follows the patient, see Fig. 1.1. Product care is a vital part of pharmaceutical care.

A patient may need medicines. In most countries they need a prescription from a medical doctor who thereby shares responsibility with the patient. 'The' pharmacist (community, hospital, industrial pharmacist, scientist, teacher or competent authority) is responsible for the supply of the prescribed medicines, being professionally

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_1,

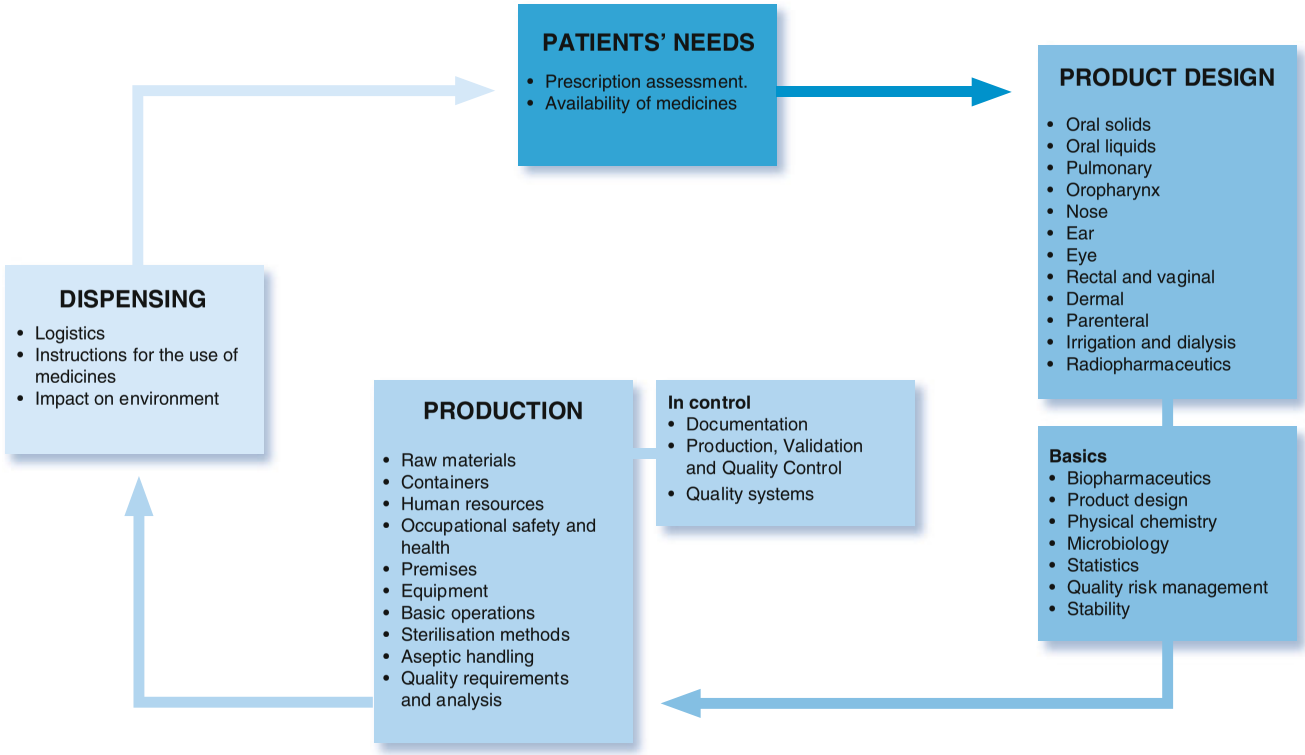

Fig. 1.1 The structure of the book.[1]

[1] The authors thank Cathrien Dijken (c.dijken@ahz.nl) for the concept.

responsible for procurement, medicines design and preparation, storage and dispensing.

The pharmacist needs to assess the doctor's prescription, for therapy reasons, but within the focus of this book also for availability and, in case of a pharmacy preparation, for safety and quality as well.

The administration route and dosage form strongly influence the design of the medicine and its method of preparation. Chapters 4–14 are written according to the route of administration. These chapters make ample use of examples from preparation in pharmacies, however the design in industrial manufacturing is basically not different. If relevant and possible industrial approaches are touched upon. All design activities need basics independent of the route of administration. These basics are dealt with in the following 7 chapters in a practical pharmaceutical context.

The actual production of medicines is a highly regulated sector of society. The 10 chapters about the different aspects clearly reflect that. Although regulations are omnipresent, the approach of these chapters stems from practice and logic. This also applies to the 3 chapters that cover the control mechanisms of production.

Before the patient can take the prepared or manufactured medicine it has to be stored, procured, and distributed. When the patient has his medicine dispensed, he has to receive labelled or oral instructions, or both, not only for therapeutic reasons but also for keeping and taking the medicine in the right way. Awareness on the impact of medicines on the environment is growing but not integrated yet.

Although many references are in all chapters, the book ends with a list of super references: textbook and hints for postgraduate education.

1.2 Definitions

1.2.1 Types of Pharmacy Preparations

The textbook started its life in the field of pharmacy preparation and although the focus of this edition is on mainstream manufactured products as well, much attention goes to provisions that the hospital or community pharmacist has to offer because not every patient fits the mainstream. It became obvious that official terminology for these peripheral activities is insufficiently discriminating. Therefore a terminology was developed as pictured in Fig. 1.2.

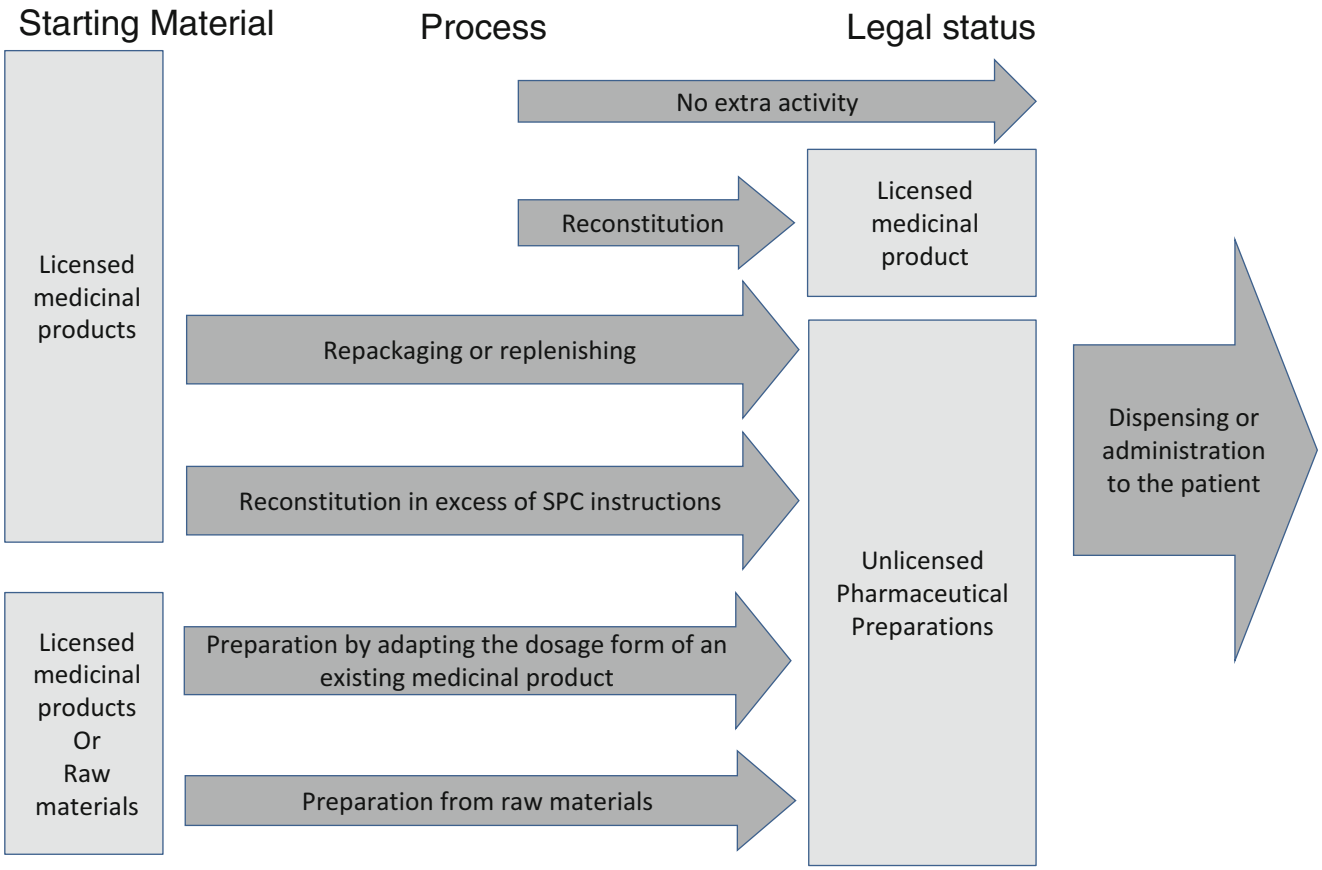

Fig. 1.2 Terminology of preparation activities

The terminology and definition of the activities is as follows:

Reconstitution: manipulation to enable the use or application of a medicinal product with a marketing authorisation in accordance with the instructions given in the summary of product characteristics or the patient information leaflet (Ph. Eur. Pharmaceutical Preparations). Often reconstitution is needed in excess of the instructions of the summary of product characteristics or the patient information leaflet, such as when a longer shelf life is assigned or when a different dilution with an infusion solution takes place. This action is legally considered as preparation. When speaking about the actual work process, that is the handling, it appears not sensible to distinguish between the processes. Therefore this book uses the term 'reconstitution' for reconstitution in the strict sense as well as for *Reconstitution in excess of the summary of product characteristics* or the patient information leaflet. If reconstitution is about parenteral medicines, as is often the case, the term 'aseptic handling' may be used in order to distinguish it from aseptic preparation or processing.

Preparation by adapting an existing product: reformulating a licensed product into a different dosage form suitable for the intended use, presented in a suitable and appropriately labelled container (after Ph. Eur. Pharmaceutical Preparations).

Preparation from raw materials: formulating active substances and excipients into a dosage form suitable for the intended use, presented in a suitable and appropriately labelled container (after Ph. Eur. Pharmaceutical Preparations).

1.2.2 Aseptic Preparation, Aseptic Handling and Reconstitution

The reconstitution of parenteral medicines in the strict sense as well in the extended sense (see Sect. 1.2.1) is very frequently performed in hospital pharmacies. The right performance of this process requires extensive precautions on procedures, premises, validation and control. However these differ considerably, due to working with closed systems, from the generally accepted precautions for aseptic processing from raw materials. The use of the term 'aseptic handling' therefore was felt justified.

1.3 Terminology

The Editors had to come to an agreement on a number of aspects that required compromise in the usage of descriptive terms and spelling.

1.3.1 Drug

The term 'drug' is not used. The reasons are because of its wider connotation in the area of abuse and because it is not discriminating between the active substance and the medicine. Instead of drug either the term 'medicine' is used or – when appropriate – 'active substance'. European legislation is thereby followed as well as international harmonisation. Only in compounded, mainly biopharmaceutical, terminology such as 'drug release' or 'drug distribution' the word 'drug' is used. The terms 'orphan drug' and 'drug shortage' are generally changed into orphan medicine and medicines' shortage (which is sometimes caused by shortage of an active substance).

1.3.2 Preparation

The Ph. Eur. defines preparation (of an unlicensed pharmaceutical preparation) as: the 'manufacture' of unlicensed pharmaceutical preparations by or at the request of pharmacies or other healthcare establishments (the term 'preparation' is used instead of 'manufacture' in order clearly to distinguish it from the industrial manufacture of licensed pharmaceutical preparations). As many situations apply to production of medicines in (hospital) pharmacies, the term 'preparation' is used most in the book. Sometimes it is quite obvious that it concerns manufacturing. 'Compounding', as a term for small-scale preparation often used in the US, is not used in this book.

1.3.3 Hazardous Substance

The definition of 'hazardous' in combination with substances follows the European Occupational Safety and Health legislation i.e. every substance that has been assigned a so-called H(azard)-statement. Carcinogenicity, Mutagenicity or Reprotoxicity (CMR) are reflected in specific H-statements, but many other types of toxicity exist. This approach should diminish the confusion that arises when 'hazardous' is considered synonym with CMR or, in other situations, even with CMR plus some specific types of toxicity. Let alone if 'hazardous substances' is considered synonym with the therapeutic class of antineoplastics.

1.3.4 Terms

Dosage forms, administration routes and containers usually follow the Ph. Eur. or are named according to the EDQM (European Directorate of Quality of Medicines) lists of

Table 1.1 Overview of the terminology used in relation to particle size reduction, mixing and de-agglomeration

Topic	Term	Description
Particles	Primary particles	Particles that consist of a single crystal
	Secondary particles	Particles are agglomerates
Particle size reduction	Milling	Particle size reduction by (different) forces
	Grinding	Milling a substance by hand
	Wet grinding	Grinding with an amount of liquid as small as possible for reasons of: preventing agglomeration, augmenting milling efficiency (grease effect) or for occupational safety and health reasons (to prevent the creation of dust particles)
	Pulverising	Smashing a material into a powder
	Comminuting	Reducing to powder (US)
Mixing and de-agglomeration	Dispersing	Distributing primary particles into a medium; may bring about the breaking up of agglomerates (de-agglomeration)
	Geometrically dilution (Triturating)	Mixing using the ratio 1:1 repeatedly
	Mixing (= blending)	Putting substances together to get a homogeneous distribution
	Rubbing	Intensely mixing (triturated) powders with a semisolid or liquid on a surface to obtain a smooth mixture
		Making into a (thick) paste
		Levigating (US)
	Triturating	Mixing a solid with a solid, semisolid or liquid substance in such a ratio and intensity that agglomerates are dispersed (de-agglomeration); de-agglomeration may take place if the right medium is chosen

standard terms. In other areas terms of the International Committee on Harmonisation (ICH), GMP and ISO are used where possible. The difference between industrial scale production and preparation in pharmacies has led to the use of other terms but they are defined, where used.

1.3.5 Dispersion

A main challenge of processing an active substance if it is not dissolved is the dispersion of the particles. This affects many dosage forms such as oral suspensions, cutaneous preparations and suspension-type suppositories. It appeared that this process could be performed in different ways on a small scale, making a difference in the result. It was felt justified to use different words for these different ways. Table 1.1 (also as Table 29.4) shows the result.

1.4 Spelling and Notation

1.4.1 Active Substances

The quality of specified active substances and excipients has to meet, in Europe, the European Pharmacopoeia criteria and thus are named according to the English monograph titles. If not included, another reference pharmacopoeia is given.

1.4.2 Spelling

As in European legislation the GB English spelling is used.

Commas are used to separate thousands in numbers instead of a space as in the European Pharmacopoeia and the stop sign that is common in many European Countries.

In some instances English words have been created, such as hydrophilise as a verb (instead of the description: making hydrophilic), considering that a French and German reader for instance will immediately understand what is meant.

1.4.3 Gender Neutral

Any reference, in the text, to the word ‘he’ should be taken to be gender neutral and to include ‘she’.

1.4.4 Greek Letters

Greek letters are indispensable part of specific formulas or equations. But in running text they better be changed into Latin. So: “α” becomes “alpha”. The reason behind is that with moving and copying texts between different word processing programs, as happens in editing and with using electronic books, symbols easily get lost or disfigured. The only exception is the chapter Statistics that definitely needs Greek letters as symbols, and μm that will not lead to misunderstandings.

1.5 Formulations

The book is not intended to be a formulary but many preparations' formulas are included in order to exemplify principles described in the texts. Some readers may wish to use the formulas in practice, however for that purpose more information is necessary, such as the detailed method of preparation, stability data, appropriate containers, background information and justification, etcetera. The original source formulary, e.g. FNA (see Sect. 39.4.5) or NRF (see Sect. 39.4.2) should be consulted to meet that demand.

The amounts in formula-tables are virtual amounts, that is: they are not meant as "to be weighed" or to provide a preparation instruction. They are used to illustrate the percentages of all substances.

1.6 Examples, Guidelines, Legislation, Ph. Eur.

Most information in the book is universally applicable in the field of preparation and manufacturing of medicines. Focus on specific items has been guided by European legislation and guidelines, and by country-specific examples put forward by the authors and an editorial advisory group. Most Countries in Europe have produced Guidelines, Publications and Textbooks to cover aspects of pharmacy that is of particular interest to their unique practice. The emphasis in each Country differs, usually as a result of some historic incident, which focused efforts in a particular direction. This means that a single textbook for all will cover topics and practices, which may be new to some, but old to others. The main legislative starting point for this book is the Ph. Eur. especially the monograph Pharmaceutical Preparations. Other basic legislation used is the EC legislation on medicines, the EU-GMP (Good Manufacturing Practice) and guidelines of ICH (International Conference on Harmonisation).

If the Ph. Eur. is referred to it is always the current edition at time of closing the manuscript (September 2014) that is meant.

Comments on the interpretation of regulation is always offered as a snapshot in time and is only valid as long as the wording of the legal texts is unchanged compared to the cited reference.

1.7 References

It was noted that scientific publications in this field are sometimes lacking where practical experience, guidelines as well as procedures may be widespread. Therefore some literature quotes in the original Dutch book have been retained even though, as they are in Dutch, they cannot be considered truly available to all. In cases where there is no literature we rely on a scientific base, sound thinking and explanation, then best practices and then regulations. The aim is to provide our colleagues with the systematic knowledge that gives them the tools to act professionally in whatever situation they will find themselves.

Prescription Assessment

2

Andrew Lowey and Stefanie Melhorn

Contents

Abstract

Upon receipt of a request from a prescriber for a pharmacy preparation, the pharmacist must decide whether the request is appropriate and reasonable, and judge the level of risk associated with proceeding with the request. The pharmacist must also consider the risks of not supplying a medicine which may lead to the patient not receiving treatment. Further discussion with the medical team may be needed. This chapter approaches the risk assessment of the prescription in a structured way, referring to procedures and forms from different countries. The assessment also includes the feasibility of producing a preparation of appropriate pharmaceutical quality and with all necessary clinical information.

Pharmacy legislation defines the framework in which pharmacists can prepare medicines, however there are other legislative and quality frameworks that they must be aware of if other categories of products are requested, such as biocides, medical devices, or placebo's, or agents used for euthanasia Veterinary and homeopathic medicines are also dealt with, as are raw materials, especially hazardous materials and precursors.

Keywords

Risk assessment • Prescription • Preparation • Reasoned assessment

2.1 Pharmacy Preparation: Way Out or Unjustified

Case Suppositories with Hydrocortisone

Prescription states: Hydrocortisone suppositories 240 mg, 6 units

Dosage – Use 1 suppository when required as directed

(continued)

Based upon the chapter Beoordeling recept by André Wissenburg en Frits Boom in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_2,

The parents of a 2 month old girl Klaartje come to the pharmacy with this prescription. The suppositories have been recommended by an endocrinologist at the hospital. Upon inquiry it appears that Klaartje suffers from a condition known as Prader Willi syndrome, a hereditary disorder which affects hypothalamic function; the adrenal cortex produces insufficient corticosteroid at times of stress.

An intramuscular injection with a licensed pharmaceutical preparation that contains hydrocortisone sodium succinate would constitute a major treatment option. However, the child's parents do not want to give an injection to their child. Klaartje drinks very reluctantly as all babies with the Prader Willi syndrome. The parents don't consider administration with the feeding of the contents of a capsule or of crushed tablets as a reliable option. Therefore, the doctor has suggested a rectal preparation.

This case is typical of requests for pharmacy preparations; in order to give tailor-made care, the doctor has prescribed an individual preparation instead of a licensed pharmaceutical preparation. When the oral route would have been an option, licensed oral solid medicines had to be adapted anyway because of the low dose required.

Before the pharmacist starts preparing the suppositories, he needs to perform a risk assessment to establish the likely safety, quality and efficacy of the product (in comparison with alternative treatment options).

Pharmacy preparation allows the doctor and pharmacist to provide individualised and tailor-made pharmaceutical care. The preparation of a medicine in the pharmacy fulfils a need when the licensed pharmaceutical preparation is not available (see also Sect. 3.2.2) or when a licensed pharmaceutical preparation does not satisfy a specific situation.

However, pharmacy prepared products are not subject to the same levels of scrutiny with respect to quality assurance and efficacy as licensed medicines; therefore prescribers and pharmacists cannot make the same assumptions of quality, safety and efficacy about these products as they do for licensed medicines.

This is due to the wide range of elevated risks associated with pharmacy preparation, including calculation and manipulation errors, formulation failures leading to overdose or underdose, possible toxicity from raw materials and microbiological contamination. The relative lack of pharmacovigilance or monitoring systems for pharmacy prepared products also means that the likelihood of detection for any errors that lead to side effects is low.

Despite the relative lack of information about side effects related to pharmacy prepared products, there have been reports of catastrophic errors associated with them, including an error in the US that led to a 1,000-fold overdose of clonidine in a 5 year old child [1]. A high profile error also occurred in 1998 in the UK, when a baby died following a calculation error in preparing peppermint water in a community pharmacy [2].

Therefore, upon receipt of a request from the doctor, the pharmacist must examine the situation and decide whether the request is appropriate and judge the level of risk associated with proceeding with the request. Before proceeding, the pharmacist should review all other potential treatment options. The use of a licensed product in line with its approved indication should be strongly advocated unless there is a specific reason not to use such a medicine. However, the pharmacist must also consider the risks of *not* supplying a medicine which may lead to the patient not receiving treatment. In this context, it should be recognised that some patients do have special clinical needs which cannot be met by other viable options.

The pharmacist must make every effort to ensure that the medicine produced is of appropriate pharmaceutical quality and is fit for the intended purpose; an approved or authorised formula should be used wherever possible. Where such formulae are not available, steps should be taken to minimize risk where possible e.g. restricted shelf life, fridge storage (if applicable), use of licensed starting materials etc.

The same principles apply for reviewing prescriptions for pharmacy preparations as for licensed medicinal products.

2.2 Prescription Assessment

2.2.1 Alternative Treatment Options

Before a pharmacist decides to prepare a product, he must consider various alternative treatment options available.

Depending on legislative situation in the country and the relation between pharmacists and physicians, options may include:

- Use of a (licensed) medicine which is then administered by an alternative route or method e.g. use of a soluble or dispersible product or indeed rectal product in patients who have difficulty swallowing whole tablets.

- Use of an appropriate licensed formulation of an alternative medicine from the same therapeutic class (e.g. using a licensed liquid formulation of lisinopril rather than preparing a captopril oral suspension).
- Manipulation of a licensed medicine prior to each dose e.g. dispersing a tablet in a small volume of water or halving tablets (Note: the practice of dispersing a tablet in water and then using an aliquot of the liquid is associated with a high risk of inaccurate doses and is generally not recommended except in extraordinary circumstances). For the general approach of options when difficulties swallowing solid licensed medicines is the reason for the request, see Sect. 37.6.2.
- Use of a product intended for a different route e.g. use of an injection orally.
- Use of an imported product which bears a product license in its country of origin (a check should be made to ensure that the absence of a local license is not due to a revocation of a previous license).
- Purchase of a batch-manufactured unlicensed product from an alternative supplier (e.g. 'Specials Manufacturers' in the UK). Note that this practice is not allowed or highly restricted in some countries in Europe (see Sects. 3.9 and 3.12).

2.2.2 Considerations Upon Receiving a Request

When faced with a request for individualised pharmacy preparation, a pharmacist may find it helpful to consider the following questions in order to reduce or avoid risks:

- Has a risk assessment been carried out that has established pharmacy preparation as the most appropriate choice for this patient?
- Are there other more suitable alternatives, is a licensed product available, could a licensed product be adapted for each dose, are there other batch-manufactured products available, could you use an imported product that has a licence in a mutually-recognised country?
- What is the risk of not treating the patient?
- Does the active substance have a narrow therapeutic index?
- Can a peer-reviewed and evidence-based formula be used? If not, have the physico-chemical properties of the active substance been considered, and have steps been taken to minimise risk and complexity (e.g. reduce shelf-life, store in fridge, prepare a solution instead of a suspension, use commercially available suspending agents which have been tested with the active substance in question and pharmaceutical-grade raw materials)?
- Are the facilities and equipment appropriate and calibrated?
- Has a health & safety risk assessment been carried out?
- Are there systems in place to monitor the efficacy and safety of the product? Is the patient being monitored closely (if appropriate)?

2.2.3 Structured Assessments

Some pharmacists have suggested a structure approach to the decision-making process: e.g. Leeds approach, German reason check, Risk-benefit Form.

2.2.3.1 Leeds Approach

At Leeds Teaching Hospitals NHS Trust in England, the Pharmacy department has a 'catalogue' of authorised pharmacy preparations, which is periodically reviewed to ensure that other more suitable options are not available. Each of the approved preparations on the catalogue have been reviewed by a group of senior technicians and pharmacists to ensure that they have a sound evidence base and are backed by an authorised preparation instruction and agreed label.

This means that the clinical pharmacist has some assurance of the likely quality of the end product. They must, however, still judge if the individual formulae is appropriate for the intended patient. This is the difference between a product of high quality and one that is appropriate or 'fit for purpose'.

If a 'non-catalogue' (non-standard) preparation is requested, the requesting pharmacist must complete a form (see Fig. 2.1) to acknowledge that other options have been considered, along with the possible risks associated with the preparation. High risk products can still be authorised if the benefits outweigh the potential risks; however the authorisation must come from one of the senior management team in the department.

This process creates an appropriate barrier to pharmacists who might otherwise decide to authorise ad hoc or unusual formulations without considering the associated risks. The group of senior pharmacists and technicians then meet every few months to review the requests for non-catalogue preparations, and review whether other options should be pursued e.g. purchase of a licensed product from a foreign country, use of a batch-manufactured product rather than an extemporaneously-prepared product for an individual etc.

As a guide to help the risk assessment, the department provides a risk assessment matrix to highlight potential problems to the clinical pharmacist, see Fig. 2.2.

Leeds Teaching Hospitals NHS Trust
Pharmacy Services

Document EXP01

Request Form for a Non-Catalogue Extemporaneous Product

Section A: Request Details

Patients Name:…… **Consultant:** ……

Ward: ……..… **Weight:** ……

Date of Birth: ……..... **Hospital:** ……..

Pharmacist Name: …… **Date:** ……
Print Name Signature

Requesting Doctor: …… **Grade:** …… **Date:** ……

Drug Requested:

Name	Route	Dose	Approximate Duration of treatment	Inpatient/ Outpatient

Clinical Reason for use: ……..

Section B: Points to consider (please circle)

Is an alternative formulation available?	**Yes/No**
Is an alternative route available?	**Yes/No**
Is an alternative licensed product available?	**Yes/No**
Can the product be sourced from a licensed specials manufacturer?	**Yes/No**
Is an alternative method possible? (e.g. tablet crushing & dispersing in water / oral administration of injection)	**Yes/No**
Is the medicine licensed for the indication?	**Yes/No**
Could the prescription be changed to a catalogue presentation?	**Yes/No**

Comments:……
……
……
……
……
……

Fig. 2.1 Request form for a non-catalogue extemporaneous product

Leeds Teaching Hospitals NHS Trust
Pharmacy Services

Section C: Risk Assessment

Use the risk assessment matrix (EXP03) to assess risks for each category and overall risk. (Please attach evidence to form)

- Risks to Quality (Formulation & Stability) Low / Medium / High (Please circle)

  Comments:

- Clinical Risks (Safety & Efficacy) Low / Medium / High (Please circle)

  Comments:

- Health & Safety Risks (COSHH) Low / Medium / High (Please circle)

  Comments:

Overall Risk Rating: **Low / Medium / High** (Please circle)

Section D: Approval

Decision to make product: **Yes / No** **Signed:** **Date:**

For Low and Medium Risk products obtain approval from CPTL. PRINT NAME ……

For High risk products obtain approval from LEVEL D PHARMACIST. PRINT NAME……

Section E: Preparation

Notify dispensary and arrange for a blank worksheet and labels to be prepared. Authorize worksheet. **Note Worksheet authorization must occur before product is made**.

Photocopy worksheet and retain copy in the dispensary. Attach form EXP01 to the original completed worksheet and leave in appropriate wallet in 'Green Extemp File' (found in LGIIP, LGIOP, CLA, SJIP, CDH, WGH, CKE, CAH dispensaries).

If this item needs to be added to catalogue refer to the 'Catalogue Request Pack' (found in dispensary Extemporaneous Dispensing File) Also refer to the Extemporaneous Dispensing Policy.

These documents will be reviewed periodically by the Extemporaneous Steering Group/Extemporaneous Review Group.

DOCUMENT EXP03 EXTEMP PRODUCT RISK ASSESSMENT MATRIX

Assessment of Overall Risk

- Assess risk for each category: Quality; Safety & Efficacy; COSHH.
- The highest individual rating gives the overall risk category.
- For high and medium overall rating contact:
  - ❖ QC for quality issues
  - ❖ Clinical Lead for clinical issues (categorisation of drug toxicity/ TI; patient monitoring measures)
  - ❖ COSHH Team for COSHH issues

						SCORE
Risks to Quality (Consider effect of preparative process on drug stability and uniformity of dose)	Validated formula and supporting stability data available. • Published papers • Pharmacopoeia • Developed by licensed manufacturer Rating: **Low**	• Formula available, but not validated. No supporting stability data. • Evaluation of formula and shelf life from first principles by suitably experienced staff. • Experience of safe and effective use in NHS. Rating: **Low**	• Formula available, but not validated. • No supporting stability data or evaluation. • Experience of safe and effective use in NHS. • Reduced shelf life (max 7 days). Rating: **Medium**	• Formula available, but not validated. • No supporting stability data or evaluation. • No evidence of safe and effective use in NHS. Rating: **High**	No Formula available. Rating: **High**	
Risks to Safety/Efficacy (Consider effect of formulation on drug bio-availability)	Low Toxicity. Short term use Rating: **Low**	Wide Therapeutic Index (TI) Short term use Rating: **Low**	Wide Therapeutic Index Maintenance Therapy Rating: **Medium**	Narrow Therapeutic Index Short term use Bioavailability could be significantly changed by crushing tablet Rating: **High**	Narrow Therapeutic Index Maintenance Therapy Bio-availability could be significantly changed by crushing tablet Rating: **High**	
H & S Risks (see extemp COSHH Guidance)	Full supporting COSHH data Control measures in place Rating: **Low**		Inadequate supporting COSHH data No control measures in place. No COSHH assessment carried out. Rating: **High**			

Overall Risk Assessment: HIGH MEDIUM LOW

Low Risk: Prepare worksheet & make in accordance with local SOP's. Use licensed or QC approved starting materials only.

Medium Risk: Make for short-term use only and monitor patient for clinical effect and ADRs. Consider outsourcing to a specials unit or alternative therapy for long term use.

High Risk: Consider all alternatives before making - only make as last resort. Monitor patient closely for clinical effect, toxic effects and ADRs.

Document EXP03 Second Edition April 2009

Fig. 2.2 Extemporaneous product risk assessment matrix

2.2.3.2 German Reason Check

In Germany, pharmacists must perform 'reason checks' (Plausibilitätsprüfung) to establish the likely safety, quality, and efficacy of the product they want to prepare. The Pharmacy Practice Order (Apothekenbetriebsordnung, ApBetrO) specifies parameters of the preparation formula that must be checked, whether it is a doctor's prescription or self-medication on patient's request. Beyond that, the guideline recommends that the pharmacist considers the overall rationale for treatment.

A form has been developed (Fig. 2.3) for the performance and documentation of the reason check. Some parts will be dealt with.

Regarding "Qualitative and quantitative composition": Substances used as active substance or as an excipient in pharmaceutical preparations have to be described in an individual monograph of the European Pharmacopoeia or comply with the requirements of the relevant general monographs (see also Sect. 23.1). Cosmetics and medicinal products may only be used if the required quality is documented. In Germany it is not allowed to change or add any active substances without permission of the prescriber. This does not apply to excipients that have no pharmacological effect.

Regarding "Compatibility": if components of a prescribed preparation are not compatible (or there is a lack of evidence), it does not mean automatically that it should not be prepared. The preparation needs to show sufficient compatibility up to the in use expiry date; it may be possible to produce a preparation with a shortened but useful shelf life. Interactions between the active substances and excipients can however make it impossible to produce a preparation of sufficient quality. These incompatibilities can be visible or invisible during preparation. The attending pharmacist has to verify if incompatibilities are apparent. More information about incompatibilities is to be found in references such as Fiedler (Sect. 39.2.2), Handbook of Pharmaceutical Excipients (Sect. 39.2.3), Martindale (Sect. 39.2.4), Handbook of Extemporaneous Preparation (Sect. 39.4.6), Kommentar zum Arzneibuch (Sect. 39.4.8) and Trissel's Stability of Compounded Formulations (Sect. 39.4.14).

Regarding "Stability and shelf life": These items are amply discussed in Chap. 22 Stability. Stability is influenced by the solubility of all substances in the preparation, pH of the base, pH at which the active substances are stable, and the influence of oxygen and light. Shelf life is restricted due to:

- Chemical, physical, physico-chemical reactions
- Rheological changes
- Formations of toxic degradation products
- Microbiological growth
- Decrease in concentration of the active substance
- Incompatibilities or issues caused by the container

2.2.3.3 Risk-Benefit Form [4]

A risk-benefit form has been elaborated for extemporaneous and for stock preparation (Figs. 2.4 and 2.5). They enable the pharmacist to list and balance the benefits and risks of the clinical and pharmaceutical qualities of the required pharmacy preparations. The form follows the process for handling of requests for preparation, and defines decisive steps, levels of evidence of decisions, individuals concerned and responsibilities.

Possible benefits include:

- Unique therapeutic value if there is no comparable authorised medicine available
- Improved patient friendliness and therefore a better compliance with therapy
- Improved safety of health care processes (using preparations that don't need any reconstitution steps on the wards or in nursing homes)
- Improved occupational safety and health (OSH) of health care personnel (by diminishing exposure from hazardous active substances)
- (Lower price)

Possible risks include:

- Uncertainty about therapeutic safety and efficacy
- Design failure causing quality defects, like poor bioavailability or poor content uniformity
- Preparation risk: if the actual pharmaceutical quality system cannot guarantee that the preparation will fully meet specifications
- Discouraging the marketing of authorised of medicines

The forms for extemporaneous and stock preparation use the same benefits and risks. With extemporaneous preparations the balance refers to an individual patient. With stock preparations the balance results in the definition of the group of (anonymous) patients for whom, or care situation in which, the benefits may outweigh the risks.

Clinical benefits and risks are assessed on the front of the form by the attending pharmacist, who decides if the request adds enough value to be considered further. On the back the preparatory pharmacist assesses the risks of design and preparation. He also checks the feasibility: if necessary conditions are met such as availability of starting materials or sufficient control of the health and safety risk of the pharmacy personnel. Over-all it is the preparatory pharmacist who decides:

- In case of an extemporaneous preparation if he accepts the request(or not)
- In the case of a stock preparation on the conditions on which he will make this preparation available.

Balancing benefits and risks (see Fig. 2.6) is not a matter of mathematics but of professionalism, responsibility and transparency. The forms therefore are transparent about the decisions and show who made them.

Checklist for Reason Check			Actions Notes
1. Sufficiency and readability of the prescription			
Is the prescription complete?	□ yes	□ no	
Is everything readable?	□ yes	□ no	
Are there any perceivable mistakes?	□ yes	□ no	
2. Safety and treatment concept, dosage and dosage instructions			
Are there questionable ingredients?	□ yes	□ no	
Is the treatment concept obvious?	□ yes	□ no	
Is the dosage sensible?	□ yes	□ no	
Are the dosage instructions sensible?	□ yes	□ no	
3.Qualitative and quantitative composition			
Is the concentration of the active substances higher than the indicative concentration?	□ yes	□ no	
Is the concentration of the active substances within the normal dosage range?	□ yes	□ no	
Are all ingredients available in the required pharmaceutical quality?	□ yes	□ no	
Does the prescription conform to a standard formulation?	□ yes	□ no	
If so, please specify the source:			
Are there any similar standard formulations?	□ yes	□ no	
If so, please specify the source:			
4. Compatibility			
Are the ingredients compatible?	□ yes	□ no	
If no, please specify the incompatibilities:			
5. Stability and shelf life			
Is there a need for an added buffer?	□ yes	□ no	
Is the microbiological stability sufficient for the targeted shelf life?	□ yes	□ no	
Is the prescribed preparation stable enough for the targeted shelf life?	□ yes	□ no	
Additional assessments			
Date, Signature Responsible Pharmacist/Delegate			

Fig. 2.3 Form for German reason check ([3] translated). Further explanation about items 3, 4 and 5 is given in Sect. 2.2.3.2

Request for extemporaneous preparation	
	Final formulation or action
☐ Availability as authorised medicine checked	
Patient (name, details):	
Name physician or GP, specialism, date, discussion:	
Indication:	
Standard therapy:	
Reason of request	
☐ Non-availability authorised medicine ☐ Unique therapeutic value ☐ Improvement patient-friendliness ☐ Improved health and safety health care personnel ☐ Different: ……	Comments / references / literature / attachments:
Level of consensus about evidence	
☐ National (authorisation, guidelines, consensus), that is: …….. ☐ Regional: …….. ☐ Local: …….. ☐ Individual physician, GP, pharmacist: …….. Experience with this therapy: ……	
Conclusion Request will (not) *) be considered subsequently.	Assessed by attending pharmacist: …… (name, initials)

*) delete where not applicable

Design	
Design of formulation and of preparation process	☐ Analogous to …… ☐ From literature: …… ☐ Own design, based on: …… Attachment(s): ……
Is the design well-considered enough if balanced with the added value for the patient?	Yes / No*) Comments: Discussion with attending pharmacist: …… ……..

Feasibility		
Raw materials available?	yes/no*)	Comments:
Sufficiently stable for clinical use?	yes/no*)	
Is the health and safety risk of the pharmacy personnel controllable?	yes/no*)	
Other preconditions	yes/no*)	
Another aspect: ……		
Conclusion: preparation is (not) *) feasible		

Decision about request	
☐ To prepare for this individual patient (p.t.o.) ☐ No preparation: no well-considered design available ☐ No preparation: the request adds value for the patient indeed, the design is well-considered but the preparation is not feasible ☐ Other . ……	
Result discussed with:	Attending pharmacist (name, date): …… ……
Signature: Preparatory pharmacist (name, date, signature): ……	

*) delete where not applicable

Fig. 2.4 Form for balancing risks and benefits of an extemporaneous preparation; front and back side (see Sect. 2.2.3.3)

Stock preparation	
(formula, strength, administration route, dosage form)	
Indication:	
Patient population:	
Standard therapy:	
☐ Availability as authorised medicine checked	
Reasons for preparation	**Level of consensus about evidence**
☐ Non-availability authorised medicine ☐ Unique therapeutic value ☐ Improvement of patient-friendliness ☐ Improved safety of health care processes ☐ Improved health and safety of care personnel ☐ Authorised medicine available but not reimbursed ☐ Different: ……	☐ National (authorisation, guidelines, consensus), that is: …….. ☐ Regional: …… ☐ Local: ……... ☐ Individual physician, GP, pharmacist: …… Experience with this therapy: ……
Comments / references / literature / attachments:	
Conclusion Risk/benefit assessment is in*)/sufficiently founded to continue the assessment.	Assessed by pharmacist: …… (name, initials)

*) delete where not applicable

Design	
Design of formulation and of preparation process	☐ Analogous to …… ☐ From literature: …… ☐ Own design, based on: …… Attachment(s): ……
Is the design well-considered enough if balanced with the added value for the patient?	Yes / No*) Comments:

Feasibility		
Starting materials available?	yes/no*)	Comments:
Sufficiently stable for clinical use?	yes/no*)	
Is the health and safety risk of the pharmacy personnel controllable?	yes/no*)	
Other preconditions	yes/no*)	
Another aspect: ……		
Conclusion: preparation is (not) *) feasible		

Decision about suitability for stock preparation	
☐ To prepare only for patients from the own pharmacy ☐ To prepare for patients nationwide ☐ No preparation: no well-considered design available ☐ No preparation: the preparation is valuable and the design is well-considered but the preparation is not feasible ☐ Other . ……	
Result discussed with:	…… ……
Signature: Preparatory pharmacist (name, date, signature): ……	

*) delete where not applicable

Fig. 2.5 Form for balancing risks and benefits of a stock preparation; front and back side (see Sect. 2.2.3.3)

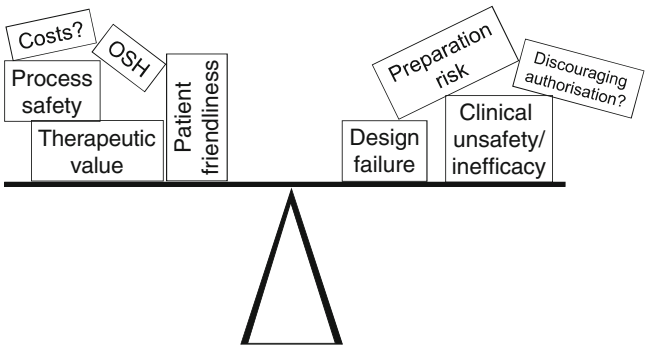

Fig. 2.6 Balancing benefits and risks of specific pharmacy preparations (see Sect. 2.2.3.3)

2.3 The Prescription

2.3.1 Legal Requirements

A prescription is a request from a prescriber (usually a doctor) to a pharmacist to dispense a medicine in the stated amount, strength and method of use. Each country has its own medicines law which will define the exact requirements of a prescription. However, there is a standard data set used with the European Economic Area (European Union plus Lichtenstein, Norway and Switzerland) as given in Table 2.1.

In some countries, the list of prescribers may include 'non-medical prescribers' such as nurses, pharmacists or chiropodists. These other prescribers may have limited formularies in some countries. However, the law varies between different countries; the validating pharmacist must takes steps to assure themselves that the prescriber is appropriately registered to prescribe.

The pharmacist should consult the prescriber if it is possible or more appropriate to use a different medicine. A licensed medicinal product should be used in preference to a pharmacy preparation, if an appropriate product is available.

When a pharmacist considers that the delivery of a medicine carries an unacceptable level of risk, he can refuse to dispense the medicine to the patient, as pharmacists have a duty of care to the patient. In this situation, they must contact the prescriber to discuss possible alternatives.

2.3.2 Consultations with the Prescriber and the Patient

2.3.2.1 Consultation About a Prescription

When there are doubts about the pharmaceutical options, consultation between the pharmacist and the prescriber takes place. The pharmacist can advise on the options for treatment following consideration of the diagnosis and pathophysiology by the doctor.

A discussion between the pharmacist and the patient (or carer) may also be needed in order to make the most appropriate treatment decision. This is often the case in paediatrics, and the parent or carer may require some assurances about the need for medication, especially if the treatment is long term.

Table 2.1 Non-exhaustive list of elements to be included in medical prescriptions in the EEA [5]

Identification of the patient	Surname(s)
	First name(s) (written out in full, i.e. no initials)
	Date of birth
Authentication of the prescription	Issue date
Identification of the prescribing health professional	Surname(s)
	First name(s) (written out in full, i.e. no initials)
	Professional qualification
	Details for direct contact (email and telephone or fax, the latter both with international prefix)
	Work address (including the name of the relevant Member State)
	Signature (written or digital, depending on the medium chosen for issuing the prescription)
Identification of the prescribed product, where applicable	'Common name' as defined by Article 1 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
	The brand name if:
	(a) the prescribed product is a biological medicinal product, as defined in point 3.2.1.1.(b) of Annex I (Part I) to Directive 2001/83; or
	(b) the prescribing health professional deems it medically necessary; in that case the prescription shall shortly state the reasons justifying the use of the brand name
	Pharmaceutical formulation (tablet, solution, etc.)
	Quantity
	Strength, as defined in Article 1 of Directive 2001/83/EC
	Dosage regimen

Adherence to treatment regimens is influenced by a number of other factors, including the formulation (e.g. solid or liquid), administration route (e.g. rectal or oral), dosage size and frequency, and the organoleptic qualities of the medicine chosen (e.g. smell, appearance, flavour). By choosing a formulation that is easy to administer and by giving good information and instruction, the patient is more likely to comply with their treatment regimen.

Case – Vitamin ADEK Mixture

Pim is 14 years old and suffers from cystic fibrosis. Due to his illness, he cannot absorb fat-soluble vitamins well. The paediatrician recommends that Pim needs treatment with vitamin A, D, E and K in various oral preparations. The licensed pharmaceutical preparation consisting of 400 IU vitamin D is no longer available, meaning Pim potentially has to take even more tablets than previously.

The parents express concern to the paediatrician that Pim is unlikely to comply with his treatment. Therefore, the paediatrician requests a pharmacy preparation in which all vitamins are combined.

The pharmacist designs an oral liquid based on a standard formulation for an oral vitamin D solution. The mixture contains, per millilitre, 750 IU vitamin A, 250 IU vitamin D, 50 mg vitamin E and 0,25 mg vitamin K.

The pharmacist chooses an aqueous solution, because of the better availability of fat-soluble vitamins in patients with absorption disorders, such as cystic fibrosis patients. Due to a lack of data about the shelf life of the mixture and the absence of a stability-indicating analytical assay, a shelf life of 1 month in the refrigerator is assigned.

Pim now only has to use daily 4 mL of the oral solution that the pharmacy prepares for him every month.

Various national formularies exist and may be useful to consult during discussions with the relevant doctor e.g the Dutch national child formulary (www.kinderformularium.nl) [6] contains various pharmacy preparations, which are included in the Dutch pharmacists Formulary (FNA, see Sect. 39.4.5).

Such national formularies are good starting points for formulations as they may have been tested or supported by published or validated formulae. A second example is the German Formulary (Neues Rezeptur-Formularium, see Sect. 39.4.2). In the UK, the Handbook of Extemporaneous Preparation (see Sect. 39.4.6) also lists a selection of 50 commonly used formulae, and the British Pharmacopoeia has a small number of formulations detailed. The existence of validated formulae then allows for the potential for batch manufacture and suitable quality control testing.

Another advantage of using a national formulary is that it is kept up to date, with obsolete formulations removed or replaced regularly. This may be due to a change in recommendations (e.g. an excipient is no longer considered appropriate) or when a suitable licensed formulation becomes available.

Ferrous chloride oral drops had been removed from the Dutch formulary as there are now sufficient alternatives like Ferrous fumarate oral suspension 20 mg/ml as a licensed pharmaceutical preparation. That product however is so viscous that a small volume, which is necessary for young children, cannot be measured accurately. In the FNA therefore a Ferrous chloride oral solution 45 mg/ml has been reintroduced. This oral solution contains 20 mg iron (II) per ml which is suitable for children and it is not viscous. So the necessary small amounts can be easily measured.

2.3.3 Dose

The doctor writes the dose on the prescription and the pharmacist checks or 'validates' this dose. The validation process may take place with the help of a pharmacy computer system or electronic prescribing system. The usual support offered by pharmacy computer systems is limited if local formulae are used, and the pharmacist may need to consult a range of reference sources when considering the appropriate indications, doses, likely side effects and contra-indications. Extra care is required with some patient populations, such as children and the elderly.

2.3.3.1 Dosage Expression

The way in which the prescriber writes the dose is dependent on the administration form. Capsules and suppositories are given in an amount (usually milligrams) per dose unit followed by the number of units and the daily or weekly dose. For example:

R/ Folinic acid capsules 10 mg
x 10
1 capsule once a week

In the case of oral liquids, the doctor will write the strength in milligrams per millilitre followed by the amount and dose. In the case of electrolytes the strength is often written in millimol per millilitre because the dosages of electrolyte are based on blood concentrations. For example:

R/ Magnesium gluconate oral solution 0,1 mmol/mL
300 mL
1 mmol 3 times a day

For the preparation and the dose check, it may be necessary to convert the strength to milligrams per millilitre. In case of the oral solution in this prescription magnesium gluconate dehydrate is used. Therefore, the equivalent strength is 45 mg/mL. The above prescription can then be read as:

R/ Magnesium gluconate oral solution 45 mg/mL (Magnesium 2,43 mg/mL)
300 mL
10 mL 3 times a day

In the case of medicines for cutaneous use (e.g. dermatology medicines), the concentration of the active substance is usually written as a percentage. The prescriber writes the amount and the frequency with which the dermatologic medicine has to be applied. The doctor usually writes the part of the body on which the patient should apply the preparation. In this way the pharmacist can check whether the prescribed amount is sufficient. Furthermore it is also important to know whether the cutaneous medicine has to be applied thickly (liberally) or thinly. A practical device for dosing a cutaneous preparation is the fingertip unit (FTU), see Table 12.3. In Germany, the Neues Rezeptur-Formularium for doctors [7] contains a useful outline figure for the prescriber to mark the area of application (Fig. 2.7).

The pharmacist must look carefully at the chemical form in which the active substance (see Sect. 23.1) of the preparation is prescribed (or meant to be prescribed), because the active substance may be available in various forms such as a base, ester or salt. Also the amount of water of crystallisation in the raw material may vary. E.g. folinic acid is dosed as the calcium salt. The doctor may use a brand name in the prescription, in this case Leucovorine®. This contains 15 mg folinic acid in the form of calcium folinate.

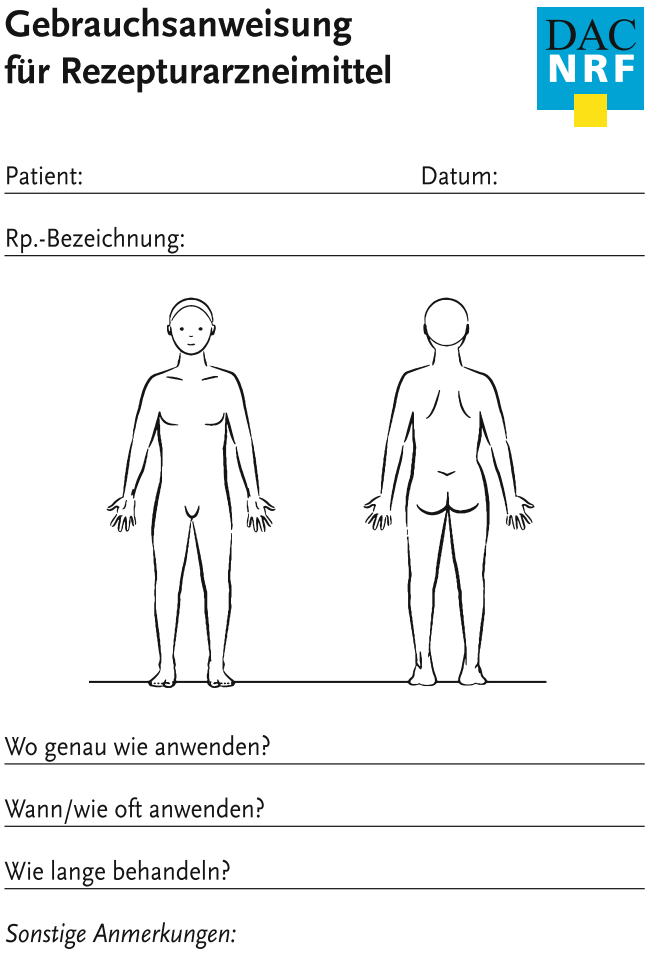

Fig. 2.7 Form for the instructions for use of dermatological medicines, © GOVI-Verlag Pharmazeutischer Verlag

2.3.3.2 Paediatric Population

Children regularly get prescribed medicines that are licensed only for adults or are licensed for use in other indications in children. This is called 'off-label' use and in this case the medicine is used in an 'unlicensed' manner.

Unlicensed medicines used in children are usually prepared by utilising raw materials or through adapting a dosage form designed for an adult population. Often there is limited data available about the dose and side effects in children. This means that consultation between the prescriber and pharmacist may be necessary.

In 2007 the Nederlands Kenniscentrum Farmacotherapie bij Kinderen (NKFK) was founded. It was established to help improve information available about medicines use in children. One of the activities of the NKFK is the compilation and publication of the national children formulary in the Netherlands) [6]. In the UK, the Medicines for Children Research Network [8] has been established to investigate formulation quality and the practice of manipulation of dosage forms before administration e.g. cutting tablets, opening capsules etcetera It is preferable to use an active substance that has been used previously in a pediatric population, as information about the dose, pharmacological effect and side effects will already be available. Doses for babies and children are commonly expressed in mg per kg body weight. For medicines with a large therapeutic window, this approach is satisfactory. However, it must be recognised that during the growth and development of a child, the pharmacokinetic parameters change continuously. Children are not small adults and neonates are not small children. When considering active substances with a narrow therapeutic window, a dose in m^2 body surface may therefore be a more accurate basis for dose calculation and adjustment. This is because some physiological parameters, which are directly related to the elimination of medicines, are better correlated to body surface e.g. hepatic and renal function.

Various formulae for calculating body surface area can be found in literature [9]. For example, the Dutch kinderformularium [6] uses the Mosteller formula as below:

$$\text{Body surface}\,(\text{in}\,\text{m}^2) = [\text{length}\,(\text{in}\,\text{cm}) \times \text{weight}\,(\text{in}\,\text{kg})/3{,}600]^{0.5} \quad (2.1)$$

Tables with length, weight and body surface of children of different ages with normal proportions [6] are convenient when one does not have the length and weight of the child. The British National Formulary (BNF) for Children in the UK also has tables for guidance, using the Boyd equation [10]. Finally the result has to be rounded to a practical strength for the product to be prepared.

Case Hydrocortisone Suppositories 240 mg

X 6

1 suppository when required

The pharmacist consults reference sources which suggest a rectal dose of 100 mg/m^2 body surface for stress situations in children with adrenal cortex disorder.

Klaartje is 2 months old and a girl of that age has an estimated body surface of 0.27 m^2. This means that the prescribed dose is too high. Discussions with the prescribing endocrinologist confirm that a prescribing error has been made. Hydrocortisone suppositories of 24 mg should have been prescribed.

In some cases, it may be necessary to estimate or derive a paediatric dose from a proportion of the adult dose, using a comparison of relevant body surface areas. However, this is a very approximate calculation, and further discussion with the prescriber will be needed to agree a final dose.

Usually the frequency of administration is similar to that of adults. However, this does sometimes require amendment. E.g. fluconazole dosing frequency varies with age, due to the changes in elimination.

2.3.3.3 Cutaneous (Dermal) Medicines Used in Children

Children and particularly babies have a large relative body surface area. Premature babies also have a thinner skin than adults, and lack the outer skin layer known as the horny layer or stratum corneum. In a young child with eczema, the skin may also be more damaged than in an adult with eczema. Therefore, the skin functions less well as barrier. Furthermore, application of any creams or ointments under a nappy or diaper prevents trans-epidermal water loss and leads to an increased absorption of the active substance.

Due to the larger risk of adverse effects and toxicity, certain medicines are not administered on the skin of young children. e.g. Salicylic acid is preferably not used on children younger than 2 years old and certainly not on large surfaces. Less potent corticosteroids are preferred as they are associated with a smaller risk of systemic adverse effects. Other options include a decreased dosing frequency to limit adverse effects e.g. application every other day rather than every day.

2.3.3.4 Elderly Population

Body composition, homeostasis, body tissues and organs change as people age. Therefore, this has consequences for the pharmacokinetic and pharmacodynamic processes associated with the active substance. E.g. due to a larger percentage fat tissue, the volume of distribution of lipophilic substances such as diazepam increases in elderly patients. The decrease of blood flow through the liver also has an effect with substances that have a high level of hepatic elimination e.g. morphine. Furthermore, two thirds of the elderly population has some degree of renal impairment. This has consequences for the dose of medicines with mainly renal elimination and a small therapeutic window e.g. digoxin, lithium. Skin also tends to be thin somewhat with advancing age.

The pharmacokinetic and pharmacodynamic changes usually become clinically more relevant over the 75th year of life. There are however large intra- and interindividual differences in aging of organ functions. Therefore, it is difficult to predict the exact pharmacological response of a given elderly patient. As with licensed medicines, it may be necessary to adjust doses of pharmacy prepared medicines carefully and cautiously in elderly patients.

Elderly patients are more sensitive to certain medicines and often use more medicines at the same time (sometimes called polypharmacy). This means that elderly patients are more vulnerable to adverse effects [11]. To avoid overdose and subsequent adverse effects, a lower starting dose may be used.

However, lower strengths are not available for every medicine and not every licensed pharmaceutical preparation is available as a tablet that can be divided e.g. coated tablets. In this situation, it might be necessary to produce a lower strength oral liquid that could be used for careful dose titration (see Sect. 5.4).

2.3.4 Contra Indications, Interactions and Intolerances

In addition to the validation of the dose, each preparation has to be reviewed in terms of possible contraindications, interactions and intolerances or allergies.

2.3.5 Narcotic and Psychotropic Substances

Based on United Nations conventions [12] most European countries have extra requirements or controls which are applied to medicines with narcotic and psychotropic substances. Requirements vary between countries but may include:

- Name, initials, full address and phone number of the prescriber
- Date of prescribing
- Name of the medicine and amount, written completely in letters
- Name, initials and full address of the patient or of the owner of the animal
- Clear description of the use, among what the maximal total drug use per 24 h, "use known" or "if necessary" is not correct
- If necessary: the amount of repeat doses

A prescription on which one or more raw materials fall under these regulations has to comply with these requirements.

In Germany the use of narcotic or psychotropic substances is not appropriate if the intended purpose can be achieved in other ways, e. g. with medicines with other active substances.

Some active substances falling under these regulations are exempted from the requirements associated with administration and prescribing, such as for preparations with codeine. However, for the raw material codeine, the administrative obligations mentioned in the law do apply in Germany.

2.3.6 Standard Amounts

The amount of a pharmacy preparation requested can vary widely, depending on the indication and area for use. The pharmacist should assess whether the amount is right for the use (see Fig. 2.7), the length of the treatment and the shelf life. In some countries, there are systems for standardising amounts used in order to improve consistency of products and maximise efficiency in the pharmacy setting. In addition in some countries the amounts are limited by the health insurance.

2.4 Special Categories of Prescriptions

Not every request for a pharmacy preparation is by definition a medicine. Examples include biocides, medical devices, starting materials and chemicals. It is important to make this distinction, because with that it becomes clear under which regulation the pharmacy preparation falls. The legal requirements varies with the category. The relevant national regulations should be consulted before any such items are prepared.

Depending upon the item in question, the pharmacist may be obliged to ensure that the product is suitable for use in humans, for instance does not contain any material of animal origin that may transmit any known diseases e.g. Transmissible Spongiform Encephalopathies (Creutzfeldt-Jacobs Disease), see Sect. 19.3.1.

2.4.1 Herbal Medicines

The regulation of herbal medicinal products is complicated and differs between countries[1]. Roughly speaking, herbal products can be considered as medicinal products with medicinal claims, but also as food or dietary supplements without medicinal claims. The status will generally depend on the level of scientific evidence supporting their use. A detailed overview of the regulations concerning herbal medicinal products worldwide can be found in Herbal Medicines [13].

Herbal medicinal products are not explicitly mentioned in the Ph. Eur. but herbal raw materials are included. The reason is that any pharmacist should be able to judge the safety of herbal medicines but not the efficacy of the products. According to EC legislation [14], "a herbal medicinal product is any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations." Herbal medicinal products are also referred to in the international literature as herbal medicines, herbal remedies, herbal products, phytomedicines, phytotherapeutic agents or phytopharmaceuticals. The use of herbal medicinal products for the treatment and prevention of disease is called phytotherapy [13].

Few herbal medicinal products are on the market as authorised medicines in the EU, fulfilling the same stringent requirements that count for conventional medicinal products. This is largely due to the limited availability of randomised controlled trials to support the quality, safety and efficacy of herbal medicinal products. More often they are licensed as traditional herbal medicinal products, following an adapted and simplified registration wherein efficacy is made plausible based on available scientific data (well-established use) or long-term historic use in the EU (traditional use). Sufficient data to underpin the safety should be available in all cases and the quality of the herbal

[1] Contribution by Herman Woerdenbag, Groningen, The Netherlands.

medicinal product must always be demonstrated. A vast majority of herbal products however, are unlicensed (not medicinal products) despite the fact that they are frequently intended for health improving purposes [13, 15].

2.4.2 Agents Used for Assisted Suicide

In countries with legislation that allows for assisted suicide, pharmacists will be involved in preparing and dispensing the products. These pharmacists are then faced with ethical, moral, and practical questions. Is a pharmacist obliged to dispense these agents or is he allowed or even obliged to refuse in specific situations, and if so, based on which moral and ethical principles? How is professional information about pharmacologically effective agents and preparations distributed among pharmacists? These and similar questions have to be discussed in a social and legal context with the purpose of improving the difficult situation of patients and caregivers.

In the Netherlands a "Guidance for the management of euthanasia and assisted suicide" was developed by doctors and pharmacists and it covers the path from the patient's request onto the arrival of the autopsist. The use of this Guidance is closely monitored [16]. This Guidance demands that any decision on dispensing the agents can only be made after oral consultation between the doctor and the pharmacist. The pharmacist must be ethically and morally independent in his decisions, like the doctor, which may eventually lead to the pharmacist refusing to dispense. The pharmacist has to be informed about all relevant backgrounds, in order to be able to make his decision and to be able to give the doctor or the patient relevant pharmacologic and practical information. The relevant products are prepared by the pharmacist and he will dispense them personally to the doctor, accompanied by oral or written information about their practical and technical administration. The standard advises pharmacist and doctor making general arrangements before an actual patient's request will occur.

2.4.3 Homoeopathic and Anthroposophic Medicines

The law regarding the supply of homoeopathic and anthroposophic medicines varies between countries. In some countries, a pharmacist can refuse to dispense such an item and refer the patient to an alternative pharmacy.

In Europe the German Homeopathic Pharmacopoeia is available for the regulation of the quality of these medicines. If prescribed it usually is a licensed medicine but occasionally – mainly in cases of non-availability – a pharmacy preparation may be requested. A general pharmacist will not be able to assess the efficacy of a homeopathic or anthroposophic prescription but he will be able to judge the safety, for instance following these recommendations:

- The pharmacist should only fulfill a request for a pharmacy preparation when the prescription comes from a homeopathic or anthroposophic doctor and relates to a single medicine of a non-animal or non-microbiological source and with dilution $\geq$1:10,000, for oral or external use.
- When the medicine does not belong to these groups then the preparation is outside the competence of the regularly educated pharmacist. If that is the case it is recommended to get in touch with a pharmacy that specialises in preparing homoeopathic or anthroposophic medicines.

At all times, pharmacists should only practice within their sphere of competence.

2.4.4 Veterinary Medicines

In relation to the administration of medicines for animals, the pharmacological differences and local laws have to be observed. The pharmacokinetics of every active substance is different in each species. For animals, especially cats, the toxic concentration of many human medicines is lower than the therapeutic dose in humans due to differences in metabolism of medicines. For example, in cats, the administration of acetaminophen (paracetamol) very quickly leads to intoxication with methemoglobin formation, anemia, hemoglobinuria and liver damage, as they may metabolise the medicine poorly.

The European Commission (EC) has acknowledged that insufficient authorised veterinary medicinal products are available for the treatment of every clinical case in every species. Therefore, Directive 2001/82/EC allows, under Articles 10 and 11, veterinary surgeons to prescribe products that are not authorised for the relevant clinical case or for the relevant species, this provision is known as the Cascade. This is a derogation from the main requirement in the EU legislation to use authorised veterinary medicines. Therefore the Cascade increases the range of medicines that a veterinary surgeon can use [17]. The Cascade allows the veterinary surgeon to use medicines designed for other species, only if there is no licensed medicine for the species and the indication and the animal is critically ill. The use of medicines as part of the Cascade system has to be carried out in the order specified:

- Licensed Animal medicine, which has a different indication
- Licensed Animal medicine, which is licensed for a different species
- Licensed human medicine or EU licensed animal medicine
- Extemporaneous preparation

There are further regulations for animals bred for human food.

2.4.5 Medical Devices

As for the regulations which apply to medicines, the regulations for medical devices include consideration of the following issues: diagnosis, prevention, surveillance, treatment or relief of illnesses. However, the set-up of the regulations for medical devices differs essentially from the one for medicines. In the case of medicines licensing, the government is responsible for managing medicines regulation. However, in the case of medical devices, the company itself is responsible for risk assessing the product before it enters the market [18, 19]. Medical devices are classified in four different risk classes [18, 19].

The manufacturer has to decide in which risk class the device falls: I, IIa, IIb or III; the higher the class, the more risks are associated with the use. Therefore devices in class IIb or III have to be assessed in advance by a competent authority a so-called Notified Body. This is an independent organisation, designated by the national government. When the device belongs to class I or IIa, the producer only has to inform that authority of the device.

How does one handle the request of a hospital ward for the preparation of sodium citrate solution 30 % in ampoules? Concentrated sodium citrate solutions are used as catheter locks on dialysis wards of hospitals. By filling the lumen of the catheter with such a solution the formation of blood clots is prevented and the flow is maintained. Sodium citrate solution is an alternative for a concentrated heparin solution and should be preferred because of the anti-microbiological effect [20]. Citra-Lock® is available as a medical device. This product contains 46,7 % sodium citrate and is CE registered class IIb. Are there justifiable reasons to prepare the solution? This could be for example when the marketed product is associated with more side effects due to the higher concentration, or is delivered in a container that is hard to use in practice. If those reasons are absent, then the marketed product is to be preferred.

Information about medical devices is not as accessible as about licensed medicines. If a pharmacist has to decide about a medical device being used in a way that is not included in the instructions for use, he has to contact the manufacturer.

The European Commission has made proposals for new guidelines in September 2012. This means that all medical devices will have to undergo thorough, independent assessment of safety and performance before they can be sold on the European market. Also new rules on traceability are proposed and public information on products available on the EU market [21].

2.4.6 Biocides

Biocides (also called disinfectants) are active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to destroy, deter, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism by chemical or biological means. A pharmacy may get a request for the preparation of a disinfectant. This may be difficult to handle because different laws are appropriate.

Disinfectants for the skin of patients, such as chlorhexidine in alcohol, are regarded as medicines for humans. When the same preparation is used in the hospital for disinfection of the hands of nurses and other staff, it is considered as a biocide and falls under the applicable EC legislation [22]. Disinfectants that are used in combination with specific medical devices fall under the regulation for medical devices and should have a CE identification mark. Disinfectants for inanimate surfaces fall under the legislation for biocides. When delivering such a disinfectant the pharmacist has to comply with this regulation, that is with the following requirements.

1. Generally only registered products should be used. This is indicated by a number or registration code on the packaging.
2. Registered biocides products must be delivered in the original package with the approved legal instructions and with the relevant danger symbols and safety recommendations.
3. A pharmacy preparation is allowed ‘if necessary’ but uses an allowed disinfectant and excipients.
4. Operations such as diluting, addition of a buffering agent or dispensing should be executed in accordance with the instructions and with due regard for the required precautions for preparation and labelling.

Practice Example: Sodium Hypochlorite

When the pharmacist obtains a request for the preparation of a sodium hypochlorite solution 2 %, the indication for use must be clear. A dentist may use such a solution for root treatment as a disinfectant and because of the tissue-dissolving effect. The prescription is from a dentist and therefore it is a medicine, so falling under Medicine law. When using a sodium hypochlorite solution for the disinfection of the floor, the biocides legislation applies. The pharmacist firstly has to examine whether there is a registered product which could be used instead. If this is not the case, then he is allowed to prepare the solution on the condition that there is a recognised use. That is to say that the use is described in guidelines or other reliable sources. In case of doubt, consultation with the authorities is recommended.

2.4.7 Raw Materials (Chemicals)

2.4.7.1 General

Chemicals only become recognised as medicines if they have been incorporated into a dosage form or when a medical indication is claimed. Chemicals can, if handled inexpertly, become dangerous to the health and in that case have to be labelled as hazardous substances (see Sect. 26.3). It is the responsibility of the pharmacist to assess whether he will supply raw materials. When delivering to members of the public (without a doctor's request) he should know the potential dangers, assess the intentions of the person who requests the item, and inform that person about the possible dangerous qualities. It is recommended to document such supplies via a request form. Data recorded on this form should comprise the identity of the person who makes the request, data about the delivered starting material (name and amount) and the indicated use. For the delivery of some raw materials separate legal regulations apply if the risk of abuse is considered to be substantial, such as with precursors. See further down.

Two Examples of Requests

Strong hydrochloric acid

A request for a bottle of strong hydrochloric acid for hobby purposes will raise doubt about the intended use. When the use seems to be acceptable, this raw material may be delivered but robust documentation of the request is strongly recommended, also to prevent problems in the context of the precursor legislation (see further down). Furthermore, the legally obliged safety information has to be present on the package (see Sects. 26.3.2 and 26.6.3). By supplying Concentrated Hydrochloric Acid Ph. Eur. the quality is guaranteed.

Sodium sulfate

Sodium sulfate may be delivered on request of a citizen. Delivery is analogous to the hydrochloric acid example. The situation is different when sodium sulfate is required on a doctor's prescription. Supplying a measured quantity of sodium sulfate in a bottle on prescription renders this raw material into a medicine and it has to be labelled as such.

2.4.7.2 Hazardous Substances

Hazardous raw materials are chemicals that provide a hazard to safety or health because of the chemical characteristics. Substances are defined as hazardous if at least one H(azard) statement (see Sect. 26.3.2) is attributed. They must only be delivered in a container that is labelled with the legal safety information such as Hazard and Precautionary statements. A Material Safety Data Sheet (MSDS) must accompany delivery.

2.4.7.3 Precursors

Precursors are raw materials that may be used at the synthesis of narcotics and psychotropic substances ('drugs'). For this group of raw materials, the EC regulations [23], lay down measures to be taken to discourage the diversion of certain substances to the illicit manufacture of narcotic drugs and psychotropic substances. These regulations recognise 3 categories of substances of which only category 1 has a practical significance for pharmacy preparation. That category contains ephedrine, ergotamine and ergometrine. Pharmacies require special licences for ordering and possessing these substances. This special licence is only valid for the use of precursors "within the scope of the official duties of the operators". A licence is not required to supply pharmacy preparations that contain such substances.

2.5 Essentials

Pharmacy preparation allows the doctor and pharmacist to provide individualised and tailor-made pharmaceutical care. The preparation of a medicine in the pharmacy fills a need when the licensed pharmaceutical preparation is not available or when a licensed pharmaceutical preparation does not satisfy a specific situation.

Upon receipt of a request from the doctor, the pharmacist must examine the situation and decide whether the request is appropriate and judge the level of risk associated with proceeding with the request. However, the pharmacist must also consider the risks of not supplying a medicine which may lead to the patient not receiving treatment. Further discussion with the medical team may be needed.

The pharmacist must make every effort to ensure that the medicine produced is of appropriate pharmaceutical quality and is fit for the intended purpose. An approved or authorised formula should be used wherever possible. Where such formulae are not available, steps should be taken to minimise risk where possible e.g. restricted shelf-life, fridge storage (if applicable), use of licensed starting materials etc.

The usual support offered by pharmacy computer systems is limited if local formulae are used, and the pharmacist may need to consult a range of reference sources when considering the appropriate indications, doses, likely side effects and contra-indications.

Whether the request is for a medicine or other type of preparation, the pharmacist is responsible for ensuring that the final product supplied is of acceptable quality and backed by the best possible evidence base.

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Availability of Medicines

3

Helena Jenzer and V'lain Fenton-May

Contents

Abstract

Fundamental changes and new challenges have been emerging in the last decades as a result of the globalisation of markets and of production, new economic doctrines, tight budgets as well as the development of information technology. This has brought with it a shift in the security of supply, which now has to cope with drug shortages to prevent a decrease in safety and a worse outcome for the patients.

Medicines are made available as authorised medicines, pharmacy preparations, or investigational medicinal products. For many diseases active substances are available, and yet groups of 'neglected' patients or special patient groups will not receive the medicines they need. If a patient needs a medicine, which is not on the national market, it may be imported from abroad or prepared in a pharmacy. The complicated rules, which are nationally determined, for reimbursement (in some Countries) and long procedures render importation a laborious way to make medicines available for the patient. To be reimbursed some Countries require that medicines are to be shown to be efficacious, appropriate and economic.

Specials (unlicensed medicines) are being produced according to GMP and PIC/S guidelines to cover these shortages. The European Association of Hospital Pharmacists (EAHP) has dedicated a big effort to animating and harmonising pharmacy production. The need for flexibility in preparation and manufacturing processes and the added value of a broad range of pharmacy production have been clearly underlined by the Council of Europe's resolution CM/ResAP (2011)1.

Keywords

Globalisation of pharmaceuticals • Security of supply • Medicines shortages • Authorised medicines • Pharmacy preparations • Investigational medicines • Medicines for orphan diseases • Importation • Unlicensed medicines • Added value of polyvalent hospital pharmacy production

Based upon the chapter 'Apotheekbereiding in de geneesmiddelenvoorziening' by Yvonne Bouwman-Boer and Reinout Schellekens in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_3,

3.1 Introduction

Medicines are available for patients as authorised medicines or as pharmacy preparations (unlicensed medicines). Market logic ensures that only medicines with sufficient return on investment will be marketed. However, health care logic requires pharmacists to provide their patients with necessary medicines. There are regulations that cover medicines for clinical research, marketing authorisation and import, as well as traffic between European countries (parallel imports). If medicines are not available as authorised medicines, various options such as compassionate use or parallel trial programme can be considered. The authorisation of medicines for orphan diseases is promoted by the orphan drug regulations. The system of reimbursement will be discussed briefly due to its special situation at the interface of both public health and social insurances.

Preparations prepared in pharmacies may serve as the last choice to provide patients with their necessary medicines. The European Ministers have formally confirmed "that the preparation of medicinal products in pharmacies, which may be required as a consequence of the individual or medical condition of the patient in the absence or unavailability of appropriate medicinal products on the market, is indispensable for accommodating the special needs of individual patients in Europe [1]." Mainly special patient groups need pharmacy preparations. Another need for pharmacy preparation arises from drug shortages.

3.2 The Pharmacist's Mandate to Provide Medicines

3.2.1 Mandate

Based on an acceptable cost-benefit and risk-benefit-assessment for both public and individual health, a pharmacist is mandated for the legal provision of medicines used to treat his patients. This scope is defined by Acts, Ordinances or Decrees, national or regional needs, and, in hospitals, is formalised in the formulary, normally defined by a medicines committee. This formulary includes medicines, controlled medicines, devices, chemicals, disinfectants, and ethanol in various concentrations and presentations. Each pharmacy should be responsible for ensuring that a locally agreed list of products should be available to meet the needs of the business even in times of accidents and catastrophes (Table 3.1). This list is adapted and recalculated from a list of a Swiss University Hospital, which has been agreed by emergency and ICU, anaesthesia, and hospital pharmacy [2]. For comparison see WHO model list [3]. The performance of the hospital pharmacy has to be available all time without any disruption.

As a rule, medicines used in bigger amounts in hospitals are commercially supplied by industry, smaller amounts and ad hoc orders by wholesalers, see Chap. 36. Some tasks delegated to the hospital pharmacist may be fulfilled by centralised services for allied partners due to economic or effectiveness reasons. The frame for this duty has to be flexible enough to attain a fast track distribution within the institution and thus a fast dispensing of medicines to the patient. Thus, not only drug supply, but also the medication process and consequently the prevention of medications errors, which are multidisciplinary processes within patient care, are to be considered as integral parts of the mandate [4].

The mandate has not changed throughout decades. It has even become more challenging as new pharmacokinetic and pharmacodynamic knowledge has been emerging and as biopharmaceutic relevant characteristics of highly active ingredients and products can be better anticipated (interactions, drug monitoring, adverse drug events). Therefore, in addition to pure logistics, the hospital pharmacist has to focus more and more on rational and economic drug use and to participate in pharmacotherapy and pharmacovigilance. Mainly in hospitals, medicines use is assessed more and more critical and differentiated. The mandate is even enlarged where suitable, according to special skills of the pharmacist.

The traditional role of the hospital pharmacist still covers production, analysis and assessment of the quality and safety of medicines, which includes the whole supply chain from purchase to pharmacotherapy, and even to disposal of wastes of unused drugs. The complex environment of public health is particularly evident in hospitals. Supply, reconstitution, preparation from raw materials or through adapting products and correct use are a matter of multidisciplinary contributions of many professionals to the benefit of the patient. They require a specialisation as well as life-long learning to remain in a strong and competent position within a care team. Graduate pharmacists have to pass a post-graduate specialisation to get ready to cope with challenges and tasks, which are inherent to the hospital domain (see Sect. 25.4.2).

Fundamental changes and new challenges have been emerging in the last three decades as a result of the globalisation of markets and of production, of new economic doctrines as well as of the development of information technology. This has brought with it a shift in the security of supply and in the hospital pharmacist's requested and mandatory tasks (Table 3.2).

Table 3.1 Preparations recommended to be kept minimally on stock for provision in case of accidents and catastrophes (minimum amounts stored for a 500,000 people region, varying depending on further regional resources and supply time)

Product	Minimal amount stored
Acetaminophen/paracetamol 10 suppositories 600 mg	40
Acetaminophen/paracetamol 16 Tbl. 500 mg	400
Acetaminophen/paracetamol infusion solution 1 g 100 ml	9,600
Acetaminophen/paracetamol infusion solution 500 mg 50 ml	1,800
Albumin infusion solution 20 % 5 × 50 ml	10
Amoxicillin/clavulanic acid 1 g Ad 20 Tbl	180
Amoxicillin/clavulanic acid infusion solution 1.2 g 5 Ad Amp	750
Amoxicillin/clavulanic acid infusion solution 2.2 g 5 Ad Amp	350
Atracurium besylate injection solution 5 Amp 2.5 ml	100
Basic infusion solution G5-K PP 500 ml	600
Bupivacaine injection solution 0.25 % 5 Amp 20 ml	50
Bupivacaine injection solution 0.5 % 5 Amp 20 ml	30
Ceftazidime vial 2 g	250
Ceftriaxone 2 g vial	800
Cefuroxim injection solution 1.5 g i.v. vials	2,800
Ciprofloxacin infusion solution 0.2 g 100 ml	400
Clarithromycin injection solution 500 mg i.v. Amp	150
Clindamycin injection solution 600 mg 3 Amp	100
Desflurane 6 bottles 240 ml	8
Dihydralazine mesylate 25 mg 5 Amp	25
Diphtheria tetanus toxoid combination pre-filled syringe	300
Dobutamine concentrate infusion solution 250 mg	180
Epinephrine/adrenalin injection solution 1 mg/ml 10 Amp 1 ml	150
Epinephrine/adrenalin injection solution 1 mg/ml 10 Amp 10 ml	20
Etomidate injection solution 10 ml 10 Amp	40
Fentanyl injection solution 0.05 mg/ml 10 Amp 2 ml	300
Fentanyl injection solution 0.05 mg/ml 5 Amp 10 ml	600
Flucloxacillin injection solution 1 g 10 vials	150
Glucose 5 % NaCl 0.9 % 2:1 PP 1,000 ml	1,800
Glucose 5 % NaCl 0.9 % 2:1 PP 500 ml	1,800
Glucose 5 % PP 1,000 ml	350
Glucose 5 % PP 250 ml	500
Glucose 5 % PP 500 ml	800
Glucose infusion solution 5 % PP 100 ml	100
Haloperidol injection solution 5 mg i.m./i.v. 5 Amp 1 ml	100
Hydroxyethyl starch 6 % infusion solution 500 ml	2,000
Imipenem/cilastatin 500 mg 10 Amp 20 ml	60
Isoflurane inhalation solution 250 ml	80
iv Line set	15,000
Ketamine injection solution 10 mg/ml 5 vials 20 ml	20
Ketamine injection solution 50 mg/ml 5 vials 10 ml	15
Lactated Ringer's solution infusion solution 1,000 ml	500
Lactated Ringer's solution infusion solution 1,000 ml	1,800
Lactated Ringer's solution infusion solution 500 ml	1,500
Lactated Ringer's solution infusion solution w/o air 1 L	1,800
Lactated Ringer's solution infusion solution w/o air 500 ml	600
Lidocaine CO_2 injection solution 2 % 10 Amp 20 ml	30
Lidocaine injection solution 1 % 10 Amp 5 ml	400
Lidocaine injection solution 2 % 5 ml w/o cons 10 Amp	120
Lorazepam 20Tbl 1 mg	400
Lorazepam injection solution 4 mg/ml i.v. 10 Amp	75
Mefenamic acid 500 mg 100 Tbl	50

(continued)

Table 3.1 (continued)

Product	Minimal amount stored
Mepivacaine HCl 10 mg/ml 100 ml	800
Mepivacaine HCl 10 mg/ml 50 ml	500
Mepivacaine HCl 20 mg/ml 50 ml	100
Metamizole sodium injection solution 50 % i.m./i.v. 10 Amp 2 ml	500
Metronidazole infusion solution 500 mg 100 ml	1,400
Midazolam injection solution 15 mg/3 ml i.m./i.v. 5 Amp	80
Midazolam injection solution 5 mg/ml i.m./i.v. 10 Amp	100
Midazolam injection solution 50 mg/10 ml i.m./i.v. 5 Amp	50
Morphine HCl 10 mg/ml 10 Amp 1 ml	500
NaCl 0.9 % irrigation 1,000 ml	600
NaCl 0.9 % irrigation 250 ml	1,400
NaCl 0.9 % infusion solution 1 L	1,800
NaCl 0.9 % infusion solution 100 ml	15,000
NaCl 0.9 % infusion solution 250 ml	300
NaCl 0.9 % infusion solution 500 ml	100
NaCl 0.9 % infusion solution w/o air 1 L	600
NaCl 0.9 % infusion solution w/o air 500 ml	1,000
Norepinephrine/noradrenaline injection solution 0.1 % 10 Amp 10 ml	10
Norepinephrine/noradrenaline injection solution 0.1 % 10 Amp 1 ml	80
Pancuronium bromide injection solution 2 mg/ml 50 Amp 2 ml	50
Pentothal sodium 2.5 g 12 vials	8
Piperacillin/tazobactam 2.25 g vial	120
Propofol injection solution 1 % 5 vials 20 ml	300
Propofol injection solution 1 % vial 50 ml	10
Propofol injection solution. 2 % vial 50 ml	1,500
PVP iodine 10 Gauze pads 7,5 × 22.5 cm	20
PVP iodine alcoholic solution 5 × 1,000 ml	75
PVP iodine solution standardised 500 ml	150
PVP iodine solution standardised120 ml	250
Ringer's solution irrigation 1,000 ml	1,600
Rocuronium bromide injection solution 50 mg 12 vials	15
Ropivacaine injection solution 0.2 % 5 Bag 200 ml	25
Ropivacaine injection solution 0.75 % 5 Amp 20 ml	25
Sevoflurane liquid 250 ml	60
Silver sulfadiazine cream 50 g	100
Silver sulfadiazine cream 500 g	10
Succinolated Gelatine infusion solution 500 ml	80
Sulfamethoxazole/trimethoprim forte 10 Tbl.	150
Sulfamethoxazole/trimethoprim injection solution i.v. 10 Amp 5 ml	80
Suxamethonium 100 mg 2 Amp 2 ml	80
Tetanus hyper gamma globulin 250 units syringe 1 ml (or corresponding amount of gamma globulin)	15

Table 3.2 Weighting over time of hospital pharmacists' contributions to shared responsibility and improved outcomes

	1960	1980	2000	2020
Clinical pharmacy	+	++	+++	+++
Production, quality control, quality assurance	+++	++	++	+++
Provision and supply chain	++	+	++	+++
Special tasks according to individual skills	+	++	+(+)	++

In the past 20 years, investments have often been called off in favour of outsourcing to keep fixed costs small and to optimise balances. From the 1990s, financial interests dominated more and more the patient-centred outcome objectives defended by physicians, pharmacists, other health care professionals and the patient himself. The freedom of action for the hospital pharmacist had been redefined and became more restricted.

Today, the hospital pharmacist is still mandated to control the supply chain, however there are challenges from supply chain professionals supported by those who consider medicines to be no different from any other commodity. Procurement now has to take place in an environment that has more and more budget restraints and external paralysing constraints induced by unwanted dependencies of third party suppliers and sometimes even drug shortages. If the skills are lost, important financial resources would be needed to reactivate lost know-how related to neglected technical equipment or outsourced activities. However, such time is not available in situations such as medicines shortages. Consequently, re-adaption may cost more than ever could have been saved.

3.2.2 Medicines Shortages (Also Referred to as Drug Shortages)

Shortages as a global phenomenon grew steadily and increased sharply in the USA within a few years from 2006 (70 shortages) to 2011 (267 shortages) [5–10]. It is a phenomenon that if left alone threatens to become a crisis in terms of delivering patient care. In 2012, 99 % of over 300 respondents from 27 European countries had to cope with medicines shortage problems according to a survey of the EAHP. Sixty three percent of hospital pharmacists experienced it weekly, sometimes even daily. Seventy seven percent report a worsening of the problem. In Belgium, some 30 medicines are regularly in short supply [11]. Today, in Europe not only isolated cases are in the focus, but examples representing all of the therapeutic groups. In the Netherlands, they are monitored and published on a website. From 2004 to 2011, more than 1,400 products were published. The number increased from 91 in 2004 to 242 in 2011. The duration of a shortage increased from 139 to 242 days in the same period. Substitution (62 %), alternatives (25 %) and pharmacy preparation (2 %) have been the method of choice to cope with such situations [12]. One of the biggest Swiss university hospitals experienced 172 cases of medicines shortage in 2011, i.e. 3 cases per week, with the involvement of 51 suppliers, and with multiple shortages for some products. An out of stock medicines was not available between 21 and 335 days. Classic alkylating, anti-metabolic or topoisomerase-inhibiting antineoplastics with a long time market presence and vaccines are the products for which there is the most concern on the steadily growing list. Pharmaceutical expertise succeeded in finding a suitable solution in 90 % of all cases [13, 14]. To bridge a gap arising from a case of medicines shortage will take 1–7 h [15]. In any case, as a medicine from the hospital formulary has been selected due to a favourable cost – benefit ratio, alternatives are in general cost-intensive compared to the standard product. A simple intermediate substitution of a medicine on the formulary costs 1,800 €, a definite substitution between 3,800 € and 4,690 € (figures from Germany) [16].

Small markets are particularly sensitive to shortages. High registration and regulation affairs cost for market admission may tempt suppliers to economise in countries with low volumes of sales. This is a major problem in a small country. Withdrawal from the market in a country such as Switzerland may be an alert for an upcoming critical situation in the European Union.

In 2011, the situation prompted authorities to intervene in the market and remind manufacturers and suppliers on their responsibility. US President Obama signed the Executive Order 13,588 instructing the FDA to require from manufacturers adequately advanced notices of discontinuation of certain prescription medicines and to review more quickly modifications of the production processes of these medicines [17]. These requirements comprised an obligation to notify and inform on medicines shortages, but do not include a disclosure of the reasons nor of the decisions which lead to a withdrawal of products from the market. An adequate announcement is requested in cases where only one provider for a medically necessary active ingredient is available. The FDA has created a task force for a strategic planning [18] and the EMA reflects particularly on shortages caused by GMP compliance problems [19]. As a result, 38 shortages could be prevented in 2010, 195 in 2011, and 150 in 2012 (up to November), but more has to be done to obtain a sustainable troubleshooting [20].

Relief may arise from less restricted importation frames. Import options depend on the current national legislation and are always related to a lag time for delivery, if substitution cannot be an option. For example, Swissmedic, may temporarily approve imports of EMA-admitted medicines from another European country for an intermediate interval of time in which the local supply chain is interrupted. There are further disadvantages related to importation, in addition to the

(continued)

extra administrative effort. The importing country may be causing a shortage in the exporting country if they are prepared to pay a higher price. In some countries, an imported product can be excluded from reimbursement, if the assurance company is not in agreement.

The most severe among a list of multifactorial reasons [21] which have induced a medicines shortage, were:

- Quality or availability problems related to active ingredients or to production processes or equipment (e.g. heparin contamination [22] and propofol case [23])
- Demand spikes (e.g. oseltamivir following flu pandemic scenarios [24])
- Unintended consequences of contracting by large buyers leading to the loss of small suppliers
- Overstocking due to panic buying (especially when alternatives are lacking)
- Parallel trade of medicines [25, 26]
- Discontinuation decisions taken by industry, possibly related to pricing or other macro-economic factors (like high cost and low gain)
- Globalisation of supply chains creating new vulnerabilities
- Lacking alternatives

The latter may be explained by the fact that capital bound in a stock is considered as an important item with potential to optimise a financial balance. The risk of losing capital is reinforced by the availability of new technologies and new products, which might diminish or degrade the stock's value due to a loss of demand for old products. However, medicines are not comparable to electronic or technical devices with short half-lives. There is no doubt that general economic rules are hardly applicable, one to one, for medicines and in no way for special product groups such as antidotes, narcotics, antineoplastics, total parenteral nutrition, and anti-infectives, if no equivalent and equally expensive medicine is available. Thus, commercial items and lean production are not convincing arguments for small stocks.

It is obvious that most drugs in short supply represent highly active ingredients and the shortage is linked to safety and quality issues. Deviations from GMP uncovered on inspections requiring improvements and investments in a manufacturing plant may play an important role in decision making about maintaining production or not. The risk and the consequences for the supply chain, which arises from cases of a major quality problem and paralysis of a big manufacturing plant after a merger of several smaller sites, is the more threatening as less alternatives will be available. The risk of affecting a global market will be clearly higher in case of one big facility affected instead of many smaller ones. It is even worse, if production is relocated into "low-cost" countries, which have less or no experience in a reliable industrial production free from major operational disruptions. From a delivery, security and ethical point of view, the economic pressure on medicines production has lead to a disastrous situation, which is to everyone's disadvantage (clinical, financial and health outcomes). An option for pharmacies to immediately cope with the vacuum caused by a stop of industrial manufacturing is only possible if the equipment and quality assurance of its production is regularly updated and the capacity of those still able to produce is sufficient to cover also the needs of non-producing pharmacies.

The role of pharmacists to cope with drug shortages is a determining one if consequences such as decreased safety and worse outcome is to be prevented. The Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) has edited guidelines to cope with drug shortages [27] and, supported by the most important Swiss Associations and Federations of pharmacists (Swisspharma), physicians (FMH), and hospitals (H+), has signed an agreement with the leading associations of pharmaceutical industry (ASSGP, Intergenerica, Interpharma, Scienceindustries, and Swiss Association of Importers of Proprietary Medicines (VIPS)) to readily provide pharmacies with active ingredients for extemporaneous individualised preparations and small scale stock production of commercially not available formulations or dosages [28]. Whatever the reason for a shortage may be, adaptation from both sides is highly recommended, i.e. from the supplier and from the supply chain responsible in a hospital.

All pharmacies should have an up to date, written policy for managing shortages [29, 30]. That policy should include the need for a risk assessment, which will assess the impact of the shortage and the actions that should be taken to limit those effects. Pharmacists have a responsibility not to do anything that will exacerbate a shortage situation. They have a responsibility to co-operate with any nationally agreed scheme to reduce the effect of such shortages.

3.2.3 Bioequivalence Considerations for Coping with Shortages

Substitution or alternatives, which may be required in the absence or unavailability of appropriate medicinal products on the market, are indispensable to cover the need arising from medicine shortages.[1]

[1] This section has been written by Wafa Jama, Royal Dutch Pharmacists' Association KNMP, The Hague, The Netherlands. e-mail: w.jama@knmp.nl.

Generic substitution is defined as the mutual substitution of medicinal products having the same active ingredient, the same strength, and the same dosage form. Different salt forms of the same medicinal product are considered to be the same active substance, unless the salt forms in question exhibit substantial differences in terms of efficacy and activity. Generic substitution usually involves replacing the proprietary brand or reference medicinal product with a generic or parallel-imported product.

The term pharmaceutical alternative is used to define the medicinal product with the same active ingredient, although the dosage form, salt form or strength may vary, such as substitution from a tablet with immediate release to controlled-release, or from capsule to oral solution. Therapeutic substitution is the mutual substitution of medicinal products with different active ingredients, both of which may or may not belong to the same therapeutic group.

In general, medicines, which passed bioequivalence testing, should be substitutable with their generically equivalent, when needed. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) consider products to be bio-equivalent if, based on the same molar dose, a generic substitute or pharmaceutical alternative exhibits a similar rate and degree of availability at the site of action, and can thus be said to have a similar efficacy and degree of safety.

Market approval of generic medicines requires pharmacokinetic bioequivalence studies. In bio-equivalence studies, the product to be investigated is compared to an innovator product. Products are regarded as bio-equivalent if the 90 % confidence interval of the AUC-ratio and C_{max} are within 80–125 % of the reference product. If the confidence interval is within these limits, this means that the average will deviate far less from the corresponding value found for the innovator product.

For medicinal products with a narrow therapeutic index the 90 % confidence interval of the AUC ratio must lie between 90.00 % and 111.11 %, and if C_{max} is important then this too must lie between 90.00 % and 111.11 %. The significance of this, in terms of interchangeability, is not known.

For medicinal products with large intra-individual variation (i.e. if the variation of a kinetic parameter exceeds 30 %) the 90 % confidence interval of C_{max} should be between 69.84 % and 143.19 %, while the AUC-ratio should be within normal limits. Classical bioequivalence studies have limited value in indicating equivalent efficacy and safety for biosimilars (generic version of biological medicines).

Medicines with a different dosage form are not tested for bioequivalence. These medicines have different kinetic properties and they are not bioequivalent by itself. From that viewpoint, these products cannot be substituted and caution is needed. The consequences for non-adherence and non-efficacy should be considered.

The main consideration where generic substitution is concerned with is that the efficacy and safety of substituted medicinal products should be equivalent to one another. As this is tested during the approval of generic medicinal products, on the basis of bioequivalence studies, it can be assumed that the approved generic products are just as effective and safe as the reference product. However, in conjunction with certain active substances or certain situations, it may be preferable to avoid even the slightest risk (e.g. ciclosporine).

In addition, there is a range of other issues – unrelated to bioequivalence – which can cause problems following substitution. Accordingly, there is still a need to determine the advisability of substitution on a medicine-by-medicine and patient-by-patient basis. The flow chart in Fig. 3.1 and the following directions may be helpful in this regard:

(a) On first dispensing, the problems relating to efficacy, safety and convenience for the patient are not an issue. This is not the case if the patient has already received the medicine from another pharmacy (e.g. hospital pharmacy).
(b) A precise dose titration is important. Small differences in bioavailability can have large consequences. In disorders such as psychosis or mania, patients can be distrustful of medication. Changes can damage patient adherence to the treatment.
(c) Substances with which, for reasons of safety and efficacy, it is preferable that no risks be taken are biologicals, those with a narrow therapeutic index and those with non-linear kinetics. Although substances with a narrow therapeutic index or non-linear kinetics meet the requirements for bioequivalence, and are therefore theoretically interchangeable, patient-related factors that adversely affect interchangeability may be involved.
(d) Substitution can cause safety problems when the medicinal products contains an excipient to which the patient is allergic or intolerant.
(e) The packaging of the medicinal product in question, or an associated device, significantly affects its ease of use, or compliance.
(f) Legally, there can be no substitution without the physician's consent, unless prescribed generically. In practice, this usually means that agreements have been made on this point.

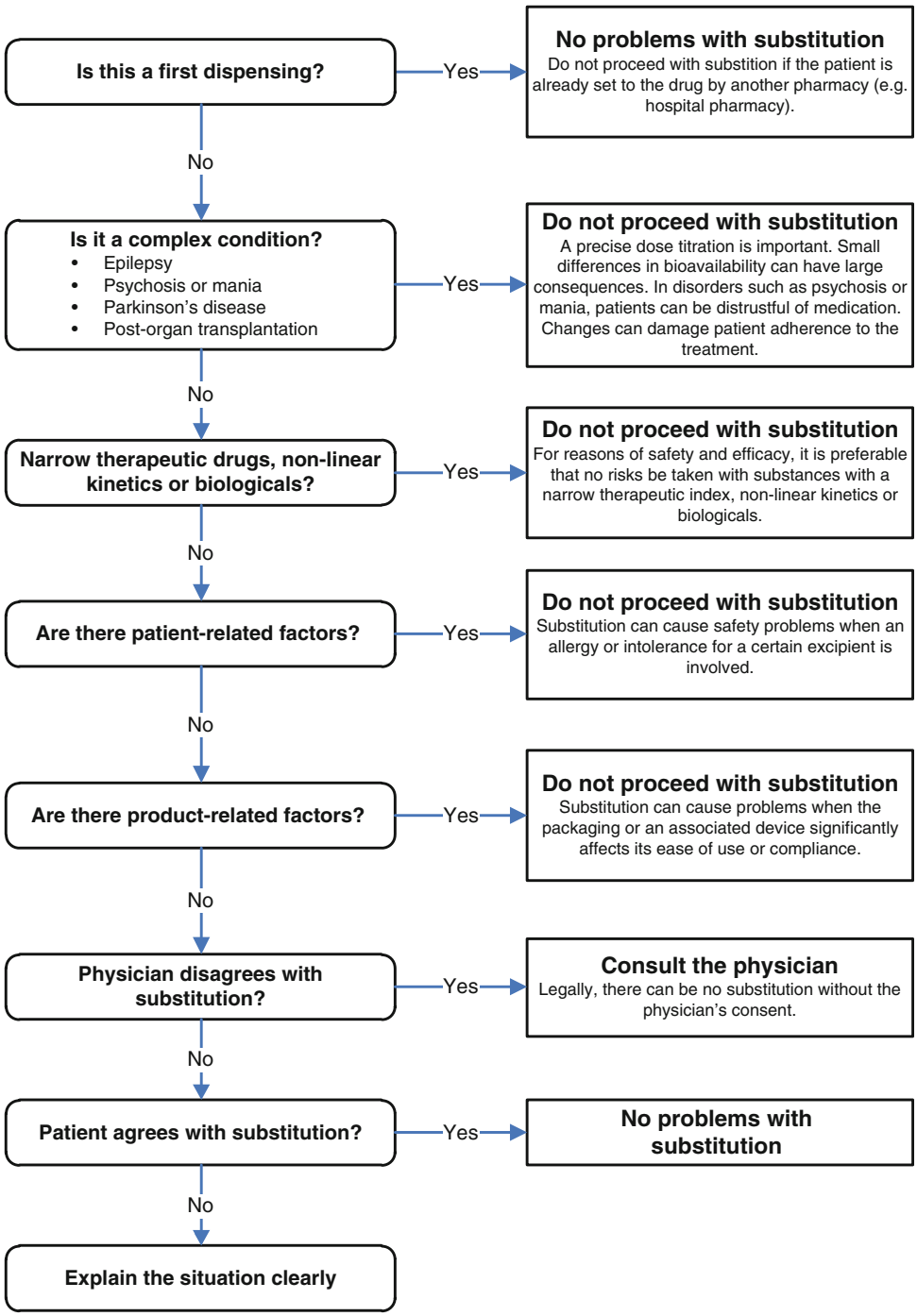

Fig. 3.1 Flowchart with decision points for substitution. Adapted from [31] by the same author. For substitution bioequivalence and additional factors are considered, especially if repeat dispensing is required. Bioequivalent proven medicinal products should be substitutable. However, for a variety of reasons this may not be the case and caution needs to be warranted

3.3 Medicines with a Market Authorisation

3.3.1 Market Authorisation (Formerly "Registration")

In Europe as in many other parts of the world, medicines can only be marketed if they are authorised [32–34]. A company, which wants to market a medicinal product, has to apply for a marketing authorisation at the European Medicines Agency for the European Union [35] or at the Medicines Agency of a country. The Medicines Agencies scientifically evaluate the medicine and grant an application if they have safety, quality and efficacy assessed positively. The process, which formerly was called registration of medicines, now is to be spoken of as granting of a Marketing Authorisation. And the company is the Marketing Authorisation Holder (MAH).

The applicant has to be authorised for manufacture, import, wholesaling, export or trading in foreign countries, according to the activities and the locations of the business. The applicant has to submit a product dossier with all necessary data defined in a guideline [36]. Such an authorisation is limited in time. It is renewed after an inspection. It nominates the Qualified Persons and specifies limitations or conditions. To be allowed to produce a medicinal product the manufacturer or the importer needs a Manufacturing License, which is bound to compliance to GMP (see Sect. 35.5.2). If the Medicines Agency judges positively, the European Commission or the National Authorities grant a Marketing Authorisation for the entire European economic area (EEA; EU Member States plus Switzerland, Norway, Iceland and Liechtenstein) or just for the country itself. Conversely, local authority's approval does not grant any authorisation for other EU member states. Non Member States ratify EU legislation such as on the pharmacopoeia to adapt national legislation and may have treaties with the EU, USA, Australia or Singapore [37, 38] European registration is possible for all medicines which meet certain requirements [39]. It is however compulsory for specific medicinal products such as biotechnologicals, orphan medicinal products, anti-neoplastics or medicines for autoimmune diseases. The product is recognisable by a EU-authorised medicinal product registration number (for example: EU/1/04/276/001).

Product information on European authorised medicines can be found at the EMA Regulatory and procedural guidance index [40]. This information comprises:

- A list of authorised presentations of the medicinal product
- The summary of product characteristics (SmPC)
- The patient leaflet and labelling of the product
- The European Public Assessment Report (EPAR)

A medicinal product with a national marketing authorisation has a national registration number, e.g. RVG 11,985 in the Netherlands. Product information about nationally authorised medicines can normally be found on national websites. National Medicinal Agencies refer to the website of the EMA if the product has obtained a European Marketing Authorisation.

3.3.2 Reimbursement

The manufacturer is allowed to market a product with a Marketing Authorisation. The company sets the price of the medicine. This is done either by a calculation which takes into account the manufacturing and marketing costs, including a profit allowance, or it is set in comparison to competing products of the same kind, especially, if the authorities negotiate with the company about that price. National pricing and financing policies are guided by a WHO policy [41].

Regulations for reimbursement are still nationally determined. In many countries the approaches are more or less the same: the type of health insurance system, pharmacoeconomic data, the effectiveness of the medicine, and the need in relation to similar medicines are determinant. The cost of a medicine for hospital patients may be regulated differently from the community situation. The inclusion in clinical guidelines of a specific medicine is of major importance in order to obtain reimbursement.

The key questions by the assessor are about an added benefit and about the medical value. In the Netherlands, the medical value is assessed unofficially by means of the Dunnings Funnel, which evaluates the candidates by defined criteria, e.g. necessity, effectiveness, safety, cost-effectiveness commonly calculated as incremental cost-effectiveness ratio (ICER), and social arguments such as budget impact or own responsibility [42]. The societies' willingness to pay for an additional quality-adjusted life year gained (QALY) is as follows [43–45]:

- Canada: $ 20,000 – $ 100,000
- United States: $ 50,000 – $ 100,000
- The Netherlands: € 20,000 – € 50,000
- Belgium: € 50,000
- United Kingdom: £ 20,000 – £ 30,000
- WHO standard: 3 * GDP (gross domestic product) per capita

The added medical benefit may be assessed in comparison with existing therapies in terms of effectiveness, adverse effects, experience, applicability and ease of use. In France, the first step of reimbursement decision and price fixing process is confirming the medical benefit obtained (SMR, service medical rendu) which determines the reimbursement percentage, whereas the second step evaluates the improvement of the medical benefit over existing medicines (ASMR, amélioration du service médical rendu), which is used for price negotiations [46]. In contrast to the methods of healthcare evaluation in other countries, the UK National Institute for Health and Care Excellence (NICE) does not evaluate all interventions as they reach the market. NICE has published guidelines on how it will select interventions for review. This includes the following key questions [47–49]:

- Is the technology likely to result in a significant health benefit, taken across the National Health Service (NHS) as a whole, if given to all patients for whom it is indicated?
- Is the technology likely to result in a significant impact on other health related government policies (e.g. reduction in health inequalities)?
- Is the technology likely to have a significant impact on NHS resources (financial or other) if given to all patients for whom it is indicated?

- Is the institute likely to be able to add value by issuing national guidance?

Many countries, e.g. Switzerland, have compulsory social accident and health insurance systems for every citizen. The choice of the insurance company is free. The insurer has to accept every request and is not allowed to reject applicants with increased risks in the basic part. Rejection is only possible for coverage by complementary insurances. Physicians, pharmacists, midwives, chiropractors, laboratories, hospitals, several institutions for acute or chronic care for in- or outpatients, policlinics, or ambulance transporters are care providers approved from the concordat of insurers. Care providers are licensed to bill the insurer for approved services at prefixed rates according to lists such as TARMED and SwissDRG (German modification) issued by the Federal Office of Public Health (FOPH) [50, 51]. To be put on the list of pharmaceutical specialties, a request has to be addressed to the Swiss Federal Social Insurance Office, which is advised by the Swiss Federal Drug Commission. Applicants have to follow a manual and submit several documents, e.g. a summary of product characteristics, the grant of marketing authorisation, key facts, clinical overview, non-clinical overview, most relevant clinical studies, epidemiologic data of the disease to be treated, clinical guidelines, and pharmacoeconomic studies [52]. It is stipulated in the Swiss federal act on health insurances, that medicines and care are required to be efficacious, appropriate and economic to be reimbursed [53]. The latter requirement is checked by means of price comparisons between the requested Swiss price and those applied in Denmark, Germany, the Netherland, Great Britain, France, and Austria [52].

The costs of materials, duration of preparation, quality control, investment in premises, training, quality assurance et cetera determine the basic cost of pharmacy preparation. As with the reimbursement of licensed medicines there is a distinction between in-patient and out-patient supply. Pharmacy preparations used in hospitals could be considered to be part of the reimbursement for the therapy as a whole. Anyhow, the hospital pharmacist normally has to find his payment within the hospital organisation. In community pharmacy most pharmacy preparations are reimbursed by the health insurer, according to the Tax price with a surcharge according to the performance cost system. Reimbursement for unlicensed medicines will be handled differently in most European Countries. There may also be differences between the reimbursement for hospital and public pharmacies.

Within the patient access and reimbursement schemes, risk sharing is fixed as outcome-based or financial-based agreement between the payer and the manufacturer. Financial-based agreements are possible on a fixed price, on a price-volume ratio, on a price by diagnosis, on capitation fee, or on dose-quantity limits. Outcome-based agreements can be divided into evidence-development-based, conditional treatment continuation-based, or performance-based schemes. Most of these schemes are applied in Europe and Australia, followed by Canada and the United States [54, 55]:

- Evidence development schemes (34 schemes in use, regrouped into coverage-with-study or coverage-with-appropriateness determination approaches)
  - Example taxanes: In 2000 in the UK, the use of taxanes for adjuvant treatment of early breast cancer was limited to randomised clinical trials.
  - Example temozolomide: In 2001 in the UK, this active ingredient was only recommended as an initial chemotherapy for patients with brain cancer included in a clinical trial.
  - Example risperidone: In 2003 in France, costs were covered, if evaluation studies on whether it helps patients stay on the medications were performed. In case of failure the manufacturer was to refund costs to the French ministry of health.
  - Example human papilloma virus quadrivalent vaccine: In 2007 in Sweden, the manufacturer was asked to provide every 6 months additional data on ongoing and planned studies in order to determinate the cost-effectiveness from a long-term perspective.
- Conditional treatment continuation schemes (10 schemes in use)
  - Example bortezomib: For the multiple myeloma indication, in the UK the manufacturer agreed in 2007 to reimburse the NHS in either cash or product for patients who did not respond, i.e. those who do not show a 50 % decrease in serum M protein, after four cycles. Responding patients received additional four cycles. In 2009, the same agreement was fixed with the Scottish Medicines Consortium.
  - Examples sunitinib and sorafenib: A hospital discount of 50 % applies in Italy to the first 3 months of treatment. For responding patients the treatment is then reimbursed and the discount dropped.

  - Examples Alzheimer's disease medicines: In Italy, during the first 3 months, patients starting Alzheimer's disease medicines are assessed for short-term effectiveness. The medicines are provided free of charge by the manufacturer. If treatment goals are met after 3 months, treatment is continued for a maximum of 2 years and the costs reimbursed by the Italian Drugs Agency (AIFA).
- Performance-linked reimbursement schemes (14 schemes in use, regrouped into pricing review, try-before-you-buy, or no cure – no pay principles)
  - Example statins: In 1998 in the US and in 2000 in the UK, rebates were agreed and refunds were promised if LDL cholesterol could not be lowered.
  - Example bosentan: In 2004 in Australia, the price of bosentan for pulmonary arterial hypertension was linked to the survival of patients followed in an observational study.
  - Example risedronate sodium: In the US in 2009, the manufacturer agreed to reimburse for the costs of treating-related fractures.

3.4 Investigational Medicinal Products

The manufacturing of investigational medicines goes together with phases I – III of the Clinical Trial Investigation, where pharmacokinetics and toxicology at different dosages is investigated and compared with the standard treatment or placebo treatment in a small group of healthy volunteers first, in a limited group of patients afterwards, and finally in a large group of patients. After completing these investigations the new medicine can be offered for approval and admission to the market (market authorisation). In phase IV Authorised Medicines are evaluated for the authorised indications, side effects and long term value and will be monitored in clinical practice. This may occur by pharmacovigilance or by outcomes research in specific patient populations. As described in Table 3.3, currently 15 years may pass until a new chemical entity reaches the market.

In the clinical phase of development of new chemical entities, medicines are developed by hospitals, universities, or pharmaceutical companies and administered to humans as "Investigational Medicinal Products (IMP)". In Europe, the administration of IMPs to human beings is regulated by Directive 2001/20/EC (which has been replaced on the 16 April 2014 by the new Regulation No 536/2014 which is to come into force no earlier than 28th May 2016), which deals with the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [56]. Each specific investigation has to be approved by an Ethics Committee. In the Netherlands, a national committee for clinical research has to assign a certificate of incorporation. Research with a non-licensed medicine without such an approval is not allowed. In Switzerland, a new act on human research entered into force as from 2014. It inserts an article into the Swiss Federal Constitution, recently voted and approved by the Swiss nation in 2010 [57].

The dossier of an IMP is called the Investigational Medical Product Dossier (IMPD). It describes the technological, pharmacological and toxicological properties of the product as well as the method of preparation. Importing or preparing IMPs by a manufacturer or a pharmacist requires a license/authorisation [58]. An authorisation as a wholesale trader in medicinal products is required, if the IMP originates from another ERA state (European Research Area). A Manufacturing Authorisation is requested, if the medicine is imported from a country outside the ERA. These authorisations are specific for a dosage form or for a preparation process. Preparation and quality control should be performed according to the IMPD. A Qualified Person (QP, see Sect. 25.3.4) has to release the product after import, preparation and quality control and to guarantee that all quality requirements are met. Pharmacies don't need a Manufacturing License if the preparation of an IMP is limited to operations such as reconstitution, dilution and

Table 3.3 Phases of clinical research

	Discovery	Clinical trials		Launching		
	Preclinical testing	Phase I	Phase II	Phase III	Drug agency	Phase IV
Years approximately	6.5	1.5	2	3.5	1.5	
Test population	Laboratory and animal studies	20–100 healthy volunteers	100–500 patient volunteers	1,000–5,000 patient volunteers	Review process, approval	Additional post-marketing testing
Purpose	Assess safety, biological activity and formulations	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use		
Yield	5,000 compounds evaluated		5 enter trials		1 approved	

labelling, which have to be performed for the purpose of administration to the patient and are defined in the IMPD. These activities however have to be carried out within the institution where this clinical trial is carried out and by a pharmacist who is employed within this institution [59]. See also Sect. 35.5.10.

3.5 Unlicensed Medicines

Unlicensed medicines are medicines, including pharmacy preparation, that don't have a Marketing Authorisation. Patients who suffer from a disease, for which no licensed medicinal product is available, may exceptionally get unlicensed medicines from a manufacturer. This happens on the legal basis of a compassionate use program either on a named patient basis or to cohorts of patients. This regulation applies to patients with a chronically or seriously debilitating disease or whose disease is considered to be life threatening. Reimbursement has to be clarified from case to case (see Sect. 3.3.2 Reimbursement).

Compassionate use is a treatment option that allows the use of an unlicensed medicine. Compassionate use programmes are for patients in the European Union (EU) who have a disease with no satisfactory authorised therapies or cannot enter a clinical trial. They are intended to facilitate the availability to patients of new treatment options under development. To qualify for a compassionate use programme, the manufacturer calls on the national authorities for permission. The manufacturer must submit a request for the granting of a marketing authorisation or he must perform research in the context of a research programme with a cohort. Compassionate use procedures are also applicable for unlicensed medicines withdrawn from the market or for off-label use of licensed medicines.

Several options to get authorisations for named patients have been applied in the past and still are in practice in order to maintain the supply chain with the most important medicines. As long as they are classified as IMPs and thus not allowed on the market, patients may be treated in some countries, e.g. Switzerland, in a parallel trial programme or within an extended access. Procedures follow those for compassionate use and requests have to be submitted to the ethical committee as well. A parallel trial programme will always require Ethical Approval and would therefore be a Clinical trial in the UK. Single cases different from compassionate use have to be authorised but do not need an ethical committee approval.

No marketing authorisation is needed, if the required medicine is a part of an approved formulary (formula magistralis or formula officinalis) produced on a small scale [60], or if it is produced according to an own formula in small scale for own clients. Medicines from foreign countries made available to tourists from the same country to continue an existing treatment, is free from authorisation request as well. In case of life-threatening urgencies, health professionals have the obligation to assist the affected person. If procedures will not resolve a problem in time, the use of unlicensed medicines may be approved by phone or mail contacts of inspectorates or of another direct supervising authority [61].

Off-label use of a licensed medicine and unlicensed use of not-admitted or not-marketed medicines have several uncertainties in common. For neither one of them the intended use is described nor approved by the authorities (different indication, different dose, different application mode, different patient population, different pharmaceutical items, e.g. expiry date, solvent, etc). Thus, the responsibility is attributed to the treating physician and to the producing pharmacist, if he is or can be aware of the indication for which the medicine is given. They act under the obligation and duty of care and have to consider the state of the art. Adverse events have to be notified to the authorities. The legitimation of having acted the selected way must be justified. Informed consent of the patient must be available. Information about reimbursement granting or rejection must have been given. The pharmacist's duty is to validate the prescription, to consult the prescriber, to produce according to GMP, PIC/S or approved quality guidelines, and be responsible for the formula (Table 3.4), in the case of a prepared medicine [62].

3.6 Orphan Medicines and Neglected Patients

The pharmaceutical industry decides on the basis of a cost-benefit analysis, if the development and placing on the market of a medicinal product is profitable. The development of medicines for rare illnesses or for minority special patient populations ("neglected patients"), therefore generally does not get funded. Industrial providers however offer innovations for very small groups of patients at very high prices, e.g. products from recombinant technologies e.g. coagulation factor VII, monoclonal antibodies, and many more. Governments have designed programs to stimulate the development of these medicines.

3.6.1 Orphan Medicines

Disorders which are rare, are called orphan diseases and the medicines intended for these diseases are called orphan

Table 3.4 General requirements for off label and unlicensed use of medicines. Authorisations may differ according to national and local ordinances

Type	Authorisation status	Legal basis	Requirements
Off label use			
I	Medicine with a market authorisation in the own country (Market Admission covering local use)	No special authorisation needed Prescription and dispensing according to approved state of the art of pharmaceutical and medical sciences	Responsibility of treating physician Obligation and duty of care Information of the patient Liability Notification
II	Medicine with market authorisation in a foreign country	Special authorisation needed Authorisation for import needed	
Unlicensed use (compassionate use, parallel trial, extended access, individual case, medicines withdrawn from market)			
I	Medicine not admitted to own market, but admitted in an extra-European country (USA, Canada, Australia, New Zealand)	No special authorisation needed Authorisation for import needed To be used within the approved indications Physicians and pharmacist with allowance for retail trade	Small amounts Responsibility of treating physician Obligation and duty of care Information of the patient Liability Notification
II	Medicine not admitted to own market, but admitted in an extra-European country (other than USA, Canada, Australia, New Zealand)		
III	Medicine without market authorisation worldwide		
Market authorisation not needed			
Formula magistralis medicine according to prescription for individual patient or patient group			
Formula officinalis medicine according to an approved monograph			
Own formula medicine produced in small amounts for own clients or patients			
I	Active ingredient known, used according to scientifically approved indication	Authorisation to produce needed	Strictly small scale Manufacturing according to c-GMP/PIC/S guidelines Responsibility, obligation and duty of care attributed to physician and pharmacist Liability Notification
II	Active ingredient known, used in an indication beyond scientifically approved knowledge		Documentation of scientific knowledge on the active ingredient Strictly small scale Manufacturing according to c-GMP/PIC/s guidelines Responsibility, obligation and duty of care attributed to physician and pharmacist Liability Notification
III	Active ingredient not yet rated "for human use"		Notification to ethical committee Documentation of scientific knowledge on the active ingredient Strictly small scale Manufacturing according to c-GMP/PIC guidelines Responsibility, obligation and duty of care attributed to physician and pharmacist Liability Notification

medicines. An orphan disease is a serious, life-threatening or chronically debilitating condition which affects less than 5,000–10,000 patients in the 750 million inhabitants in the EU [63]. Governments try to stimulate the development of orphan medicines with economic incentives through legislation on orphan medicines. It was hoped that this stimulant would encourage the market. However, the market is failing in this respect [64]. In trade, sellers get paid for what they sell. In care, providers get paid for what they do. No orphan medicinal product will be available without

economic encouragement, at least the coverage of development and production costs. The European legislation is based on the economic motivation to put a medicinal product on the market. Public health arguments are secondary. If the market fails, health care and tax payers should take over and care for the patient in another way, e.g. by attribution opportunities and flexibility to prepare medicines in a pharmacy. Many case studies support a simplified handling for pharmacy prepared compounded medicines with a long history of effective use [65].

In some countries, enterprises can be commanded to provide a medicine. This had been the case in the nineties with cladribine (2-CdA, 2-chlorodesoxy-adenosine), which was provided first by a current industrial supplier in the USA to treat hairy cell leukaemia as an alternative to interferon-alfa. Cladribine was not available in Europe at that time, neither as a product nor as an active substance. It took several weeks until the six-step synthesis was developed and a hospital pharmacy product could be made available. The US-price of the marketed syringe was some 20 times as much as could be attained later by hospital pharmacy production with the specially synthesised substance [66].

Today, the EU encourages the development of orphan medicines [67] with:

- Advice and support on research protocols
- EU-funded research
- Free pre-submission meetings with persons or companies ("sponsors") on authorisation applications
- Reduction on the registration fee
- Centralised EU procedure
- Market exclusivity for 10 years
- After-designation support

To be eligible for these incentives, products should be designated through the orphan designation procedure. The EMA through its Committee for Orphan Medicinal Products (COMP) assesses at request by the manufacturer, if a substance might be designated as an orphan drug for a specified orphan disease. The whole orphan designation procedure comprises the following steps [68]:

- Sponsor notifies the Agency of intent to file.
- Pre-submission meeting/ teleconference.
- Submission of application; validation by the Agency (day 1).
- Assessment/COMP meeting/ possible hearing/COMP opinion adopted (by day 60 or 90).
- Opinion sent to the European Commission.
- Commission decision granted (within 30 days).
- Publication in EU Register on the Commission's website; publication of public summary of opinion on the Agency's website.

After a positive assessment the manufacturer must follow the normal registration procedure, albeit that the clinical studies normally will be continued after the market authorisation has been granted due to the small number of patients. National incentives may be provided, e.g. reimbursement options. In Portugal, France and Belgium, all orphan medicinal products are reimbursed, in the Netherlands most of them (95 %) [69].

Designated orphan products, indications and more than 1,224 active substances are registered. Sixty are authorised for 52 rare diseases, 25 are withdrawn or suspended, 9 expired. Oncological products dominate. Within this class, no orphan medicinal product authorisation has been attributed to axitinib, crizotinib, erlotinib, gefitinib, lapatinib, pazopanib, vandetanib, vemurafenib. An orphan medicinal product authorisation has been assigned to dasatinib, imatinib, nolotinib, sorafenib [70].

3.6.2 Neglected Patients

For many diseases active substances are available, and yet groups of patients will not receive the medicines they need. This refers not only to patients who cannot pay for the medicines, but also to various special patient groups, e.g. children and elderly. They need doses or dosage forms which differ from the available licensed medicines. In the wake of the WHO and DNDi, following the World Health Assembly in 2012 [71–73], the EU, national Governments and universities call for attention to be given to the development of appropriate medicines for these neglected patients. For the development of more medicines for children funding programmes have been started such as ERA-NET PRIOMEDCHILD in the EU [74] and in the Medicines for Children Research Network (MCRN) in the Netherlands and the UK [75].

From the WHO-report Priority Medicines for Europe and the World [76, 77]:

> . . . There is a wide range of existing evidence-based, very often off-patent, technologies that are heavily underutilised. Such technologies could be used to improve the 'patient-friendly' performance of a number of existing medicines, the use of medicines in paediatrics and geriatrics, and other areas where individualised time-dosing of medicines is required, e.g., patients with impaired liver or kidney functions, or patients with compromised immune systems. . .

Whereas agreements on patents and authorised production can be negotiated in cases of shortages (see section on shortages), this has so far not yet been possible in cases of national versus pharmaceutical industry interests on behalf of neglected patients. Patented medicines block the production of more affordable generic versions while more and more patients become sick or die because the medicines they need to stay alive are simply too expensive. Recently, much attention has been attracted by India's efforts to increase access to medicines and implement a patent system

in line with its public health needs. India is a critical producer of affordable medicines. Competition among generic producers in India has brought the price of medicines to treat diseases such as HIV, tuberculosis and cancer down by more than 90 %. The majority of the antiretroviral medicines purchased by the U.S. government's global AIDS program come from India, and more than 80 % of the HIV medicines non-profit aid organisations use to treat more than 280,000 people with HIV in 21 countries are generics from India.

The policies and decisions by India's patent offices and courts to limit abusive patenting practices and increase access to affordable generic medicines are subject to increased political pressure from the US government and pharmaceutical industry. Among the critical decisions can be found a 7-year-battle to claim a patent on the salt form of the cancer medicine imatinib, judged by the Indian Supreme Court as non-patentable, and a generic version of a kidney cancer medicine, which was made available for 97 % less than the patented version. India's health ministry has set up an independent expert committee to identify exorbitantly-priced medicines for which further compulsory licenses may be issued, relying on the Agreement on Trade Related Aspects of Intellectual Property (TRIPS) and the Doha Declaration on TRIPS and Public Health, both of which defend access to existing medicines by allowing countries to use flexibilities such as patent oppositions and compulsory licenses to overcome intellectual property barriers.

The country must now deal with pressure from the multinational pharmaceutical industry trying to sue India in a foreign tribunal. The US Government has a policy of negotiating and exerting pressure on governments to give foreign investors the right to sue governments 'known as Investor-State Dispute Settlement' for high amounts of damages if a law or policy harms their investment [78].

3.7 Medicines Import

If a patient needs a medicine, which is not on the national market, it may be imported from abroad or prepared in a pharmacy.

In 2013 the following medicines had to be made available in the Netherlands in 2013 by import [79]:

- Isoniazide tablets 200 mg (Isozid®)
- Sucralfat oral suspension 200 mg/ml (Ulcogant®)
- Chinidine sulphate 200 mg tablets (Kiniduron Depot®)
- Mitoxantron injection various strengths (Onkotrone®)
- Riboflavine 10 mg tablets (Beflavine®)
- Adrenaline injection various strengths (several manufacturers)
- Phentolamine injection 10 mg/ml (Regitine®)
- Hyaluronidase injection (Hylase®)
- Biperidene injection 5 mg/ml (Akineton®)
- Tinidazole tablets (Fasigyn®)
- Bismuth oxide tablets (De-nol®)
- Fluphenazine coated tablets (Moditen®)
- Dihydralazine injection solution (Nepresol powder for injection®)

From those medicines prepared in one of a selection of European hospital pharmacies, half to three-quarters are available in the market in another EU country, North America or Australia [80]. Although the European legislation has been aimed at decreasing trade barriers since 2001, the purchase of medicines from other countries is anything but simple. A patient is allowed to travel abroad and buy an authorised medicine for personal use and import it into Europe, however, a pharmacist can only import a medicinal product if he has a wholesale import authorisation. The complicated rules for reimbursement (in some Countries) and the amount of time the whole process takes, renders import a laborious way to make medicines available for the patient.

If an imported medicinal product has been granted a Marketing Authorisation, the pharmacy can purchase it from a wholesaler established in the country or from the manufacturer. The packaging must meet the labelling requirements in the subject country, and the patient leaflet has to be written in one of the country's languages. In a hospital, the patient leaflet and/or usage information are less important if information and skill is more readily available from a permanent pharmaceutical assistance and documentation than outside of a hospital. The pharmacist will then dispense the product to the patient. As a second option, a pharmacist or a wholesaler or a manufacturer can ask permission to import from the Competent Authority under the terms of the named patient regulation and on the following conditions:

- The physician considers it necessary that the patient belonging to his medical practice is treated with the medicinal product.
- There is no adequate alternative medication for the medicinal product on the market.
- The physician has requested a pharmacist to deliver the medicine in writing using the national model form.
- The pharmacist has presented the written request of the physician to the Competent Authority.
- The quantity of the medicinal product and the period during which it may be delivered to the doctor, has been determined by the Competent Authority.

- The manufacturer, wholesaler or pharmacist keeps track of the quantity of the medicinal product, the name of the physician, the number of patients for whom it is intended, and on the medicinal side effects observed.

The costs of medicines purchased from abroad have to be borne by the budget of the institution. In some Countries these imported medicines are not reimbursed from a social health insurance, unless the patient has an allowance or is covered by an extra private insurance, specifically for that medicinal product.

3.8 Preparation of the Remaining Necessary Medicines

A patient may need medicines which are not commercially available, neither in the country nor abroad, or which are temporarily not available, although a Marketing Authorisation is granted. To provide the necessary care to the patient, these medicines may be prepared by the pharmacist, either from raw materials or through adapting a licensed product. The need for this combined production-and-care task of the pharmacist is endorsed worldwide. Various references and lists from hospital pharmacy production units are published online [81]. The Formularium der Nederlandse Apothekers (FNA, see Sect. 39.4.5) contains formulations for 200 medicines, which are prepared in the pharmacy because they are frequently needed but not on the market. It does not contain all the required pharmacy preparations. The total number of required, rational medicines which pharmacies have to prepare out of raw materials is estimated at 50 to more than 500. The estimate depends on the concepts 'required' and 'rational' (see Table 3.5 for examples of the vast variety of medicines provided by a Swiss University hospital pharmacy). Specials (unlicensed medicines) are being produced according to GMP and PIC/S guidelines and are becoming more and more important to produce, whereas extemporaneous preparations, prepared according to less strict standards, are becoming less common. There is a need for consensual standards of preparation practices and common monographs for preparations [82, 83]. The development of standard formulations is costly, but considerably cheaper than developing a medicine with a Marketing Authorisation (Table 3.4).

3.9 Organisation of Pharmacy Preparation

Pharmacy preparation not only covers preparation from raw materials, but also the adaptation of licensed medicines and reconstitution in excess of the instructions of the SPC. Such preparation also happens outside the pharmacy, e.g. on the ward or in patient's homes. Circumstances such as legislation, logistics, regulation, and reimbursement have caused the development of several types of preparing pharmacies, which differ in organisation, size, types, and batches. The organisation of pharmacy preparation should guarantee good product and patient care. This is the scope of the legal basis of pharmacy preparation.

3.10 Importance of Pharmaceutical Production in Hospitals

All those hospitals, which have decided to run a hospital pharmacy without access to production, are deprived of an important scope for action to overcome shortages. If own manufacturing has not been spectacular enough in the past to underline its importance and justification to exist, it should be recognised by now that flexibility counts and is one of the determinant element for hospital pharmacists to fulfil their duty (Table 3.6). Grouping of geographically closely situated production units may be an option to economise.

In the 1990s, the justification of hospital pharmacy production has been reassessed due to economic reasons and due to the severe GMP-requirements requiring important investments. Economic reflections have dominated rational ones and anticipation of supply problems. Administrators did not realise that only a few pharmacy-issued products were commercially available. In-house products have been compared to standard industry-derived products as far as comparisons existed. Some infusion solutions were commercially available at low prices due to the large numbers produced by scaling up. Some of these infusions were produced in medium or low numbers by hospitals to put pressure on prices, to keep installations running, and to continuously exercise technical staff. Their contribution to coverage was judged as being insufficient. Intermediate and small-scale production of not commercially available products has not been included in the economists' figures, as there were no commercially available products to be compared to.

In 1996, in one of the biggest hospital pharmacies of a Swiss University Hospital, an internal cost assessment of hospital production revealed that there was no financial loss, but rather an income of around 165,000 CHF had been achieved with internally prepared stock products, if every product including small scale serial stock production and extemporaneous production had been included in the calculation. As a result of own figures, around 15 % only of the assortment of pharmacy products could be compared to marketed brands and 85 % not. Outsourcing of the latter would have cost 2.9 times the amount of the cost billed to internal users. These considerations and the mandate to provide medicines have helped to prevent the closure of hospital pharmacy production [84].

Table 3.5 Examples from a Swiss University Hospital of the vast variety of medicines provided by pharmacy preparations only. Some may be prepared by contract manufacturing depending on the amounts used

Sterile products (large volume liquids ≥ 100 ml, aseptic process)	**Indication, use**
Alumen irrigation	Astringent for hemorrhagic bladder
Cardioplex injection solution	Cardioplegia for open heart surgery with cardiopulmonary bypass
Ethanol 70 % irrigation	Irrigation
Hydration infusion solution standard bag EVA	Pretreatments to carboplatin treatments
Hydrogen peroxide 2 % irrigation	Irrigation
PCA Fentanyl 20 mcg/ml injection solution	PCA
Total Parenteral nutrition all-in-one solution	TPN
Sterile products (large volume liquids ≥ 100 ml, autoclaved)	**Indication, use**
Aluminium acetotartrate irrigation	Irrigation
Basic infusion solution G5-K Perf PP 500 ml	Basic infusion
BSS irrigation	Irrigation
Calciumchloride 170 mmol/l infusion solution	Infusion by pump
Chlorhexidine 2 % irrigation	Irrigation
Glucose 40 % with Ethanol 10 % (V/V) irrigation	Irrigation
Glucose 7.5 %, 10 %, 12.5 %, 15 %, 30 % infusion solution	Infusion volume and concentration adapted
Glycerol 85 % solution sterile	Urethral use at extra-corporal shock-waves lithotripsy; Osmotic dehydration of oedematous cornea
Hank w/o Ca/Mg solution sterile	Not injectable, *in vitro* use
Mepivacaine HCl 0.5 %, 1 % injection solution	Local anesthesia
Mixed infusion for neonates	Infusion volume and concentration adapted
NaCl 2.5 % infusion solution	Infusion volume and concentration adapted
NaCl 20 % irrigation	Irrigation
Neomycin 0.5 % irrigation	Irrigation
Novesin 1 % irrigation	Irrigation
PCA Ketamin 5 mg/ml infusion solution	PCA
PCA Ketamin 2 mg/ml/MORPHIN 2 mg/ml infusion solution	PCA
PCA Morphine HCl 2 mg/ml infusion solution	PCA
PDA forte (or standard) infusion solution	Epidural analgesia
Polyelectrolyte infusion concentrate	Component for TPN compounding
Ringer lactate infusion solution	Infusion volume and concentration adapted
Sterile products (small volume liquids < 100 ml, aseptic process)	**Indication, use**
N-Acetylcysteine 1 % eye drops monodoses	Ocular mucolytic eye drops
Alteplase 12.5 mcg/0.1 ml syringe	Ready-to-use syringes or vials made from commercial product, plasminogen activator for fibrinolysis
Amphotericin B 0.15 % eye drops	Eye drops
Bevacizumab 25 mg/ml injection solution	Anti-angiogenetic agent for intravitreal application
Bleomycin injection solution 1,000 I.U./ml syringe	Therapy-resistant warts
Carbicarb injection solution concentrate	Injection concentrate
Cefazolin 33 mg/ml eye drops	Eye drops
Cefuroxime injection solution 10 mg/ml	Intracameral injection solution
Ciclosporin 2 % eye drops	Eye drops
Cocaine HCl 2 %, 10 % eye drops monodoses	Eye drops
Cysteamine HCl eye drops 1.5 mg/ml	Cystinosis
Ethanol 96 % infusion solution	Antidote at methanol or ethylene glycol intoxication
Ethanol water free 99 %	Antimicrobially filtrated, not for direct injection
FITC-Dextrane 25 % injection solution syringe	Diagnostic agent, for microlymphography, subepidermal injection
Glucose 30 % solution oral sterile 10 MD	Calmative for neonates
Lidocaine 2 % eye drops	Eye drops
Methacholine HCl 2 mg/ml or 10 mg/ml inhalation solution	Diagnostic for lung diseases
Mitomycin C 0.2 mg/ml eye drops or syringe	Eye drops or syringe for ophthalmic use
Mixed eye drops tropicamide 0.5 %, phenylephrine HCl 2.5 %	Eye drops
Novesin 0.2 % eye drops	Eye drops
Paraffin liquid sterile solution	Dipping bath for sutures

(continued)

Table 3.5 (continued)

Sterile products (small volume liquids < 100 ml, aseptic process)	**Indication, use**
Phenol 6 % injection solution syringe	Intra-articular injection solution at neurolysis
Phenol orthopedic kit sterile solution	Instillation at bone tumors
Pilocarpin 0.125 % pH 6.5 Eye drops monodoses	Glaucoma (less irritating than commercially available products)
Polyhexanide 0.02 % eye drops	Eye drops
Tobramycin 6.6 mg/ml eye drops monodoses	Eye drops
Sterile products (small volume liquids ≤ 100 ml, autoclaved)	**Indication, use**
Adenosine 3 mg/ml injection solution	Test for blockages in the coronary arteries after adenosin exposition at scintigraphy
Buffer pH 7.0 injection solution additive/amphotericin B stabiliser	Stabilization of amphotericin B infusion solution
Carbachol 2.5 mg/ml inhalation	Diagnostic at lung function test
Clonidin HCl 6 mg/mL infusion solution concentrate	$Beta_2$-Sympatholytic to treat high blood pressure, anxiety disorders, panic disorders, withdrawal symptoms
Cocaine HCl 5 %, 10 % sterile solution	At local application for anesthesia and vasoconstriction
Dextrane T70 20 % sterile solution	Additive to Hank w/o Ca/Mg at cryoconservation of stem cells
Dextran riboflavin kit	Keratoconus therapy: Corneal collagen cross-linkage with riboflavin and UV-A
Glycerol 85 % eye drops	Eye drops
Histamin injection solution 1:10'000	Diagnostic for intradermal and inhalation provocation
Komplexon III 3 % eye drops	Eye drops at local ophthalmic use
Mepivacaine HCl 1 %, 2 % injection solution in sterile package	Local infiltration anesthesia, epidural block
Morphine HCl 2 mg/ml // 4 mg/ml // 40 mg/ml injection solution	Analgesia
Zinc 7.6 μmol/ml infusion solution concentrate	Concentrate for infusion solution or component of TPN
Sterile products (semisolids)	**Indication, use**
Lubricant for catheter syringe, bottle	Lubricant various presentations
Methocel 2 % gel sterile	Lubricant, various indications
Sterile products (solids)	**Indication, use**
Talcum (sterile powder)	Pleurodesis
Non-sterile products (liquids)	**Indication, use**
Chlorhexidine tincture (or 0.02 % in glycerol)	Irrigation
Codeine phosphate 2 % oral solution(1 ml = 19 gtt = 20 mg)	Antitussive
Copper sulfate 20 mg/ml oral solution	Oral copper supplement
Dessicating ear drops	Ear drops
Ethanol 30 %	Dermatological use for wetting dressings and cooling
Fuchsine ethanolic solution	Dye
Hydrogen peroxide 3 %, 10 % solution	Disinfectant, oxidiser
Individualised oral liquids from solids (active ingredient in ora-sweet® or ora-blend® or ora-blend® vehicle) [83]	Patients with swallowing difficulties or dose determining with children
Joulie solution (5 ml = 337 mg phosphate = 110 mg P = 3.55 mmol P)	Oral phosphate supplement
KCl 1 mmol/ml solution	Oral potassium supplement
Ketamine 25 mg/ml nasal spray	Analgesia and bronchodilatation
Lugol solution 2 %	Oral iodine supplement
Methoxsalen 0.15 % solution (10 gtt = 0.3 mg)	PUVA therapy
Midazolam 5 mg/ml nasal spray	Sedative in pediatrics at short interventions
Morphine HCl 0.1 % oral solution (1 ml = 20 gtt = 1 mg)	Analgesia
Morphine HCl 1 % oral solution (1 ml = 20 gtt = 10 mg)	Analgesia
Morphine HCl 2 % oral solution (1 ml = 20 gtt = 20 mg)	Analgesia
Oral thrush prevention solution	Thrush prevention
Pepsin wine 2.5 mg/ml	Pepsin supplement at achlorhydria
Phenobarbital 10 mg/ml 15 ml oral solution (1 ml = 15 gtt = 10 mg)	Anticonvulsive
Phenol 80 % solution	Topic solution
Potassium permanganate 5 % solution	Dermatologic use: to dilute 0.5 ml – 1 ml in 1 L water
Resorcin ear drops	Ear drops

(continued)

Table 3.5 (continued)

Non-sterile products (liquids)	Indication, use
Salicylic acid Oil 5 %, 10 % or petroleum Jelly 20 %	Dermatologic use as keratolytic
Silver nitrate 1 % solution	Cutaneous solution at therapy-resistant warts
Trichloroacetic acid 40 % solution	Cutaneous solution at therapy-resistant warts
Non-sterile products (semisolids)	**Indication, use**
Aqua dalibouri solution	Disinfectant, adstringent
Calciumgluconate 2.5 % Gel	Antidote: cutaneous gel, HF burns
Capsaicin cream 0.075 %	Pain relief at peripheral neuropathy e.g. post-herpetic neuralgia or shingles, reduction of itching and inflammation at psoriasis
Chloral hydrate suppository	Sedative at CT scans
Coal tar in pasta leniens 10 %	Treatment of dandruff, psoriasis, head lice
Duret ointment	Psoriasis on the scalp
Esophagus paste	Diagnostic for CT images of the gastrointestinal tract
Hydrocortison oxytetracyclin paste	Local anti-infective
Lubricant with chlorhexidine 0.05 %	Non-sterile lubricant
Nasal ointment own formula	Nasal ointment
Urea (carbamide) 20 % fatty cream	Dermatologic use at rehydration and further indications
Wart ointment NRF	Ointment at therapy-resistant warts
Non-sterile products (solids)	**Indication, use**
Dexamethason 20 mg, 40 mg capsules	Corticosteroid therapy
DHEA 10 mg, 25 mg, 100 mg capsules	Supplement for many indications (schizophrenia, improving skin appearance, systemic lupus erythematosus, sexual dysfunction, muscle ache, mouth ulcers, osteoporosis)
Hydrochlorothiazide 0.5 mg, 1 mg, 3 mg, 5 mg capsules	Pediatric cardiology
Estradiol 0.4 mg 100 capsules	Physiologic induction of puberty with very low-dose, e.g. in Turner syndrome
Fordtran solution and aromatiser powder	Osmotic laxative, pretreatment of diagnostic or surgical intestinal intervention
Gentamicin/Polymyxin 20 capsules	Selective intestinal decontamination
Hydroxycarbamide 100 mg, 300 mg, 500 mg capsules	Non-marketed dosage
Maltodextrin powder 0.5 g, 1 g, 2 g, or 5 g	Pediatric use
Misoprostol 25 mcg vaginal capsules	Medical abortion, treatment of miscarriage
Paracetamol 30 mg suppositories	Non-marketed dosage
Spironolactone 0.5 mg, 1 mg, 3 mg, 5 mg capsules	Pediatric cardiology
Thalidomide 50 mg 30 capsules	Multiple myeloma
Repacked products (liquids)	**Indication, use**
HIV-PEP-Set	Post-exposition prophylaxis HIV infection after accidental injection
Spinal-Set Bupivacain long acting	Spinal anesthesia
Spinal-Set hyperbar	Spinal anesthesia at Caesarean section
Suxamethonium HCl (Succinylcholine) 5 %	Depolarising neuromuscular blocker

Closing scenarios are influenced by the lack of financial resources needed for investments, typically calculated for a pay-back-time of 10–15 years. Generally, hospitals do not have such sums at their disposal to match those of industry, where 10–15 % reinvestments of the annual volumes of sales are current. Benchmarking with industrial production cannot be more than a virtual cost comparison, because the two markets differ fundamentally and most of the products of hospital production do not compete with industrial ones. In trade, sellers get paid for what they sell. In care, providers get paid for what they do. As a result, it is even not important to analyse and compare cost structures. Some components of cost are only, or mainly, found in industry but not in hospital pharmacies, e.g. gains (around 10 % of the ex-factory price), advertising (4 %), distribution (9 %), medical information (11 %), research and development (15 %).

It is generally recognised that production should be taken over and scaled-up by industry as soon as a hospital's capacity is exhausted. The contrary is seen today as well. Hospital should be able to provide products made in house as soon as the industrial scale is not reached any more and withdrawal from the market is imminent. In times of good economic prosperity and when medicine shortages were exceptional occurrences, and in order to reduce the risks arising from non-industrial production, some countries and governments favoured limiting hospital pharmacy production and support industrial production. Another approach was to limit the number of units producing on a small-scale depending on a

Table 3.6 Arguments for pharmaceutical production in hospitals

High added value for public health from a global point of view
Traditional role as a central item of public health
Favourable cost-benefit-ratio
Mandate to provide medicines
Independence from unreliable suppliers
Preservation of know-how, returns and employment in the region
Responsibility for the patient mix from the region
Reasons for various kinds of logistics of medicines
Indispensable logistic resource
Active substances either not commercially available or not available in the required dose or patient friendly form
Individual pharmacotherapy (paediatrics, ICU, etc)
Choice of most suitable container
Option to adapt formula or container or both
Unstable medicines: short shelf lives
Emergency situations following accidents, crises, catastrophes
Local clinical trials
Medicine safety items
Know-how in times of medicines shortages
Know-how for medicine selection and formulary definition of industrial standard products
Know-how for extemporaneous preparation and magistral formulations
Individual pharmacotherapy (paediatrics, ICU, etc)
Quality assurance (high quota of professional staff)
Multidisciplinary shared responsibility and assistance of pharmacotherapy
Protection from hazardous influences and incidences (antineoplastics)
Small patient population, e.g. suffering from hypersensitivity or contraindication to substances
Direct dispensing and application to personally known patients, to promote patient adherence
Optimal stocks (no intermediate stocks)
Economic values
Adapted and polyvalent intermediate chain production
Low transport cost
No setting aside of reserves for risks
No cost for intermediate trade margin
No advertising and marketing cost
Low cost for storage of standard products
No or low cost for research and development
Ecologic values
Recycling
Reduction of waste volume
Simplified disposal of waste
No unnecessary transports
Different objectives of industry (returns) and hospital (public health service)
Ad hoc production not for stock, but adapted to needs
Assortment of many products in small amounts rather than of few products in big amounts
Physicians as initiator of orders (patient-oriented), not management or shareholder (yield on shares)
Mandate for provision is also applicable for unviable products

risk assessment estimated from application, amount produced per year, active ingredient, production process, and client or patient respectively. No flexibility based on the number of beds or on the number of allied institutions was planned. Above this quota, a market admission would be requested [85, 86]. Excepted from the need for a market admission are still the magistral or officinal formulations, products produced according to a formula published in professional literature, and products not equally available on the market and distributed to the own patient or client.

The EAHP has dedicated big efforts for animating and preventing hospital pharmacy production from decline. The need for flexible unimpeded preparation processes, the option to bridge gaps between pharmacy and industry

preparation, and the added value of polyvalent hospital pharmacy production have been clearly underlined at the 17th EAHP Congress in a seminar on the harmonisation of quality requirements according to the EC resolution CM/ResAP (2011)1 [1, 87].

3.11 Legislation of Pharmacy Preparation

Local laws may define preparation in a pharmacy as the complete or partial manufacture of medicinal products or the packaging or labelling of them. As a result, a pharmacy comprises premises in which medicines are prepared, stored, and dispensed, or just stored to be dispensed.

The allowance of preparation of medicines in the pharmacy is not self-evident. The main aim of EU legislation is to ensure that medicinal products have a license. This requirement results in a comprehensive external control of the efficacy, effectiveness and safety of the pharmaceutical quality. Medicines prepared in the pharmacy don't have a license and but pharmacy preparation is an allowed exception to this rule. The reason for this exception is the need for some medicines which are not available with a license. The exception is only applicable to the patients of the pharmacist, which should have a prescription from the treating physician. The essence of the exception is limiting the patient's risk of getting an ineffective, inefficient and unsafe medicine by:

- Restricting the medicines to patients the physicians and the pharmacist actually care for
- Putting the responsibility on physician and pharmacist

Laws covering patient's rights adds the patient's own involvement to the responsibilities of physician and pharmacist. A physician has to exercise due care in prescribing and act according to the professional standard and to inform the patient about the nature and purpose of the treatment and about possible side effects. The pharmacist is liable for the quality of pharmaceutical products prepared in the pharmacy in accordance with national laws and guidance on quality of care and for checking the reasonableness of the prescription.

Informing the patient about the nature of pharmacy preparations is not yet common practice in many countries. In the UK patient leaflets on this topic are available [88]. They explain both the preparation in the pharmacy and off label prescribing of licensed medicinal products. Both situations have in common that physician and pharmacist will of course act according to disease-specific professional guidelines or following a documented risk assessment.

The legal limitation of the risks of pharmacy preparations to the patient focuses mainly on pharmacotherapeutic aspects. The government manages this risk by limiting the application and responsibility of pharmacy preparations to the triangle patient-physician-pharmacist. The supply of pharmacy preparations from a preparing pharmacy to other pharmacies therefore is usually not allowed unless they are part of the same business and unless the ordering pharmacist, obtaining a preparation from elsewhere, is considered as the manufacturing pharmacist in terms of responsibility. However, the centralisation of manufacturing facilities may ensure more control over the product quality and lead to economic advantages. This awareness actually has led, in many countries, to the situation that not every pharmacy is able, any more, to prepare all medicines. In the Netherlands, the Health Care Inspectorate allows pharmacies to supply other pharmacies with pharmacy preparations, on condition that these preparations are efficient, effective and safe according to professional standards. In the UK such centralised units are licensed as manufacturing facilities by the Competent Authority (see Sect. 3.12). These centralised pharmacies need to fulfil further quality requirements. Only the own pharmacy is allowed to prepare the pharmacy preparations that do not need to have an equally highly documented level of quality control.

3.12 Preparations' Categories

Preparation in the pharmacy involves more activities than preparation from raw materials only. It comprises (see Fig. 3.2):

- Preparation from raw materials
- Preparation through adapting a medicinal product
- Reconstitution (in the strict sense as well as in excess of the SPC)
- Repackaging/Replenishing of medicines

The definitions are as follows:

Reconstitution: manipulation to enable the use or application of a medicinal product with a marketing authorisation in accordance with the instructions given in the summary of product characteristics or the patient information leaflet (Ph. Eur. Pharmaceutical Preparations). Often reconstitution is needed in excess of the instructions of the summary of product characteristics or the patient information leaflet, such as when a longer shelf life is assigned or when a different dilution with an infusion solution takes place. This action is legally considered as preparation. When speaking about the actual work process, that is the handling, it makes no sense to distinguish between the processes. Therefore this book uses the term 'reconstitution' for reconstitution in the strict sense as well as for reconstitution in excess of the summary of product characteristics or the patient information leaflet. If reconstitution is about parenteral medicines, as is often the case, the term 'aseptic handling' may be used in order to distinguish it from aseptic preparation or processing.

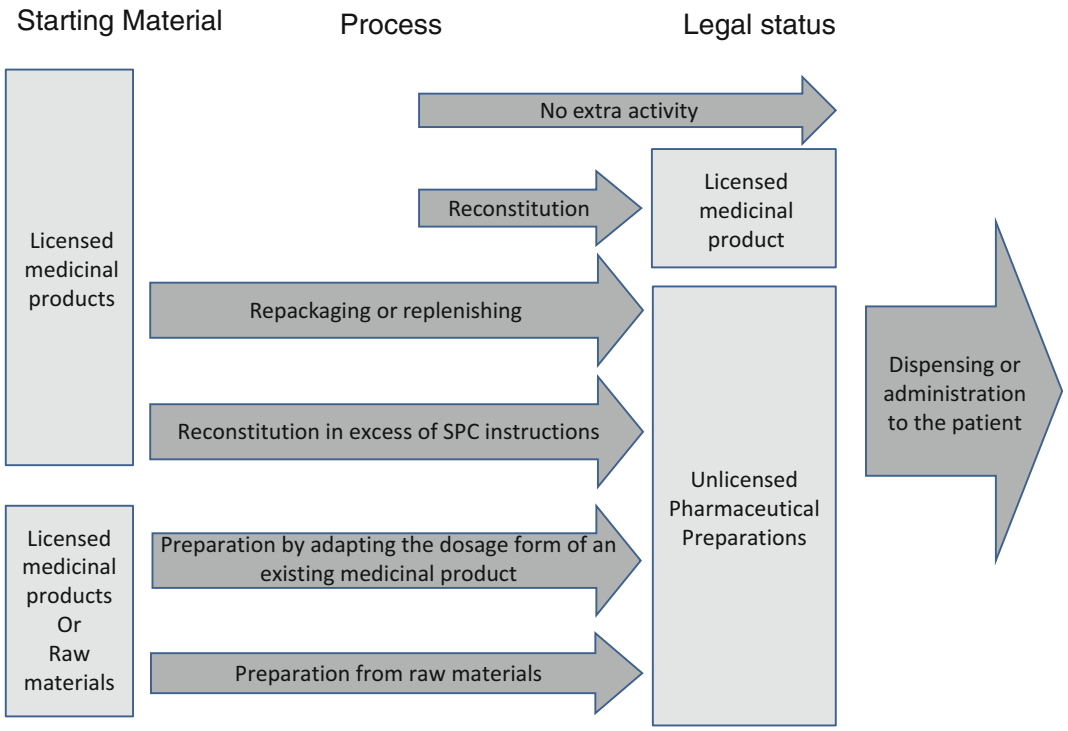

Fig. 3.2 Preparation types

Preparation through adapting a product: reformulating a licensed product into a different dosage form suitable for the intended use, presented in a suitable and appropriately labelled container (after Ph. Eur. Pharmaceutical Preparations).

Preparation from raw materials: formulating active substances and excipients into a dosage form suitable for the intended use, presented in a suitable and appropriately labelled container (after Ph. Eur. Pharmaceutical Preparations). Apart from raw materials also concentrates or intermediate products may be used.

Preparation from raw materials is not performed in every community pharmacy any more. Not every hospital pharmacy prepares in full extent either. The community pharmacist who is not preparing himself could think of referring the patient with a prescription which demands preparation to a preparing pharmacy. Referring seems undesirable, however, because pharmacotherapeutic assessment of the prescription, any potentially necessary adaptations of the dosage form, dispensing and instructions is best to be performed by the pharmacist who is in contact with both the physician and the patient. Hospital pharmacies are often requested to supply products, which should be made available for patients after discharge. In the UK, there are a number of hospital units and commercial companies preparing medicines under Manufacturers (Specials) Licence (MS) which allows the preparation of medicines according to a prescription or order from a pharmacy. The facilities are inspected for compliance with GMP by the Competent Authority, but the efficacy and safety of the products are under the responsibility of the Pharmacist/Physician.

From the preparation point of view, the following types of pharmacies have evolved:

- Non-preparing pharmacies with the ability to perform non-sterile reconstitution, and to counsel patients and carers on this process as well on the right way to handle their medicines
- Pharmacies which prepare for their own patients and often for other pharmacies with which they have a care-link (both community and hospital pharmacies)
- Nationwide supplying pharmacies under special terms: these pharmacies could be hospital pharmacies as well as manufacturing sites which have the legal status of public pharmacies as in the Netherlands or commercial organisations as in the UK
- Pharmacies with a distribution or packaging machine, which supply on demand from other pharmacies repackaged licensed medicines in units per administration for named patients

There are several special situations in some European countries. In the United Kingdom and in the Scandinavian countries, most preparations are prepared at and supplied by central pharmacies. In Belgium, Germany and Portugal, such a supply is prohibited, so pharmacies have to prepare for their own patients. In France, a large hospital pharmacy in Paris provides many other pharmacies with preparations.

In the US and in Brazil preparing pharmacies have been established. Patients have to refer themselves with their prescription to such a pharmacy.

3.13 Feasibility of Pharmacy Preparation

Gain for industrial manufacturer and suppliers or cost for the clients are: price per unit × amount. Thus, in industrial production the profits depend on the size of the patient population, the uniqueness of the medicinal product and the price which the society or the insurance is ready to pay. The frame of reference for the quality to be achieved is the requirements of the registration authorities, many of which are laid down in the directives of the Committee for Proprietary Medicinal Products (CPMP) [89] and of the ICH (the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) [90].

In pharmacy preparation technical limits play the largest role in assessing the feasibility. Health gain, including the number of patients who need the preparation, could in fact give an objective starting point, but subjective opinions of physicians, pharmacists and patients play a more direct role. Preparation facilities represent the health care task under the personal responsibility of physician and pharmacist.

Breaking points are the availability of the raw materials and primary containers of reliable suppliers, the feasibility of analysis of the drug substance and the preparation and the availability of equipment. As an example, preparation processes such as tableting, freeze-drying or aseptic production are accessible in a few pharmacies. The preparation of oral solids with controlled release is not possible in pharmacies mainly to lacking equipment (fluidised-bed techniques and instrumental analysis, etc). Working with radiopharmaceuticals also requires very specific facilities, as is the case with preparation of solid dosage forms with hazardous substances.

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Oral Solids

4

Minna Helin-Tanninen and João Pinto

Contents

Abstract

This chapter provides the pharmaceutical basis of common solid dosage forms and discusses biopharmaceutical aspects related to their formulation. There is a need for customised capsules and powders, usually when the required dose is not available as a licensed product and this dose cannot be obtained by splitting of tablets, as it is in paediatrics. Swallowing problems may be another reason. The aspects related to the excipients to be used and factors affecting the processing of materials, and thus, the performance of the final product are discussed in this chapter. The design of formulations and quality control of powders and capsules are presented in detail. Attention is also given to a specific area of solid dosage forms namely, cachets and herbal teas.

The pharmacist can prepare capsules or powders from the pure active substance or, when this is not available, from pulverised tablets and the contents of higher dosed capsules. Non-coated tablets can usually be pulverised. Modified-

Based upon the chapter Oral Solids by Christien Oussoren and Gerad Bolhuis in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_4,

release tablets or enteric-coated tablets can be processed in only a limited number of cases. Critical steps in the preparation of solid oral dosage forms are discussed which are the preparation of a homogeneous powder mixture and evenly dividing the powder mixture over the dosage units.

Keywords
Cachet • Capsule • Herbal tea • Powder • Formulation • Preparation • Solid dosage form • Tablet • Content uniformity • Excipients • Adapting oral dosage forms

4.1 Orientation

Solid oral dosage forms are dosage forms that are usually swallowed to release the active substance at one or more sites of the digestive tract mainly for a systemic effect [1]. Solid dosage forms can be a powder or a mixture of powders, often further processed into tablets or hard capsules. The latter are the most common dosage forms delivered to patients [2].

The structure of this chapter is such that after orientation on the application of oral dosage forms and their definitions, at first the general aspects of formulation and preparation of powder mixtures are dealt with. Specific information about the respective dosage forms are then given in separate sections on capsules and powders (single dose, multidose and cachets).

This chapter discusses the formulation and methods of preparation of the most used solid dosage forms that can be prepared in hospital or community pharmacies. The formulation of licensed medicines, particularly tablets and capsules, is discussed to such an extent as it is necessary to understand how they are made in case they may have to be adapted for the preparation of other oral preparations in pharmacies.

Powders as such or encapsulated into hard shells (capsules) are alternatives to tablets. They are needed for example to obtain appropriately sized dosage units for children. Both powders and capsules are relatively easy to prepare on a small scale. Often, pharmacists use commercially available medicines as a starting point to prepare the dosage forms, rather than starting ab initio from the active pharmaceutical substance with selected excipients. Pulverised tablets (if possible) can be used for the preparation of capsules with a lower dose than the one present in tablets intended for adults. Alternatively, the contents of capsules can be diluted to provide the dose required by the patient.

Stability is one of the main advantages of solid dosage forms compared to liquid ones. There is no need for preservatives or other excipients (e.g. antioxidants) to enhance stability. Capsules, cachets and powders can be prepared with few and safe excipients. Tablets, capsules and powders present unit dosage forms, which diminish the risk of giving wrong doses to patients.

Normally hard capsules are swallowed whole, but when they need to be administered to infants, pharmacy-prepared capsules may be opened before administration and the contents mixed with a small amount of suitable liquid or soft food. However, solid dosage forms that provide flexible dosing, such as fast dissolving granules (sprinkles) and uncoated mini-tablets may be preferable for paediatric patients because taste and smell can be masked and therefore compliance may improve [3].

Most industrially manufactured herbal medicinal products are oral dosage forms. Liquid preparations (fluid extracts, tinctures) have advantages as to dose flexibility but an unacceptable taste can be a problem in clinical practice. The latter can be circumvented by using solid oral dosage forms containing a dry extract of the herbal medicine. Tablets and capsules with pulverized herbal active substances are also available commercially. Some herbal medicines have to be taken as loose powders. A tea can be prepared from pulverized herbal medicines, either loose or in teabags, or from an instant herbal tea [4, 5].

Further details on the characteristics and use, advantages and disadvantages of the respective oral dosage forms will be given in the separate Sects. 4.6 (capsules), 4.7 (powders) and 4.8 (cachets).

4.2 Definitions

Solid oral dosage forms are described in the Ph. Eur. as oral powders, granules, capsules and tablets.

Oral powders are "preparations consisting of solid, loose, dry particles of varying degrees of fineness. They contain one or more active substances, with or without excipients and, if necessary, colouring matter (...) and flavouring substances. They are generally administered in or with water or another suitable liquid. They are presented as single-dose or multidose preparations" [6].

Similarly, granules are solid, dry agglomerates of powder particles [6]. The Ph. Eur. distinguishes effervescent granules, coated granules, gastro-resistant granules, and modified-release granules, according to the stability of the medicine and purpose of administration.

Capsules are solid preparations with hard or soft shells of various shapes and sizes, which contain a single dose of one or more active substances, with or without excipients [6]. The Ph. Eur. describes hard capsules, soft capsules, gastro-resistant capsules, modified-release capsules and cachets.

Cachets consist of a hard shell containing a single dose of one or more active substances with excipients. The cachet shell is made of unleavened bread usually from rice flour and

consists of two prefabricated flat cylindrical sections. The Ph. Eur. considers cachets to be a category of capsules [6].

Tablets are defined in the Ph. Eur. as "solid preparations each containing a single dose of one or more active substances" [6]. Tablets are prepared by compressing uniform volumes of particles or by another suitable manufacturing technique, such as extrusion, moulding or freeze-drying (lyophilisation). The Ph. Eur. distinguishes various types of tablets; the most important being uncoated tablets, coated tablets, effervescent tablets, dispersible tablets, gastro-resistant tablets and modified-release tablets.

Modified-release tablets are defined in the Ph. Eur. as preparations with a modified drug release rate, place, or time at which the active substance is released compared to standard tablets [6]. Modified-release tablets include prolonged-release, delayed-release and pulsatile-release tablets.

4.3 Biopharmaceutics

Active substances are only absorbed from the gastrointestinal tract in the dissolved state (see Sect. 16.1.5). Dissolution of the active substance should occur as fast as possible after administration if an immediate effect is intended. When an active substance is administered as a capsule or tablet, it will not be immediately in contact with the surrounding fluid. Thus, rapid dissolution of an active substance from a capsule or tablet requires the rapid disintegration of the dosage form. The disintegration rate depends on the quantity and type of excipients and the processing conditions, as well as on the active substance itself, particularly when present in high fractions. Hydrophilic excipients improve the penetration of water into the powder bed, hence the wetting of the preparation (Fig. 4.1).

Problems may arise in the presence of hydrophobic active substances or excipients that are not wetted easily. In these cases it may be necessary to add a disintegrating agent to the formulation.

The choice of a diluent may influence the absorption of an active substance, which was seen in the 1960s in Australia. The diluent of phenytoin sodium capsules was changed from calcium sulfate dihydrate to lactose, which strongly enhanced the bioavailability of phenytoin sodium. Plasma levels of phenytoin increased up to fourfold, which led to an increased reporting of adverse events [8, 9]. This case drew worldwide attention and resulted in an increased awareness of the importance of pharmaceutical availability and bioavailability of active substances in the development of solid oral dosage forms.

Capsules release their contents when at least a part of the capsule shell is dissolved. The Ph. Eur. requires that capsules disintegrate within 30 min [6]. However, the shell of gelatine capsules usually dissolves within 3–15 min in the aqueous, acidic gastric lumen. The powder in capsules prepared in the pharmacy has not been subjected to a compression stage, as is the case of most industrially manufactured capsules. Therefore, the content of pharmacy prepared capsules is usually released more quickly than industrial prepared capsules.

Oral powders (single-dose or multidose) and the contents of opened capsules do not require the release of the active substance from the dosage form. Therefore, only the dissolution rate of the active substance itself is important, provided no agglomeration is observed and the crystalline structure of the active substance has not changed during manipulation and exposure to air. Consequently, pharmaceutical availability and absorption rate of sparingly soluble or slowly dissolving powders are comparable to those of oral suspensions. Effervescent powders and powders that dissolve well in water (preferably dissolved prior to ingestion) have a bioavailability which is (almost) equal to oral solutions.

Tablets are compressed preparations, and therefore, require a disintegrating agent to promote their disintegration by swelling, dissolving or becoming effervescent in contact with water. Furthermore, the hardness of a tablet is important. The Ph. Eur. requires that non-coated tablets disintegrate within 15 min in water. Currently available disintegrating agents allow the preparation of tablets which disintegrate within a few minutes.

In addition to the disintegration of a capsule or tablet, absorption rate is determined by the dissolution rate of the active substance. The dissolution rate of the active substance depends on various factors, for example the solubility, the particle size and shape, the crystal morphology, and wetting ability. Section 18.1 discusses the effects of these factors on the absorption of the active substance.

Ingestion of a tablet should not always lead to a rapid release. In a number of cases it may be preferred that the active substance is not released directly, for example [10]:

- The active substance degrades in gastric juice, or irritates the stomach wall (e.g. valproic acid).
- The active substance should exert its effect in a specific part of the intestine or should reach undamaged a specific part of the intestine for absorption (e.g. mesalazine).
- Absorption of the active substance should be spread out evenly over a period of time to reach an appropriate plasma concentration (e.g. morphine, theophylline).
- The therapeutic benefits from a specific release pattern over time (e.g. methylphenidate, for which it may be therapeutically relevant to have an immediate release of a small fraction of the dose whereas the largest fraction is controlled released).

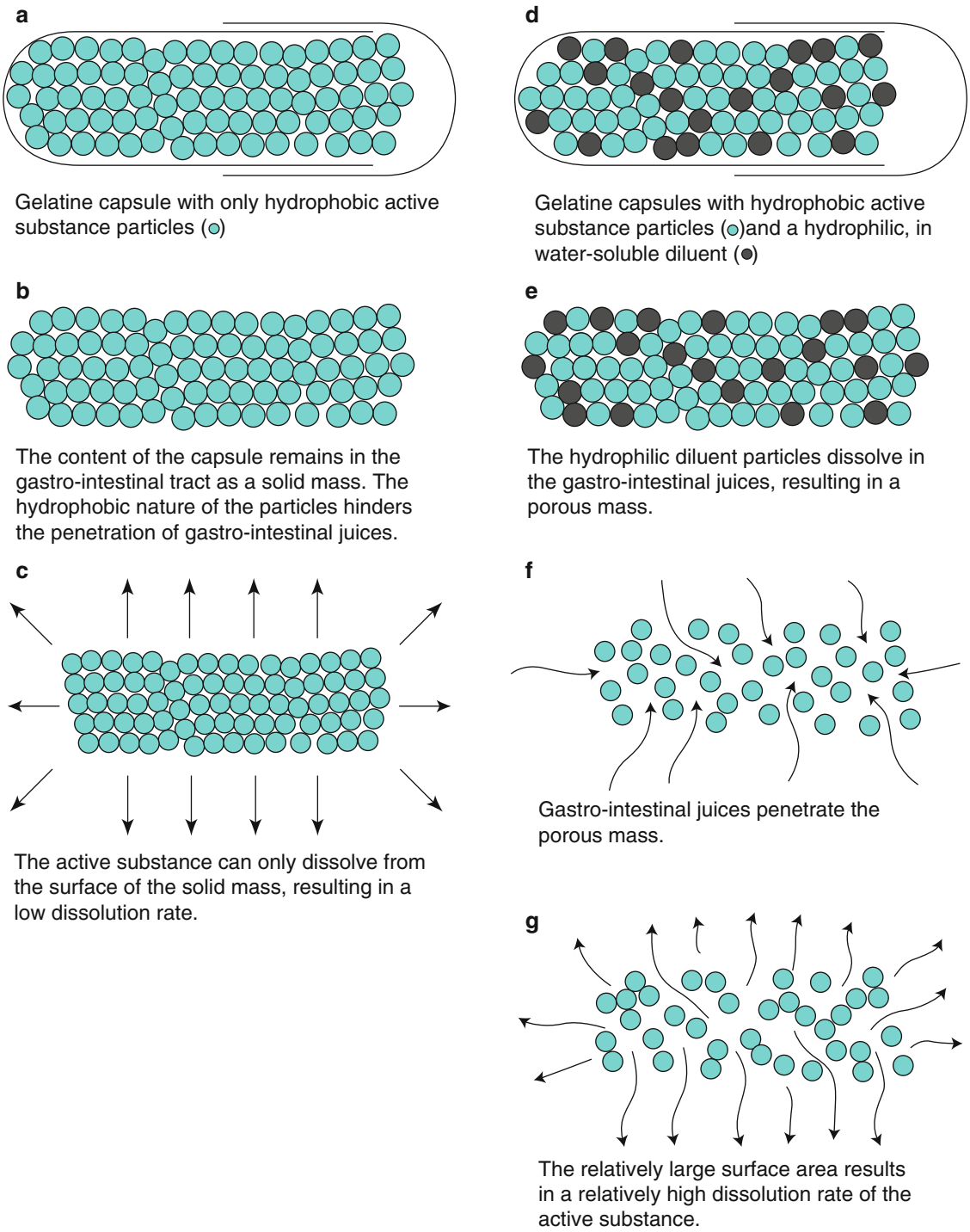

Fig. 4.1 The effect of a hydrophilic diluent on the dissolution rate of a sparingly soluble, hydrophobic active substance in a gelatine capsule (from McConell and Basit [7], with permission).

a–c: Gelatine capsule with only hydrophobic active substance particles.
d–g: Gelatine capsules with hydrophobic active substance particles and a hydrophilic, in water-soluble diluent

- The patient benefits from a less frequent dosing regimen, i.e. the release occurs over an extended period of time (e.g. clomipramine). Modified-release tablets or enteric-coating tablets do not release the active substance directly, but do so in a specific part of the gastro-intestinal tract, either delayed or with a specific release pattern. The release of these tablets is adjusted to therapeutic needs of the patient.

Pentasa® microgranules are an example of a dosage form designed to release the active substance (mesalazine) in a specific part of the intestines. Pentasa® tablets disintegrate into microgranules following oral administration, whilst Pentasa® sachets contain the microgranules as such. The release rate of mesalazine from the microcapsules is pH dependent (faster release at higher pH), which results in a continuous release of mesalazine in the small and large intestines at all enteral pH conditions. After one 1,500 mg dose, approximately 60 % is released in the small intestine, and 40 % is released in the large intestine. Mesalazine is partly metabolised by the intestinal mucosa to acetylmesalazine. About 30 % of the ingested dose is absorbed in the small intestine, and 25 % in the colon (predominantly as acetylmesalazine) [11].

4.4 Product Formulation

The design of the formulation of capsules and oral powders and that of tablets are similar in some respects, but there are also some important differences. In this section, the general aspects of formulation design are discussed.

4.4.1 The Need for Excipients

It is usually not possible to prepare a capsule, oral powder or tablet from an active substance without the addition of any excipients. Firstly, the volume of the active substance is often very small; a diluent is necessary in order to handle the powder mixture. Secondly, the active substance may not have good flow properties; these can be improved by addition of a glidant. Another reason to use excipients is that a preparation, consisting only of an active substance, may not disintegrate well in the gastro-intestinal tract; a disintegrating agent can improve this. Many excipients combine a number of such functions so the number of different excipients can be limited and the potential interactions between materials can be minimised [12]. The next sections discuss these functions in relation to the required properties of solid oral dosage forms.

The intrinsic properties of the active substance are difficult to change, but the pharmacist can choose the right excipients and preparation techniques to overcome or decrease the impact of limitations. Although excipients should be pharmacologically inactive, they may cause adverse effects. The European Paediatric Formulation Initiative (EuPFI) project is considering the suitability of excipients for paediatric formulations. The results have been published in the STEP database [13]. For example many colouring agents have been associated with hypersensitivity and other adverse reactions.

4.4.2 Active Substance

Solid oral dosage forms are preferably prepared with the active substance as such. The particle size of active substances in fast-release preparations should preferably be not larger than 180 μm to reach a compromise between dissolution rate and flowability. If the raw material consists of particles that are too large, the particles should be reduced in size (see Sect. 29.2).

When the active substance is not available as raw material, tablets containing the active substance may be used, providing that both the tablet and the active substance are suitable for processing into a capsule. Sometimes the active substance is extracted by dissolution into a liquid but unfortunately these solutions (especially aqueous liquids) cannot be further used in the preparation of capsules because they affect the gelatine shell. However, there are exceptions such as macrogols of small chain lengths [14], which do not affect the gelatine.

Any processing of the active substances (e.g. milling, hydration), which may occur during preparation, can modify their physical properties. This is probably not being noticed by the pharmacist as he will not have methods at his disposal to confirm changes of the active substances [15]. For this reason, preparation of dosage forms should preferably be carried out starting from the raw material of which the quality meets the requirements. Thus, the availability of pure qualified active substances is advantageous for the preparation of adapted doses and reduces the risk of manipulations of licensed products.

Highly soluble salts (for example sodium fluoride, potassium chloride, potassium citrate) are preferably not prepared in a capsule at all, since rapid dissolution can result in a high local concentration that may be harmful to the mucosa of the gastro-intestinal tract. An enteric coating on capsules and tablets can protect the gastric mucosa from irritating active substances. But the preparation of an oral solution of the active substance may be a better alternative.

4.4.3 Dilution and Flowability of the Powder Mixture

Solid oral divided dosage forms are prepared by dividing a mixture of the active substance and excipients evenly over a dosing mould, so every unit corresponds to one dose. In the case of capsules or oral powders, the powder is spread over the capsule shells or powder papers, respectively. Moulds should be filled evenly. Therefore, good flowability is required.

The flowability of a powder (mixture) can be tested in several ways but a relevant impression for small-scale preparation is obtained from observation during mixing [16]. When the mixture is dusty, sticky, or when segregation of components occurs, other excipients should be used or a glidant has to be added. Even if the mixture looks all right, powder flow may not be good enough. Insufficient flow will lead to uneven filling of the separate capsules and tablet moulds, and ultimately result in too large a weight variation. By preparing trial batches with various filling agents and glidants, and comparing the weight distributions, the powder formulation with the best flow properties can be selected. Flowability of powder can be measured directly (flow through an orifice) or indirectly (angle of repose or tapped and bulk densities) [17].

Powder flowability is influenced by [18]:

- The particle size: powders consisting of many small particles tend to show a poor flow.
- The particle shape: a more regular shape promotes good flow properties, particularly the spherical shape.
- The surface of the particle: a smoother surface results in better flow properties. Furthermore, the surface of particles can be modified to improve the flow properties.
- The moisture content of the powder (this can vary under ambient conditions): the powder flows better when the moisture content is low, but too low will generate static electricity.
- Electrostatic charge: removing the charge improves the flow properties.

4.4.3.1 Diluents

Addition of excipients such as a diluent with good flow properties may improve the flow properties of a powder. Diluents are added to powder mixtures also to increase the mass and volume of the active substance. Very small amounts of active substances often require a carrier to ensure their uniform distribution in the dispensed product, and to guarantee an accurate dose [19].

The most often used diluent for capsules and powders is microcrystalline cellulose (Avicel PH 102 or Pharmacel 102, see also Sect. 23.4.1). Microcrystalline cellulose has both proper flow and disintegrating properties. However, microcrystalline cellulose has some drawbacks. For instance it is insoluble in water forming a suspension. Secondly, the active substance may adsorb onto cellulose particles, which may reduce both solubility and dissolution rates of sparingly water soluble active substances, and thereby the active substance's relative pharmaceutical bioavailability. Microcrystalline cellulose causes no systemic adverse effects, because humans do not absorb it [12, 20].

Lactose (alfa-lactose monohydrate) (see also Sect. 23.4.4) has somewhat less favourable flow properties than microcrystalline cellulose PH102. A disadvantage of lactose is its incompatibility with primary amines. An advantage compared to microcrystalline cellulose is that it is water soluble, which makes lactose suitable for capsules where the contents have to be dissolved. Capsules containing lactose disintegrate as a result of the dissolution of lactose (Fig. 4.1). Its use might be limited in patients with lactose intolerance [12].

Dried (corn, rice or potato) starch (see also Sect. 23.4.1) has good flow and disintegrating properties. It is used occasionally as a diluent in capsules for the processing of hygroscopic substances. Starch is extracted from plant material and subsequently dried. The water content should be below 5 %. During a few hours of exposure to air with a relative humidity of about 60 %, dried starch will take up 5 % of water.

4.4.3.2 Glidants

If not enough diluent is present, or if the powder does not flow sufficiently despite the presence of a relatively large quantity of diluent, the addition of a glidant can be considered. When a glidant is required for the preparation of capsules, preferably colloidal anhydrous silica (Aerosil 200 V) is used in a fraction of 0.5 %. However, it has a tendency to adsorb onto active substance particles, so the application should be investigated beforehand. Magnesium stearate can be used as an alternative, but it is not preferred because its hydrophobic nature may negatively influence the wetting and dissolution rate of the active substance.

A glidant does not always improve the powder flowability, for example when the active substance is micronised. The cohesion forces between the small particles may be too large to be overcome by a glidant. Moreover, when the poor flow properties of the powder are due to irregular particle shapes, a glidant will not have much effect either.

Addition of a glidant could be counterproductive because of [21]:

- Segregation: glidants may displace the active substance particles that are bound to a carrier by ordered mixing (see Sect. 4.5.1). The small particles that are displaced may decrease the flowability and the powder mixture may segregate.

- Segregation and loss: a glidant may also increase the flowability too much. Small particles may move too easily between the large particles, which may lead to segregation of the powder with the large particles on top and the small particles at the bottom. Moreover, particles may fall between the capsule shell and the capsule filling apparatus, resulting in loss of active substance content.
- Incompatibilities: glidants may cause degradation of other substances. For example, magnesium stearate may react with acids.
- Reduced dissolution rate: magnesium stearate is hydrophobic and forms a hydrophobic layer on the surface of the powder particles. Therefore, the dissolution rate of the active substance may be reduced.
- Reduced pharmaceutical availability: colloidal silicon dioxide has a large surface area, which may facilitate adsorption to the active substance. This may reduce the pharmaceutical availability of the active substance.

4.4.3.3 Binding Agents

Binding agents combine the diluent function – and thus improve flowability – and the binding function mainly used in direct compression of tablets. These excipients increase the mass and promote the bonds between particles of other materials in the formulation, so in fact they lead to, desired, agglomeration. In direct compression the powder mixture is not granulated before compression. Therefore, binding agents should improve flowability without segregation of the mixture.

In direct compression tablets, microcrystalline cellulose of various grades is used as a binding agent. Generally the PH101 grade with a mean particle size of 50 μm and the PH102 grade with a mean particle size of 90 μm are used. The PH101 grade flows poorly, not only because of the small particle size, but also because of the needle like particle shape. The PH102 quality flows better because half of the particles are granulated.

Calcium monohydrogen phosphate dihydrate is used in granulated grade as a binding agent in tablets prepared by direct compression. Since the binding properties are quite poor, it is usually combined with another binding agent. In capsules calcium monohydrogen phosphate dihydrate is used when none of the common diluents are suitable, for example for the processing of corticosteroids (Table 4.1). In spite of its hydrophilic nature calcium monohydrogen phosphate dihydrate has neither disintegrating properties, nor it is water-soluble, therefore, addition of a disintegrating agent is required. Primojel Capsule diluent FNA is a diluent for capsules that contains, besides calcium monohydrogen phosphate dihydrate, the disintegrating agent sodium starch glycolate A (Primojel®) and the glidant silica colloidal anhydrous (Table 4.2).

Table 4.1 Prednisolone Capsules 10–40 mg [22]

Prednisolone micronised	10–40 mg
Primojel capsule diluent (Table 4.2)	>200 mg
Capsules size 2	

Table 4.2 Primojel Capsule Diluent [22]

Calcium hydrogen phosphate dihydrate, heavy[a]	94 g
Silica, colloidal anhydrous compressed	1 g
Sodium starch glycolate (type A)[b]	5 g
Total	100 g

[a]Di-Cafos® DC 92–14
[b]Primojel®

During an investigation into the optimal formulation of a well flowing powder for the preparation of Prednisolone capsules, microcrystalline cellulose with anhydrous colloidal silica failed to give a mean content meeting the requirements [22]. Apparently the electric charge was not neutralised and prednisolone was lost through flying up and through the exhaust. Calcium monohydrogen phosphate dihydrate in combination with colloidal silicon dioxide gave the best results. However, due to the lack of disintegrating properties of calcium monohydrogen phosphate dihydrate, a solid mass remained after dissolving of the capsule shell. Only capsules with prednisolone, calcium monohydrogen phosphate dihydrate, silicon dioxide and the disintegrating agent sodium starch glycolate disintegrated giving a desired dissolution rate.

4.4.4 Disintegration

Capsules disintegrate when the capsule shell dissolves and the powder mixture is wetted. Hydrophilic excipients promote the wetting of the powder bed (Fig. 4.1). Due to the low compaction of the encapsulated powder, and the easy dissolution of most diluents for capsules, the addition of a disintegrating agent is often not needed for pharmacy preparations. However, when excipients compact easily (e.g. calcium monohydrogen phosphate dihydrate) a disintegrant is recommended.

Disintegrating agents act through swelling or by promoting water penetration through capillary action or even by the production of a gas (e.g. effervescence) (see Fig. 4.1). Highly compressed powders or granulates in tablets are more difficult to disintegrate, thus, the addition of a

disintegrating agent is often required for immediate release of the active substance.

The diluents microcrystalline cellulose and lactose have some disintegrating properties. When these diluents are used in capsules, the addition of a separate disintegrating agent may not be necessary, or it is used only in smaller fraction than in tablets. However, when a diluent without disintegrating properties is used, such as calcium monohydrogen phosphate dihydrate, a disintegrating agent has to be added, particularly 5 % of sodium starch glycolate [23]. For instance sodium starch glycolate exerts its disintegrating effect by strongly swelling in the presence of water, which leads to the breaking of bonds in the powder bed or tablet. Lactose disintegrates powder beds by dissolution in water. However, tablets for immediate release of active substances always contain a disintegrating agent.

4.4.5 Incompatibilities

The most important incompatibility in capsules is the adsorption of active substances to excipients and vice versa. Sparingly water-soluble active substances may adsorb to non-water soluble excipients such as microcrystalline cellulose (diluent). On the other hand, the very fine glidant, colloidal anhydrous silica, can adsorb onto active substance particles. Especially for low dosed active substances, relatively large fractions may adsorb or be adsorbed. Such adsorption may delay the dissolution of the active substance, resulting in a delayed or incomplete release of the substance. This may lead to a reduced pharmaceutical availability and ultimately a lower therapeutic activity. Substances known to adsorb to microcrystalline cellulose are ethinylestradiol and dexamethasone [24].

Due to the absence of water, which catalyses many chemical reactions, chemical incompatibilities rarely occur in dry dosage forms. One exception is the incompatibility of the excipient lactose with primary amines, such as amphetamine and lisinopril. The rate of the reaction (Maillard reaction) is slow in absence of water, but may lead to yellow discolouration during storage [25].

Thus the pharmacist must be careful when choosing the excipients. Pre-formulation studies to identify incompatibilities can be time-consuming but are required to prove that no instability of the active substance will occur during preparation and storage. In the case of the use of licensed products to prepare capsules or powders, it might be difficult to obtain information from the manufacturer. Thus, it is usually safe to dilute crushed tablet with the excipient that is used in the tablet formulation, based on the market authorisation holder who has ensured their compatibility.

4.4.6 Colouring and Flavouring

A capsule or tablet that is swallowed as such is almost tasteless, because only a small part of the active substance comes into contact with the palate. Therefore taste masking is generally not necessary. If taste masking is required for tablets, a coating can be applied. Patients who cannot swallow capsules receive either a powder or the contents of a capsule. The direct contact between powder and palate results in a distinct taste sensation. Many active substances have an unpleasant taste and thus flavouring, sweetening and even colouring of the powder are vital to patient compliance. Taking the powder with food – e.g. yoghurt or custard – can also be an adequate way to mask the taste, particularly for children, which are very sensitive to organoleptic properties. One of the scopes of a large European research project on children's medicines is to discover more about masking taste and smell in oral dosage forms [26].

One cannot simply add a flavour to a dosage form containing a unpleasent tasting active substance and expect it to taste good because the strength of tastes are different or different receptors are sensitised. Flavours are complex mixtures that are made up of many chemicals. Flavouring agents can be natural (essential oil, derivatives from fruit vegetable juice) or artificial (see Sect. 5.4.10). In particularly, natural flavours may have dozens of different types of molecules, which may interfere with the active substance.

In some cases it may be desirable to colour the tablet or capsule, for example to prevent a mix-up of medicines or to prepare placebos with an appearance identical to the original tablets for use in clinical trials. In case of capsules, it is possible to use coloured capsule shells, or to prepare a coloured powder mixture in transparent capsules. Colouring agents should be used with caution, because they can cause allergic reactions. The use of coloured capsule shells is preferred, but if it is necessary to colour the powder mixture, a colouring agent can be added. Section 23.11 lists colouring agents for powder mixtures. Tablets can be coloured by using soluble (for wet granulation) or insoluble (for direct compression) colouring agents. Moreover, tablets are often coloured by processing of a colouring agent in the coating.

Patients with Addison's disease or Cushing's syndrome take steroids two or three times a day in various doses, depending on the time of the day and the situation. Commercially available tablets may not always contain the dose they need. Moreover, tablets with different doses are not always easy to distinguish. For these patients, capsules with a dose-related colour can be a solution [27].

4.5 Method of Preparation

The preparation of solid oral dosage forms consists of two steps. The first step is the preparation of a homogeneous powder mixture, and the second step is the even distribution of the powder mixture over the dose units. Mixing of solids to obtain a homogeneous mixture is in principle the same process whether capsules, powders or tablets are prepared. However, the requirements regarding the filling of the dose units are different for the three types of preparation.

Mass for oral powders is easy to prepare but time-consuming to divide. The solids are mixed together and subsequently the powder mixture is divided evenly over the powder papers. The same applies to cachets. The preparation of capsules is quick but somewhat more complex, because the powder mixture should have a fixed volume, which is determined beforehand. Next, the powder mixture has to be divided evenly over the capsule shells. The preparation of tablets is in this regard more complex. Tablets are made with a tableting machine (see Sect. 28.7.3 for some brands), which imposes extra requirements to the flowability of the powder mixture. To minimise flow and segregation problems, powder mixtures are often granulated before compression.

4.5.1 Homogeneous Powder Mixtures

4.5.1.1 Particle Size

Particle size of the constituents for powders range commonly from 10 µm up to 180 µm. For the preparation of a homogeneous mixture, the solids preferably have comparable particle sizes, densities, shapes and equal mixing ratio (see Sect. 4.4.2). Particles with unequal sizes mix poorly and may segregate easily. Segregation, for example during the filling of the capsules, may lead to a large weight variation and a bad content uniformity. In practice, the maximum particle size for the active substance is 180 µm, unless a delayed release effect is envisaged. Larger particles have a relatively small surface area, which may result in a too low dissolution rate (see Sect. 18.1). When the particles of the starting material are larger than 180 µm, the material should be ground and, if necessary, sieved. However, grinding by hand (triturating) of materials that are already fine enough should be avoided, because it may introduce agglomerates.

4.5.1.2 Starting from Tablets or Capsules

Real challenges for the preparation of the powder mixture arise from the situation in which tablets or capsules are needed to get access to the active substance. In the first place the pharmacist has to consider the suitability for grinding or crushing of the tablets or capsules and then he has to develop a reliable method to produce the required dilution of the ground mass; this dilution sometimes having to be quite considerable, even a 100-fold.

Coated tablets, such as enteric-coated tablets, and modified-release tablets are better not split or pulverised, because their specific features may be lost. If it is absolutely necessary to break them then the pharmacist must know beforehand the implications on the stability of the medicine and on its therapeutic effect (see Sect. 4.9). A controlled-release tablet that has been split may overdose. Splitting may also expose the taste of the medicine, which had originally been masked in the coated tablet. Only standard, non-coated tablets shall readily be processed into a powder mixture.

To obtain the required amount of active substance the equivalent amount of whole tablets are counted. It is preferable to use several tablets to level out content differences between tablets. In principle there are two ways: take an exact, counted number of tablets to pulverise, or to use an excess of tablets in pulverising and then weighing the required quantity. If an exact number of tablets is used, the resulting mean content of active substance in the final product has to be validated.

A strict method of grinding is needed to avoid the loss of active substance for example due to static charges or to sticking of tablet components to utensils such as mortar, pestle and tablet crusher device. This loss of active substance can be compensated beforehand by taking an excess of tablets. Note, however, the risk of calculation errors in that case. There is some loss of active substance also during administration, i.e. taking the powder from folded paper or emptying the capsule, and the loss seems to be higher in low-weight single-dose powders (Fig. 4.2).

Tablets are crushed manually in a non-porous mortar with a pestle. After careful grinding the resulting powder may be more or less homogeneous (Fig. 4.3).

The properties of all excipients present in the tablet must be considered for their possible effects on the final preparation, such as weight variation, disintegration time, dissolution characteristics and *in vivo* performance. The lower the proportion of the active substance present in the mixture, the more difficult it is to achieve a sufficient homogeneity. In Sects. 4.9 and 4.10, the formulation of tablets and the possibilities to process coated or modified-release tablets in capsules are discussed.

4.5.1.3 The Mixing Process

Geometric dilution is used to ensure that small quantities of ingredients are uniformly distributed in the powder mixture, starting with the ingredient in the smallest quantity. Then a volume of powder equal to the volume of the powder mixture in the mortar is added and triturated with a pestle to a uniform mixture. Then the mixture of the two components is mixed again with an equal quantity of diluent. This process is repeated until all solids are mixed. Triturating and small-scale mixing is performed in a mortar with pestle (Sect. 28.6.4). For larger quantities a mixing apparatus needs to be used.

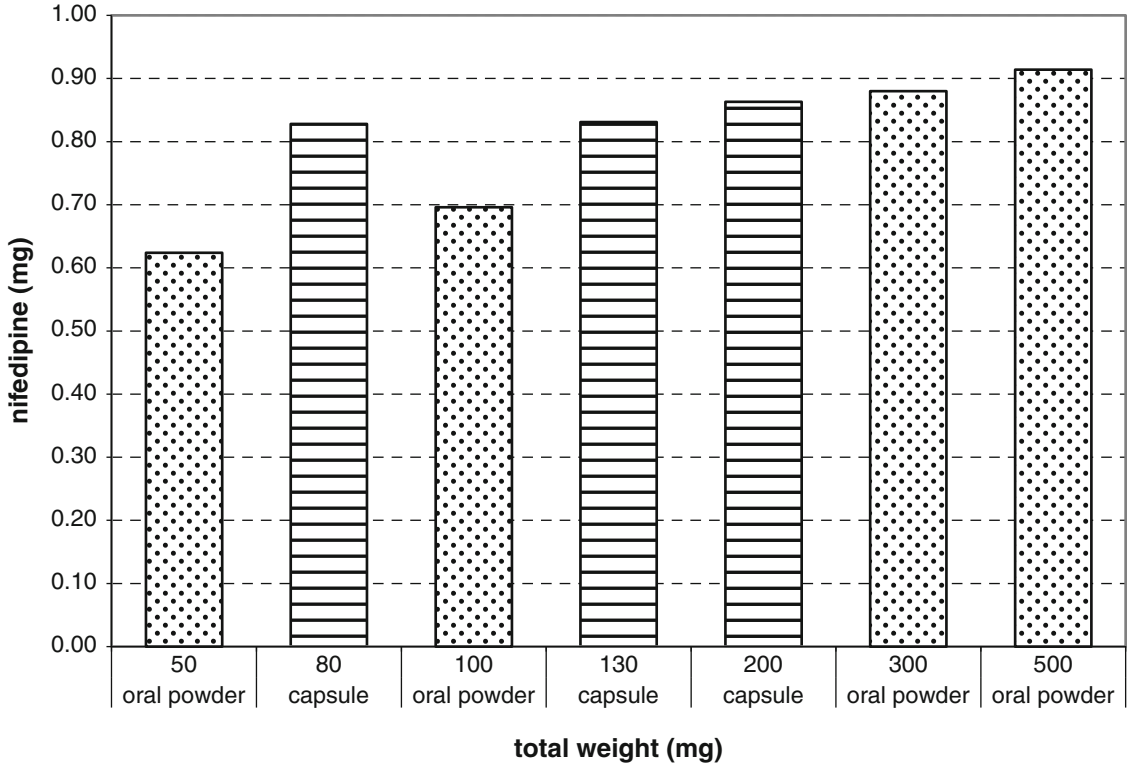

Fig. 4.2 Nifedipine contents in single-dose powders or capsules that were meant to contain nifedipine 1 mg as active substance (from crushed tablets Adalat® 10 mg retard) and microcrystalline cellulose (MCC) as a diluent. The batch size was 50 single-dose powder or capsules and no excess tablets were used. Capsules number 4 (80 mg MCC), 3 (130 mg MCC) and 1 (200 mg MCC) are compared to oral powders weighing 50 mg, 100 mg, 300 mg and 500 mg. Mean values are shown (n = 10). The higher content of nifedipine can be observed in all sizes of capsules compared to oral powders of 50 mg or 100 mg. According to this study the use of different sizes of capsules would lead to an acceptable content while oral powders should weigh at least 300 mg [28]

Fig. 4.3 Particle size variation in the manually (in a mortar with a pestle) crushed Nifedipine tablet (Adalat® 10 mg retard). Scale bar in SEM is 100 μm [29]

Mixing should be performed in such a way that the following problems are avoided:

1. Adsorption of the active substance to the pestle, mortar, measuring cylinder or the mixer. Adsorption of active substances may be reduced by minimising direct contact with utensils. Therefore, the active substance is best put in between the utensils and the excipient ('wrapping method', see Sect. 4.6.2). Mortars need to be non-porous so that no active substance remains in the pores to decrease the dose or to contaminate the next product to be prepared.
2. Suctioning of the statically charged active substance with the airflow, since mixing of powders is generally performed in the presence of dust extraction. If it is assumed that substances are selectively suctioned when they become statically charged, this can be avoided by selecting excipients (e.g. colloidal anhydrous silica) that can neutralise the static charge, by reducing the mixing time to the minimum, and by avoiding whipping too much air into the mixture. A powder that is too fluffy can be compacted slightly to change the surface properties by the addition of a few drops of alcohol, water or liquid paraffin.

In the past, homogeneity of powder mixtures was assessed by processing a colouring agent in the powder mixture. It was assumed that when the colour was spread homogeneously over the mixture, the entire mixture was homogeneous. However, this method may not be suitable for two reasons. First, a homogeneous distribution of a colouring agent is not a guarantee that the active substance is distributed evenly over the mixture as well. The physical properties of solids, such as particle size and adsorption onto other substances, determine the quality of the mixing. Differences in properties of colouring agent and active substance may result in a different distribution for both substances. A second reason is that colouring agents may cause hypersensitivity.

4.5.1.4 Solvent Method

Mixing of powders with unequal volumes often results in non-homogeneous mixtures, because it takes more patience to obtain a homogeneous mixture than when two equal parts are mixed. However, small amounts of active substances simply need to be mixed with a large quantity of diluent to obtain a processable powder mixture. In case of an inconvenient mixing ratio, the solvent method might be applicable, if validated carefully. The method has to be investigated for a specific active substance and standardised formulation. Unfortunately the solvent method often appears not to be appropriate because there is no suitable solvent, or because the active substance is not stable in solution.

The solvent method basically distributes a small quantity of active substance (5 mg or less per dose unit) over a diluent. The active substance is dissolved in a suitable, volatile solvent, usually in a stainless steel mortar to be able to check if dissolution is completed. -Subsequently, the solution is mixed with a carrier that does not dissolve in the solvent. The moistened powder is triturated –until the solvent has completely evaporated. The powder mixture now consists of carrier particles with a coating of the active substance. This method is in fact a combination of simultaneous particle size reduction and mixing. Another advantage of this method is the reduced loss of the powder mixture during mixing.

The solvent should comply with a number of requirements:

- The active substance has to dissolve well in the solvent, but not the carrier.
- The solvent has to be volatile enough in order that the powder will dry within a limited period of time.
- The solvent has to be non-toxic, because a residue of it will always remain in the powder mixture.
- The active substance has to be stable in solution.

For practical examples of this method see Sect. 4.6.2.

4.5.2 Colouring of Powder Mixtures

Capsule contents can be coloured by using a coloured powder mixture as diluent. Powders can be coloured with water-soluble, or water insoluble colouring agents (see Table 23.26). Water-soluble colouring agents should be dissolved in order to produce an even distribution over the diluent. The use of water to promote the dispersion of the water-soluble colouring agent may cause granulation of particles. To prevent or minimise this event the addition of the solution to the powder must be slowly and with continuous stirring. Water is a safe solvent for everyone, but evaporates slowly. Ethanol in a concentration of more than 90 % evaporates quickly, but the use of organic solvents has to be considered carefully because of the possible residues. Water-insoluble colouring agents, on the other hand, mix well with the diluent in the dry state.

4.6 Capsules

Capsules are probably the most versatile dosage form prepared in the pharmacy. Capsules may contain one active substance or a mixture of active substances, usually a diluent and sometimes a glidant or a disintegrating agent or both. Capsules are easy to swallow and can enclose active substances with an unpleasant taste. Capsules can be prepared in the range of few units up to hundreds of thousand units. Further advantages, namely by comparison to tablets, are the small number of excipients required to prepare capsules, and the possibility of having non-compressed powders, allowing a faster dissolution of the active substance.

4.6.1 Capsule Shells

Capsules consist of a shell made of a structural polymer (e.g. gelatine, hypromellose, starch) together with other excipients that allow the preparation of the shell itself (e.g. plasticizers) or provide some functionality to the shell (e.g. titanium oxide for making capsules opaque). Gelatine is often extracted from animals (e.g. pig), that is why some people doesn't want to ingest them. The pharmacist must consider possible interactions between the active substance or the excipients and gelatine. Alternatively, 'vegetarian' capsules exist, which consist of gelatine from algae or of a cellulose derivative.

Empty capsule shells are stored at room temperature in tight containers that maintain a constant, adequate relative humidity. The Deutsche Arzneimittel Codex (DAC) describes the test for dissolution of capsule shells: empty

capsules should dissolve or at least open in less than 15 min [30]. Incorrectly stored capsules do not dissolve, they just swell. Furthermore cycles of high and low humidity and temperature damage the shells irreversibly.

In pharmacies hard capsule shells consisting of a body and a cap with a locking mechanism are by far the most used. These shells come in various sizes: size 5 being the smallest and size 00 the largest. Many patients experience difficulty in swallowing large capsules. Usually capsule sizes 1 or 2 for adults and size 3 or 4 for children are used in pharmacy preparation. In some cases the patient is instructed to open the capsules to take the contents with food or dissolve it in water, provided that capsules can be opened and the drug can be given without the protection of the capsule shell.

A way to determine the volume of capsule shells to resort to if all other information has been lost, is by filling them with a liquid of known relative density, such as ethanol 96 % V/V. Ethanol of high concentration evaporates quickly, so the lower concentrations can also be used. If pure water is used, a pharmacist must be fast in a measurement because capsule shell begins to dissolve. From the weight of the capsules and the density of the liquid, the absolute volume can be calculated. The filling volume determined following this method does not depend on the filling procedure or the diluent; it is the volume usually provided by manufacturers. Alternatively, one can use liquid dropping from a pipette and the volume of liquid used corresponds to the volume of the shell's body.

4.6.2 Different Methods for Preparing the Powder Mass

As an addition to the general method of preparation of a powder mixture, for capsules some specific directions apply. Capsules are filled by volume, therefore, the powder mixture should be prepared to obtain a specific volume. The correct volume depends on the capsule size and the number of capsules to be filled (Table 4.3).

The volumes in the table are derived from filling capsules with microcrystalline cellulose by tapping lightly or no tapping at all. For small batches of small sized capsules no numbers are given because preparation cannot be performed reliably. However, even under these circumstances the volume may slightly vary. Moreover, filling capsules with a different diluent or according to a different method, may influence the filling volumes.

Smaller capsule sizes should not be prepared in small batches, because a relatively large loss during mixing and filling may result in a too low content. Moreover, the mass deviation and thereby content deviation may become too large for such batches, because a small quantity of powder is hard to divide evenly over the capsules.

Table 4.3 Volumes of microcrystalline cellulose filled in hard gelatine capsule shells (in cm^3)

	Capsule size				
Number	00	0	1	2	3
20	18	13			
30	28	20	14	11	
50	46	34	24	19	14
60	55	40	29	22	17
90	83	60	43	33	25
100	92	67	48	37	28

Four methods will be described for the preparation of powder mixtures for capsules. These methods are about mixing of varying ratios and the preparation of a powder mixture from capsules and tablets.

4.6.2.1 High Dose Method

For capsules with a relatively high dose (>50 mg), first the active substances and, if necessary, the glidant are mixed following the geometric dilution method (see Sect. 4.5.1.). Next, the volume of this mixture is determined using a measuring cylinder, and a diluent is added up to the required volume without too firmly tapping to prevent too much compression of the mixture. This mixture is emptied from the cylinder and mixed again. For this method, it is assumed that the losses are relatively small and relatively little amount of diluent is needed. The method is based on the bulk density of the powder mixture, i.e. the density of a bulk which volume has been measured in a volumetric cylinder, for instance.

4.6.2.2 Low Dose Method

The preparation method for capsules with a relatively low dose of active substance (≤50 mg) has been developed to prevent loss of the active substance. Losses occur mostly during determination of the volume of the active substance in a measuring cylinder. Mixing the active substance beforehand with a known volume of diluent can reduce this loss. So, the volume is determined after mixing of the active substance and diluent. There are two methods of mixing. The traditional method of equal parts, geometric dilution, can be used for capsules with 10–50 mg active substance. For less than 10 mg active substance, it is advised to use the wrapping method. The wrapping method is meant to minimise loss of substances that are static, sticky or coloured. For this method, at first a layer of diluent is placed in the mortar. The active substance is added on top, and is covered with

Table 4.4 Solvent method developed for some low dose capsules

Active substance and dose:	Solvent and amount	Deposition and ratio:	Diluent	Reference
Colchicine	Methylene chloride 2 × 9 mL for 162 mg colchicine	Diluent 100 times the amount of colchicine	Microcrystalline cellulose	[31]
Diazepam	Methylene chloride 2 × 3 mL for 120–300 mg diazepam	Diluent 20 times the amount of diazepam	Microcrystalline cellulose	[32]
Ethinylestradiol	Acetone 2 × 3 mL for 100 mg ethinylestradiol	2 g Colloidal anhydrous silica, compressed, for 100 mg ethinylestradiol	Lactose	[32]
Hydrochlorthiazide 0.5–5 mg	Acetone 2 × 3–5 mL for 15–150 mg hydrochlorthiazide	3 g diluent	Mannitol with 0.5 % m/V Colloidal anhydrous silica, compressed	[33]

another layer of diluent. The two layers of diluent that surround the active substance prevent direct contact with the pestle and mortar, thereby reducing losses.

4.6.2.3 Solvent Method

The solvent method is preferably used for mixtures with very unfavourable mixing ratios (<5 mg active substance). This method (see Sect. 4.5.1) needs careful testing and validation. For some active substances the solvent method has been developed (Table 4.4). If the substance is not listed, the powder mixture can only be prepared following the low dose method.

For illustration of the solvent method, the preparation process of Hydrochlorothiazide capsules NRF [33] is quoted:

- Hydrochlorothiazide is rapidly dissolved in the first portion of acetone in a metal mortar while mixing (in process controls: no undissolved crystals; not more than 50 % acetone has evaporated).
- First portion diluent is mixed with the hydrochlorthiazide solution, avoiding excess force. The mixture has to be loosened from the side of the mortar and the pestle at least two times. The mixture has to be removed from the mortar and kept aside (in process controls: powder mixture should be fine again and not smelling of acetone).
- Second portion of acetone is used to rinse mortar and pestle.
- Second portion of diluent is mixed with the rinsing solution, avoiding excess force. The mixture has to be loosened from the side of the mortar and the pestle at least two times. The mixture has to be removed from the mortar and kept aside (in process controls: powder mixture should be fine again and not smelling of acetone).
- Mixing of both powder mixtures avoiding excess force.
- Etcetera (adding diluent, mixing, filling capsules).

4.6.2.4 Preparation from Tablets

The tablets may be crushed and the resulting powder used as a source of active ingredient following a low dose method (see Sects. 4.5.1 and 4.6.1). Addition of a glidant is generally not necessary, because it is already present in the tablet. The final product also contains excipients from the original dosage form, which would have not been necessary if a preparation from the pure active substance was considered.

When encapsulating tablets for blind studies, the tablet containing the active substance is concealed in a capsule designed for clinical trials. Tablet as a whole may, or may not be embedded in powder that has been placed previously into a capsule shell.

4.6.2.5 Preparation from Other Capsules

Capsules available as authorised medicines can be the source of the active substance. The capsules have to be opened and emptied to obtain the active substance that will be processed further into the new capsule. Sealed capsules can be difficult to open. If so, use a blade to open the capsule, or smash the capsules in a mortar and sieve the contents to remove the smashed shell pieces.

4.6.2.6 Supplementing to Volume

For all methods described above, the final step is to add a diluent up to the required volume. Mixing may result in volume contraction, which means that during mixing the total volume becomes smaller than the sum of the volumes of the separate powders. Volume contraction results from small particles creeping in between larger particles. As a consequence a relatively large amount of diluent is needed to bring the powder mixture to the volume required, i.e. the total volume of the bodies of the shells to be filled. An uneven distribution over the capsules may be obtained when the volume of the powder mixture is too small. Therefore, it is important to adjust the volume prior to filling the capsules.

It must also be pointed out that the measurements in a measuring cylinder should be made with care, particularly to avoid tapping the cylinder, otherwise the bulk density may be increased too much and thus ensuring a failure of the capsule filling process. This may result in a considerable

fraction of the mixture no longer fitting into the available volume.

4.6.3 Filling of Capsule Shells

In the pharmacy, capsule filler equipment for 60 or 100 units is used most frequently, but equipment able to fill up to 300 shells are available. For the filling of smaller numbers of capsules, the holes in the filler can be partly covered with paper or tape. An even distribution of the powder mixture over the filler is essential, which can be obtained by good flowability of the powder mixture and a correct spreading technique: the placing of a large quantity of powder on top of only a section of the capsule bodies in the equipment should be avoided. The method to fill capsules using capsule filler equipment is described in Sect. 28.7.3.

One dose of voluminous powders or high dose active substances sometimes will not fit into one capsule. Therefore, 'densified' or 'heavy' qualities of these substances may be available, such as for tetracycline hydrochloride. For high doses of paracetamol the problem can be solved by using a mixture of large and small particles, designated (in the Netherlands) as paracetamol (500–90). This type of paracetamol has a relatively high bulk density, because the small particles fill up the spaces between the large particles.

4.6.3.1 In Process Controls

The following in-process controls are essential for the preparation of capsules:

- Noting the tare weight prior to adding up with diluent to weight or volume.
- The absence of lumps or agglomerates: simple visual control is sufficient to determine whether lumps or agglomerates are present or not.
- A visual test on homogeneity or evenness of the mass: this test is performed after mixing or sieving of powder mixtures.
- The yield (number of capsules).
- When the mixture has to be divided over more than one portion, every portion (including the last one) must be weighed.

4.6.4 Preparation of Coated Capsules

In some cases, it may be desirable to coat capsules, for example to make them resistant to gastric juices (enteric coating). For this, specialised equipment is required. More information on the large-scale equipment for coating capsules can be found in the literature [14].

4.6.5 Release Control and Quality Requirements

This section discusses the non-destructive controls on appearance, average weight and weight distribution. When capsules comply with these specifications, and when they are filled with a homogeneous powder mixture, they comply with the Ph. Eur. monograph 'Capsules'. When the capsules do not comply, either the batch should be rejected, or a full analysis according to the Ph. Eur. should be performed. After this analysis, the batch can either be approved or rejected. More information on the quality requirements for capsules can be found in Chap. 32 (for instance Table 32.2) and in Sect. 20.4.6 on the distinction between content variation due to inhomogeneity or to weight variation.

4.6.5.1 Appearance

A simple visual control is sufficient to determine on homogeneity of the mass, and whether lumps or agglomerates are present or not. Filled capsules should be free of dust and well closed after preparation. Moreover, they should not be dented. A dent may lead to a too low dose delivered to patients.

4.6.5.2 Average Weight

The average weight is used to check whether the right capsule size has been used and to get an impression of the loss of powder mixture. The average weight is determined on ten capsules (see Sect. 32.7.1). It is advised to sample selectively by taking the capsules from the centre and the corners of the capsule filler. If the amount of powder mixture is insufficient to fill all the capsules, the ones in the corners usually will not be filled completely.

The average weight is calculated by subtracting the average weight of ten empty shells from the average weight of ten filled capsules. The theoretical weight is calculated from the weighed quantities of raw materials and the added diluent. A difference of more than 3 % between the theoretical weight and the average weight implies in practice that the formulation is not optimal or that the preparation was not successfully accomplished. For determination of the empty capsule weight, it is important to use capsules of the same batch and with the same moisture content as the ones used for the preparation.

4.6.5.3 Uniformity of Mass

The uniformity of mass is expressed as the relative standard deviation and is determined by dividing the standard deviation of the weight of the filled capsules by the average weight of the content. The Ph. Eur. (see Sect. 32.7.1) asks

to weigh 20 units individually. For capsules with a content weight less than 300 mg not more than two capsules should deviate more than 10 % of the average and none more than 20 %. For capsules with a content weight equal to or more than 300 mg these values are 7.5 % and 15 % respectively.

From experience can be stated that a batch will meet the Ph. Eur. requirements when weighing ten capsules and calculating the average weight and standard deviation: for capsules containing less than 300 mg, the relative standard deviation should be below 4 %. For capsules containing more than 300 mg, the relative standard deviation should be below 3 %.

4.6.5.4 Homogeneity

The average weight and the uniformity of mass are indicators for the weight distribution of the powder over the capsules. The weight distribution depends on the flowability of the powder, the completeness of filling and the operator's precision. However, it does not give information on the active substance content per capsule. Due to mixing variation there will never be a perfect content uniformity.

An assay on separate capsules gives direct information on the mean content of active substance in the capsules and its variation between capsules. In pharmacy preparation such assays are usually performed during the validation of a formulation and during routine examination of large batches of standardised preparations. But for extemporaneous preparations in-process controls and non-destructive end controls have to be sufficient. The requirements for the mean content and content uniformity of capsules are described in Sects. 32.4 and 32.7.2.

The combined results of the controls on weight and the assay give information on the preparation method. If capsules do not comply with the specifications for uniformity of mass, it can be concluded that the powder was not divided evenly over the capsule shells. This may be caused by loss of powder mixture (the average weight is too low), or by insufficient flowability of the powder (the average weight may still comply). When both the average weight and the uniformity of mass comply with the specifications, but the content uniformity does not, the cause is a non-homogeneous powder mixture. In the latter, it can be concluded that the mixing of the solids was insufficient. Generally the variation coefficient after mixing should be less than 5 % [34].

4.7 Powders

4.7.1 Single-Dose Powders

Single-dose powders are measured quantities of a solid mass packaged in paper or, in the case of industrially manufactured products, in sachets. Single-dose powders are traditionally prepared for children and elderly because of difficulties in swallowing tablets or capsules. Another reason for dispensing single-dose powders is to prevent a high local concentration of the active substance in the oesophagus and the stomach, as might be the case with capsules or tablets. Powders with active substances with bitter or salty taste can be presented as effervescent granules [17].

Powders should be dissolved or suspended in a glass of water or milk or mixed with a small amount of suitable soft food before ingestion, to prevent aspiration into the lungs, as well as to promote direct dissolution of the active substance. Unlike tablets or capsules, powders provide a rapid onset of action because they are readily dispersed. They have a large surface area, and they do not disintegrate but rather just dissolve before absorption.

A disadvantage of single-dose powders is that preparing each individual dose is time-consuming. Another disadvantage is that the patient may have problems opening the folded paper without spilling and losing all powder from the folded paper. The total mass of a single-dose powder may be too large for neonates, even when mixed with milk, and undissolved particles may clog small-lumen nasogastric feeding tubes.

> Carbasalate calcium is irritating to the gastric mucosa. Therefore, it cannot be administered in capsules. It is administered as single-dose powders in sachets instead. The powders should be dissolved in a glass of water before ingestion. When carbasalate calcium powders are prepared in a pharmacy, the poor flow properties of the active substance may result in a relatively low uniformity of mass. The poor flow of the powder is probably due to an irregular shape of the carbasalate calcium crystals and perhaps also to a relatively wide size distribution of the raw material.

4.7.1.1 Product Formulation and Method of Preparation

Divided powders usually contain one or more active substances and excipients. If the quantity of active substance per powder is low, it is supplemented with diluent up to a manageable quantity. A weight range of about 200 mg as a minimum to 500 mg per powder is widely used and assumed to bring along minor loss of active substance during the process (Fig. 4.2) [28].

The formulation and preparation of the powder mixture for single-dose powders is to a great extent similar to the one described previously (see Sects. 4.5 and 4.6.2). Excipients that are used for single-dose powders are diluents, and in case of poor flow properties, a glidant. A disintegrating agent is not needed due to the loose packing of particles in the powder.

After all solids are mixed, the powder mixture is divided over the dose units. For single-dose powders this is done by weighing the powders individually on waxed powder papers. Each paper is folded. Powder filling and folding machines are no longer used in most countries. Packets (papers) should be checked to see that they are uniform in weight.

Effervescent powders contain, besides the active substance, a combination of an acid and a carbonate or bicarbonate. When the powder is added to a glass of water, carbonic acid and carbon dioxide are formed and the latter produces effervescence. During this chemical reaction often a soluble sodium salt of the active substance is formed. Moreover, the effervescence serves as a natural stirring process, which may enhance the dissolution rate.

The in-process controls for the preparation of the powder mixture are the same for single-dose powders as for capsules.

4.7.1.2 Release Control and Quality Requirements

For single-dose powders, the average weight and the uniformity of mass are determined. The specifications for content uniformity are discussed in Sect. 32.7.2.

Often, as is the experience in the Netherlands, the pharmacist can directly, after preparation, have a good perception of the quality of the batch by assessing the average weight and weight variation. It appeared that the mean weight of powders will normally not deviate by more than ±5 % from the theoretical weight, which is different from the deviation met in practice with processing for capsules (±3 %). The uniformity of mass could be expressed, for practical purposes, as the relative standard deviation as determined by dividing the standard deviation of the weight of the powder content by the average weight of the content. For powders with a content of less than 300 mg, the relative standard deviation usually will be less than 4 % and that of powders with a weight of more than 300 mg, will normally not be higher than 3 %. See Sects. 32.6 and 32.7 for the Ph. Eur. test.

4.7.2 Multidose Powders

Multidose powders for oral use are mainly used when the patient has to take large quantities (grams) of an active substance. These powders usually contain non-potent active substances that should be taken in large quantities, such as calcium salts (e.g. calcium gluconate and calcium citrate) and certain nutrients. Multidose powders are dispensed to the patient in a bulk container. Multidose powders are usually dosed by a measuring spoon or cup. Traditionally spoons and cups used as cutlery presented standard measures, but nowadays, designers are changing the sizes, thus, the volumes. To prevent variations of volume, patients should be given a measuring device with the medicines. It will be obvious that the dose accuracy is not as good as in single-dose powders, tablets or capsules.

The preparation of the powder mixture is analogous to the preparation of single-dose powders (see Sect. 4.5), but the flow properties are less critical, because the powder mixture does not have to be distributed evenly over dose units. A diluent is generally not necessary, but in case it is required, lactose is often used. Bulk or multidose powders can be packaged in glass, plastic, metal or other containers that have a wide mouth to allow the handling of the powder-measuring device.

> Sodium sulfate is an example of multidose powder, which is used as laxative in case of intoxication: the patient should take several grams. To make this preparation more patient-friendly, the required quantity of Sodium sulfate decahydrate can be weighed into a dry bottle, which basically makes it a divided powder. Prior to use, the required amount of water is added to dissolve the powder. This may be done in the pharmacy or elsewhere by the patient or the caregiver. An advantage of a powder over an oral solution is that the preparation has a long shelf life without the need for a preservative.

4.8 Cachets

A cachet is a type of shell made from starch. Before administration, the cachets are immersed in water for a few seconds, placed on the tongue and swallowed with a draught of water. Cachets were used in pharmacies prior to the introduction of gelatine capsules, and in most countries they are considered obsolete and not in use anymore due to stability problems and difficulty in industrial manufacturing. However, for example in Poland they are very popular, in contrast to gelatine capsules, which are rarely used. Recently it has been considered as a reference in the production of new hard starch shells resembling hard gelatine capsules, on providing an alternative polymer to gelatine.

The sizes range from no. 1, the smallest, to no. 6, which is the largest (Table 4.5). In contrast to hard gelatine capsules,

Table 4.5 Sizes and volumes of the cachets

Size	Volume (cm^3)
6	1.8–2.0
5	1.5–1.6
4	1.2–1.3
3	1.0–1.1
2	0.7–0.8
1	0.5–0.6

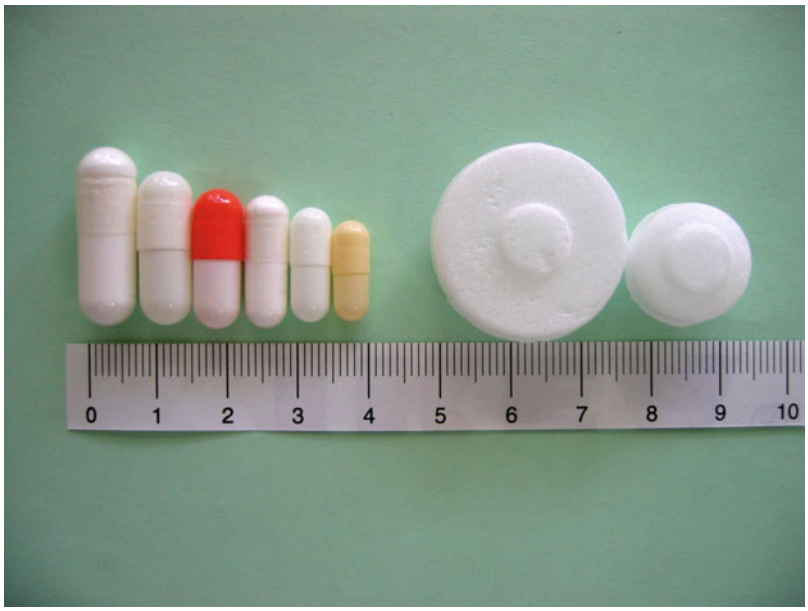

Fig. 4.4 Dimensions of cachets compared to capsule shells, © Department of Pharmaceutical Technology GUMed Gdansk

they are bigger and flatter in shape (Fig. 4.4). Like the gelatine hard capsules, cachets consist of two shells: a cap and a body. Cachets are manufactured by moulding a mixture of starch and water, after which the capsules are dried ("baked"). Separate moulds are used for caps and bodies, and they are supplied separately as well. The empty cachets should be stored in dry place.

4.8.1 Filling of Cachets

In pharmacy, cachets are hand-filled with dry powder mixtures. Active substances often require adding a diluent to the active substance to achieve the minimum mass of 100–300 mg as in single-dose powders (see Sect. 4.7.1). Lactose is the most common agent used for this purpose. The powder has to be divided into individual cachets by weight, which is time-consuming. Afterwards the caps are fitted manually onto the bodies to close the cachets. Although special filling apparatus were developed, they are not commonly used.

4.8.2 Patient Instruction

In spite of their large size, adult patients can swallow cachets upon moistening with water making them soft, elastic and slippery. If the size is too big the patient may take the powder after removing it from the cachet. This is a way to administer them to children.

4.8.3 Stability

Cachets are sensitive to moisture that causes softening of the shell, improve the potential for chemical degradation, and microbial growth. When stability is not confirmed experimentally, the beyond-use date is, generally, not longer than 30 days. The preparation is stored at room temperature, in paper or plastic bags or other containers. If the powder is hygroscopic, a tight closure is required.

4.9 Tablets

4.9.1 Orientation and Definitions

Tablets are the most popular pharmaceutical dosage form with many advantages: simple and accurate administration of the correct dose, convenient delivery of active substances, easy handling and good stability. Degradation of the active substance occurs usually slowly and the microbiological quality of the dosage form is almost guaranteed. Moreover, tablets can be prepared at both laboratory and large scale. However, they present little flexibility on dosage which makes them inappropriate for patients with special needs, even if they are manufactured with score lines to divide them into halves or quarters (see Sect. 37.8.3). The majority of tablets are swallowed whole. Less common are tablets that need to be dissolved or disintegrated before ingestion, or that fizz when in contact with water (effervescent tablets) (Table 4.6).

Other types of tablets may require chewing by the patient or dissolution of the active substance in the mouth. The formulation of tablets is discussed to such an extent as is necessary to support the adapting of these products into other oral dosage forms in pharmacies. The preparation of tablets is complex and specialised, hard to perform on a small scale and is therefore beyond the scope of this book. The

Table 4.6 Types of tablets (Based on the definitions of the Ph. Eur.)

Type of tablet	Characteristics
Non coated tablet (conventional tablet)	Is designed to be swallowed by the patient
	Releases the active substance in the stomach, immediately after administration
Coated tablet	A coat was applied to a tablet (e.g. protection from the environment)
Enteric coated tablet	A gastroresistant coat is applied to the tablet
Effervescent tablet	Is prepared by compression
	Contains mixtures of weak acids (e.g. citric acid or tartaric acid) and sodium bicarbonate or carbonate, which release carbon dioxide when dissolved in water
	The prepared solution becomes the delivery system of the active substance to the patient
Soluble tablet	Tablet to be dissolved in water prior to administration; may or may not be coated
Dispersible tablet	Tablet to be dispersed in water prior to administration; may or may not be coated
Orodispersible tablet	Tablet designed to disintegrate in the mouth within seconds
Tablet for sublingual application	Dissolves rapidly in the mouth
	Is designed for sublingual absorption of fast release medicines
	Often contains lactose or other excipients easily soluble in water
Tablet for buccal application	Is placed in the cheek pouch where the active substance can be absorbed in the mouth
	The active substance can be released immediately or, slowly, particularly when adhesive tablets are designed
Chewable tablet	Designed to be chewed
	Is formulated to have a pleasant taste, without leaving an unpleasant after taste (e.g. by including mannitol, sorbitol or sucrose)
	Is formulated with a high mechanical strength to prevent fast disintegration in the mouth
Modified release tablet	Is designed to be swallowed whole
	The release of the active substance is not immediate but controlled

preparation method is however discussed briefly, because it partly determines the possibilities of adapting.

4.9.2 Formulation

4.9.2.1 Diluents

Diluents are added to tablets that are prepared by either wet granulation or direct compression to increase the mass. These agents should comply with the same specifications as diluents in capsules. Generally milled lactose or microcrystalline cellulose grade PH101 are used as diluents; sometimes mannitol or calcium monohydrogen phosphate dihydrate act as such. Some of these substances are described in the section on capsules (see Sect. 4.6). Good flow properties of diluents are less important for tableting by wet granulation compared to capsule filling. For this reason (milled) lactose 100 mesh, with good flow properties, is used in capsules, whilst the rather poorly flowing (milled) lactose 200 mesh is used in tablets prepared by wet granulation (see Sect. 23.4.4).

Nowadays some tablet excipients present multi functionalities. New excipients are designed to allow a fast and effective mixing with the active substance prior to compression. Although more expensive, they save production time and diminish difficulties on designing a new formulation.

Diluents with binding properties are used in tablets that are prepared by direct compression. They are meant for increasing the mass, but have binding capacities as well. Since the powder mass is not granulated, they should exhibit good flow properties. Furthermore, diluents should not segregate easily. The most often used binding agents are microcrystalline cellulose (especially type PH102), various grades of lactose, and calcium monohydrogen phosphate dihydrate.

Various qualities of lactose (see also Sect. 23.4.4) are used as diluents in tablets. For instance alfa-lactose monohydrate 100 mesh is a sieved product with good flow properties, although the binding properties are quite poor. Consequently it is often combined with another binding agent such as microcrystalline cellulose PH102. Granulated alfa-lactose monohydrate has better binding properties than lactose 100 mesh. Anhydrous beta-lactose is an agglomerated product with good flow and binding properties. Spray-dried lactose also has good flow and binding properties, but contains about 15 % of amorphous lactose, which makes it somewhat hygroscopic. Mannitol is a binding agent that can be used in tablets; it is a polyalcohol, available as binding agent in a granulated grade (e.g. Pearlitol®). Mannitol is mainly used as substitute for lactose. Co-processed products can also be used for the production of tablets. These are agglomerates of two different excipients. The best known are Cellactose® (75 % alfa-lactose monohydrate and 25 % cellulose) and StarLac®

(85 % alfa-lactose monohydrate and 15 % corn starch). These products exhibit good binding and flow properties. More information on binding agents can be found in the literature.

4.9.2.2 Disintegrants

Disintegrating agents for tablets are either classical disintegrating agents or super-disintegrating agents. The most often used classical disintegrating agent is corn starch in fractions between 10 % and 20 %. Starch, which does not compress well, cannot be used for direct compression. In that case super-disintegrating agents are used, which are already effective in concentrations between 2 % and 6 %. Super-disintegrating agents are used in tablets when required independently of the preparation by wet or dry granulation or, simply direct compression of excipients and drug. The ones that are used are:

- Sodium starch glycolate (type A) (Primojel®). This product swells strongly in water and thereby breaks bonds within the tablet.
- Sodium croscarmellose (Ac-Di-Sol®) has about the same properties as sodium starch glycolate, but is effective in even lower concentrations.
- Crospovidone (Polyplasdone® XL) swells sparingly in water. Its mechanism of action is based on capillary forces, which allow for fast penetration of water into the tablet. In tablets with a high content of highly soluble compounds, such as anhydrous beta-lactose, it is more effective than both other super-disintegrating agents.

It is essential to choose the right super-disintegrating agent for direct compression. For tablets containing sparingly or poorly soluble binding agents, sodium starch glycolate and croscarmellose are suitable. For tablets containing soluble binding excipients, crospovidone is the better choice.

4.9.2.3 Binders

Binders provide binding in tablets that are prepared by wet granulation. Binders are polymers that transform into a sticky mass in presence of water. They can be added to the powder mixture as a solid or in solution. When added as a solid, the mixture is subsequently wetted with water; when dissolved in water, or another convenient non-toxic solvent, the powder mixture is wetted with the binder solution. The latter approach maximizes the binding property of the binder. In the past, mainly natural polymers were used, such as starch or gelatine. Nowadays, the most commonly used binders are:

- Polyvinylpyrrolidone (povidone, PVP)
- Cellulose ethers, such as hypromellose (HPMC), methylcellulose (MC), hydroxypropylcellulose (HPC) and carmellose sodium (CMC-Na)
- Cold swellable starch

4.9.2.4 Glidants

Glidants promote the flow of granules and tableting powder mixtures. This causes a more uniform filling of the mould, and thus a higher uniformity of mass. For tablets prepared by wet granulation, generally talc is used. Talc also reduces adhesion to the punches and moulds. For direct compression a glidant is often not necessary. If it is desirable to use glidant, colloidal anhydrous silica is used (Aerosil® 200 V). Magnesium stearate also promotes flow, but is mainly used as a lubricant.

4.9.2.5 Lubricants

Lubricants are used to minimise friction between particles and between the particles or the tablet and the mould during tableting. The most often used lubricant is magnesium stearate in concentrations between 0.5 % and 2.0 %. Magnesium stearate functions as an anti-adhesive agent: it reduces adherence to the punches and mould. A disadvantage of magnesium stearate is its negative effect on the binding properties of the powder mixture. Moreover, it increases the disintegration time of tablets due to its hydrophobic nature. Alternatives to magnesium stearate, such as stearic acid and hydrogenated fats, are sparingly used because these compounds are less effective.

4.9.2.6 Mechanical Strength

Tablets should be formulated to have sufficient mechanical strength to prevent breakage or crumbling during transportation or further processing, because damaged tablets contain less active substance, may be more difficult to deliver to patient and be regarded as a defective product by the patient.

4.9.2.7 Disintegration and Dissolution Rate

Most types of tablets should disintegrate in water within a certain time limit (see Sect. 32.9). Disintegration of tablets is a prerequisite, but not a guarantee for a good bioavailability, for which a good dissolution rate is essential as well.

4.9.3 Method of Preparation

Tablets are prepared by compression of uniform volumes of particles (powder mixtures) or granules. The choice of excipients depends on the preparation method: wet granulation or direct compression.

The problem that arises with tablets is that it is hard to produce small batches of tablets of good quality. Mixing, granulation (often required) and tableting equipment are suitable for the manufacturing of tablets on a larger scale than required in most pharmacies. Only a few pharmacies are equipped for the preparation of tablets, which are usually not commercially available. Alternatively one can use a mechanical press to prepare individual tablets, although

reproducibility may be a problem. Traditionally small-scale tableting has not been common practice in pharmacies, but new equipment is allowing the preparation of small batches.

In the past, tablets used to be prepared by wet granulation, but nowadays, more and more tablets are prepared by direct compression of a powder mixture. Both methods have advantages and disadvantages. Tablets that are prepared by wet granulation usually contain a diluent, a binder, a disintegrating agent, a glidant, and a lubricant. The process includes mixing, wet granulation, drying, mixing again and tableting and takes quite some time. Tablets that are prepared by direct compression contain one or more binding and diluent excipients that have a binding capacity in the dry state. The process runs faster as mixing of powders prior to compression is often sufficient. Direct compressed tablets usually contain additionally a disintegrating agent, a glidant and a lubricant. Both types of tablets may also contain other excipients, such as colouring agents and wetting agents. Modified-release tablets contain different excipients and are prepared following a different method. This type of tablets is described in Sect. 4.10.

4.9.3.1 Flow

For even filling of the moulds, it is important that the powder mass flows well. A classical method to improve the flow properties of a powder is granulation. The flow properties of the substances that are present in the granules are irrelevant, only the flow properties of the granules themselves matter. Direct compression, however, requires good flow properties. This can be achieved by use of the right binding agents. Tableting of high dose active substances requires good flow properties of these substances as well. The addition of a glidant may be necessary.

4.9.3.2 Mixing

It is essential that a powder does not segregate during mixing or tableting to achieve a good content uniformity. Granulation is one technology that can be used to prevent segregation of powders. For direct compression, choosing the right particle size for the active substances and the excipients can prevent segregation. Micronised active substances are generally distributed over one of the excipients by means of ordered mixing (see Sect. 4.5.1) prior to subsequent mixing. Another method to distribute micronised particles over excipients is by dissolving them first in a suitable solvent (solvent method, see Sect. 4.5.1).

4.9.4 Release Control and Quality Requirements

Once manufactured, tablets will be controlled for weight and weight variation, appearance, disintegration active substance content, content uniformity, friability and dissolution rate (see Chap. 32). Most of these requirements are to be found in the Ph. Eur.

4.10 Modified-Release Tablets and Capsules

Solid oral dosage forms can be modified in various ways to alter the release profile of the active substance. Preparations with such an altered release profile are called modified-release preparations. Some of the reasons have been presented previously (Sect. 4.9.1).

Modified-release preparations are discussed for several reasons. At first, a pharmacist should know that such modifications on active substance release exist, and that he may dispense medicines with a specific release profile. Secondly, some active substances are only available as a modified-release preparation. Thirdly, the administration of a modified active substance release profile from a tablet might be due to the properties of the active substance. These are some aspects that must be considered before such a tablet is crushed or a capsule is emptied. Enteric-coated tablets and capsules are not described as modified release preparations in the Ph. Eur. [6] but the same care must be taken not to damage the coat when using it for the preparation of other dosage forms.

Formulation and preparation method of modified-release tablets is tuned to the desired release profile, and thus differ from conventional tablets. The complex nature of this formulation and preparation can only occur in large-scale industrial production.

4.10.1 Pharmacokinetics

Not all active substances are suitable for a modified-release tablet. In general, an enteric coating on an ordinary tablet requires no specific properties of the active substance. However, other types of modified-release may require certain pharmacokinetic properties:

- The pharmacokinetics of the active substance should be known: an active substance with a long half-life in a slow release preparation has little added value. An active substance with a short half-life may be appropriate for a modified-release dosage form, unless a large dose is required to achieve the therapeutic effect. In that case, then the size of the dosage form may be too large to be swallowed by a patient.
- The dissolved active substance should be sufficiently absorbed in the small and large intestines, depending on the site of their release, requiring the dosage form to remain over time in a specific location (e.g. mucoadhesion).

4.10.2 Physico-chemical Mechanisms on Active Substance Release

Various physico-chemical mechanisms can be applied to delay the release from a solid oral dosage form. These mechanisms are usually applied in combination:

- Delayed dissolution and diffusion: water (needed for dissolving the active substance) and, after dissolving, the active substance solution have to pass a barrier: through narrow pores or a viscous mass.
- Delayed dissolution by applying a layer that dissolves at a higher pH.
- Erosion: the mass that contains the active substance should first erode for the active substance to come into contact with water and dissolve.
- Swelling: excipients swell in contact with water, which hinders diffusion of the active substance.
- Complex formation: the active substance cannot be released due to binding to insoluble excipients.
- Osmosis: a semi-permeable membrane containing holes of a certain diameter surrounds the active substance and an osmotic active agent. In contact with water, the osmotic active agent attracts water, which results in release of the content through the holes.
- Physical blockade of transportation: the tablet is or becomes so large that pylorus passage is delayed (gastro retention).

4.10.3 Desired Release Rate

The desired release profile can be based on various physico-chemical mechanisms, supplemented with the mechanical effect of the dosage form itself. The mathematical equations for the release profile in combination with *in vitro* research can help on directing the development of new preparations.

However, the release profile *in vivo* is hard (often impossible) to predict. Beneficial is a release profile with little dependence on physiological and anatomical factors, such as the degree of filling of the gastro-intestinal tract, the rate of passage, the type of food, the pH, physical activity, age, etc. These parameters exhibit large inter- and intra-individual variation. Residence times in the different parts of the gastro-intestinal tract may vary greatly: stomach: 0.5 – > 8 h; small intestine: 2–6 h; large intestine: 4–30 h.

The independence from such factors can be tested to a certain extent *in vitro*, by determination of the dissolution rate under influence of (a simulation of) the variables. The tests described by the Ph. Eur. are limited, namely to the influence of pH [6]. The USP also requires testing for the influence of 15 % ethanol on the dissolution rate (see also Sects. 32.10 and 16.2.3).

4.10.4 Dosage Form

The described physico-chemical mechanisms are applied in various combinations in licensed medicines. The different modified-release dosage forms can be classified in many ways, which can be found in literature.

Licensed medicines delivering the same active substance with a modified release profile rarely have the same formulation. What can be distinguished is whether the preparation consists of a matrix, a reservoir system, or a combination of both. An example of a combination of a matrix and a membrane is a coated hard gelatine capsule filled with small matrix pellets (mini matrices). When using these complex systems for the preparation of other dosage forms, each component should be dealt with differently and independently.

It can also be distinguished whether the dosage form is monolithic (one part) or multi-particulate (consisting of multiple small particles). A monolithic dosage form remains intact or erodes during its residency in the gastro-intestinal tract. A multi-particulate system, on the other hand, disintegrates and spreads.

Over the last 30 years many studies have addressed the problem of transit time and active substance site absorption. Factors such as, dosage form size, density, shape, the fed versus fast status of patient have been studied using different techniques (e.g. gamma-scintigraphy). Generally low size and low density dosage forms present a faster transit than large and dense tablets [35]. Overall the time of a modified release dosage form in the stomach varies with the presence or absence of food, from minutes to 2–4 h. The stay in the small intestine is quite constant at 3–4 h and in the colon from a few hours to days.

The advantages of a multi-particulate capsule or tablet in comparison to a monolithic dosage form are:

- Transportation is independent of the filling of the stomach (assuming that the particles are < 2 mm).
- Spreading of the content over the stomach and intestine reduces the chance that the dose is (unintentionally) released at once, which could lead to damage of the gastro-intestinal wall.

The disadvantages are:

- The surface area is large, and thus the dissolution rate is higher (see Sect. 18.1), which requires a larger delay.
- In the case where the particles contain hydrophilic and inert polymers, there is a chance that the capsule does not disintegrate, and thus acts as a monolithic dosage form.

4.10.5 Matrix Systems

In a matrix, the active substance is dispersed in compressed excipients (usually polymers) that retain its shape reasonably long after ingestion. The active substance should be released through pores in the matrix, or the matrix should erode. The matrix can be hydrophilic; then swelling is the main delaying mechanism. A matrix consisting of inert plastic requires the active substance to diffuse through narrow pores. Matrices can also consist of fat, for which erosion is the main principle of delayed release of the active substance.

Matrix systems may contain the following excipients [36]:

- Polymers for hydrophilic matrices
- Semi-synthetic: hypromellose, hydroxypropylcellulose
- Synthetic: polyvinylalcohol, copovidone (polyvidone/vinyl acetate)
- Polymers for inert matrices: ethylcellulose, aminomethacrylate (Eudragit® RS), polyvinyl acetate/polyvidone (mixture, no co-polymer)
- Polymers for a fatty matrix: glycerol behenate, glycerol palmitostearate, waxes, cetyl alcohol

4.10.6 Reservoir Systems

A reservoir system consists of an active substance and a membrane, and therefore is also known as a membrane controlled system. A membrane or coating can be applied to a whole tablet or capsule, or to a tablet core. Granulates and even crystals can be coated as well, which are then processed into tablets or capsules. Enteric-coated dosage forms have an acid-resistant coating, which dissolves when the pH is increased. An osmotic system may be regarded as a particular reservoir system, because it has a semi-permeable membrane that is provided with holes with an exact diameter.

For reservoir systems and coatings, the following polymers can be used for the base of the coating [36]:

- Polymethacrylates (Eudragit® series, Kollicoat® series)
- Cellulose derivates, such as ethylcellulose, cellulose acetate, cellulose acetate butyrate (Ethocel®, Aquacoat®, Surelease®)
- In acid soluble polymethacrylates and cellulose derivates, Shellac
- Fats and waxes, such as carnauba wax, glycerol monostearate, hydrogenated ricin oil, for coating with molten polymers

Examples of plasticisers to improve the workability of the polymer, are:

- Hydrophilic plasticisers: triethyl citrate (TEC), triacetine (GTA), macrogol, propylene glycol, sodium lauryl sulfate, polysorbate 80, water
- Lipophilic plasticisers: dibutylsebacate (DBS), tributyl citrate (TBC), acetyl-TBA, acetyl-TEC, stearic acid, ricin oil, medium chain triglycerides, acetylated monoglycerides (acetem)

Other compounds that may be present in a reservoir system are a dispersion medium of solvent, glidants or anti-adhesive agents (titanium oxide, talc, magnesium stearate, etc.), and agents that further influence the release (various water soluble, but also fat-soluble compounds.

4.10.7 Adapting Modified-Release Preparations

When a patient cannot swallow tablets or capsules, has a feeding tube, or requires a lower dose of the active substance than present in a commercial product, the pharmacist should find a way to administer the active substance. Sections 37.6.2 and 37.8.3 discuss various strategies to modify conventional (fast-release) tablets or capsules, such as the opening and emptying of a capsule, or pulverisation of a tablet and subsequently mixing it with a diluent or liquid.

However, these modification strategies may not be possible to apply to modified-release preparations. Questions such as the following should be answered: is it possible to split the dosage form without destroying its function? Is it possible to mix the content of a capsule without grinding? Can the dosage form be modified into a liquid preparation? And if so, should the dose or dose frequency be adjusted?

A modified-release preparation should be administered as such to have its intended effect. Splitting is not an option, unless this is provided by the manufacturer and is specified in the product details. Sometimes, asking the manufacturer may give the desired information, but not all manufacturers are able or willing to help with the particular situation of an individual patient.

The product details of many licensed products do not specify what to do when a patient is not capable of taking the capsule of tablet, or requires a different dose. However, propositions have been made to improve the situation [37]. The EMA has made the

(continued)

following changes in the guidelines on the content of the Summary of Product Characteristics (SPCs):

- For scored tablets, the product details should include whether the tablets may be broken to obtain half doses, or only to ease the ingestion.
- When the manufacturer has information on alternative methods for ingestion, this should be stated as clearly as possible in the product details; for example, whether the tablet can be pulverised or broken, the capsules be opened, or the content be mixed with food or liquid. The manufacturer should also account for patients who receive gavage feeding.
- An advice on the handling of a dosage form should be supplemented with a clarification, such as: 'do not chew the tablet, because of the unpleasant taste', 'do not split the tablet, because the coating protects the stomach', or 'do not split the tablet, because the coating modifies its release profile'.
- For a preparation that can be applied for children in a modified form, the manufacturer should provide detailed instructions on how this should be done, including the container that should be used and the shelf life.

A graph of the release profile in the product details would also benefit the application of modified-release preparations, as well as information on the dependence on physiological and anatomical factors.

In a specific situation, the pharmacist first studies the Summary of Product Characteristics (SPC) to check whether a preparation may be modified and if so, how [37]. Normally, this can be found in its Sect. 4.2 Posology and method of administration. When the information on modification is negative or absent, a pharmacotherapeutic alternative is the most obvious choice. Such an alternative may be a different dosage form of the same active substance or a different active substance with a comparable therapeutic effect. Clinical and pharmacokinetic background of the modified-release profile is paramount for making a justified decision. Clinically superfluous modified release can also be concluded with such a literature search.

4.11 Herbal Oral Medicines

The use of herbal medicines has attracted attention in recent years[1]. Following the millenary use of natural products worldwide, for instance as teas, their conversion into solid dosage forms is a current practice. The main advantage is the standardisation of the active medicines (often a family of chemically similar compounds) presented to patients in a stable dosage form as a tablet, which can be coated. Their production can be difficult due to variations on the herbal medicine as a raw material (e.g. powdered dried seeds, leaves or liquid or solid extracts) and their transformation into a compressible material [38, 39]. Even the dry extracts can exist as a very fine powder, poorly compressible, and hygroscopic. Furthermore the disintegration time of high fraction dried extract tablets can be too long [40]. As a consequence it is possible to manufacture solid dosage forms in a small scale, it is also possible to design formulations for herbal medicines, but care and hard work on designing the formulation and defining the processing conditions are required. Both the USP-National Formulary and the European Pharmacopoeia present a series of preparations from natural products, namely Aloes (extract), American Ginseng (powder, extract, capsules or tablets), Belladonna leaf (dried extract, tincture or powder), Chamomila (flower heads), Garlic (powder) or St John's Wort (extract, powder).

Pharmacy preparations from herbal medicines include herbal tea mixtures, from which the user to whom it is dispensed prepares a tea using (boiling) water. According to the Ph. Eur., herbal teas consist exclusively of one or more herbal medicines intended for oral aqueous preparations by means of decoction, infusion or maceration. The patient prepares the herbal tea immediately before use. Instant herbal teas consist of one or more herbal medicine preparations (primarily extracts with or without added essential oils), and are intended for the preparation of an oral solution immediately before use. Example of formulae for oral solid herbal pharmacy preparations can be found in [41] (Table 4.7).

Table 4.7 Cough and Bronchial Tea II [42]

Aniseed	20 g
Lime flower, cut	50 g
Mallow flower, cut	5 g
Primrose flower DAC	5 g
Thyme, crushed	20 g
Total	100 g

4.12 Complementary Information

4.12.1 Containers and Labelling

Many active substances are sensitive to light, and therefore, oral solid dosage forms have to be packaged in a light-protecting container. This is especially relevant to capsules with a transparent shell. Powders are packaged in a carton

[1] This section was contributed by Herman J. Woerdenbag, Groningen, The Netherlands.

box, plastic jar or plastic sachet. For packaging of licensed medicines, light-sensitivity of the active substance is generally taken into account. When such products are repackaged for automated dispensing systems, the function of the original container should be considered and taken up: for example protection against light or moisture.

Single-dose powders are packaged in a suitable powder fold box, a plastic bag with locking clip or, in case of an authorised medicine, in sachets.

Containers of solid oral dosage forms should be provided with a label. When the preparation has a primary and a secondary container, both containers should be labelled. The label should meet the requirements described in Sect 37.3.

4.12.2 Storage and Stability

The chemical, physical and microbiological stability of solid oral dosage forms is generally good (see Sect. 22.7.1). Chemical reactions and physical degradation processes hardly occur in the absence of water together with the potential growth of micro-organisms in the materials.

The amount of water in solid oral dosage forms can vary from less than 1 % up to 10 %. This water exists due to the exposure of materials to the environment. Some active substances may degrade at high relative air humidities (e.g. carbasalate calcium), or are hygroscopic and attract water (e.g. potassium iodide). Degradation reactions such as hydrolysis may occur. In these cases an excipient with water absorption properties (e.g. silica oxide) should be added to the formulations. However, hard gelatin capsule shells normally contain about 12–16 % water and moisture can diffuse through the gelatin wall [36]. The preparation may be prevented from attracting moisture by keeping it in a dry place or by packaging it in a material that protects against moisture, such as sealed sachets. Once the problem of instability in the presence of small amounts of water has been solved, the shelf life of solid oral dosage forms is long.

Capsules, powders and tablets should be stored at relative air humidity between 35 % and 60 %. Capsules dehydrate and become brittle at lower relative humidity, while at higher values they absorb moisture and become sticky and flaccid. Consequently, capsules should be stored in dry places at room temperature rather than stored with a desiccant.

Multidose powders have their containers opened several times while used, and thus, stability might become a problem. As a suggestion, when the chemical and physical stability are unknown, the maximum shelf life of the powders is limited to 6 months and the user informed towards a careful use of the container, particularly on having it open for the shortest possible time.

Carbasalate calcium is a relatively unstable solid active substance, as it degrades through hydrolysis in the presence of moisture. Upon degradation, salicylic acid and acetic acid are formed. The latter can be smelt in very low quantities. To prevent patients becoming needlessly worried, carbasalate calcium powders should be packaged in lightly ventilating material such as paper.

4.12.3 Advices on Use

Orally administered medicines require the pharmacist's advice on when (before, with or after the meal) and how (with a full glass of water, no milk, etc.) to take the medicine. When single-dose or multidose powders are dispensed, patients must be taught on the exact technique for measuring the dose to be administered and the proper mode of administration. Should the powder be mixed in a liquid? What liquid and volume? Can the powder be mixed with food (hot or cold)? How long it can be kept after mixing?

Medicines can interact in many ways with food or liquids. First, food or drinks may interfere with the performance of the dosage form, namely on sustaining its migration throughout the gastrointestinal tract. They may also affect the absorption of released active substances due to geometry and structural effects (tablets or capsules versus pellets or granules) [43], see also Sect. 16.1.6. Food or drinks, as such or one of the ingredients can influence the stability of the active substance e.g. calcium ions present in the milk may chelate some active substances [44]. The absorption of the active substance may be compromised, for instance when its absorption requires a common cellular membrane transporter to some component of food or beverage.

Capsules or tablets that get stuck in the oesophagus may lead to severe oesophageal irritation particularly if the active substance is released. Furthermore the therapeutic action may be compromised. Preparations of active substances with a high risk of damaging the oesophagus (e.g. risedronate, alendronate, doxycyline) require the text "Take in an upright position with a full glass of water" in the label.

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Oral Liquids

5

Antje Lein and Shi Wai Ng

Contents

Abstract

Oral liquid medicines may be a good choice of dosage form for patients who have problems with swallowing tablets and capsules, or if they have an enteral feeding tube, or for whom the required dose does not fit with the available tablet(s) or capsule(s) such as is often the case with children and elderly people. A liquid dosage form is easy to measure and administer.

Compared to tablets and capsules, oral liquids have some disadvantages as well. Their extemporaneous formulation and preparation is not so easy. They may have an unpleasant taste, the use of solvents and preservatives is restricted due to their toxicity (especially for children), and the safe use of suspensions requires proper shaking.

The properties of the active substance dominate and often restrict the choice of the type of oral liquid. Oral liquids are classified according to their physical properties as solutions, suspensions, emulsions and solubilisates. Solutions and suspensions are treated in depth because they are most often dealt with in daily practice.

Keywords

Solutions • Suspensions • Emulsions • Solubilisates • Oral liquids • Syrup • Flavour • Acceptable daily intake • Colour • Taste • Feeding tube • Preparation • Formulation

5.1 Orientation

Oral liquids have some advantages compared with tablets and capsules. They are more easily ingested by patients having problems with swallowing or having an enteral

Based on the chapter Oraal vloeibaar by Christien Oussoren and Doerine Postma in the 2009 edition of Recepteerkunde.With advices from Mark Jackson, Liverpool U.K.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_5,

feeding tube. An adult dose is easily adapted for children or for elderly patients.

In nursing homes psychoactive medicines are commonly administered as drops. If there is no oral liquid form available, the pharmacist may receive a doctor's prescription for the adaptation of an oral solid into an oral liquid. Tablets may be pulverised or capsules can be emptied and administered with semisolid food. However, there may be other solutions such as improving swallowing technique or a different administration route. Even for patients with an enteral feeding tube there may be alternatives or at least points of attention.

Oral liquids may have several disadvantages like an unpleasant taste and an insufficient physical, chemical and microbiological stability. It may be complicated to formulate an oral liquid that complies with quality specifications. And the relative ease of administration may lead to abuse or overdose, especially with children.

After mentioning the relevant definitions this chapter firstly discusses the assessment of prescriptions for oral liquids, especially if inadequacy of the corresponding oral solid is the reason for the request. Also the choice between solutions and suspensions should be made carefully.

Biopharmaceutical aspects are shortly dealt with, followed by formulation and preparation method of oral solutions, suspensions, emulsions and solubilisates.

5.2 Definitions

Oral liquids are included in the European Pharmacopoeia as 'Liquids for oral use', distinguishing the following categories of preparations.

Oral solutions, emulsions and suspensions are defined as being supplied in single-dose or multidose containers. Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 mL or multiples thereof or an oral syringe for other volumes.

Powders and granules for the preparation of oral solutions and suspensions generally conform to the definitions in the monographs on Oral powders or Granules as appropriate. They may contain excipients, in particular to facilitate dispersion or dissolution and to prevent caking. After dissolution or suspension, they comply with the requirements for oral solutions or oral suspensions, as appropriate.

Oral drops are solutions, emulsions or suspensions that are administered in small volumes such as drops by the means of a suitable device. Because dosing in drops is less accurate than dosing with a dosing syringe and because using general dropper bottles requires extensive validation, drops are not dealt with separately. Drops preferably are replaced by oral liquids, of which a small volume can be dosed with a suitable dosing syringe (1 mL).

Powders for the preparation of oral drops generally conform to the definition of Oral powders. They may contain excipients to facilitate dissolution or suspension in the prescribed liquid or to prevent caking. After dissolution or suspension, they comply with the requirements for oral drops.

Syrups are aqueous preparations characterised by a sweet taste and a viscous consistency. They may contain sucrose at a concentration of at least 45 % w/w. The sweet taste can also be obtained by use of other polyols or sweetening agents. Syrups usually contain aromatic or other flavouring agents. Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 mL or multiples thereof.

Powders and granules for syrups generally conform to the definitions in the monograph on Oral powders or Granules. They may contain excipients to facilitate dissolution. After dissolution, they comply with the requirements for syrups.

Apart from these categories this chapter also covers:

Solubilisates for oral use: colloidal solutions of a liquid active substance in an immiscible liquid; this term is not on the list of EDQM standard terms.

A few of the 'herbal drug preparations' of the Ph. Eur. are oral liquids: teas and extracts such as tinctures (extracts with ethanol-water mixtures). Teas are dealt with in chapter Oral solids because they are dispensed as solids, see Sect. 4.11. Liquid extracts are dealt with in chapter Raw materials, see Sect. 23.12.

An oral dosage form frequently has to be adapted into an oral liquid to meet the needs of a patient. The action that has to be exerted may be called 'manipulation'. But mentioning the actual action (such as crushing) is to be preferred.

5.3 Biopharmaceutics

Active substances that are dissolved in water are, if they remain in solution, immediately available for absorption after taking on an empty stomach. If they precipitate in the acidic environment of the empty stomach the precipitation will often be so fine that it easily passes the closed pylorus and re-dissolves, after which rapid absorption is still possible. The pharmaceutical availability (actually the dissolution rate of the solid substance) of suspensions for oral use depends on many factors including solubility *in vivo*, the crystal modification and the particle size and the viscosity of the suspension. In practice it occurs that an active substance (such as phenobarbital) may be formulated as a suspension in water or as a solution in a lipophilic solvent such as acetem (see Sect. 23.3.6). Beware that changing from a suspension into a solution may cause a great increase in absorption rate and thus cause a change in pharmacodynamics.

The absorption of active substances from a lipophilic solvent varies widely and is difficult to predict. The amount and rate of absorption are largely determined by the release of the active substance from the lipid phase. This depends on the solubility of the active substance in the lipid phase and the composition of the intestinal contents. If the partition coefficient is large (the medicine resides mainly in the lipid phase, see Sect. 16.1.4) the absorption is slower. Bile salts provide a fine distribution of the lipophilic active substance, which promotes the absorption. Some lipophilic solvents promote the release of bile acids resulting in a quick absorption of the active substance. Other lipophilic solvents slow down the absorption. A deficiency of bile salts can lead to impaired fat absorption and decreased absorption of lipophilic active substances. In those cases the administration of lipophilic active substances in the form of a solubilisate is more suitable (see Sect. 5.4.7).

5.4 Product Formulation

First, the reason why a prescriber may require an oral liquid is discussed. If no standard formula is available, one of the main choices regards whether an oral solution is to be formulated or an oral suspension.

The formulation of a dispersed system is not easily accomplished. With reference to useful physico-chemical principles practical guidelines are given.

The general aspects of stability, packaging, labelling and dosage delivery devices conclude this section.

5.4.1 Assessment of the Prescription

A prescription for an oral liquid can be assessed as discussed in Sect. 2.2. A request for a standard oral liquid formulation will appear to be reasonable in many cases. However, if the request for an oral liquid comes from swallowing problems with oral solids, some alternatives should be considered before the formulation of an oral liquid is started.

5.4.1.1 Request Because of Swallowing Problems with Oral Solids

If the request for the preparation, whether standardised or not, originates from swallowing problems with oral solids, some specific alternatives should be taken into consideration before starting the formulation and preparation. These alternatives are:

- Improving the swallowing technique (see Sect. 37.6.2)
- Choosing a medicine that uses an alternative administration route (oromucosal, rectal or transdermal, or parenteral if the administration by doctor or nurse can be organised)
- Instructing the patient how to process the oral solid for ingestion (see Sect. 37.6.2)

5.4.2 Choice of the Oral Liquid Dosage Form

Different oral liquid dosage forms offer the possibility to adjust the dosage form optimally to the requirements. The options are solutions, suspensions, emulsions or solubilisates. The flow scheme in Fig. 5.1 shows a route to the oral liquid form that is to be preferred due to the qualities of the active substance, particularly solubility, stability and taste. The required concentration influences the choice as well.

The main choice will be between an oral solution and an oral suspension. For some active substances an emulsion or solubilisate is the appropriate form. However in some cases (e.g. because of an intermediate solubility of the active substance) the pharmacist will have no other option than to dispense an oral solid dosage form and instruct the patient how to manipulate it safely (see Sect. 37.6.2). Proper consideration of the options may prevent formulation mistakes with probably severe consequences. This especially applies to the unreflected use of ‘suspending bases’ for rendering an oral solid into an oral liquid.

If the patient has an enteral feeding tube, specific requirements have to be taken into consideration (see Sects. 5.4.3 and 37.6.3).

An aqueous solution is the first choice because of high dosage accuracy and homogeneity. If an active substance is not sufficiently water-soluble, a solution may be achieved by adjusting the pH, by adding co-solvents or the use of a more soluble salt. A disadvantage of a solution can be the unpleasant taste or insufficient stability.

A suspension is the first choice if the aqueous solubility is low. Also substances with a very unpleasant taste or substances that are not stable in an aqueous solution can better be processed as a suspension. The taste sensation is less prominent and they are less susceptible to degradation when dispersed and not dissolved. However, as a suspension is a disperse system, much attention has to be paid to homogeneity at dosing. This risk has to be considered for potent medicines.

Active substances with intermediate solubility may cause the greatest challenge. When the solubility is too low for a solution but too high for a suspension (because the risk of crystal growth, see Sect. 18.1.6) the best option seems to be to choose a solid dosage form in combination with instructions for the patient how to handle in case of swallowing problems.

For lipophilic liquid active substances an emulsion or solubilisate seems the only option; if a high amount has to be processed, an emulsion is the best choice; if low amounts are present a solubilisate may be an option.

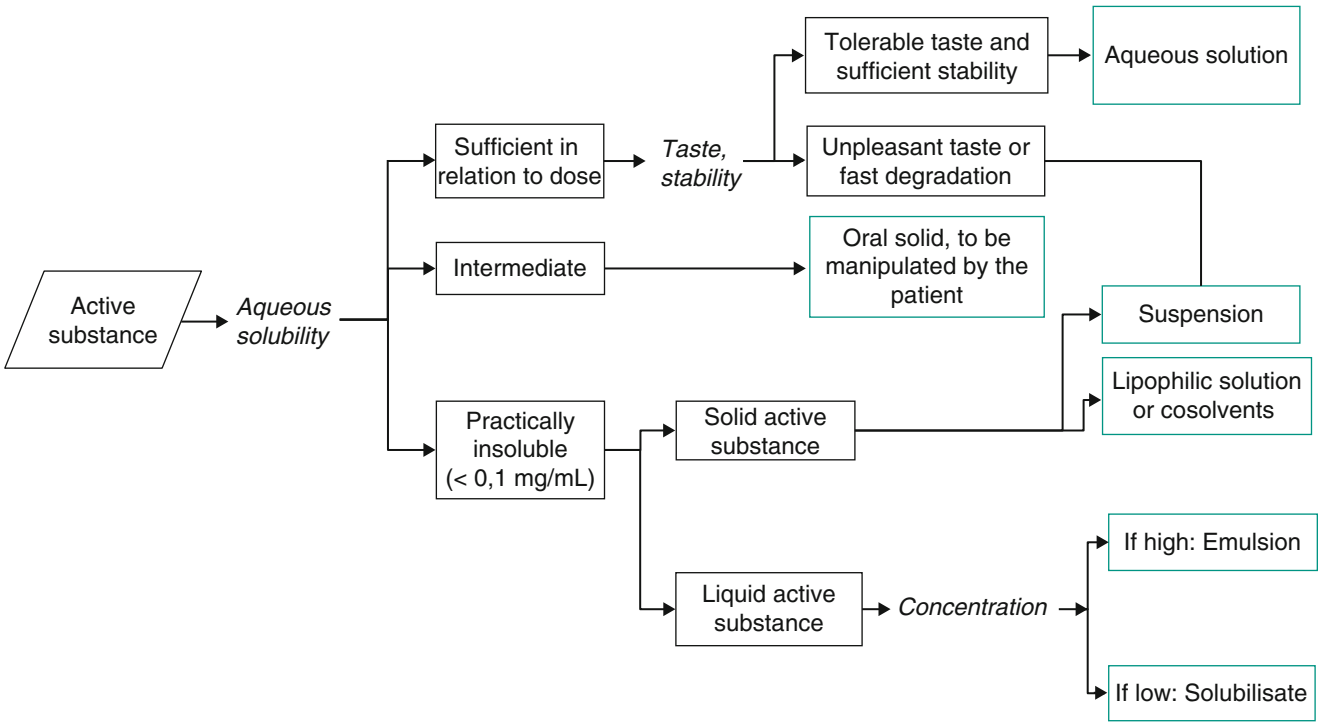

Fig. 5.1 Decision tree relating to the oral liquid form

The choice of a dosage form finally has to be taken into account that the dose range must be feasible with appropriate volumes and for ease of calculation concentrations such as 1, 2, 5 or 10 mg/mL will be preferred.

A hydrochlorothiazide oral liquid has to be formulated for children, especially for neonates. Because of the limited solubility of hydrochlorothiazide in water (0.6 mg/mL) and to avoid the presence of organic solvents such medicine may be formulated as a low concentrated solution or a higher concentrated suspension. The concentration should be calculated keeping the amount of fluid for dosing low. The solution has a concentration of 0.5 mg/mL below the limit of solubility (Table 5.1).

Table 5.1 Hydrochlorothiazide Oral Solution 0.5 mg/mL [1]

Hydrochlorothiazide	0.05 g
Citric acid monohydrate	0.87 g
Disodium phosphate dodecahydrate	0.835 g
Orange essence (local standard)	0.052 g
Methyl parahydroxybenzoate	0.045 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	32 g
Water, purified	73.88 g
Total	107.7 g (= 100 mL)

5.4.3 Additional Formulation Demands when the Patient is on Enteral Feeding

There are additional requirements for an oral liquid administered via a nasogastric feeding tube:

- It must not block the feeding tube
- It must not interact with the enteral feeding
- It must not interact with the material of the feeding tube

5.4.3.1 No Blocking the Tubes

Enteral feeding tubes can be very narrow, especially those for children. The minimum external diameter is about 1.3 mm, with the internal diameter depending on the wall material: polyvinyl chloride (PVC) being the thinnest, closely followed by polyurethane (PUR), and by silicone that being relatively thick does not leave much room for the internal diameter.

Diameter Feeding Tubes

The external diameter of feeding tubes is expressed using the Charriere (Ch) or French (Fr) unit (1 Ch = 333 μm = 1 Fr). The external diameter of the narrowest tube is Ch 4; the external diameter of the thickest tube is Ch 20, with Ch 8 or 10 being the most used.

The viscosity of the oral liquid has to be low enough to be administered through an enteral feeding tube. If necessary they have to be diluted with water. However, some solutions may precipitate upon dilution, e.g. because they contain co-solvents. Dilution also causes a decrease of the solubility of the active substance. Therefore solutions with co-solvents have to be administered undiluted.

The particles of the active substance in oral suspensions are required not to exceed 180 μm and should therefore not block the tube. Larger particles may be encountered however if ground tablets or the contents of capsules are used. In that case water-soluble fillers (such as lactose) will diminish the risk of blocking.

Flushing the feeding tube with 20–30 mL of fresh potable water before and after each addition of medicines can prevent clogging. But take care: many patients who are being tube fed require frequent monitoring of the fluid balance. The amount of water used to administer medicines (as an oral liquid and to flush the tube) may be subject to restrictions and should be recorded in that case. Carbonated fluids can exacerbate tube clogging by causing feed to coagulate or protein and amino acids to denaturise. Therefore they should not be used to flush the tube.

5.4.3.2 Incompatibility with Tubes

The relatively short time that the active substance is in contact with the feeding tube may be long enough for adsorption to the tube. When using lipophilic solvents there is also a risk of the leaching of plasticisers from the tube. This depends on the material of the feeding tube.

The use of PVC feeding tubes is limited. PVC is firm but can be uncomfortable for the patient. The plasticisers in PVC dissolve when exposed to gastric juices. As a result, the feeding tube becomes hard and fragile and can therefore be used for a maximum of 10 days [2]. In practice the use is limited to 1 week. Lipophilic medicines easily adsorb to PVC. Lipophilic solvents, such as acetem (see Sect. 23.3.6) when administered through PVC feeding tubes may cause plasticisers (phthalates) to dissolve and the feeding tube to crumble.

Polyurethane (PUR) feeding tubes can remain in the patient up to a maximum of 6–8 weeks. PUR is a rather flexible and inert material that offers more comfort for the patient than PVC. However, the greater flexibility can make the insertion more difficult. Adsorption of active substances rarely occurs.

Silicone feeding tubes are even more flexible than PUR and thus more difficult to insert. These feeding tubes are used when the tube should remain in the patient longer than 4–6 weeks. Silicone is highly resistant to gastric juices. However, silicone feeding tubes are weaker than PVC or PUR tubes [3].

5.4.3.3 Microbiological Quality

Enteral feeding does not contain preservatives because of the large volume being administered. Although tube feeding is used by vulnerable patients, sterility is not necessary. However, the food is often sterilised to get a sufficient shelf life.

If the oral liquid has been prepared from an oral solid using potable water, it has to be added immediately after preparation, thereby causing no larger microbiological load than that of potable water. Oral liquids made from raw materials are preserved in most cases and thus have a low bioburden.

5.4.4 Active Substance Solubility

Aqueous solutions can be formulated if the active substance is soluble in the desired concentration. The solubility may be enhanced by adjustment of the pH, addition of organic solvents (so-called co-solvents) or the use of a better soluble salt or ester. Some active substances only dissolve in lipophilic vehicles, see Sect. 5.4.5.5.

5.4.4.1 Sufficient Solubility

An active substance such as metoprolol tartrate, which is very soluble in water, may be processed in a simple aqueous base (Table 5.2).

5.4.4.2 pH

In general salts dissolve well in water but the solubility often depends on the pH (see Sect. 18.1.1). A high pH may not be a good option because an oral solution with a high pH is not tolerated by the gastrointestinal tract and tastes unpleasant. A furosemide oral solution may serve as an example (Table 5.3). The solubility of furosemide in water is less than 0.1 mg/mL but it increases at alkaline conditions. The solubility at pH 8 is more than 100 mg/mL [5]. An oral solution containing 2 mg/mL can be formulated by setting the pH at 6.6–8.0 with trometamol.

5.4.4.3 Co-solvents

The solubility in mixtures of water with organic solvents (co-solvents) can be predicted (see Sect. 18.1.3) but is in practice determined by experiment. Information on solubility in water or organic solvents may be available [7–10], but solubility in solvent mixtures is not. It is not correct to make

Table 5.2 Metoprolol Tartrate Oral Solution 1 mg/mL [4]

Metoprolol tartrate	0.1 g
Potassium sorbate	0.14 g
Citric acid, anhydrous	0.07 g
Water, purified	99.69 g
Total	100.0 g (= 100 mL)

Table 5.3 Furosemide Oral Solution 2 mg/mL [6]

Furosemide	0.2 g
Methyl parahydroxybenzoate	0.15 g
Saccharin sodium	0.1 g
Trometamol	0.1 g
Water, purified	99.8 g
Total	100.4 g (= 100 mL)

Table 5.4 Phenobarbital Oral Solution 4 mg/mL with Ethanol and Propylene Glycol [11]

Phenobarbital	0.4 g
Bitter-orange-epicarp and mesocarp tincture	1 mL
Ethanol (96 %)	20 mL
Propylene glycol	10 mL
Saccharin sodium	0.1 g
Sorbitol, liquid (crystallising)	60 mL
Orange essence (local standard)	1 mL
Water, purified	98.9 g
Total	100.4 g (= 100 mL)

an assumption about solubility based on the solubility in one of the solvents because all components of the mixture influence it.

An example of increasing the solubility by using co-solvents is a phenobarbital oral solution with ethanol and propylene glycol (Table 5.4). The formula is only suitable for use of limited duration in adults. Both solvents make the solution unsuitable for children. Prolonged use can make the amount of propylene glycol also too high for adults.

5.4.4.4 Better Soluble Salt or Ester

Several salts or derivatives (e.g. esters) of active substances are more soluble in water than the parent substance (see also Sect. 18.1). Well-known examples are the sodium salts of the phosphate esters of prednisolone and dexamethasone (Table 5.5).

5.4.4.5 Low Solubility: Suspension

As said (Sect. 5.4.2) an active substance that does not dissolve sufficiently to be administered as an aqueous solution can be processed in a suspension. But the solubility of the active substance should be sufficiently low, taking into account the desired concentration of the active substance in the suspension. Too high a percentage of dissolved active substance can lead to crystal growth of the suspended particles. Large particles settle faster, which can cause insufficient physical stability of the suspension and a lower dissolution rate.

Ideally, for a stable suspension, the solubility of the suspended substance should be not higher than 0.1 mg/mL and the proportion of the dissolved substance should be not higher than 0.1 % of the total amount of the oral liquid. If this is not quite to be achieved, extra attention to the particle size of the active substance should be paid. Crystal growth will more likely occur with very small particles or a high spread in the particle size. This is called Ostwald ripening (see Sect. 18.4.2.3).

Table 5.5 Dexamethasone Oral Solution 1 mg/mL (as Sodium Phosphate) [12]

Dexamethasone sodium phosphate	0.143 g
Bananas essence (local standard)	0.1 g
Disodium edetate	0.1 g
Disodium phosphate docecahydrate	1.9 g
Methyl parahydroxybenzoate	0.15 g
Sodium dihydrogen phosphate dihydrate	0.21 g
Sorbitol, liquid (crystallising)	25.8 mL
Water, purified	78.4 g
Total	106.8 g (= 100 mL)

For the indications epilepsy, diuresis, increased intracranial pressure and glaucoma with children an oral liquid dosage form with acetazolamide 5 mg/mL was required. The aqueous solubility of acetazolamide is 0.1–1 mg/mL, pK_a is 7.2 and the stability is optimal at pH 4. To obtain a solution with the concentration 5 mg/mL the pH has to be fixed at 8 but that caused a 20 % degradation of acetazolamide within 2 weeks. For an oral suspension the solubility is relatively high; for about 2–20 % of the substance would be dissolved, giving quite some cause for crystal growth. A solid dosage form would be a better option but the physicians definitely wanted to be able to adjust the dose immediately. An oral suspension was designed (see Table 5.6). However, a concentration of 10 mg/mL was used to decrease the relative percentage of dissolved acetazolamide and thus risk for crystal growth. During storage the dissolution rate appeared to decrease which may be a sign of crystal growth. Therefore, the shelf life has been limited to 3 months.

Table 5.6 Acetazolamide Oral Suspension 100 mg/mL [13]

Acetazolamide	1 g
Aluminium magnesium silicate	0.89 g
Carmellose sodium M	0.89 g
Citric acid monohydrate	0.37 g
Methyl parahydroxybenzoate	0.07 g
Raspberry essence (local standard)	0.3 g
Sodium citrate	4.7 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	33.3 g
Water, purified	72.5 g
Total	109 g (= 100 mL)

This phenomenon of crystal growth is a very realistic risk in practice if active substances, whether as raw material or as crushed tablets, are processed in a universal 'suspension base' without noticing that the actual solubility is too high for a suspension. These bases are often not clear and therefore, it cannot be controlled whether the active substance dissolves or not. If the crushed tablets are processed, the control of an eventual dissolution is impossible anyway because of the insoluble excipients.

5.4.5 Vehicles

The most commonly used vehicle is water, for solutions as well as suspensions, emulsions and solubilisates. If a solution is required, co-solvents may be added (see Sect. 5.4.4) such as ethanol, glycerol 85 % and propylene glycol. Their toxic and adverse effects should be fully considered. They are miscible with water and often have an antimicrobial effect as well. Lipophilic active substances may be brought into solution by a lipophilic solvent such as acetem. Another way of processing lipophilic solvents is to convert them into an emulsion.

5.4.5.1 Water

Usually purified water (Aqua purificata) is used. Because of the chemical and microbiological quality it is preferred over potable water (see Sect. 20.3.1) although the taste of potable water may be better due to presence of ions. Water is a good growth medium for micro-organisms, so aqueous oral liquids generally have to be preserved, see Sect. 5.4.9.

Water has a low viscosity and high surface tension, which causes an uneven 'flow' when dosing the oral liquid from bottles and dosage devices. Thickening agents, especially cellulose derivatives, may be added to improve this.

5.4.5.2 Ethanol

Ethanol is used as co-solvent in a concentration up to 20 % in oral solutions. If present in a concentration of at least 15 %, it also serves as a preservative.

In babies ethanol can lead to convulsions. According to the WHO [14] ethanol has to be avoided in oral preparations for children less than 6 years. Chronic exposure to ethanol (>1 week), even in small doses, is in principle contraindicated in children aged less than 6 years and should be limited to 2 weeks in children aged over 6 years, if a positive risk-benefit balance is not demonstrated.

The influence of ethanol on the responsiveness can especially be a problem for all ages. Pharmacy preparations should be labelled with a warning indication as it is directed for licensed products. Guidelines concerning the content of ethanol and how to deal with in high-risk groups (e.g. patients with liver diseases, alcoholism etc.) and in the handling of machinery are given by the EMA [15].

> Children, especially under the age of 6 years, are more vulnerable to the effects of ethanol.
>
> Adverse effects on the central nervous system are already evident at blood ethanol concentrations of 10 mg/100 mL in children. Higher peak ethanol blood concentrations are also observed in children than in adults for a similar intake [15].

5.4.5.3 Propylene Glycol

Propylene glycol is used as co-solvent in a concentration up to 20 %. It has preservative properties when used in concentrations of 15 % or higher. The taste is unpleasant. The acceptable daily intake (ADI) of propylene glycol is 25 mg/kg bodyweight per day without mentioning any age group [16]. Because of the limited hepatic and renal function in preterm and term neonates the application of medicines containing propylene glycol may lead to accumulation and serious adverse effects. Data in chronic use for children are not available and reports about the tolerance in patients of different ages are usually based on IV application. A daily IV dose of about 34 mg/kg bodyweight is reported to be tolerated in neonates in short time use [17]. As long as there are no data available for oral use the amount tolerated in IV application may be an indication for oral consumption as well.

5.4.5.4 Glycerol 85 %

Glycerol 85 % is used as co-solvent, preservative, sweetening agent and viscosity-increasing agent in a concentration up to 60 %. Its sweetening power is about 0.5 times that of sucrose. It functions as a preservative at a concentration higher than 30 %. The osmotic effect of high concentrated glycerol has to be considered in paediatric use and in patients with enteral feeding tubes because of gastrointestinal adverse effects (diarrhoea).

5.4.5.5 Lipophilic Solvents

Lipophilic solvents may be used for dissolution of lipophilic active substances. This option is less desirable because most lipophilic solvents do not taste very well and may render the preparation (or the labels) a bit messy at use. But for formulating an oral solution when toxic organic solvents such as ethanol or propylene glycol are not suitable, such as in paediatric use, the use of a lipophilic solvent such as acetem (see Sect. 23.3.6) may provide a useful preparation. Acetem is allowed in food, also for babies, and there is no restriction on the daily intake. The taste of acetem is

Table 5.7 Phenobarbital Oral Solution 4 mg/mL with Acetem [18]

Phenobarbital	0.4 g
Peppermint oil	0.04 g
Saccharin	0.05 g
Acetem (Myvacet 9–08)[a] (local standard)	98.4 g
Total	98.9 g (= 100 mL)

[a]Distilled acetylated monoglycerides, see Sect. 23.3.6

unpleasant; therefore saccharin and peppermint oil are added as flavouring agents. A phenobarbital oral solution may serve as an example (Table 5.7).

Lipophilic solutions contain less excipients. By the lack of water there is no grow of micro-organisms and no decomposition reactions occur. Preservatives, antioxidants and buffers are thereby not necessary.

Lipophilic solvents can be brought into an emulsion, see Sect. 5.4.7.

5.4.6 Suspending Agents

As is explained in Sect. 18.4.2 the following conditions are favourable for the formulation of an oral suspension:

- Primary particles, no agglomerates or lumps
- Right particle size (not too large but not too small either)
- Vehicle with increased viscosity and increased density
- Intermediate between a flocculated and deflocculated sediment (in order to enable safe dosing through easy resuspendability and a not too fast settling)

The achievement of the right particle size is discussed in Sects. 29.2 and 29.3. The primary particle size of substances processed in suspensions is generally < 180 µm. Wetting agents may be necessary to break up agglomerates, mainly through making hydrophilic (hydrophilising).

To increase the density of water sugar syrup can be added. An increase of the viscosity can also be achieved by the addition of viscosity enhancing substances. The character of the sediment may be influenced by electrolytes or surfactants.

Often substances are used that combine different favourable properties such as increasing viscosity, decreasing surface tension, hydrophilising the particles of the active substance etcetera. It depends on the properties of the active substance and the other components of the suspension, how a substance influences the character of the sediment (see Sect. 18.4.2).

This subsection describes three groups of substances rated by their main quality: wetting agents (including hydrophilic excipients and surfactants), thickening agents and flocculating agents. Their effect on the stability of a suspension has to be determined carefully and in combination.

Table 5.8 Phenytoin Oral Suspension 15 mg/mL [20]

Phenytoin	1.5 g
Aluminium magnesium silicate	1 g
Carmellose sodium M	1 g
Citric acid monohydrate	0.05 g
Methyl parahydroxybenzoate	0.09 g
Raspberry essence (local standard)	2 dr
Silica, colloidal anhydrous, compressed	0.25 g
Sodium citrate	4.7 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	30 g
Water, purified	ad 107.5 g (= 100 mL)

They may interact and turn a positive effect of the other substance into a negative effect. As an example cellulose derivatives may increase viscosity and wettability but decrease resuspendability. The effect of particle size, settling rate, resuspendability of the sediment and dissolution rate may be tested by applying the tests of the British Pharmacopoeia, as described in the general monograph Unlicensed Medicines [19].

5.4.6.1 Wetting Agents (Hydrophilic Excipients)

Substances with high surface energy are sometimes difficult to wet (see Sect. 18.3.2) which makes them difficult to disperse: they float on the liquid or form lumps. Such a substance should be mixed with a hydrophilic substance before dispersion. Appropriate hydrophilic substances are: thickening agents, sugar syrup, or silicon dioxide. The addition of a surfactant, for example polysorbate or polyvidone, to the aqueous phase can improve wetting as well.

The phenytoin in Table 5.8 is a poorly wettable substance. Therefore it is mixed with colloidal anhydrous silica and subsequently triturated with sugar syrup.

5.4.6.2 Wetting Agents (Surfactants)

Wetting of the active substance can be improved by the addition of a small amount of surfactant to the aqueous phase. A surfactant reduces the surface tension between the water and the solid. A surfactant will also play a role in the character of the sediment. An example is polysorbate 80 that is processed in a griseofulvin suspension 25 mg/mL (Table 5.9). The disadvantage of surfactants in general (particularly polysorbate) is the unpleasant taste.

Polyvidone K30 is used for wetting in a clioquinol suspension 100 mg/mL (Table 5.10). The addition K30 refers to the chain length and the extent to which it influences the viscosity in water. This substance has many uses including thickening agent, wetting agent and improving dispersion.

Table 5.9 Griseofulvin Oral Suspension 25 mg/mL [21]

Griseofulvin	2.5 g
Aluminium magnesium silicate	0.88 g
Carmellose sodium M	0.88 g
Citric acid monohydrate	0.066 g
Methyl parahydroxybenzoate	0.066 g
Polysorbate 80	1 g
Saccharin sodium	0.2 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	30.5 g
Water, purified	69.9 g
Total	106 g (= 100 mL)

Table 5.10 Clioquinol Oral Suspension 100 mg/mL [22]

Clioquinol	10 g
Carmellose sodium M	0.5 g
Citric acid monohydrate (crystalline)	0.1 g
Methyl parahydroxybenzoate	0.07 g
Polyvidone K30	2.5 g
Saccharin sodium	0.05 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	30 g
Water, purified	63.8 g
Total	107 g (= 100 mL)

5.4.6.3 Thickening Agents

Increasing the viscosity of water by the addition of thickening agents reduces the settling rate of particles (see Sect. 18.4.2). For thickening agents reference is made to Sect. 23.7 regarding their chemical composition, general use and their way of processing. In Table 5.11 the most commonly used thickening agents in oral liquids are listed. Apart from being used for decreasing the settling rate in suspensions, they may also be used for shielding the taste buds from an unpleasant taste and for improving the flow of the oral liquid from the bottle or the dosing device.

Using thickening agents of natural origin such as agar, tragacanth or gum Arabic the microbiological quality requires constant attention. The sterilisation of the raw materials with ethylene oxide is not allowed in pharmaceutical use and autoclaving a thickened base may decrease viscosity. Therefore an effective preservation is very important.

Xanthan gum and carrageenan are contained in the suspending base Ora-Plus®.

Some examples of the use of thickening agents are given.

In a potassium hydrogen tartrate suspension (Table 5.12) methylcellulose 15 mPa.s is applied as thickening agent. The pH of this suspension is 3.0–3.5. Cellulose derivatives, such as methylcellulose, may hydrolyse at low pH. The polymer chain is broken down and the viscosity will decrease. The shelf life is therefore limited to 3 months.

A naproxen oral suspension (Table 5.13) is an example for using tragacanth as a thickening agent. It is combined with sucrose and for taste improvement sodium chloride is added.

Ferrous fumarate can be brought into a suspension with colloidal aluminium magnesium silicate (Table 5.14), which also acts as a flocculating agent.

Table 5.11 Thickening Agents in Oral Liquids

Thickening agent	Concentration (%)	Comment
Carmellose sodium (middle viscous)	0.5–1	Incompatible with cations
Carrageenan	0.1–0.75	Needs cations (e.g. calcium, potassium, etc.) for gelling [23]
Aluminium magnesium silicate	0.5–2	Provides electrolytes as well (for flocculation)
Hydroxyl ethylcellulose (HEC) 300–560 mPa.s	1–1.5	
Hypromellose (HPMC) 4,000 mPa.s	1–1.5	
Methylcellulose 15 mPa.s	2.5	
Tragacanth	0.5	
Xanthan gum	1–3	Incompatible with polyvalent cations

Table 5.12 Potassium Hydrogen Tartrate Oral Suspension 188 mg/mL [24]

Potassium hydrogen tartrate	18.8 g
Bitter-orange-epicarp and mesocarp tincture	1 g
Ethanol (96 %)	3.3 g
Methylcellulose 15 mPa.s	2.5 g
Sorbic acid	0.2 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	25 g
Water, purified	63.9 g
Total	114.7 g (=100 mL)

5.4.6.4 Flocculating Agents

Flocculating agents are added for creating an open and large volume sediment that can be resuspended easily; they prevent ‘caking’: the occurrence of a compact sediment on the bottom of the bottle (see Sect. 18.4.2). In suspensions with negatively charged particles, multivalent cations, such as aluminium ions, may cause flocculation. On positively

Table 5.13 Naproxen Oral Suspension 50 mg/mL [25]

Naproxen	5.0 g
Sucrose	22.0 g
Sodium chloride	0.5 g
Potassium sorbate	0.15 g
Citric acid, anhydrous	0.35 g
Tragacanth	0.6 g
Water, purified	81.4 g
Total	110.0 g (=100 mL)

Table 5.14 Ferrous Fumarate Oral Solution 20 mg/mL [26]

Ferrous fumarate	2.15 g
Aluminium magnesium silicate	2 g
Raspberry essence (local standard)	0.05 g
Sorbic acid	0.1 g
Sorbitol, liquid (crystallising)	28 g
Water, purified	76.2 g
Total	108.5 g (= 100 mL)

Table 5.15 Sulfadiazine Oral Suspension 100 mg/mL [27]

Sulfadiazine	10 g
Aluminium magnesium silicate	0.54 g
Carmellose sodium M	0.54 g
Citric acid monohydrate	0.63 g
Methyl parahydroxybenzoate	0.07 g
Raspberry essence (local standard)	0.3 g
Sodium citrate	4.7 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	30 g
Water, purified	67.2 g
Total	114 g (= 100 mL)

Table 5.16 Paraffin Oral Emulsion [28]

Paraffin, liquid	5.15 g
Benzoic acid	0.1 g
Citric acid monohydrate	0.1 g
Methylcellulose 15 mPa.s	1 g
Peppermint oil	1 dr
Saccharin sodium	0.005 g
Water, purified	92.7 g

charged particles anions such as citrate ions may also have this effect.

Aluminium and magnesium ions may be added by means of the thickening agent aluminium magnesium silicate. This substance forms a colloidal solution and gives a low concentration cations that keeps the sediment flocculated (see example in Table 5.15).

Citrate ions are usually added in the form of sodium citrate or citric acid. Apart from creating a flocculated sediment they create a buffer. An example of a suspension in which citric acid and citrate are applied is given in Table 5.15.

The choice of the right flocculating substances, the combination and the concentration depend on the properties and concentration of the active substance. Adding too many ions can influence the settling behaviour and the resuspendability even negatively.

The combination of carmellose sodium with aluminium magnesium silicate is a common combination in oral suspensions. Carmellose enhances the viscosity and is easy to process. However, it cannot always avoid a compact sediment. Aluminium magnesium silicate creates an open sediment that is easy to disperse. It also has some viscosity enhancing properties.

The base for oral liquid Ora-Plus® contains a combination of xanthan gum and carrageenan as thickening agents, with citric acid as flocculating agent.

The effectiveness of both combinations of thickening agents and flocculating agent has to be investigated in practice with the active substance concerned. This concerns both the physical and the chemical stability.

5.4.7 Agents for Emulsifying and Solubilising

Emulsions for oral use are predominantly of the type o/w. In that way the disadvantage of messiness and unpleasant taste of lipids is partly overcome. Emulsifying occurs by reducing the droplet size of the lipid phase and increasing the viscosity of the outer phase generally with use of a thickening agent (that lowers the interfacial tension). Thickening agents (see Sect. 5.4.6.3) that are used for emulsifying, such as methylcellulose, hypromellose, methylhydroxylethylcellulose and hydroxypropylcellulose, possess interfacial tension-reducing properties.

An example of an emulsion for oral use is paraffin emulsion (Table 5.16).

Solubilisates are colloidal solutions of a liquid in another liquid that is not miscible with it (see Sect. 18.3.3). The fat-soluble vitamins A, D and E are to be administered as solubilisates to patients with impaired fat absorption, such as patients with cystic fibrosis, to get the vitamins absorbed. Fat-soluble liquid active substances can be solubilised using surfactants, whereby colloidal particles, micelles, are formed. Relatively high concentrations of surfactants are necessary because they have to exceed the critical micelle concentration. Polysorbate 80 (see also Sect. 23.6.4) is

Solubilisates of vitamin A and E may be prepared in a simpler way if other chemical forms of these vitamins are used. Vitamin A is described as a mixture with a solubilisating substance as raw material in the Ph. Eur.: Synthetic Vitamin A concentrate (solubilisate/emulsion). This raw material contains vitamin A, solubilising agent(s) and may contain preservatives and antioxidants.

Vitamin E is available as tocopheryl polyethylene glycol succinate (TPGS). Tocopherol is esterified via succinate to polyethylene glycol. This substance can be dissolved in a high concentration in water under micelle formation. For the formation of micelles no excipient (but a preservative) is needed because the TPGS has surfactant properties (Fig. 5.2).

Fig. 5.2 Structure of TPGS

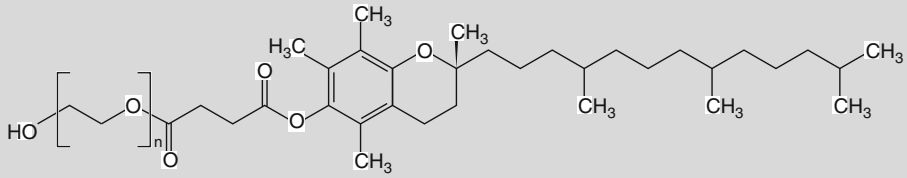

Table 5.17 Vitamin A Oral Aqueous Solution[a] 50,000 IU/mL [29]

Vitamin A concentrate (oily form), synthetic 1,000,000 IU/g	5 g
Citric acid monohydrate	0.24 g
Polysorbate 80	12.5 g
Potassium sorbate	0.3 g
Star anise oil	0.22 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	12.5 g
Water, purified	73 g
Total	104 g (= 100 mL)

[a]This solution is actually a solubilisate

commonly used as a surfactant for pharmacy prepared solubilisates.

The proportion between oil and surfactant has to be determined in practice. In a vitamin A oral aqueous solution containing 50,000 IU/mL the proportion oil:polysorbate 80 of 1:2.5–3 is used (Table 5.17). This appeared also to be applicable to the analogous cholecalciferol oral aqueous solution 50,000 IU/mL.

5.4.8 pH

The pH of an oral liquid is important for the flavour, solubility and stability of the active substance and for preservation. The preferred pH for an oral solution is between 5.5 and 7.5. A pH < 5.5 often tastes better, but may degrade the tooth enamel although the total amount of free acid plays a role as well [30]. A pH above 8 often gives an unpleasant taste.

The solubility of active substances often depends on the pH (see Sect. 5.8.1). By adjusting the pH, a solution or a suspension may be prepared (see Sect. 19.1.1). The pH can affect the stability of an active substance or excipient. For example, the hydrolysis rate of esters depends on the pH (see Sect. 22.2.1). The pH must be taken into account for the preservation of an oral solution. The preservative sorbic acid is only effective at a pH < 5.5 and the preservative methyl parahydroxybenzoate undergoes hydrolysis at pH > 8.

The pH can be adjusted with buffering agents. The most used buffering agents in oral fluids are phosphates or citrates. Citrates may be used for the pH range 3–6, phosphates for the pH range 5–8. To adjust to an even higher pH, trometamol can be used, which as a solid has the advantage above NaOH solution that it can be weighed.

5.4.9 Preservation

Water supports the growth of micro-organisms, therefore oral aqueous solutions, suspensions, emulsions and solubilisates in multidose containers should be preserved. Preservatives may be used for that purpose as well as excipients with preservative properties, such as propylene glycol. See Sect. 23.8 for extensive information on preservatives. Table 5.18 summarises preservatives with properties especially relevant for oral liquids.

The choice of the preservative is determined by the pH, the presence of antimicrobial co-solvents, the presence of a lipid phase and whether, because of the adverse effects, the liquid is intended for adults or neonates or children. It is shown that oral liquids with a pH > 8 are difficult to preserve, apart from giving taste problems.

Table 5.18 Preservatives for Use in Aqueous Oral Liquids

Preservative	pH range	Concentration in the aqueous phase (% g/v)	Suitability for neonates and children
Benzoic acid	<5	0.1–0.2	Not appropriate: incomplete metabolism in neonates; may cumulate in the central nervous system
Ethanol	Whole range	15–20	Not suitable for young children, see Sect. 5.4.5.2: Unpleasant taste should be considered
Glycerol 85 %	Whole range	30	Appropriate, osmotic effect to consider
Methyl parahydroxybenzoate	<8	0.1–0.2	Appropriate in every age group [31]
Propyl parahydroxybenzoate	<8	0.1–0.2	No data in children <2 years, may influence the maturation of the reproductive system [31]
Propylene glycol	Whole range	15	Strict limitation in preterm and term neonates [17]
			Unpleasant taste should be considered
Sorbic acid	<5.5	0.1–0.2	Appropriate in every age group

How to Preserve Antacid Suspensions

The pH of antacid suspensions is between 7.7 and 8.2. This pH range is very unfavourable for the stability and effectiveness of methyl parahydroxybenzoate and no other preservatives are available for that pH range. Propyl parahydroxybenzoate can be added but additional measures are needed to achieve a reasonable shelf life: the use of raw materials with a low bioburden, preventing contamination during preparation, storage in the fridge, small bottles, limited usage period.

5.4.9.1 Methyl and Propyl Parahydroxybenzoate

Methyl parahydroxybenzoate (MOB or methylparaben) is most widely used in oral liquids. As an ester it is stable between pH 3 and 6. Outside these pH limits methylparaben will hydrolyse, which amounts for example to 25 % in 12 months in an oral solution with pH 7.0–7.5 (prednisolone oral solution, see Table 23.23) at room temperature.

At pH 7–8 methylparaben is less stable and also less effective. Propyl hydroxybenzoate can be added to increase the preservative effect. If the pH > 8, methylparaben is of no use any more.

The solubility of methylparaben in water is about 1 in 400 (0.25 %) but will be decreased by the presence of dissolved salts, causing methylparaben to precipitate. In oral liquids usually 0.15 % of the aqueous phase is used, but 0.1 % in the presence of a high concentration of salts (see Sect. 23.8.5).

In chloral hydrate oral solution 100 mg/mL (Table 5.19) methylparaben in a concentration of 0.15 % would precipitate because of the high concentration of chloral hydrate. Methylparaben is not added separately to this solution, it originates from the added marshmallow syrup. The concentration methylparaben in the solution is 0.085 %.

Table 5.19 Chloral Hydrate Oral Solution [32]

Chloral hydrate	10 g
Peppermint oil	0.04 g
Water, purified	10 g
Marshmallow syrup (local standard)	109.9 g
Total	129.9 g (= 100 mL)

Methylparaben must not be combined with polysorbate or used when a lipid phase is present. It forms micelles with polysorbate, making it ineffective. If the preparation contains a lipid phase (in the case of an emulsion or solubilisate), methylparaben will dissolve in it rendering the aqueous phase insufficiently preserved.

Disadvantages of both methyl and propyl parahydroxybenzoate are allergic reactions and an unpleasant tingling sensation experienced by several patients when the solution contacts their tongue.

5.4.9.2 Benzoic Acid and Sorbic Acid

Benzoic acid contains a carboxyl group (pK_a 4–5) making it only effective at pH < 5. It may cause allergic reactions and is notorious for its toxicity in neonates and babies. Because of these disadvantages benzoic acid is rarely used in oral liquids.

Sorbic acid is preferably used at pH 4.5–5.5 and is not related to allergic reactions with oral use. For easy processing and obtaining the right pH, sorbic acid is often applied as combination with potassium sorbate.

Sorbic acid has a more suitable fat-water distribution than methylparaben, which makes it better applicable in emulsions. For solubilisates there is however a problem to overcome because sorbic acid adsorbs onto polysorbate, which is often used as a solubilising agent. Therefore the processed quantity of sorbic acid should be larger than the solubility of sorbic acid in water. Potassium sorbate is used to achieve this. Potassium sorbate is dissolved in water and then converted to sorbic acid using citric acid. Part of the sorbic acid dissolves in the lipid phase and adsorbs to the polysorbate. The free sorbic acid serves to preserve the aqueous phase [33]. See further Sect. 23.8.6.

5.4.9.3 Other Preservatives

Co-solvents such as ethanol, sugars, polyols, propylene glycol and glycerol, also have preservative properties if they are present in sufficient concentration (see also Sect. 23.3). Propylene glycol at 15 % is not quite as effective as sorbic acid or methyl parahydroxybenzoate and tastes unpleasant. Glycerol 85 % in concentration 30 % preserves less well than propylene glycol but tastes slightly sweet.

Sucrose (present in syrups, see Sect. 23.4.4) preserves in concentrations above 63 % m/v. Usually syrups contain 0.1–0.15 % methyl parahydroxybenzoate.

Ethanol preserves in concentrations above 15 % v/v. If sufficient ethanol is present in oral preparations, no other preservatives are needed. See Table 5.19 however for the restrictions for oral liquids for children.

5.4.10 Excipients and Children

As mentioned in Table 5.18, some of the excipients are not suitable for children. The information available on the acceptability of excipients for paediatric age groups is sparse and distributed over various sources. Hence, European (Eu) and United States (US) Paediatric Formulation Initiatives (PFIs) are collaboratively creating a database Safety and Toxicity of Excipients for Paediatrics (STEP). This STEP database provides specific safety and toxicity data on target age groups, route of administration, treatment duration, concentration, maximum daily excipient intake and exposure extracted from selected information sources. The data in the STEP database would be derived from publicly and commercially available information sources together with any information shared by the industry. It will be accessible freely online thereby facilitating paediatric formulation development.

Currently, a pilot version of the STEP database compiling the data for 10 prioritised excipients, for example propylene glycol, ethanol and benzyl alcohol, is in process. If the pilot is proved to be successful, the database will be expanded to a fully released database and will eventually include many excipients [34].

5.4.11 Flavour

Dissolved substances directly touch the taste buds, much heavier than when present in oral solids. An unpleasant taste can give, especially in children, a tremendous resistance to taking the medicine. This makes taste masking of oral liquids very important. Taste masking in oral liquids is often needed to improve palatability of the medicine. Children have a well-developed sensory system for detecting tastes, smells and chemical irritants. They are able to recognise sweetness and saltiness from an early stage and are also able to recognise a sweet taste in oral liquids and the degree of sweetness. Children seem to prefer sweeter tastes than adults do. The unpleasant taste of an active substance, e.g. bitterness or a metallic taste, is, therefore, often masked in an oral liquid by the use of sweetening agents and flavours. However, a child's preference for particular flavours is determined by individual experiences and culture.

The target for taste masking needs not necessarily to be good-tasting medicines; it should simply be a taste that is acceptable [35].

The taste can be improved by the addition of flavouring agents, by shielding the taste buds and by adjusting the taste of the active substance.

5.4.11.1 Flavouring Agents

A flavouring agent includes the existing taste in a flavour that is experienced as less unpleasant. Apart from a suitable flavour also a smell suiting the basic taste has to be added. For example, if an unpleasant bitter or sour tasting oral liquid has a smell that suggests the bitter, respectively sour taste, the preparation will be experienced as less unpleasant. The colour may also play a part by arousing a particular taste.

For taste improvement some general principles can be applied:

- Sour flavours can be improved with acid flavours probably in addition with sweet flavourings. Also substances that suggest a sour taste by smell or colour (for example, lemon + yellow or raspberry + red) can be used.
- Bitter flavours can be improved with flavourings with a pleasant bitter taste, probably in addition with sweet flavourings, for example chocolate/vanilla.
- Sweet flavours can be improved with peppermint, probably in combination with sour or bitter flavours. Corrigents that suggest a sweet taste by smell or colour can be added, such as vanilla and fruits.
- Salty flavours can be improved with ethanolic anise extract or liquorice or with tomato juice.

Non-cariogenic sweeteners and flavours are preferred.

Most essences only influence the odour; they influence the taste if they are combined with a basic taste (usually a sweet substance).

Table 5.20 summarises taste improving substances.

Table 5.20 Substances that may improve specific tastes

Sweet	
Sugars	Sucrose, glucose, fructose
Sugar containing products	Syrups (10–20 % of the oral liquid), honey, lemonade, fruit juices
Polyols	Sorbitol (available as sorbitol solution 70 %), mannitol, xylitol, glycerol
Artificial sweeteners	Saccharin sodium (0.01–0.5 %; mostly 0.1 %), aspartame, acesulfame potassium and sodium cyclamate
Sour	
Dilute organic acids	Tartaric acid, but mainly citric acid and carbonic acid (for example created by effervescent powders)
Products with acids	Raspberry syrup, poppy syrup and diluted inorganic acids such as dilute hydrochloric acid, dilute sulfuric acid and dilute phosphoric acid
Bitter	
Orange peel	Orange peel syrup, orange peel tincture
Cinnamon	Cinnamon syrup or ethanolic extracts
Cacoa	Cacoa and cacoa syrup
Other	
Essential oils	Peppermint oil (1–2 drops per 100 mL), anise oil, lemon oil, cinnamon oil, sweet orange oil
Other volatile, aromatic substances	Vanillin, piperonal
Essences	Orange, cherry, raspberry, lemon, banana, vanilla, vanilla-cocos, cognac
Ethanol or alcoholic oral liquids	Cognac, brandy

In literature standard concentrations may be stated but they usually refer to foods and beverages, not to bad tasting active substances. The necessary concentration very much depends on the taste and concentration of the active substance, pH etcetera, and only can be determined experimentally. For testing the performance of taste correction specific methods have been developed.

For children up to about 4 years sweet oral liquids with banana or raspberry essence are preferred [36]. A midazolam hydrochloride oral solution (Table 5.21) usually applied in the premedication of children before surgery or clinical diagnostics contains sucrose as sweetening agent and raspberry flavour, which is favoured by younger children.

Syrups (see Sect. 23.4.4) are widely used for the improvement of unpleasant tasting active substances. A disadvantage of using sucrose-containing syrups is that these are cariogenic: bacteria in the mouth convert sucrose into acids, which cause cavities.

Another disadvantage is supposed to be the caloric value that diabetics have to take into account. However, with the increased use of blood glucose monitors and relatively simple insulin delivery devices it has become easier to match the carbohydrate intake to the blood sugar level, especially for patients with type I diabetes. Apart from that the contribution of sugar through medicines is small and it is actually not necessary to develop special sugar-free medicines for diabetics.

A 70 % sorbitol solution can be used for its sweetness if no sugar is desired. It has the disadvantage of being an osmotic laxative because it is only absorbed slowly from the gastrointestinal tract. To avoid this effect the daily allowance for adults must be limited to 20 g. The sorbitol dose that leads to diarrhoea in children is 0.5 g/kg [38].

Table 5.21 Midazolam Hydrochloride Oral Solution [37]

Midazolam hydrochloride	0.222 g
Sucrose	25.0 g
Potassium sorbate	0.15 g
Citric acid, anhydrous	0.2 g
Raspberry essence	0.11 g
Water, purified	83.918 g
Total	109.6 g (= 100 mL)

Some patients consider the energetic value of sugars or sorbitol as a problem and demand artificial sweeteners in their medicines. Their effect depends very much on the active substance in the oral liquid and cannot be derived from usual concentrations in soft drinks.

Investigations of the Laboratory of Dutch Pharmacists regarded the replacement of sugar syrup in several oral solutions as pharmacy preparations. It was shown for instance that in the 'sweetness area' of 10–100 % sugar syrup the combination sodium cyclamate with acesulfame potassium (4:1) tastes good, while the corresponding sweetness amount of sodium cyclamate as well as the corresponding sweetness amount of saccharoid sodium taste bitter. The latter also applies to the combination saccharoid sodium/sodium cyclamate 1:10.

Table 5.22 ADI-value of some Sweeteners [39]

Sweetener	ADI
Acesulfame potassium	9 mg/kg
Aspartame	40 mg/kg
Sodium cyclamate	8 mg/kg
Sodium saccharin	2.5 mg/kg

For the application of artificial sweeteners in medicines that are taken for a long time, the 'Acceptable Daily Intake' (ADI) must be taken into account [39]. For some common sweeteners the ADI-values are shown in Table 5.22.

5.4.11.2 Shielding the Taste Buds

A simple method for improving unpleasant tastes is local anaesthesia of the taste buds. This can be achieved by taking the oral liquid immediately from the fridge or by adding menthol (peppermint oil, peppermint syrup). Menthol has a slight local anaesthetic effect. Taking an oral liquid with fruit juice, lemonade (syrup), fruit concentrate or food also masks the taste buds. Increasing the viscosity by syrups, gels and emulsions is a last option. Enhanced viscosity decreases stimulation of the taste buds and change the 'taste experience' of an oral liquid.

5.4.11.3 Adjusting the Taste of Active Substances

An alternative approach for the improvement of the taste of an oral liquid is to improve the taste of the active substance. This can be achieved by physico-chemical changes:

- Formulating a suspension from the slightly soluble salt or less soluble component (see Sect. 18.1). Examples are: taking ferrous fumarate instead of ferrous sulfate, taking amitriptyline pamoate [40] instead of its HCl salt, which is also applicable to other phenothiazines. Of course bioavailability has to be assessed anew.
- Decreasing the dissociation. As an example: the bitter taste of magnesium sulfate is caused by the magnesium ion. The addition of dilute sulfuric acid reduces the dissociation and the number of free magnesium ions, thereby improving the taste.
- Complex formation. An example: complex formation of ferrous ion with citric acid, which reduces very much the concentration of ferrous ions.

5.4.12 Colouring Agents

Colouring agents, as flavourings, are used to make the medicine more acceptable for the patient. Sometimes colouring agents are used to prevent mix-ups, which however is contrary to the principle that the label always should be read well. Colouring agents are also used to protect light-sensitive medicines or to prevent patients' concerns about irrelevant degradations. It should of course not be used to mask a relevant decomposition (see Sect. 22.2.2).

Only water-soluble colouring agents are processed in oral liquids (Table 23.11). They are, whether or not through a dilution, dissolved in the preparation. Colouring agents that do not dissolve in water (often inorganic substances: pigments) cannot be processed in liquid forms.

5.4.13 Incompatibilities

Incompatibilities in oral liquids can take place between active substances and excipients, among active substances and among excipients. It may regard to formation of insoluble salts or adsorption by thickening agents. Another type of incompatibility is the change of pH brought about by an active substance, causing the preservative becoming ineffective. Well-known is the incompatibility of negatively charged thickening agents (carmellose sodium, xanthan gum) with positively charged active substances or excipients.

Incompatibilities may become relevant from a solution that contains more of the dissolved substance than could be dissolved by the solvent under normal circumstances (supersaturated). To avoid these incompatibilities the order of dissolving and mixing should be so that no high concentrations are created during preparation. For example the relative incompatibility (precipitation) between lidocaine cation and phosphate anion can be circumvented by dissolving lidocaine hydrochloride after sodium phosphate has been dissolved instead of adding both substances to purified water at the same time. Substances of vegetable origin can cause precipitations and discolouration.

5.4.14 Chemical Stability

See Chap. 22 for information on Stability. Dissolved substances are more accessible and thus sensitive to degradation than if present as particles in suspension. Most stability issues arise for that reason in aqueous solutions. The two main degradation reactions are hydrolysis (see Sect. 22.2.1) and oxidation (see Sect. 22.2.2). The rate and degree of hydrolysis is pH-dependent.

In prednisolone sodium phosphate oral solution (see Table 23.23) the main degradation reaction is hydrolysis of the corticosteroid-phosphate ester catalysed by hydrogen ions. The phosphate group is split off. At pH 7–8 this hydrolysis is minimal [28], therefore the

(continued)

pH of the oral solution in Table 23.23 is 7.1. At this pH, however, the preservative methyl parahydroxybenzoate hydrolyses as well. After 12 months, the concentration methylparaben has dropped by 25 %.

Oxidation, in oral liquids, in practice is inhibited by removal of oxygen from water by boiling, reduction of headspace by completely filling of bottles, addition of a chelating agent (sodium edetate) for the removal of catalysing traces of metals and the addition of antioxidants, such as ascorbic acid (see Sect. 22.2.2).

Sugars may also protect against oxidation through their reducing properties. In addition, when using a concentrated sugar solution less oxygen will be dissolved in it.

Examples of oxidation reactions in oral liquids can be found at ferrous salts, morphine salts and phenothiazine derivatives.

Ferrous salts are easily oxidised in solution into the inactive ferric salts. This can be inhibited by complex formation with citric acid, addition of reducing sugars, reducing the amount of air oxygen by completely filling of the bottles and by exposing to light.

Morphine salts are converted to the inactive pseudomorphine at pH $>$ 4.5 in the presence of oxygen. Therefore in the example formulation of Table 5.23 the solution is acidified with citric acid to pH 2.5–3.5. Disodium edetate is added for further protection against oxidation.

Phenothiazine derivatives and related compounds oxidise rapidly if dissolved. This degradation can be inhibited by the addition of 0.5 % ascorbic acid.

5.4.15 Physical Stability

Oral solutions can be physically unstable through crystallizing of dissolved solids, which in practice may occur when solutions are put in the fridge. The solubility of most active substances is lower at low temperature than at higher temperatures (see also Sect. 18.1). And if they are dissolved in a concentration that is just below their solubility crystallising will easily occur. With low-dosed substances any crystals or precipitate will not always be visible. Crystallisation may lead to underdosing and, at a later stage, to an overdose as the settled crystals are taken at the last dose. This is the reason why some oral liquids need to be stored at room temperature (15–25 °C). Crystallisation and storage temperature not only concern the active substances but also preservatives. The crystallisation of methyl parahydroxybenzoate is described in Sect. 5.4.9.

Suspensions are physically unstable preparations: sedimentation occurs at storage. The monograph Unlicensed medicines in the British Pharmacopeia describes how to assess the settling and resuspendability (see Sect. 32.7.2).

Table 5.23 Morphine hydrochloride Oral solution 1 mg/mL [41]

Morphine hydrochloride	0.1 g
Citric acid monohydrate	0.04 g
Cognac essence (local standard)	0.17 g
Disodium edetate	0.1 g
Ethanol (96 %)	8.1 g
Methyl parahydroxybenzoate	0.15 g
Water, purified	90.6 g
Total	99.3 g (= 100 mL)

5.4.16 Containers and Labelling

Oral liquids are usually delivered in glass or plastic bottles. Generally brown glass is used to protect the content from light. Glass vials may be equipped with a pouring ring. General guidelines for the packaging and labelling are mentioned in Chap. 21. Oral suspensions as well as oral emulsions have to be delivered in bottles that leave enough headspace for shaking. A suspension can also be filled into single-use (oral) syringes with a closure but only if the settling behaviour allows easy redispersion.

Packaging in Specific Situations

Some ferro salts are delivered in bottles of uncoloured glass because oxidation of ferrous to ferric ion is inhibited by light.

For supplying oral liquids such as methadone oral solution to drug addicts single-use plastic cups have to be preferred to prevent abuse. They cannot pretend they have broken a glass bottle or to be tempted to sell part of the liquid.

An oral gel (for instance a hydrogel with lidocaine hydrochloride) is best packed in a plastic bottle with spout or dosing dispenser because of its rather high consistency.

The label must meet the requirements as mentioned in Sect. 37.3.1. The label of suspensions and emulsions should mention “shake well before use”.

5.4.17 Dosage Delivery Devices

Most liquid oral medicines are dosed in millilitres. These are measured with a measuring cup (24.4.19.3) or an oral syringe (see Sect. 24.4.16). The volume of the dosage device

or a multiple thereof should match the dosage or should be clearly readable in millilitres. See Sect. 37.4.3.

Some liquid oral medicines are dosed in drops. This may be practical but the doses that are administered in the form of drops should meet the requirements for uniformity of weight and content. For pharmacy preparations the requirements for oral drops of the Ph. Eur. cannot be achieved with the available dropper devices. See further Sect. 24.4.19.4–6.

5.4.18 Storage

See Sect. 22.7 for the general approach. For standard preparations the storage temperature and shelf life of an unopened container and after opening (in use period) should be determined during the design phase. For non-standardised preparations with a reliable preservation but with an uncertain chemical or physical stability it is recommended to limit arbitrarily the shelf life after opening to a maximum of 1 month.

If preservation is not possible due to hypersensitivity or toxicity (for example in premature infants or when a large volume is taken at once), or very impractical (if preparing large amounts of bottles cough syrup from a concentrate), the oral liquid should not be kept longer than 14 days, and preferably in the refrigerator. Some oral preparations have to be stored in the refrigerator (2–8 °C) because of the chemical or microbiological stability. Storage in the refrigerator is not always possible if active substances and excipients are about to crystallise (see Sect. 5.4.9). In addition, preservatives work less well at low temperatures (see Sect. 23.8).

5.5 Method of Preparation

The preparation of oral liquids generally follows the basic operations such as dissolving, mixing and dispersing described in Chap. 29. The method depends on the characteristics of the formulation: solution, suspension, emulsion. This section discusses as well the increasing non-availability of the active substance as a raw material.

Preparation processes (or steps or unit operations) are treated as well as in-process controls, release control and quality requirements.

5.5.1 Availability and Pre-treatment of the Active Substance

5.5.1.1 Pulverising the Raw Material

If the active substance is available as raw material, it sometimes has to be pulverised to obtain smaller particles. They may be needed for increasing the dissolution rate when processed for oral solutions, or for improving homogeneity and decreasing settling rate when processed in an oral suspension. For pulverising see Sect. 29.2.

5.5.1.2 Use of a Solution Licensed for a Different Route

If there is no raw material available but a liquid preparation is available with the same active substance as licensed product, it may be able to use that preparation. A parenteral preparation is usually the best option. But especially if the oral liquid is meant for children, be careful with some excipients of which children could be especially sensitive.
Points to work out when adapting:

- Does the demanded concentration require dilution?
- Are the excipients safe?; will particularly complexing agents, antioxidants, co-solvents and organic solvents irritate the gastrointestinal tract or, if administered by an enteral feeding tube, will they be compatible with the tube components?
- Will the shelf life be different?; will active substances in parenterals that are filled under nitrogen oxidize after opening?
- Will the pH of the parenteral solution cause irritation or decrease absorption?

5.5.1.3 Adapting Oral Solid Dosage Forms

If the active substance is not available as raw material it may be processed from oral solid dosage forms by adapting those. Not all solid dosage forms however are fit for such an operation. Tablets with a gastro-resistant coating or modified-release tablets should not be crushed unless the product information confirms its suitability, see further Sect. 4.10.7.

If there is no problem in adapting the oral solid, several methods of processing present themselves: crushing or pulverising in a mortar, (half-)mechanically pulverising, dispersing in water.

5.5.1.4 Crushing and Pulverising Oral Dosage Forms

Crushing a tablet in a mortar has some disadvantages:

- Loss of active substance because of crushed particles flying off or because of adherence at the mortar's wall.
- The operator may get exposed to the active substance; hazardous substances demand specific ventilation or the use of personal protecting equipment (see Sect. 26.4.1).
- The need of muscular strength for crushing; RSI (repetitive strain injury) problems may occur in nursery homes if caregivers have to crush tablets for many patients.

These drawbacks are less severe if a mechanical crusher or pulveriser is used such as the Pill Drink (see Fig. 37.5).

5.5.1.5 Dispersing in Water

Oral solids can be dispersed in water. Effervescent tablets immediately disperse in water. Granulates and granules, tablets and orodispersable tablets (melting tablets) are to be dispersed by shaking with lukewarm water (35 °C), for instance 20–30 mL. If dispersing takes more time, as is the case with coated tablets, it is better to use water with a higher temperature. Capsules should be opened before dispersing.

The solubility of the active substance determines if the active substance will be dissolved or dispersed, see Sect. 5.4.2. Because most tablet excipients are insoluble, the oral liquid will become a suspension of excipients anyhow.

5.5.2 Dissolving

In general, soluble solids, such as buffers and antioxidants, are dissolved separately in the vehicle. The solution process can be speeded up by stirring, by using smaller particles (see Sect. 23.5), or by heating if the active substance withstands it. Dissolving by heating of substances that are not soluble at room temperature is not reasonable. These substances will crystallise once the 'solution' is cooled down.

In many oral liquids the preservative methylparaben is used. Its dissolution rate can be increased by heating or by using concentrated solutions in organic solvents such as propylene glycol (see also Sect. 23.8.5).

Dissolution under boiling improves the microbiological quality of the water. The risk of superheating (followed by boiling over) however, causing breakage of the glassware, may overshadow this advantage especially when large vessels are involved. The addition via a concentrated solution is preferred in practice.

Methylparaben Concentrates in Practice

Methylparaben may be used as a concentrate, such as: methyl parahydroxybenzoate 15 g with propylene glycol 91 g (= 100 mL). Although weighing a quantity is generally to be preferred over measuring the volume (see Sect. 29.1.2), in case of the addition of a methylparaben concentrate to oral liquids, volume measuring has some advantages. These advantages become clear by the following directions.

- The liquid has to be shaken immediately after the addition to get the methylparaben dissolved; therefore the necessary amount of methylparaben needs to be weighed or measured beforehand.
- The low necessary amounts would require a balance able to weigh milligrams.

Mind that the concentrate has to be transferred quantitatively, which is easier with a plastic syringe with plunger than from a (glass) weighing beaker.

Rinsing (with propylene glycol; water causes precipitation in the syringe or beaker) is not to be recommended because it will increase the amount of propylene glycol of the liquid.

The concentrated methylparaben solution can be added to a volume of maximal 500 mL at once, after which the liquid should be shaken vigorously immediately. Processing larger volumes manually may lead to precipitation due to supersaturation. In that case it is better to add the methylparaben solution gradually while continuously mixing.

If sorbic acid is used as preservative, it is dissolved in water under boiling. During dissolution, the vessel must be covered to avoid evaporation of the sorbic acid with steam.

After processing all materials, the liquid should be made up with the solvent to 100 % volume. This is because usually a volume unit is dosed. However, it is highly recommended to state the required end weight because this is more accurate and weighings can be recorded unmistakably. If the specific gravity is not known, the liquid has to be made up to volume, preferably by using a measuring cylinder.

5.5.3 Mixing

Different liquid excipients are mixed with each other if possible. Volume amounts are preferably converted to weights (see Sect. 23.1.6). The liquids can be directly weighed into the vehicle. If necessary the quantities can be measured with a measuring cylinder or a pipette and transferred into the bottle. The measuring cylinder should be rinsed. The pipette is not rinsed, except for highly viscous liquids (Sect. 23.1.6).

For (highly) viscous liquids additional attention has to be paid to the mixing process because these liquids are difficult to mix. If 'strings' in the solution are visible, it is a sign that the solution is not sufficiently homogenised.

Insufficient mixing at the preparation of a mixture of phytomenadione with arachis oil (for the oral solution of Table 5.24) caused large variations of content between the vials of the same batch. Only if phytomenadione was mixed with small portions of arachis oil and the homogeneity was checked (inhomogeneity may look like trails or strings) after each addition, sufficient homogeneity was obtained. By mixing in a translucent barrel a better visual control on the homogeneity after mixing is possible.

(continued)

Table 5.24 Phytomenadione Oral Solution 10 mg/mL [42]

Phytomenadione	1 g
Arachis oil, refined	90.2 g
	91.2 g (= 100 mL)

5.5.4 Dispersing

Dispersion will take place in a mortar or by means of a rotor-stator mixer, see further Sect. 29.7.1. An alternative method may be the use of the precipitation method (see Sect. 29.2.3).

In most oral liquids thickening agents are used. They have to be hydrophilised and dispersed in the liquid before they can be dissolved. If not, lumps may be created that block the dissolution process. The processing of thickening agents is discussed in Sect. 23.7.

An example of a method for dispersing is given in Table 5.25. The active substance nitrofurantoin is hydrophilised by mixing it with silica. The thickening agents are processed into a base solution. Subsequently the hydrophilised substance is dispersed in that base. The example uses a rotor-stator mixer preparation method.

5.5.5 Emulsifying

For the small scale preparation of oral emulsions the liquid active substance is added to base gel. The base gel can be prepared by processing a suitable thickening agent in the aqueous phase. For the dispersion method of the thickening agent see Sect. 23.7. The liquid that has to be emulsified is added drop by drop to the base gel under mixing. With a rotor-stator mixer a finer divided dispersed phase is obtained. Water is added in small portions and mixed carefully for the dilution and making up to the right volume.

5.5.6 Solubilising

At small scale solubilisates can be prepared by mixing firstly the surfactant and the solubilising liquid in a mortar. Subsequently this mixture is mixed with sugar syrup and diluted gradually with parts of the aqueous phase in which the potassium sorbate has been dissolved. Then a solution with citric acid is added and filled up to the right volume. The mortar should be carefully degreased prior to the preparation to avoid that the extra fat prevents the formation of a solubilisate. But aggregates may be formed instead of micelles if the proportion between the amounts of surfactants and fat has been disrupted, for example by incorrect calculation, inaccurate weighing or the use of a greasy mortar. These aggregates are larger than the micelles.

5.5.7 In-Process Controls

For the preparation of oral solutions and suspensions the following in-process controls may be appropriate:

- Record the tare or calibrate the utensils if the preparation needs to be complemented on weight or volume.

Table 5.25 Nitrofurantoin Oral Suspension 10 mg/mL [43]

Nitrofurantoin macrocrystals (USP)	10 g
Aluminium magnesium silicate	9 g
Carmellose sodium M	9 g
Citric acid monohydrate	0.67 g
Methyl parahydroxybenzoate	0.67 g
Silica, colloidal anhydrous, compressed	2.5 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	336 g
Water, purified	703 g
Total	1,071 g (= 1,000 mL)
Method of preparation with a rotor-stator mixer:	
Dissolve the methyl parahydroxybenzoate in 600 mL purified water while heating to 100 °C	
Disperse the colloidal aluminium magnesium silicate in the hot solution of methyl parahydroxybenzoate	
Disperse the carmellose sodium as well	
Dissolve the citric acid monohydrate in about 50 mL purified water	
Mix the citric acid solution with the solution: suspension base	
Triturate the nitrofurantoin macrocrystals with the colloidal anhydrous silica in a rough mortar	
Disperse this mixture of solid substances in the sugar syrup	
Mix the solid substances-syrup mixture with the suspension base	
Make up with purified water and mix	

- Check on replenishment of evaporated water.
- Measurement of the temperature, for instance, at the dissolution under heating of thermolabile substances and when checking for sufficient cooling.
- Record the start time and end time of cooling down (in the refrigerator) of some gels and sometimes at dissolution under heating.
- pH value of aqueous preparations as a check on the correct composition; as such an in-process control the pH measurement may be performed with a pH indicator strip.
- Clarity after each dissolution process.
- Homogeneity (absence of mixing strings) after mixing liquids.
- Total weight or yield, the total weight after supplementing with water or other solvent.
- Control of cleaning the utensils after use.

In addition, for suspensions, the following in-process controls may be useful:

- Checks for the absence of lumps or agglomerates; a simple visual inspection may be sufficient; if using a rotor-stator mixer, there should not remain any lumps on the shaft.
- A visual test on homogeneity after mixing.

In addition, for emulsions, the following in-process controls may be useful for testing the dispersion homogeneity:

- The absence of large oil drops on the surface: a simple visual inspection is sufficient to determine this.
- A visual test on homogeneity or evenness of the mass.

In addition for solubilisates:

- A solubilisate should be clear or slightly opalescent (not resembling diluted milk).

5.5.8 Release Control and Quality Requirements

See Chap. 32 and Table 32.2 for background information and an overview.

Oral liquid preparations should be checked after preparation and packaging on appearance, labelling and container. Depending on the type of preparation the clarity, resuspendability or colour additionally should be checked.

5.5.8.1 Solutions

Solutions should be clear and practically free of particles. The oral liquid should be colourless unless an active substance or excipient has its own colour.

Some solutions for oral use cannot meet the requirement of clarity. They may be lightly opalescent due to insoluble ingredients of herbal origin. Cough syrup in the Netherlands is for instance made from raw glycyrrhizae extract that contains small amounts of water-insoluble substances. It also contains ethanolic anise extract that not fully mixes with water and turns the liquid lightly opalescent.

5.5.8.2 Suspensions

The monograph Unlicensed Preparations of the British Pharmacopoeia gives quality requirements for oral suspensions. See also chapter Quality requirements, sections on particle size (Sect. 32.11), dissolution (Sect. 32.10) and resuspendability (Sect. 32.13). As is said in Sect. 32.1 these qualities are mainly design qualities and should be defined specifically per product.

Suspensions should be homogeneous and well resuspendable and not settle (too) fast. Absence of lumps can visually be checked after shaking. To determine the homogeneity of oral suspensions a method is described in the British Pharmacopoeia (see Sect. 32.7.2).

5.5.8.3 Emulsions

Emulsions are visually checked for homogeneity and evenness. They should not contain large droplets and no phase separation should occur. The drop size of emulsions can eventually be measured with particle counters, see Sect. 35.9.3.

5.5.8.4 Solubilisates

A solubilisate is clear to weak opalescent and contains no particles. If aggregates are formed instead of micelles the solubilisate will not be clear but has the appearance of (diluted) milk.

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Pulmonary

6

Anne de Boer and Ernst Eber

Contents

Abstract

The two main determinants for medicine deposition in the respiratory tract are the aerodynamic size distribution of the aerosol and the manoeuvre with which the aerosol is inhaled. They govern the mechanisms that are responsible for particle deposition in the lungs. By varying the inhalation manoeuvre, not only the distribution in the airways for the same aerosol is changed; in many cases also the amount and properties of the delivered fine particle dose are affected. The complex interplay between inhalation manoeuvre, aerosol properties and site of deposition has led to many misconceptions regarding the best inhaler choice for individual patients and the way these inhalers need to be operated to achieve optimal therapy for the patient. In this chapter the medicine deposition mechanisms for inhaled aerosols are explained as functions of the variables involved. In addition, the working principles of different inhaler types are described and it is discussed how their performance depends on many inhalation variables. Finally, some persistent misconceptions in the literature about the most preferable dry powder inhaler properties and performance are unravelled.

Keywords

Deposition mechanisms • Inhalation manoeuvre • Pulmonary administration • Pulmonary drug delivery • Therapeutic aerosol • Biopharmaceutics • Particle size • Dry powder inhaler • Metered-dose inhaler • Nebuliser • Novel liquid inhaler

Based upon the Chap. 28 Luchtwegen by Anne de Boer and Liesbeth Ruijgrok in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_6,

6.1 Orientation

Pulmonary administration of medicines currently has the primary objective to achieve local effects in the respiratory tract of patients with chronic diseases like asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF). For half a century, inhalation therapy has been the cornerstone in the management of these diseases and the often life-time therapies aim to suppress inflammatory processes and bacterial infection in order to reduce hospitalisations and to improve the patient's quality of life. They also give relief to the patient in moments of bronchoconstriction. The advantages of pulmonary administration of medicines for local treatment are well known. The active substances are delivered directly to the site of action which leads to a faster response than via the systemic route. It may also result in higher local active substance concentrations and this could reduce the total dose by as much as a factor 10 compared to oral or intravenous administration. This has the advantage that systemic side effects are reduced and in combination with being a non-invasive method of administration, inhalation therapy may lead to better patient compliance.

More recently, it has been recognised that pulmonary administration of medicines may be a good alternative for other therapies too. The respiratory tract is the port of entry for many bacteria and viruses and infectious diseases like influenza, tuberculosis and measles which can be prevented or treated effectively with inhaled vaccines, antibiotics and anti-viral medicines respectively. Lastly, the respiratory tract can be used for delivering systemically acting medicines which are not effectively absorbed by the gastro-intestinal tract or are rapidly metabolised by the first-pass-effect in the liver. Inhalation can potentially replace the more invasive parenteral routes of administration used for these active substances to increase their bioavailability and the adherence to therapy. An example is loxapine for acute treatment of agitation in patients with bipolar disorder or schizophrenia which has only 30 % bioavailability after oral administration, versus 90 % after intramuscular injection. Very recently (2012), approval for an inhaled loxapine formulation has been received which has a very high absorption of $>$ 90 % within seconds (Adasuve®, Alexza Pharmaceuticals). Currently many more devices and formulations for such new applications are in development or being tested and it may be expected that in the very near future several of them will be introduced to the market. Because most inhaled products are registered combinations of an active substance or a combination of substances and a suitable administration device, their manufacturing is not described in this chapter. Instead, their principles of operation are explained in relation to the variables that influence their performance. Basically these variables are the same as those controlling particle deposition in the human respiratory tract and the underlying mechanisms for that will be discussed as well.

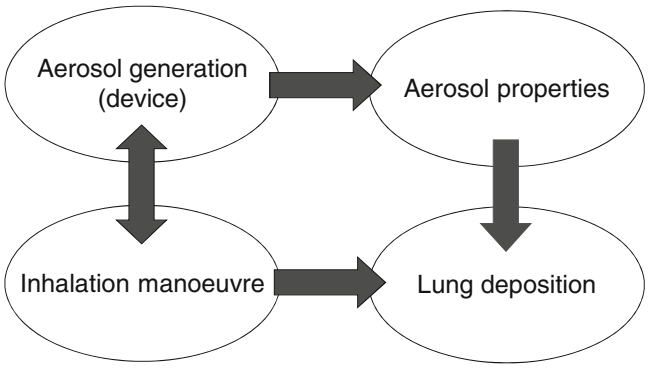

Fig. 6.1 Principle variables and interactions in pulmonary administration of medicines

In contrast with oral administration of tablets or capsules, pulmonary administration is a complex process with many variables involved as well as several interactions between these variables depending upon the type of aerosol generation device used. The most basic scheme of variables and interactions is presented in Fig. 6.1.

For many inhalation devices, the inhalation manoeuvre has an influence on the aerosol generation process. Either the air stream through the aerosolisation device delivers the energy for the aerosolisation process (e.g. for passive dry powder inhalers), or it alters the aerosol properties from the device (e.g. by coalescence or evaporation of droplets from nebulisers and metered-dose inhalers). The aerosol generation device may also influence the inspiratory flow manoeuvre by its resistance to airflow. A high resistance limits the flow rate to be achieved and this influences the deposition pattern in the respiratory tract in a positive way. Generally, a poor understanding exists regarding the precise role of airflow resistance, flow rate and aerosol properties in pulmonary therapies particularly with dry powder inhalers. Therefore, it is the aim of this chapter not only to explain the influence of the inhalation manoeuvre on the working principles of various aerosol generation devices and the mechanisms that govern aerosol deposition in the respiratory tract, but also to unravel some persistent misconceptions.

Administration devices for medicines used to treat asthma and COPD are prescription products, with an exception for some nebulised (medicine) formulations. Medicines such as amphotericin B or antibiotics (colistimethate sodium, tobramycin sulphate or gentamicin) for nebulisation in CF therapy are sometimes still partly prepared by hospital pharmacists, and so are nebulised solutions for bronchial challenge testing. Although product formulation and the method of preparation of formulations for inhalation are not the main subjects of this chapter, recommendations are given in the subparagraphs about nebulisation.

6.2 Definitions and Terms

6.2.1 Definitions in the European Pharmacopoeia: Preparations for Inhalation

The European Pharmacopoeia (Ph. Eur.) describes preparations for inhalation as liquid or solid preparations intended for administration as vapours or aerosols to the lung to obtain a local or systemic effect. These preparations may contain one or more active substances and, depending on the type, also propellants, co-solvents, diluents, antimicrobial preservatives, and solubilising and stabilising agents that do not adversely affect the functions of the mucosa of the respiratory tract or its cilia. The Ph. Eur. refers to three types of administration devices for inhalation preparations: nebulisers, pressured Metered-Dose Inhalers (MDI) and Dry Powder Inhalers (DPI). An appropriate size distribution has to be delivered to the patient so that a significant fraction is deposited in the lung and fine particle characteristics are determined by one of the methods for "Aerodynamic assessment of fine particles" in the Ph. Eur. The Ph. Eur. distinguishes between "Liquid preparations for inhalation" and "Powders for inhalation".

The liquid preparations for inhalation are divided into (A) preparations intended to be converted into vapour, (B) liquid preparations for nebulisation and (C) pressurised metered-dose preparations for inhalation. They are added to hot water to obtain inhalable vapours or converted into aerosols by continuously operating nebulisers or metered-dose nebulisers, and they can be solutions, suspensions or emulsions. They may be prepared by dilution of concentrated preparations or by dissolution of powders. The pH of liquid preparations for use in continuously operating nebulisers has to be within the range between 3 and 8.5. Suspensions or emulsions have to be readily dispersible on shaking and remain sufficiently stable to enable the correct dose to be delivered.

Powders for inhalation are not defined other than that they are presented as single-dose or multidose powders and that the active substances may be combined with a suitable carrier to facilitate their use. If the powder is for a single-dose (pre-metered) inhaler, the device is loaded with powders pre-dispensed in capsules or other suitable pharmaceutical forms. For inhalers using a powder reservoir, individual doses are isolated from the bulk with a metering mechanism within the inhaler.

Important for all different preparations and delivery devices is that they meet the requirements for uniformity of the delivered dose and the number of deliveries per inhaler for multidose inhalers. Also the fine particle dose has to be tested and calculated, but there are no specifications in the Ph. Eur. to meet this most important parameter. Some specific terms and definitions related to pulmonary administration of medicines are given and explained in this paragraph. For various terms different definitions or explanations are given in the literature and specific product information leaflets and it is important to recognise the implications of that.

6.2.2 The Other Definitions

6.2.2.1 Adhesive Mixture

An adhesive mixture is a type of formulation for micronised active substances for inhalation in which the small active substance particles adhere by natural forces (mainly Van der Waals forces) to the surface of much larger carrier (or host) particles.

6.2.2.2 Aerodynamic Diameter (D_A)

The aerodynamic behaviour of aerosol particles depends on their diameter, density and shape. To compare the behaviour of particles that have different properties with each other, the aerodynamic diameter (D_A) has been introduced, which standardises for particle shape and density. By definition the aerodynamic diameter of a particle is the diameter of a sphere with unit density having the same terminal settling velocity as the particle in consideration. Only for aqueous droplets with a spherical shape and unit density the aerodynamic diameter equals the geometric diameter. For non-spherical particles, the aerodynamic diameter can be expressed in terms of equivalent volume diameter (D_E), particle shape factor (χ) and particle density (ρ) (see definitions): $D_A = D_E.(\rho/\chi)^{0.5}$

6.2.2.3 Aerosol

An aerosol is a (colloidal) dispersion of particles in a gas, which for therapeutic aerosols is air. There is no definition for the particle size distribution of an aerosol, but most airborne particles are within the size range between 0.2 and 20 μm.

6.2.2.4 Breathhold Pause

This is the period during which breathing is interrupted after inhalation of an aerosol. By not immediately exhaling after inhalation, particles in the central and peripheral airways are given time to deposit by sedimentation and make contact with the epithelial lining fluid of the airways.

6.2.2.5 Carrier Particle

See adhesive mixture. Carrier particles in marketed formulations are exclusively alpha lactose monohydrate crystals, mainly in size distributions between 20 and

150 μm, but they may contain substantial amounts of fine lactose < 10 μm.

6.2.2.6 Deposition

This is the act of bringing an aerosol particle in contact with the airway wall. Different deposition mechanisms exist and it depends primarily on the particle's aerodynamic diameter (see definition) and velocity in which part of the airways an aerosol particle is most likely to be deposited.

6.2.2.7 Deposition Mechanism

Deposition mechanisms are principles by which particles can be deposited onto airway walls. For inhaled aerosol particles only two major mechanisms are important: inertial deposition and sedimentation (see definitions). In the literature also diffusion, interception and electrostatic precipitation are sometimes mentioned as deposition mechanisms, but these mechanisms, if occurring at all, are of lower relevance.

6.2.2.8 Deposition Modelling

Deposition modelling consists of simulation of the deposition in the lungs on the basis of deposition probability equations for inertial impaction, sedimentation, and diffusion.

6.2.2.9 Dose

The dose is the amount of active substance (to be) delivered from the inhalation device. Different definitions for the dose can be given for MDIs and DPIs. Basically, there is a difference between the label claim (also: nominal dose) and the delivered dose (also: emitted dose). The label claim is the dose as measured into the dose compartment of the device (for single-dose or multiple unit dose dry powder inhalers) or as measured by the device (for MDIs and multidose DPIs which both have a metering chamber). The delivered dose is the amount of active substance leaving the mouthpiece of the inhaler, which is lower than the label claim due to inhaler (mainly in the mouthpiece) retentions (for MDIs and DPIs) and incomplete emptying of the dose compartment (for DPIs only). Some manufacturers of DPIs weigh between 10 % and 20 % more than the label claim into the dose compartments to compensate for the inhaler retention, whereas others use an average delivered dose as label claim. This shades the difference between label claim and delivered dose. Delivered doses vary not only between devices; for DPIs they mostly also depend on the flow rate for the same type of device. A special situation concerns nebulisers where the delivered lung dose may not only depend on the retention in the nebulisation cup, but also on aerosol losses during periods of exhalation. Next to (nominal or delivered) dose, the fine particle dose (or fraction) is important (see FPD and FPF).

6.2.2.10 Drag Force (F_D)

Particles moving relative to the surrounding air are subjected to a resisting force by collision with air molecules. This force is the same whether the particle moves through the air or the airflows past the particle. For small airborne aerosol particles the resisting force, or drag force (F_D), is described by Stokes' law: $F_D = 3.\pi.\eta.U.D$, to which several correction factors may be applied (as for the shape factor: see definition). In this equation η is the dynamic viscosity of the air, U is the particle velocity (relative to the air) and D is the particle diameter.

6.2.2.11 Equivalent Volume Diameter (D_E)

The equivalent volume diameter (D_E) of an irregularly shaped particle is the diameter of a sphere having the same volume as the particle in consideration. The equivalent volume diameter is used to describe the dynamic particle behaviour of non-spherical particles in combination with the shape factor (see definition).

6.2.2.12 Fine Particle Dose (FPD) and Fine Particle Fraction (FPF)

Fine particle dose (FPD) and fine particle fraction (FPF) have to be defined by particle size (distribution). Based on their ability to target the site of action in the lungs, FPDs in the literature are frequently defined as the mass fractions of particles < 5 μm in the delivered aerosol. However, particles < 1 μm are not desired as they are exhaled to large extent, whereas for total and deep lung deposition particles in the narrow size range from 1 to 3 μm may be more appropriate. FPD is given in microgram or milligram active substance. FPF is a relative measure of FPD, expressed as percent of the dose for which both the label claim and the delivered dose can be used (see label claim).

6.2.2.13 Geometric Standard Deviation (GSD)

Geometric standard deviation (GSD) is a measure of the distribution of particle sizes which can be used for log-normal volume (or mass) distributions as function of the diameter:

$$GSD = (D_{84.13}/D_{15.87})^{0.5}$$

$D_{15.87}$ is the diameter corresponding with 15.87 % cumulative volume (or mass) and $D_{84.13}$ is the diameter corresponding with 84.13 % cumulative volume (or mass).

6.2.2.14 Impaction Parameter (IP)

The impaction parameter (IP) of an aerosol particle is the product of the particle density (ρ), the square of the particle's (aerodynamic) diameter (D) and its velocity (U):

$$IP = \rho.D^2.U.$$

The parameter predicts the chance of impaction against an obstruction in the flow direction of the particle and can for instance be used to predict oropharyngeal deposition. Practically, instead of particle velocity sometimes the flow rate (Φ) through an inhaler is used, but this does not enable comparative evaluations between different inhalers when the cross sections for airflow in the mouthpieces are different between the inhalers as this will result in different velocities.

6.2.2.15 Impactor

Multistage impactors or cascade impactors are used for aerosol particle size analysis. By drawing a constant flow rate through an impactor nozzle, airborne particles may or may not be collected on an impaction plate underneath the nozzle depending on their aerodynamic diameter and velocity. The cut-off diameter of an impactor varies with the flow rate through the nozzle, and by placing impactors with decreasing nozzle diameters in serial arrangement a mass distribution as function of the aerodynamic diameter can be obtained. The United States and European Pharmacopoeias show different types of impactors to be used for aerosols of which the nine-stage Andersen impactor is most popular in the USA and the seven-stage Next Generation Impactor (NGI) is most frequently used in Europe.

6.2.2.16 Inertial Impaction

One of the two dominant deposition mechanisms for aerosol particles in the respiratory tract (see definitions) is inertial deposition or impaction. Inertial deposition is based on the particle's inertia or momentum, which is the product of particle mass (m) and velocity (U). Inertial deposition occurs particularly in the upper respiratory tract where air velocity is high and the largest aerosol particles are still airborne.

6.2.2.17 Inspiratory Flow Rate

The volume of air per unit time through an inhaler during inspiration is the inspiratory flow rate, which is expressed in L/min. Generally, the flow rate through an inhaler quite rapidly reaches a maximum value (peak inspiratory flow, PIF) followed by a slower decrease to zero flow. As a general rule, the average flow rate equals approximately 70 % of PIF. From the average flow rate and the total inhalation time the inhaled volume (V) can be computed. The flow rate influences the particle size distribution in the aerosol and the deposition pattern in the respiratory tract.

6.2.2.18 Label Claim

The label claim of DPIs and MDIs is the amount of active substance corresponding with a unit dose. Different label claims are used and there is a tendency in Europe to change from metered dose to delivered dose for the label claim, which is an estimated value for the amount of active substance leaving the mouthpiece. For fine particle fractions (FPFs) it is important to know which type of label claim has been used as reference, or a comparative evaluation between different devices will be impossible.

6.2.2.19 Median Diameter

The median diameter corresponds with the 50 % value of a cumulative number, volume or mass percent distribution as function of the diameter. Fifty percent of the volume (number or mass) of the aerosol is in larger, and 50 % is in smaller particles than the median diameter. For a volume distribution it is the volume median diameter, for a mass distribution the mass median diameter. When the mass percent is expressed as a function of the aerodynamic diameter, reference can be made to the mass median aerodynamic diameter (MMAD).

6.2.2.20 Mass Median Aerodynamic Diameter (MMAD)

The MMAD is a parameter frequently used to characterise therapeutic aerosols. MMAD alone is not very useful however, as it provides no information about the size distribution in the aerosol and the mass fraction of the dose (label claim) processed into a suitable aerosol. Fine particle dose and fraction are more meaningful parameters, particularly for DPIs (see definitions).

6.2.2.21 Monodisperse Aerosol

In a monodisperse aerosol all particles have the same diameter. In practice, monodisperse aerosols are very difficult to obtain and therefore, aerosols are considered monodisperse when their geometric standard deviation (GSD) is smaller than 1.2 (see definition).

6.2.2.22 Plume Velocity

The plume velocity is the velocity with which an aerosol is released from an MDI. Generally, the plume velocity from hydrofluoroalkane (HFA) holding MDIs is much lower than that from chlorofluorocarbon (CFC) holding MDIs, but this may depend on the presence of a co-solvent.

6.2.2.23 Polydisperse Aerosol

In a polydisperse aerosol the particles have different diameters and the size distribution is such that the geometric standard deviation (GSD) has a value larger than 1.2 (see definitions).

6.2.2.24 Resistance (Against Airflow)

Inhalers are flow constrictors which reduce the flow rate (Φ) to be achieved during inhalation. Their behaviour in this respect complies with the general equation for orifice types of airflow resistances ($\Phi = Fu(A).\sqrt{dP}$), where Fu(A) is a

function of the cross section (A) for airflow and dP is the pressure drop across the inhaler (in kPa). Fu(A) may be complex but fairly constant over a wide range of flow rates and contains flow coefficients depending on the precise inhaler design. The reciprocal value of Fu(A) is the inhaler's resistance to airflow (R).

6.2.2.25 Sedimentation

One of the two dominant deposition mechanisms for aerosol particles in the respiratory tract (see definitions) is sedimentation or stationary settling. Sedimentation occurs under influence of the force of gravity and settling (falling) particles reach a terminal (stationary) settling velocity once the force of gravity is in equilibrium with the drag force (see definitions). The terminal settling velocity (U_{TS}) is proportional to the square of the particle diameter (D) and also depends on particle density (ρ) and shape factor (χ: see definitions):

$U_{TS} = (\rho.D^2.g.C_c)/(18\eta.\chi)$ in which g is the acceleration of gravity, C_c is the Cunningham correction factor for slip flow and η is the dynamic viscosity of the air.

6.2.2.26 Shape and Shape Factor (χ)

Only aqueous aerosol droplets and some particles obtained from (spray) drying of droplets are perfectly round. Most solid aerosol particles have other shapes, and also when spherical particles cluster together their shape changes from round into irregular. The shape of a particle affects its drag force (see definition) and in particle dynamics shape is characterised by a (dynamic) shape factor. This factor for a non-spherical particle is defined as the ratio of the actual resistance force to the resistance force of a sphere having the same volume and velocity relative to the air. The factor is applied to make corrections for Stokes' law for the drag force (see drag force) which influences both inertial impaction and sedimentation.

6.2.2.27 Stopping Distance

The stopping distance or inertial range is the distance a particle will travel in still air with all external forces eliminated, except for the drag (resistance) force of the air which decelerates the particle to zero velocity. The stopping distance depends on the particle's momentum, which is the product of particle mass and velocity (m.U).

6.2.2.28 Target Area

The target area is the area in the respiratory tract where the action of the inhaled medicine is most needed. The target area may either be part of the respiratory tract or the whole lung, depending on the medicine.

6.3 Biopharmaceutics

Aerosol particles carrying the active substance have to make contact with the walls of the respiratory tract in the target area and the medicine has to be dissolved before it can become active. In this paragraph, the anatomy of the human respiratory tract is described in view of its function as transport route and target area for inhaled medicines.

6.3.1 The Human Respiratory Tract

For pulmonary administration of medicines the mouth is the port of entry (see Fig. 6.2). Inhaled air carries the aerosol from the inhalation devices past the oral cavity, pharynx and larynx before it enters the tracheobronchial tree. Starting with the trachea (generation 0) most airways branch into two (some in more) smaller airways, which comprise the following generation. The trachea branches (bifurcates) into two main bronchi (generation 1) which bifurcate further into five lobar bronchi (generation 2) and so on, until eventually the alveolar sacs (alveoli) are formed. Estimates for the number of branchings (airway generations) from the trachea to the alveoli in the literature vary between 20 and 28 and the number of airway ducts in each generation is roughly 2 to the power of the generation number; for example, in generation 8 there exist 2^8 (256) airway ducts. The number of alveoli does not comply with this geometric sequence however, and is much higher up to an estimated 300–800 million [1]. The airway system can be subdivided in many different ways. Clinically, large airways (with diameters > 2 mm) are frequently distinguished from small airways (with diameters < 2 mm). In addition, the terms upper and lower airways are frequently used, but with different definitions. From the viewpoint of fluid and particle dynamics dividing the airways into conducting, transitional and peripheral airways seems more practical. Clear definitions for these regions have never been given but on the basis of airflow velocity and functional and anatomical differences the conducting airways are referred to as the generations 0–11, the transitional airways as the generations 12–16 and the peripheral airways as the generations 17–23 in this chapter. In aerosol deposition studies with radiolabeled substances partitioning is often into central, intermediate and regional airways on the basis of two-dimensional γ-camera images. The average angle of bifurcation is 37° which from the fluid dynamics point of view is the angle with the least disturbance of the flow pattern. Lung models used for deposition simulation in the literature mostly give only 23 generations (e.g. the Weibel model) and only few are extended to 26 generations (e.g. the Hansen and Ampaya model) [2].

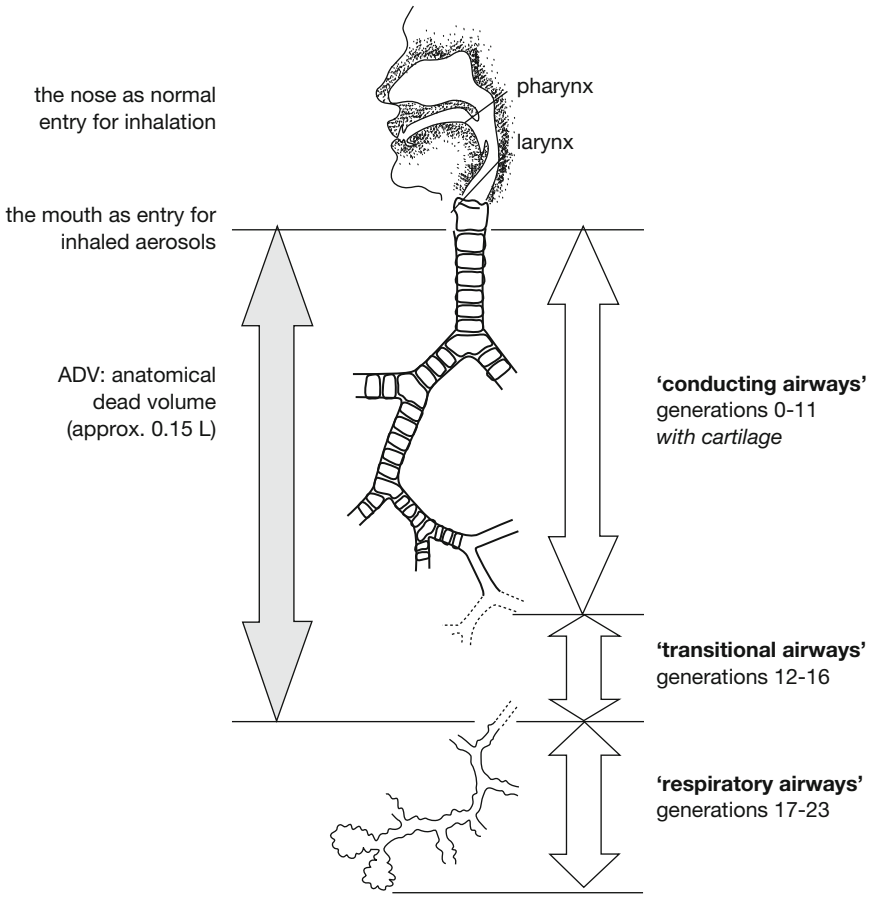

Fig. 6.2 The airways as transport route for aerosols. The anatomical dead volume of 0.15 L is for adults; the total number of airway generations (23), based on the Weibel model, is by approximation. Source: Recepteerkunde 2009, ©KNMP

From the trachea to the small bronchi cartilage is present in the walls of the airways. In the trachea cartilages are C-shaped, in the bronchi they appear as interspersed small plates of elastic tissue. The cartilages in the trachea are joined by smooth muscle which continues into the bronchi and bronchioles where the muscles encircle the airways completely. Further down the respiratory tract, smooth muscle becomes less until it is absent in the alveoli. The airways are covered with epithelium of which the type varies within the tract. There are glands (upper respiratory tract) and mucus producing goblet cells, and most of the epithelial cells (into the bronchi) are ciliated cells. The cilia beat upwards, moving mucus (including all, in the mucus, entrapped foreign inhaled particles) towards the throat where it is swallowed. In the alveoli neither mucus nor ciliated cells are present and mainly alveolar macrophages are responsible for destroying foreign material. The walls of the alveoli contain surfactant secreting cells. Surfactant decreases the surface tension of the alveolar lining fluid preventing collapse and assisting re-inflation of the lung after exhalation.

Different lung models are used to describe the human airways as transport route for inhaled aerosol particles [2]. All these models have in common that they are simplifications of reality presenting the airways as round pipes with defined lengths and diameters. From the trachea with an estimated diameter of 15–18 mm (in adults) the airway diameter decreases towards the alveolar ducts, whereas the number of airways increases. The increase in number (from 1 to approximately 8×10^6, assuming 23 generations) is much higher than the decrease in diameter (from 18 to approximately 0.4 mm). As a consequence, the cross section for airflow, after an initial decrease in the first four generations, increases exponentially towards the alveoli, which corresponds to an exponential decrease of the air velocity. In the terminal bronchioles the air stands practically still and its velocity reaches the same value as the terminal settling velocity of particles in the size range between 5 and 6 μm.

6.3.2 Spirogram and Lung Volumes

The total lung capacity (TLC) of healthy adult subjects varies between approximately 4 L (female) and 6 L (male), but during tidal breathing at rest only a fraction of this volume is refreshed: approximately 0.5 L. During severe exercise, this tidal volume (TV) increases to about 1.5–2.5 L, which means that a considerable part of the TLC is not used. In fact, a residual volume (RV = approximately 25 % of TLC) cannot be exhaled at all to prevent collapse of the lungs. Tidal breathing is not on top of the residual volume, but on top of the functional residual capacity (FRC), which after exhalation leaves a volume of about 2.3 L of air in the lungs for an adult male. The alveolar volume is about 2.1 L and this implies that during tidal breathing air refreshment by convective transport takes place mainly above the alveolar volume. Hence, to reach the alveoli effectively with an inhaled aerosol, a preceding exhalation to residual volume is necessary.

6.3.3 Target Areas for Inhaled Medicines

The precise area to target in the lungs depends on the type of medicine given and the mechanism of action for this medicine. Most of the active substances used for inhalation interact with cell receptors in the respiratory tract [3]. For asthma and COPD these include mainly β_2-adrenoceptor agonists and muscarinic receptor antagonists (anticholinergics). The distribution of receptors over the lung is an important determinant of both the clinical effect of the medicine and the desired site of deposition for the active substance. The primary action of β_2-agonists is to relax airway smooth muscle. β_2-agonists target β_2-receptors that are present in high concentration in lung tissue and localised to several cell types which, next to smooth muscle, are epithelium, vascular smooth muscle and submucosal glands [3]. They also target β_1-receptors localised to submucosal glands. There is a uniform distribution of β-receptors also on the alveolar wall with a ratio of β_1 to β_2 receptors of 2:1. The density of β_2-receptors in airway smooth muscle does not change down the respiratory tract and is the same in small and large airways. Therefore β_2-agonists may dilate all airways and this is relevant to asthma and COPD where small airways are involved. To achieve acute relief of bronchoconstriction, reaching the larger airways, which have the highest resistance to airflow, is mostly sufficient.

Inhaled anticholinergics are the most effective class of bronchodilators in COPD patients. Muscarinic receptors are localised to smooth muscle of all airways, but the density decreases down the respiratory tract. They are also localised to airway epithelium and submucosal glands [3]. Four subtypes of muscarinic receptors exist in the lungs and those mediating bronchoconstriction belong to the M_3-receptor subtype on endothelial cells which release nitric oxide (NO). Muscarinic receptors of the M_3 subtype also mediate mucus secretion and so do receptors of the M_1 subtype, whereas autoreceptors in the human airways belong to the M_2 subtype. Medicines like ipratropium bromide block prejunctional M_2-receptors and postjunctional M_3-receptors in airway smooth muscle with equal efficacy. The presence of M_2-receptors has also been demonstrated in airway smooth muscle and M_1- and M_3-receptors are both present in submucosal glands, whereas M_1-receptors can also be found in the lung parenchyma. Recently, it has been suggested that muscarinic receptors may have a much greater role in the pathophysiology of obstructive airway diseases than previously thought [4]. Active substances like tiotropium may potentially inhibit airway inflammation and remodelling, and it has recently been shown that aclidinium may play an important role in inhibiting fibroblast-myofibroblast transition, which is a key step in peribronchiolar fibrosis formation [5]. Deposition in the whole lung is therefore desirable for anticholinergics in spite of the fact that cholinergic activity in the lung is most pronounced in the large airways [6].

Inhaled corticosteroids (ICSs) are the mainstay of asthma management. Their effects are mediated by glucocorticoid receptors in target cells of the lung. Almost every cell has glucocorticoid receptors, but the number per cell varies with the type of tissue and in the airways the highest density is found in endothelial and epithelial cells [3]. Airway epithelial cells, which express multiple inflammatory proteins dominating the inflammation in asthma, may be the major target for ICSs. Because epithelial cells are present throughout the entire lung, all airways have to be targeted with ICSs.

Many specific mediator receptors are involved in asthma but they are so abundant that specific antagonists for these receptors have little effect, with an exception for cysteinyl leukotriene-1 (cys-LT_1) receptors which are distributed predominantly on airway smooth muscle and (to a lesser extent) on macrophages. Their numbers are small, however, and this may explain why antileukotrienes like montelukast and zafirlukast, which prevent predominantly leukotriene-induced bronchoconstriction, are less effective than β_2-agonists.

6.3.4 Side Effects and Toxicity

Side effects can be the result of unwanted systemic action, toxicity, irritation and hypersensitivity following sensitisation. Both the active substances and excipients can cause side effects and in addition to the chemical nature of the inhaled compounds, also physical properties can be relevant. An example can be given for salbutamol, for which it has been shown that increasing the dose may result

in increased side effects without improving the therapeutic effect [7]. Also specific salts of an active substance may be less favourable, as they can increase the degree of irritation from particle deposition on the mucosa [8]. Irritation may result in severe cough and chest tightness; both may further depend on the precise site of deposition which depends on particle size and/or flow rate. Dry powder formulations for low dose substances in asthma and COPD therapy previously contained only alpha lactose monohydrate as carrier (or diluent) excipient. In some countries, there has been concern about the use of lactose in inhaled medication because of some rare cases of bovine spongiform encephalopathy (BSE), but it is highly unlikely that the prions causing BSE can be found in this excipient. Currently, many formulations are introduced to the market which contain magnesium stearate as force control agent to improve powder dispersion (e.g. Chiesi Foster NEXThaler®, Novartis Seebri Breezhaler® and GSK Breo Ellipta®). Although the use of this practically insoluble excipient has been approved, its long term safety may be questioned. Still uncertain are also the long term effects of various excipients in high dose medicines, such as lung surfactant (dipalmitoylphosphatidylcholine, DPPC) in various particle engineered powders, hydrogenated soya phosphatidylcholine (HSPC) and cholesterol in liposomal formulations, and poly lactic acid (PLA) and poly lactic-co-glycolic acid (PLGA) in insoluble microspheres. The arguments for safety are that the compounds are not foreign to the lungs or that they do not interfere with physiological processes. However, interference for substances like DPPC are likely to depend also on their concentration, and for instance metabolic lactic acid is an important mediator of myofibroblast differentiation via a pH-dependent activation of transforming growth factor-β [9]. MDI formulations contain various excipients too, of which some have been less abundantly used since the replacement of CFC by HFA propellants. Furthermore, most HFA-MDIs have a lower plume velocity and a higher plume temperature than CFC devices which reduces the cold-freon effect and local side effects from substantial throat deposition.

6.4 Mechanisms of Aerosol Deposition and Aerosol Characterisation

6.4.1 Forces Acting on Inhaled Aerosol Particles

Aerosol particles transported in a steady laminar air stream have basically the same velocity and flow direction as the air, but in contrast with the air molecules particles have a much higher inertia. Therefore, they cannot follow rapid changes in velocity or direction of the airflow, which for instance occur in curved airways, at bifurcations or around local obstructions. In such areas or in turbulent air streams particle trajectories and velocities may differ from the stream lines of the air and under these conditions, a drag or resistance force of the air is added to the force of gravity acting on the particle. Whereas the particle's inertia tends to maintain particle motion in the original direction, the drag force tends to change this direction into that of the air stream. The tendency of a particle to maintain its state of motion in still air is expressed by its stopping distance (S) which is related to the particle momentum. For the sake of simplicity and an easier understanding, it can be imagined that a particle following a curvilinear trajectory is subjected to a centrifugal force. This adds a third force acting on particles in a bent airway as depicted in Fig. 6.3.

$$F_C = m.U_{T^2}.R^{-1} \tag{6.1}$$

$$F_D = 3.\pi.\eta.U_{PA}.D \left(\begin{array}{l} \text{for spherical particles} \\ >1\ \mu\text{m with unit density} \end{array} \right) \tag{6.2}$$

$$F_G = m.g \tag{6.3}$$

Where:
m is the particle mass
U_T is the tangential velocity
R is the radius of the bent
η is the dynamic viscosity of the air
U_{PA} is the particle velocity relative to the air velocity
D is the particle diameter
g is the acceleration of gravity

Of these forces, the centrifugal force and force of gravity are a function of the particle mass, which is proportional to the third power of the particle diameter, whereas the drag force is proportional to the first power of the diameter. The

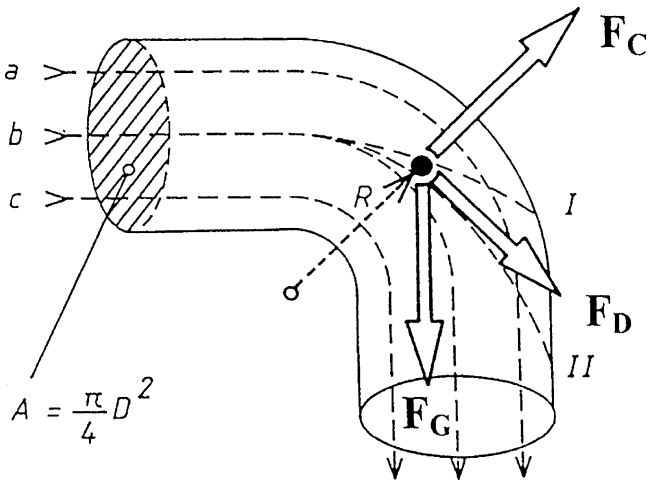

Fig. 6.3 Forces acting on airborne particles in a bent airway. Source: Recepteerkunde 2009, ©KNMP

drag force and the centrifugal force depend on the particle velocity, whereas the force of gravity does not. This has the important implication that the balance between these forces can be influenced by changing the particle diameter, particle velocity, or (as a determinant for particle mass) particle density. Because the particle shape influences the drag force, the shape factor is a fourth determinant for a particle's aerodynamic behaviour.

6.4.2 Deposition Mechanisms in the Respiratory Tract

The balance between the three forces acting on airborne particles results in dominance of either inertial impaction or sedimentation, which are the two main deposition mechanisms in the respiratory tract. Inertial impaction occurs when particles have a high momentum and the air suddenly changes its direction. This situation is met in the human throat and the upper airways where the air velocity is high and the largest particles in the aerosol are still present in the inhaled air stream. For such particles the ratio of centrifugal force to drag force is relatively high, meaning that they have a great chance of colliding with the airway wall based on their high inertia, which event is referred to as inertial impaction. As the largest particles are removed in the upper airways and the air (and thus particle) velocity decreases down the respiratory tract, particle inertia and the drag force decrease and the force of gravity becomes more dominant. This leads to settling (falling) of particles in the central and peripheral airways and when the settling time is long enough it could result in deposition by sedimentation. For a small fraction of the finest particles ($D \ll 1$ μm) Brownian motion may become noticeable. This mechanism of displacement, resulting from particle collision with surrounding air molecules, causes particle movement with a randomly changing direction which could lead to contact with the wall of an airway. However, because the displacement velocity by Brownian motion (or diffusion) is very low, and so is the mass fraction of the dose represented by particles smaller than 1 μm, this mechanism of deposition does not contribute substantially to total deposition. Also electrostatic capturing of particles is mentioned in the literature as a possibility to bring aerosol particles in contact with airway walls but for the relevance of this mechanism there is no experimental evidence. One aspect that is still relatively unexplored and needs further investigation is the possibility that particles change their mass during passage through the respiratory tract, e.g. by moisture sorption [10]. Such particles may be inhaled as small (submicrometer) to avoid high deposition fractions in the oropharynx and larger airways and increase in weight in the high humidity within the airway system to enhance sedimentation deposition in the deep lung.

6.4.3 Sedimentation Takes Time

Particle settling in the respiratory tract occurs under the influence of the force of gravity and the drag force. In the stationary situation these forces counterbalance each other and this enables to calculate the stationary or terminal settling velocity (see terms and definitions) which is proportional to the square of the particle diameter. For spherical particles with unit density in the range of diameters between 0.5 and 5 μm, which covers the range of interest for inhalation, the terminal settling velocities are given in Table 6.1.

Table 6.1 shows that particles of 1 μm, or smaller, are less favourable for inhalation because their settling time is too low. Even for a total residence time of 7.5 s in the smallest airways, the falling distance of a 1 μm particle is no more than 50 % of the diameter of that airway, if the air stands completely still. In practice, the air velocity remains much higher than the particle's settling velocity, even in these most distal airways (e.g. 2.5 mm/s in generation 22 at an inspiratory flow rate of 60 L/min), and this can influence sedimentation in a negative or positive way. Moreover, most distal airways are not horizontal ducts and a falling distance of 50 % of the airway diameter does not provide an average 50 % chance for deposition of particles entering the airway randomly distributed over its cross section. As a consequence of all this, the deposition efficiency of very fine particles is low and exponentially decreases with decreasing diameter. This is reflected in the fraction of small particles exhaled again, which is known for particles in the size range between 1.5 and 6 μm [11]. Figure 6.4 shows the relationship between particle diameter and measured exhaled fraction for monodisperse aerosols, and the extrapolation of this relationship towards particles of 1 μm. The trend computed matches very well the relationship which presents the time needed to fall a distance equal to the diameter of a peripheral airway (0.43 mm).

Table 6.1 Terminal settling velocities in still air of spherical particles with unit density

Particle diameter (μm)	Terminal settling velocity (μm/s)	Average settling time[a] (s)
0.5	7.5	30
1	30	7.5
2	120	1.9
3	271	0.8
4	482	0.5
5	753	0.3

[a]The average settling time is the time needed to fall a distance (H) that equals 50 % of the diameter of a respiratory bronchiole (H = 0.225 mm)

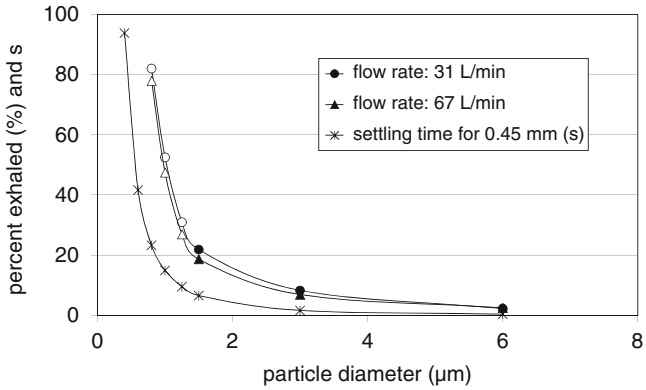

Fig. 6.4 Trends for the percentage particles exhaled and the time needed to fall a distance that equals the diameter of a peripheral airway (0.43 mm), both as function of the aerodynamic particle diameter. The percentage exhaled for 1 µm particles is obtained from extrapolation (using a second order polynomial equation); exhalation data for 1.5; 3 and 6 µm particles derived from Usmani et al. [11] and extrapolation of the correlationships towards particles of 1 µm

6.4.4 The Influence of Particle Shape and Density

The terminal settling velocities and average settling times given in Table 6.1 are for spherical particles with unit density which is the density of water (1 g/cm^3). This may well apply for wet aerosol droplets from aqueous solutions of active substances which take a spherical shape as soon as they have been formed under the influence of the surface tension. Solid aerosol particles from dry powder inhalers have different properties. Such particles may exhibit a variety of different shapes and also have different densities, depending on how they were prepared. Particles obtained from micronisation are mostly crystalline and have density values typically in the range between approximately 1.25–1.55 g/cm^3. Due to the size reduction process (breaking of larger particles) micronised particles have irregular shapes which, however, never deviate extremely from the spherical shape. This is in contrast to particles obtained with anti-solvent precipitation or super critical drying which can have shapes varying from cubic to plate or needle like. An increasing number of high dose medicines for inhalation are currently produced with spray drying techniques, yielding particles with high internal porosity or corrugated surfaces to enhance dispersion during inhalation. Such particles may largely be spherical, but they have low densities, frequently much smaller than 1 g/cm^3. Both the particle density and shape influence the aerodynamic behaviour of aerosol particles and this affects deposition in the human airways. Figure 6.3 shows that the force of gravity and the centrifugal force both depend on the particle density (ρ). All three forces furthermore depend on the particle diameter, but non-spherical particles have different dimensions in different directions and therefore, a unique diameter to characterise such particles cannot simply be given. For this reason, the equivalent volume diameter (D_E) was introduced, which is the diameter of a spherical particle with the same volume as the non-spherical particle. Finally, the drag or resistance force strongly depends on the particle shape. This does not show in the equation given in Fig. 6.3, which is therefore only valid for spherical particles. To standardise for both shape and density, the aerodynamic diameter is used, which by definition is the diameter of a sphere with unit density having the same terminal settling velocity as the irregular particle in consideration.

6.4.5 Polydisperse Aerosols and the MMAD

All currently marketed inhaler devices produce polydisperse aerosols of which the individual particles have different sizes. Therefore, they cannot be characterised by a single diameter. In fact, for most solid aerosols from dry powder inhalers the particles may have different shapes too, which is the reason to characterise them with aerodynamic diameters. To be able to express polydisperse aerosols with a single parameter, the median aerodynamic diameter (MAD) was introduced. When the aerodynamic size range which covers the population of particles in the aerosol is divided into different classes and the volume or mass fraction within each size class is expressed as function of the class mean diameter, a volume or mass distribution as function of the aerodynamic diameter is obtained. This volume or mass frequency distribution can be transferred into a cumulative percent distribution of which the 50 % value corresponds with the volume or mass median aerodynamic diameter (VMAD or MMAD). This is the diameter indicating that 50 % of the total aerosol volume or mass is in larger, and 50 % is in smaller particles. When particles of all sizes in the aerosol have the same density, which is mostly the case, then VMAD equals MMAD.

MMAD is frequently presented as the parameter characterising aerosols from inhalation devices best. This is not true however. To judge the quality of a therapeutic aerosol from a particular type of inhaler, more information is needed. The MMAD does not give any information about the size distribution of the aerosol particles. Substantial mass fractions may be outside the desired size range for adequate deposition of active substance in the target area, even when MMAD looks very favourable. Moreover, MMAD does not give information about the mass fraction of the dose (label claim) that has been delivered within the desired size range. For all types of inhalers, the delivered fine particle dose (FPD) is much lower than the label claim and this may vary from 10 % to 60 % for DPIs and up to 90 % for

MDIs. For these reasons it is best to define first the FPD in terms of desired size range and mass percent (of the label claim, yielding the fine particle fraction, FPF) and next compute the MMAD for this size range. In the literature, mostly FPF < 5 μm is mentioned as the relevant fine particle fraction, but practically FPF 1–5 μm is more meaningful because of the low deposition efficiency of submicron particles (Fig. 6.4).

6.4.6 Deposition Efficiencies and the Most Preferable Size Distribution

The deposition mechanisms mentioned previously have different efficiencies which, in addition to the particle properties, depend on the velocity with which the particles enter the respiratory tract and their residence time in the tract. The velocity is most important for inertial impaction in the oropharynx and larger (mainly conducting and transitional) airways. The likelihood of particles to be deposited in the mouth and throat or larger airways is a function of their momentum, which is the product of particle mass and velocity and can be predicted with the impaction parameter.

An experimental relationship between impaction parameter (based on inhaled flow rate) and oropharyngeal deposition from a study with monodisperse particles is shown in Fig. 6.5. The highest value in this relationship is for 6 μm particles inhaled at a flow rate of 67 L/min; the lowest for 1.5 μm particles inhaled at 31 L/min [6].

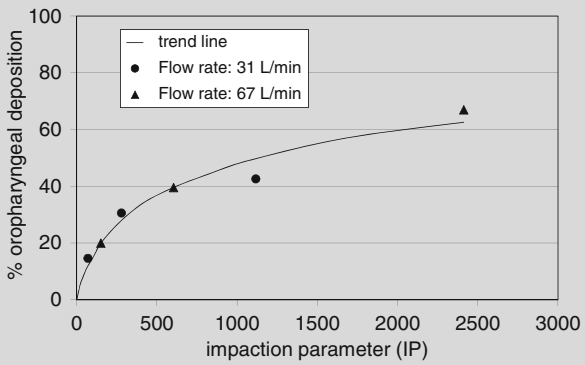

Fig. 6.5 Experimental relationship between percent oropharyngeal deposition and impaction parameter computed as $IP = D^2.\Phi$, where D is the aerodynamic particle diameter (micrometre) and Φ is the flow rate with which the particle is inhaled (L/min). Data derived from Usmani et al. [11]

The figure makes clear that substantial lung doses cannot be obtained with particles larger than 6 μm, unless they are inhaled very slowly which from dry powder inhalers is often not possible. Large particles also deposit effectively in the larger airways where initially the velocity increases (until generation 4) before it slows down. This has the consequence that particles larger than 3 μm from DPIs do not effectively enter the peripheral lung.

The residence time is more relevant to small particles which have to deposit mainly by sedimentation in the central and peripheral airways. In these regions, the flow rate is strongly reduced and large particles are not present in large numbers due to which inertial impaction is less prominent. Sedimentation takes time however, as explained above, and particularly for particles in the size range below 1.0–1.5 μm a residence time of several seconds may be needed to obtain a noteworthy deposition by sedimentation. This practically confines the diameter for most effective total lung deposition to the very narrow aerodynamic size range between 1 and 1.5 and 3 μm. Only for bronchodilators which need to target predominantly the larger airways, particles in the size range between 3 and 6 μm may be more effective [11].

6.4.7 Medicine Distribution over the Entire Respiratory Tract

One of the aspects that is often neglected, but may be of utmost importance for effective therapy, is the active substance concentration achieved in different lung regions. Most *in vivo* deposition studies with radiolabeled substances from dry powder inhalers teach that the deposition fractions in the central, intermediate and peripheral lung are very roughly one third of the total lung dose each [12–14]. This is more or less confirmed by deposition modelling studies with monodisperse particles of 3 μm inhaled at a moderate flow rate of 30 L/min [15], although a good comparison in this respect is not possible as different lung regions are defined differently in these studies. Considering the exponentially increasing internal surface area of the airways from the trachea to the alveoli, which differs roughly by a factor 130 between the generations 0–11 (conducting airways) and 17–23 (peripheral airways) based on the Weibel model, it may be concluded that there must be a dramatic difference in active substance concentration (in $\mu g/cm^2$) between these regions. A difference in definition for the different lung regions, or a considerable deviation from the deposition distribution (approximately one third of the total lung dose in each region) does not really change this conclusion. This may have the consequence that the peripheral lung is underdosed with for instance antibiotics, which need to

reach their minimum inhibitory concentration (MIC) value to become effective. In fact, not reaching the MIC value could result in bacterial resistance development and this is an aspect that will need serious consideration when changing from systemic to pulmonary administration for therapies against pulmonary infections. In this respect, also changing from approved formulation-device combinations to off-label combinations (e.g. in nebulisation) is potentially a risk when the delivered fine particle dose and the inhalation manoeuvre are not exactly the same.

6.4.8 Practical Implications for the Inhalation Manoeuvre

The optimal inspiratory manoeuvre for inhalation of a therapeutic aerosol depends on how it influences the aerosol generation process and the deposition pattern in the respiratory tract (Fig. 6.1). Its effect on the aerosol properties will be discussed in the next paragraphs in which the working principles of different aerosol generation devices are explained. From the deposition point of view particularly the (peak) flow rate, the inhaled volume and a certain breathhold pause are relevant, but good inhalation starts with exhalation to residual volume. As explained above, only with an inhalation from residual volume the alveoli can be reached effectively. Considering the dependence of inertial impaction in the oropharynx and first airway generations on the particle velocity, it may also be clear that a high flow rate during inhalation should be avoided, but the optimum in this respect depends on the performance of the aerosol generation device too. For good (dry powder) inhaler performance, even the acceleration to peak flow (flow increase rate) may be important. Inhalation should be continued until total lung capacity is reached. Premature stopping of the inhalation manoeuvre again has the consequence that the most distal airways are not reached with the aerosol, but it can also mean the total dose is not delivered. Once the smallest aerosol particles have reached the peripheral lung, they must stay there for a certain period of time to give sedimentation a chance and a breathhold pause of several seconds (preferably 5–10) is desired before starting exhalation.

6.5 Aerosol Generation Devices

Basically four different types of commercially available aerosol generation devices exist: dry powder inhalers (DPIs), metered-dose inhalers (MDIs), classic jet and ultrasonic nebulisers and a new class of high-performance liquid inhalers. Each of these categories has many different variations of the same basic design and working principle and they may also have significantly different performances. In the following paragraphs, firstly the conceptual design of the different types will be described and then their working principle will be explained. This has to be known to make the best possible choice for individual patients and to give an appropriate instruction for use. Only examples of specific devices will be discussed in more detail, because the still growing number of devices in each category is too extensive to make a complete survey.

6.5.1 Dry Powder Inhalers (DPIs)

DPIs are relatively new and their designs and working principles may not only be quite complex but also rather diverse between the different types, which easily leads to incorrect or suboptimal use. DPIs contain the active substance in the dry state which is beneficial from the viewpoint of stability. They can deliver much higher doses than MDIs and be disposable which is particularly desired for hygroscopic formulations of active substances, antibiotics against which bacterial resistance development has been reported and single-dose administrations such as vaccinations. Aerosol generation in DPIs is mostly breath activated, which eliminates the need for a good hand-lung coordination but requires the generation of sufficient flow rates and inhaled volumes to release a sufficiently high fine particle dose. DPIs have much higher airflow resistances than MDIs, which limits the attainable flow rate and by that, oropharyngeal deposition. Furthermore, DPIs can deliver higher fine particle fractions and finer aerosols at higher flow rates, which compensates to a certain extent for the increasing losses in the mouth, throat and upper airways when the patient inhales more forcefully, which results in an increased dominance of inertial particle impaction. DPIs exist not only in a large variety of different designs, they also have different performance properties and resistances to airflow. These differences in design and performance may be functional and have been chosen carefully to obtain the most optimal deposition of the active substance at the site of action. However, in many cases they may also be different for the same type (or class) of active substance(s), all having the same target area. These differences may lead to considerable variation in the delivered fine particle dose at this site of action. Differences in ease of handling, the flow manoeuvre needed and airflow resistance may be aspects to consider particularly for special patient groups, such as children and severe COPD patients. In the next paragraphs, the general design with some specific examples of DPIs will be presented and discussed in relation to their performances and the required operational procedures to obtain the best delivery of active substance.

6.5.1.1 Basic Design of DPIs

The primary functional parts of a dry powder inhaler are schematically shown in Fig. 6.6 and include a powder formulation, a dose (measuring) system, a dispersion principle for the powder formulation, a mouthpiece and a housing for all parts. Additionally, the inhaler may have various secondary features, including a dose counter, giving the number of doses left in the device, a compartment with desiccant to keep the powder formulation dry and a signalling to the patient that the inhalation manoeuvre is correct or has been completed. Different choices can be made for each of the functional parts and a good and compatible combination has to be chosen and developed to obtain the maximal result.

6.5.1.2 The Powder Formulation

The powder formulation contains the active substance in the correct aerodynamic size distribution, which for most currently marketed formulations is either obtained by micronisation or by spray drying. Both techniques produce polydisperse particles and their mass median aerodynamic diameter is preferably in the range between 1 and 5 μm, depending on the precise target area. Particles within this size range are extremely cohesive, whereas the powder masses to be measured are miniscule and mostly less than 5–500 micrograms for the active substances used in asthma and COPD treatment. Such small quantities of micronised powders cannot be delivered in a reproducible way without improving their flow properties and increasing their volume. They are formulated into free-flowing powders either by blending with coarse lactose carrier particles into so-called adhesive mixtures or by preparing highly porous soft spherical agglomerates with or without micronised lactose excipient. For high dose medicines in the range from a few to a few 100 mg, frequently special particle engineering techniques are used which produce low density particles or particles with a corrugated surface. Both types of powders, which require the use of special volatile agents or surfactants and often multi-step processes, have improved flowability and can be delivered without further dilution or formulation.

6.5.1.3 Dose (Measuring) Systems for the Powders

Basically two different types of dose principles exist for the inhalation of powders in currently marketed inhalers; preloaded single-dose compartments or multidose reservoirs with a measuring mechanism that has to be operated by the patient. Both principles have pros and cons and which type is most appropriate also depends on the properties of the powder formulation. Preloaded single-dose compartments include mainly capsules and blisters. Capsules are stored separately and inserted individually into the inhaler when needed. They have to be pierced to discharge the powder which in currently used inhalers occurs during high speed spinning (e.g. Breezhaler®) or vibration (e.g. Boehringer HandiHaler®) in

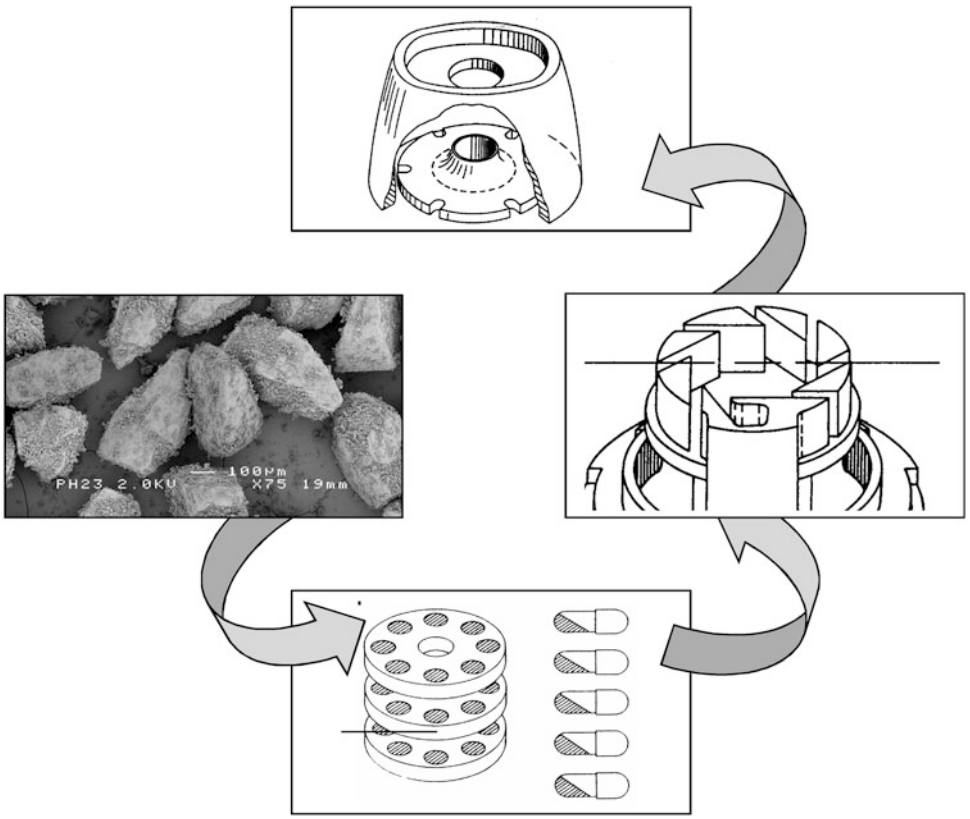

Fig. 6.6 The primary functional parts of a dry powder inhaler including a powder formulation, a dose (measuring) system, a powder dispersion principle and a mouthpiece (with flow control and aerosol directing functions)

swirl chambers or narrow channels during inhalation. Hard gelatine capsules have been the standard for more than 30 years in dry powder inhalation, but many newly developed medicines are now delivered with hydroxypropylmethylcellulose (HPMC) capsules. Particularly for moisture sensitive formulations HPMC capsules are more appropriate as they contain less water. HPMC capsules are also less prone to tribocharge during spinning and vibration and their tendency to fragment or indent at extremely low and high relative humidities of the air is considerably less when being pierced. This reduces the risk of inhalation of capsule fragments and poor capsule emptying. Gelatine capsules on the other hand have a much lower oxygen permeability. Capsules size 3 for inhalation typically contain powder masses between 5 and 45 mg depending on the type of active substance and formulation. Aluminium blisters used for inhalation are mostly smaller and contain less than 10 mg of powder. Blisters can be provided individually (e.g. Elpen, Elpenhaler®), be part of a disk (e.g. GSK Diskhaler®, with four to eight cavities), or be on a long strip for 60 doses which is coiled into a spiral in the inhaler (e.g. GSK Diskus®). Access to the powder is obtained either by piercing the blister foil and cover lid (Diskhaler®) or by separating both parts from each other (Diskus® and Elpenhaler®). For blisters on a disk or a strip, a transport mechanism is needed as part of the inhaler design. When the blister foil and cover lid are pierced, parts of the lidding strip projecting into the powder cup may prevent complete emptying of the dose. Although this is not likely to result in serious underdosing, it causes inhaler pollution which may be a burden to the patient.

In contrast to single-dose compartments, multidose reservoirs require good flow properties for the powder formulation. To isolate single doses from the powder bulk, a slide (e.g. AstraZeneca Genuair®), disk (e.g. AstraZeneca Turbuhaler®) or cylinder (e.g. Orion Easyhaler®) with small cavities is used as measuring principle making contact with the powder container. A transport mechanism displaces the measuring principle and the filling of the cavities is basically by action of the force of gravity. This requires that the inhaler is kept in the prescribed position during dose measuring to assure good powder flow into the measuring cavity. Disks and cylinders have several dose cavities along their circumference and transporting them means that a filled cavity is positioned in line with the powder channel towards the dispersion principle, whereas simultaneously an empty cavity is positioned underneath the powder container which is then filled. Slides have a single cavity which is pushed forward for the inhalation and drawn back for filling. The Turbuhaler® has a more complex dose measuring mechanism as this inhaler makes use of spherical agglomerates which are scraped into tiny dose measuring holes in a series of successive scraper chambers between the bulk container and the discharge channel. Therefore, the position in which the inhaler is held during dose measuring is less critical. On the other hand, the mechanical stability of such pellets is less than that of adhesive mixtures and this makes the inhaler more sensitive to falling or violent motions. All multi-reservoir inhalers are protected against double dosing. When the dose measuring mechanism is operated repeatedly without inhalation in between, the dosing disk or cylinder is rotated with filled cavities into which no additional powder can be measured. The only risk of not inhaling after dose activation is powder waste from the dose cavity which is in line with the discharge channel. This leads to inhaler pollution. The (Meda) Novolizer® and Genuair® have a different protection principle. Their measuring slide is put into position for inhalation with a knob and drawn back to the filling position automatically by an air valve only when sufficient flow rate is generated by the patient to guarantee good emptying and dispersion. Patients that are unable to generate this flow rate cannot use these dry powder inhalers and need to be treated with an MDI. The NEXThaler® has a similar dose measuring slide which is transported (to and fro) by the protective hood of the inhaler whereas an air triggered valve removes a plate which covers the powder cup until sufficient airflow has been generated. For extreme moisture sensitive powders, multidose reservoir inhalers may be less appropriate.

6.5.1.4 Powder Dispersion Mechanisms

As explained above, micronised particles of active substances are formulated (by agglomeration) into freely flowing powders to facilitate reproducible dose measuring. The agglomerates prepared are too large to reach the target area in the lungs and they must be dispersed (de-agglomerated). Particles of active substances blended with coarse carrier particles into so-called adhesive mixtures have to be detached from the lactose carrier particle surface onto which they adhere mainly by Van der Waals forces. In soft spherical agglomerates, cohesion (or adhesion) forces of the same nature between the small active substance (and excipient) particles have to be overcome during inhalation. Different types of de-agglomeration forces can be used and frequently emptying of the capsules and blisters and dispersion of the powder formulation occurs (at least partly) simultaneously. Most effective are inertial forces which are the result of particle collision against inhaler walls or that of high speed particle spinning and circulation. Particles may also impact with each other. Inertial forces as generated in the Novolizer®, Genuair®, (Teva) Spiromax®, (MSD) Twisthaler® and (Chiesi) NEXThaler® are proportional with the third power of the particle diameter. Drag and lift forces occur during emptying of the dose compartment or in turbulent air streams in or around special flow bodies. They are the result of considerable differences between the air and particle velocities and are largely proportional to the first power of the particle diameter. Therefore, they are much lower than inertial forces. They are also less effective when

the carrier particles have a high surface rugosity. The Turbuhaler® makes use of friction forces in addition to inertial forces. The soft agglomerates in this device pass a spiral-shaped channel in which centrifugal forces are responsible for considerable friction with the outer wall of this channel. The interaction between the drag force of the air stream pushing the particles forward and the friction forces with the inhaler wall causes internal shear which leads to disruption into smaller particles.

All dispersion forces in so-called passive (breath operated) inhalers are derived from the kinetic energy of the inhaled air stream. For well-designed inhalers with effective de-agglomeration principles this leads to a better dispersion at a higher flow rate. In addition to that, the particles in the aerosol may become finer. In contrast with what is frequently claimed in the literature [16], this is an advantage as it contributes to a more constant (patient independent) therapy. The finer particles reduce the increased deposition propensity in the oropharynx and upper airways, whereas the higher fine particle dose compensates for higher losses in the same regions. This results in a more constant central and peripheral lung deposition as has been shown for the Novolizer® in a study with radiolabeled budesonide [12]. Dispersion of the formulations is also improved by utilising the available energy within the inhaled air stream more efficiently. In most multi-dose reservoir inhalers, the powder is released from the inhaler mouthpiece within split seconds. Hence, a major part of the kinetic energy remains unused for dispersion. By keeping the particles in circulation for a certain period, a better de-agglomeration can be obtained, providing that the bulk of the aerosol is delivered within the first litre of air inhaled. The classifier types of dispersion principles in the Novolizer® and Genuair® have the longest circulation times followed by the Spiromax® and NEXThaler®, which have different circulation chambers. However for all these devices, the dose emission times remain shorter than those for most capsule inhalers. All these differences in design lead to considerable differences in dispersion efficiency and thus result in a large variation of fine particle doses at the same pressure drop across the inhaler. They also result in considerable differences in how the fine particle dose changes with the flow rate and thus, the degree of compensation for the effective flow rate on lung deposition.

6.5.1.5 The Mouthpiece

The inhaler mouthpiece can have different functions. It has been shown that minor variations of the mouthpiece geometry of an inhaler like the (Novartis) Aerolizer® may have a great effect on the throat deposition [17]. Active substance deposition in the throat is not only relevant because it reduces the lung dose but also because of possible local side effects, particularly from inhaled corticosteroids. Throat deposition is for a large part caused by carrier particles onto which a significant part of the dose remains attached during dispersion. The mouthpiece may also be used to fine-tune the total airflow resistance of the inhaler. This principle has been used in the Novolizer®, Genuair® and Diskus®. The Diskus® has two air holes on either side of the exit channel for the aerosol whereas the Novolizer® and Genuair® have a bypass that creates a clean air sheet around the aerosol to reduce deposition in the oral cavity. Compared to other DPIs, the Novolizer® and Genuair® have a different discharge pattern for the carrier particles as a consequence of which these particles are not deposited in the throat, but in the mouth from which they can easily be rinsed to prevent local side effects.

The Inhaler Resistance

Resistance to airflow is an inhaler property that is a direct consequence of its basic design, but can be fine-tuned with the mouthpiece. Persistent misconceptions exist about the inhaler resistance and hamper an optimal inhaler choice for individual patients and the correct use of DPIs. It is often postulated that operating a high resistance inhaler requires a greater effort and a higher amount of work than using a low resistance device [18]. It has also been described that patients have to inhale deeply and forcefully when using a DPI in order to receive the correct dose and that failure in this way is a common error when patients use their DPI [19]. This has resulted in the belief that patients with reduced vital capacity may have difficulties in operating high resistance inhalers effectively [16, 20]. As a response to this, the ERS/ISAM task force group has classified DPIs according to their flow rate (Φ) corresponding with a 4 kPa pressure drop across the inhaler into low resistance ($\Phi > 90$ L/min), medium resistance (60 L/min $< \Phi <$ 90 L/min), medium/high resistance (50 L/min $< \Phi <$ 60 L/min) and high resistance ($\Phi < 50$ L/min) [19]. They also explained that ‘because the internal energy in a DPI will be the same whether a patient inhales slowly through a DPI with a high resistance, or inhales quickly through a DPI with low resistance, the de-agglomeration of the powder will be the same’.

Reality is rather different, however. The amount of work for inhaling a certain volume of air through inhalers is independent of the inhaler resistance, as can be computed by expressing the energy in terms of flow rate, pressure drop and inhalation time. A lower flow rate at the same pressure drop through a high resistance inhaler is completely compensated by the longer time needed to inhale the same volume. Patients do not necessarily have to inhale deeply and forcefully to receive the correct (lung) dose. On the contrary, some inhalers are more effective when the flow rate is limited and a maximal value is not exceeded, as will be explained below. Therefore, whether patients with reduced vital

(continued)

capacity, e.g. severe COPD patients, have difficulties with operating a DPI correctly does not depend on the inhaler resistance, but on the severity of their disease. In fact all subjects, healthy or not, are able to generate a higher pressure drop across a higher resistance [21], but the value achieved at any resistance decreases with the degree of vital capacity reduction. Whether the pressure drop value achieved is sufficient for good DPI performance or not depends on the fine particle dose delivered at that pressure drop. There is no such thing as an internal energy in a DPI. What does exist is the kinetic energy of the inhaled air stream which is utilised to generate the de-agglomeration forces. Because different de-agglomeration forces are applied in different DPI designs, which may have different dispersion efficiencies, de-agglomeration cannot be expected to be the same on the basis of equal kinetic energy. In fact, fine particle doses vary considerably between inhalers at the same pressure drop and inhaled volume as will be shown and discussed in the next paragraph.

Patients with severely reduced vital capacity are often short-winded and have high breathing frequencies. Despite the fact that they may be capable of achieving sufficient pressure drop across the DPI, they may be unable to inhale sufficiently long to release the total dose from the inhaler or to transport sufficient aerosol to the central and deep lung. And inhaling against a high resistance may feel less comfortable than inhaling against a low resistance because it takes much longer before the same volume of air is inhaled, even if the amount of work is the same. Therefore, the choice of DPI resistance for a particular patient has to be balanced between patient acceptance and the benefits of a high resistance regarding lung deposition. In this respect, it should also be taken into consideration that many DPIs allow for a number of short inhalations to complete the administration of a single dose. Furthermore it has to be acknowledged that the total inhalation time including preceding exhalation and a breathhold pause is much longer than the time needed to inhale a certain volume of air and the DPI resistance has only a minor effect on that.

6.5.1.6 DPI Performance and Its Relevance to the Therapy

The airflow resistances of some currently marketed devices are presented in Table 6.2.

The difference between the highest and lowest flow rates corresponding with 4 kPa is by the factor 2.7. Although a good comparison between different inhalers cannot be made in this respect because different mouthpieces may result in different exit velocities at the same flow rate, the effect of flow rate on oropharyngeal losses for the same DPI may well be estimated from Fig. 6.5. Such a great difference in flow rates as between the extremes in Table 6.2 is likely to influence oropharyngeal losses considerably and the losses become more pronounced when the particle diameter increases. In addition to that, the lung deposition in the entire lung is shifted to larger diameters when the flow rate is increased. Whether this is disadvantageous for lung deposition or not depends on many factors, including the precise target area for the active substance, the size distribution of the aerosol and the range over which the flow rate can be varied. Lung deposition also depends on how the delivered fine particle dose changes with the flow rate. If the target area is in the larger airways the effect of the flow rate on the deposition pattern is less important than when the central or peripheral lung has to be targeted. The relatively high concentration of active substance in the larger airways compared to the peripheral lung is partly responsible for that; for most inhaled medicines the upper airways are relatively overdosed.

Table 6.2 Airflow resistances and flow rates corresponding with 4 kPa pressure drop for a number of currently marketed dry powder inhalers with asthma and COPD medication

Inhaler	Resistance ($kPa^{0.5}.min.L^{-1}$)	Flow rate at 4 kPa (L/min)
Budesonide Cyclohaler	0.019	105
Flixotide Diskus	0.026	78
Seretide Diskus	0.027	75
Budesonide Novolizer	0.028	71
Rolenium Elpenhaler	0.029	68
Budesonide Easyhaler	0.033	61
Symbicort Turbuhaler	0.034	59
Foster NEXThaler	0.034	59
Pulmicort Turbuhaler	0.037	54
Spiriva HandiHaler	0.051	39

Some fine particle doses as percent of the label claim are presented in Fig. 6.7 as function of the pressure drop for ICS from ICS-DPIs or inhalers with a combination of ICS and a β_2-agonist. The differences are rather extreme and roughly two different categories can be distinguished: inhalers with a constant fine particle output (e.g. Elpenhaler® and Diskus®) and inhalers of which the delivered FPF becomes higher when the flow rate is increased. Obviously, a high FPF is desired and most preferable is a high FPF delivered at a low flow rate. From the combination of the data in Table 6.2 and Fig. 6.7, it can be concluded that the Symbicort Turbuhaler® (29.5 %), Flixotide Diskus® (28.1 %) and budesonide Novolizer® (22.9 %) deliver the highest FPFs (<5 μm) at 2 kPa, corresponding with flow rates of 41.5, 54.5 and 50.5 L/min, respectively. The budesonide Cyclohaler® delivers the same FPF at 2 kPa as the Novolizer®, but this is at a much higher flow rate of 74.5 L/min. From Fig. 6.7 it may also be clear that inhalation through the Elpenhaler®, Diskus® and Cyclohaler® should not be forcefully, as recommended in the ERS/ISAM task force report [19], because this will not result in a higher delivered fine particle dose. On the contrary, a lower peripheral and central lung dose will be obtained due to higher oropharyngeal losses and the changes in lung distribution. For the Turbuhalers, Novolizer® and Easyhaler® the effect of inhalation effort is less critical because the losses and shift in deposition are more or less compensated by the increasing FPF, and the compensation is highest between 2 and 4 kPa. But even for the Turbuhalers and Novolizer®, an inhalation effort that will result in pressure drops higher than 4 kPa is not needed. Much more important it is to exhale deeply first before inhaling to total lung capacity, to assure aerosol penetration into the most distal airways, and finally to keep the breath for approximately 5–10 s to give sedimentation a chance.

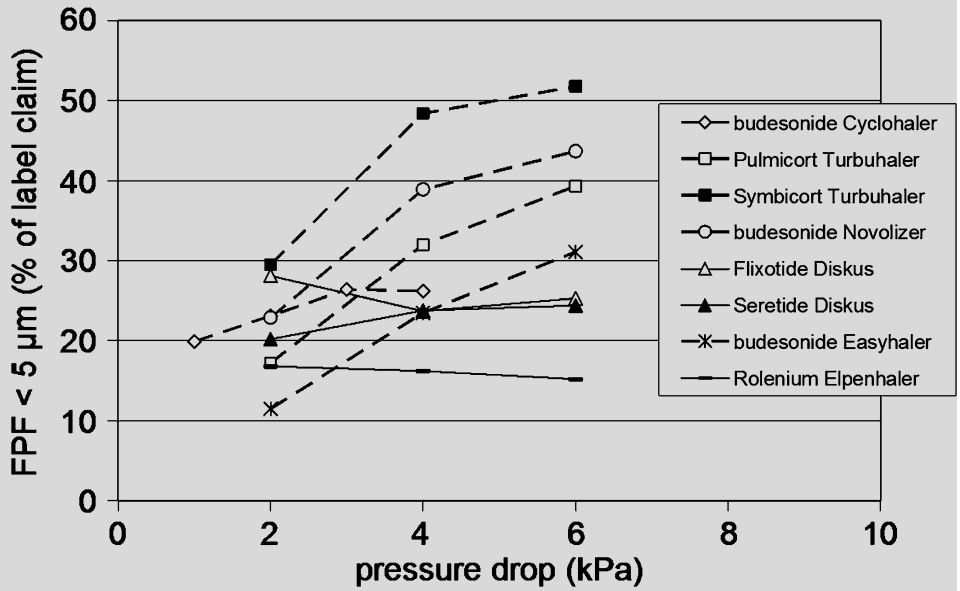

Fig. 6.7 Fine particle fractions < 5 μm (expressed as percent of the label claim) as function of the pressure drop across the inhaler

Aspects needing careful consideration when choosing a DPI for the individual patient are the ease of handling and risk of inhalation errors. Both are relevant to good adherence to the therapy and the efficacy of the treatment. In spite of numerous publications on these aspects good recommendations cannot be given because of the contradicting outcomes of the studies, of which several were reviewed by Lavorini et al. [22]. What does assist in the correct use of a DPI is signalling to the patient, as for instance given by the Novolizer® and Genuair®. Both devices give acoustic and visual signalling when the flow rate for good performance is achieved, after which the patient has to continue inhalation with the same effort for another 1–1.5 s.

6.5.2 Metered Dose Inhalers (MDIs)

In contrast to DPIs the basic design of MDI hardware is well described in the literature [23, 24]. Most MDIs apparently have a simpler design than DPIs and a key advantage of MDI systems is their low cost per dose. They are portable, convenient and have widespread acceptance by patients and clinicians. Basically they all have the same operational principle and furthermore all MDIs deliver a constant fine particle dose (independent of the flow rate). Whereas they have a relatively low resistance to airflow and this all makes the inhalation instruction less dependent on the individual type of MDI. The most relevant differences between types are in the actuator design and medicine formulation (solution or suspension), in which the type of propellant and the presence of co-solvents play an important role because of their influence on the (plume) velocity with which the aerosol is released from the actuator and rate of droplet evaporation.

6.5.2.1 Basic Design of MDIs

The general design of an MDI is shown in Fig. 6.8. The main body of an MDI is a small canister for the medicine formulation which is sized to contain sufficient volume for the labelled number of doses. The formulation contains a propellant (a gas with a high vapour pressure) which is one of the key components of an MDI. On top of the medicine formulation canister a metering valve or chamber is crimped. This has to separate a defined volume of the solution or suspension from the canister containing the amount of medicine for a single dose. The metering chamber is connected to a hollow stem that ends against the actuator orifice. On actuation of the MDI, the stem penetrates the metering chamber which becomes closed to the formulation reservoir and opens to the nozzle block in the actuator. This results in discharge of the formulation from the metering chamber through the stem and atomisation through the actuator orifice by propellant evaporation and gas expansion.

6.5.2.2 The Medicine Formulation

In contrast to DPIs, most MDIs contain a wide variety of different excipients. In the original design of the first MDIs on the market in 1957 (Medihaler-Epi™ and -Iso™, 3M-Riker), the propellant was a relatively low-pressure chlorofluorocarbon (CFC11, 12 and 114, or a mixture of these compounds). Initially, the choice of the type of propellant was rather driven by manufacturing convenience and formulation stability than by performance, and delivery to the lung was frequently as low as 5–10 % of the label claim. The Montreal protocol signed in 1987 and ratified in 1989 put an end to the use of CFCs because of their contribution to the depletion of the ozone-layer, and the CFCs needed to be replaced by hydrofluoroalkanes (HFAs) of which HFA 127 and 134a evolved as most suitable. Both HFAs used have broadly similar thermodynamic properties as CFC

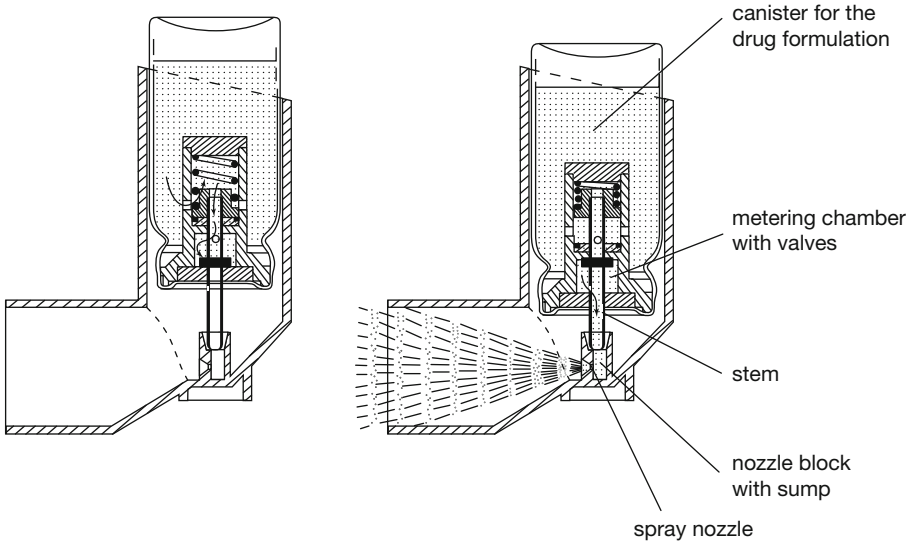

Fig. 6.8 Basic design of an MDI before (*left*) and during activation (*right*). Source: Recepteerkunde 2009, ©KNMP

12, but they are chemically different and this raised problems with certain active substances regarding solubility [25]. The active substance solubility problem is further complicated by the fact that previously used surfactants or other excipients for CFC-MDIs are insoluble in the HFAs too. For that reason co-solvents are currently often added to the formulations. Solution MDIs may have several advantages over suspension aerosols, including a higher physical stability, a more homogeneous formulation and potentially a larger fine particle dose. On the other hand, the primary co-solvent ethanol may change the size distribution of the aerosol and the evaporation rate of these droplets, whereas the excipients used in solution aerosols may also influence the pharmacological effect [25].

Suspension aerosols require that the active substance is added in a suitable size distribution to the formulation. The size distribution is obtained with the same techniques as used for dry powder inhalers, including micronisation in a fluid energy mill, spray drying and super-critical fluid drying. Whether this size distribution is the same as needed for adequate deposition in the target area depends on the concentration of active substance in the suspension. If the concentration is low, individual droplets from the actuator contain single particles of active substance and the size distribution of the suspended particles equals that required for lung deposition. If the concentration is high, droplets may contain multiple particles of active substance which cluster into small agglomerates upon evaporation of the volatile excipients. Such MDIs need finer particles in suspension. A primary concern for suspension MDIs is their physical instability due to phase separation, flocculation, agglomeration and sedimentation. Some of these processes may be irreversible and moisture ingress may negatively influence them. The active substance must also practically be insoluble in the formulation to prevent Ostwald ripening or the suspension must be thermodynamically stable if a certain level of solubility exists. Stability may further depend on the anomeric form or salt used for the active substance. In addition to co-solvents, a wide variety of other excipients may be present in the formulation, including surfactants (e.g. soya lecithin, sorbitan trioleate or oleic acid), suspending aids (e.g. PEG, PVP), bulking agents for low-concentration suspension MDIs (e.g. lactose, maltose, glycine and leucine) and traces of lubricant (silicone oil) for the metering valve.

The change from CFC to HFA propellants had consequences for delivery of the active substance to the respiratory tract. Improved delivery of beclomethasone dipropionate (BDP) from a HFA based MDI was explained by the much finer aerosol (with an average particle size of 1.1 μm) compared to CFC-BDP metered-dose inhalers, which deliver aerosols with average particle diameters of 3.5–4 μm [26]. This led to the conclusion that from a HFA-MDI only half the BDP dose is needed for the same efficacy as from a CFC-MDI [27]. More important for delivery of active substance to the lung may be the difference in plume velocity between CFC and HFA containing MDIs, however. In different studies the spray patterns [28], velocities [29] and impact forces [30] of different MDI types have been measured and the results show that CFC products have forceful plumes whereas most HFA systems produce much softer plumes. The use of HFA does not guarantee a lower plume velocity, however. The difference in velocities between CFC and HFA is for a large part due to the difference in nozzle diameters between both systems and some MDIs which use HFA propellants have a high aerosol velocity too (e.g. GSK Flixotide®).

6.5.2.3 The Metering Chamber (Valve)

The metering chamber is the MDI part with greatest complexity. To deliver a consistent amount of medicine, the valve must release a consistent mass of the bulk formulation with each actuation and the concentration of active substance in the measured mass must each time be the same. In fact the metering chamber has two valves. At rest, one (inner) valve is open to the canister to fill the chamber and this valve closes upon actuation after which a second (outer) valve is opened to release the contents of the chamber through the stem (Fig. 6.9).

The metering chamber, sealed with a ferrule onto the canister, must meet many other criteria amongst which low leakage during storage, low moisture transmission, low actuation forces and low extractables and leachables are the most important. Different designs exist for the metering chamber and many MDIs have a concept with a so-called retaining cup around the actual metering chamber. Without the retaining cup the metering chamber may drain out during storage of the MDI between inhalations or due to ‘shake out’ by the patient through the open valve between the metering chamber and the canister. The retaining cup is filled from the top of the canister when the MDI is in the inverted position (as during inhalation of a dose) and remains thus filled when the MDI is placed with the metering chamber in upright position. Retaining cups prevent not only loss of prime but also increase consistency of delivered dose when the canister approaches the end of labelled contents. Many other special

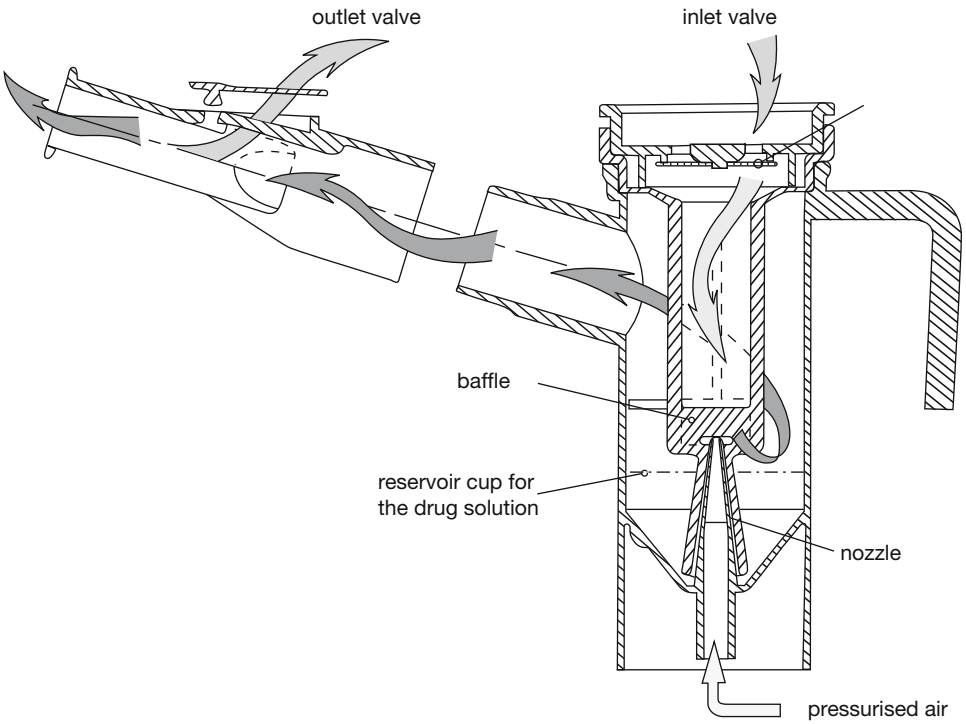

Fig. 6.9 Design of a jet nebuliser. Source: Recepteerkunde 2009, ©KNMP

metering chambers, e.g. with narrow and tortuous inlet channels, or 'fast-fill, fast empty' (FFFE) principles are in use or in development. They have been described or referred to elsewhere and will not be discussed here [31].

6.5.2.4 The Actuator

The actuator is the patient interface of the MDI in which the aerosol is formed. It is the mouthpiece of the MDI where the tip of the hollow stem from the metering chamber is positioned against a ledge in a nozzle block (Fig. 6.8). The nozzle block has a small expansion chamber (sump) which ends in a spray nozzle (also: atomisation or actuator orifice). The atomisation process is complex and starts already in the hollow stem when vapour cavities are formed in the liquid medicine formulation due to rapid expansion after the pressure is reduced compared to that in the confinement of the metering chamber. This process of expansion is continued in the sump, followed by rapid flashing of the propellant after exiting the spray nozzle [24]. Nozzle diameters are typically in the range between 0.3 and 0.6 mm and the precise geometry of the various parts of the actuator control the atomisation time as well as the size distribution of the aerosol and by that, the delivered fine particle dose. Also relevant is the geometry of the mouthpiece of which the length was originally 3–4 times longer than that for currently marketed MDIs. A long mouthpiece collects droplets that would otherwise be deposited mainly in the oropharynx. Shortening has improved portability, but it introduces the need for add-on devices (spacers or valved holding chambers). Also the mouthpiece shape and diameter affect aerosol delivery. Although several improvements have been implemented through the years, in many respects the actuator is still quite similar to its original design [31].

6.5.2.5 MDI Design and its Relevance to the Therapy

As a consequence of its push-and-breath design, MDIs require a good hand-lung coordination. Depending on the actuator design, the discharge time of a dose is typically between 0.1 and 0.5 s [24] and poor coordination may result in high losses in the mouth and throat region (in combination with the high exit velocity of the aerosol) and insufficient penetration of the active substance into the peripheral lung. Due to the extraction of heat from the mouth and throat cavity for evaporation of the propellant, patients may experience a 'cold-freon' effect which could negatively influence the inhalation manoeuvre. This cold freon-effect is particularly noticeable for CFC-MDIs having generally much lower plume temperatures (−20 °C to −30 °C) than HFA systems, although some HFA-MDIs also produce very cold plumes (e.g. Flixotide). To overcome these problems, particularly for small children and elder patients, various add-on devices can be used which either elongate the distance between the nozzle and the throat, or keep the aerosol in storage until it is inhaled. Aerosol storage in so-called valved holding chambers (VHCs) not only reduces the high throat deposition and the cold-freon effect, it also eliminates the hand-lung coordination problem. However VHCs may cause

considerable reduction of the delivered lung dose depending on how they are used, as discussed in the next paragraph. Healthcare workers giving instructions for use, should be informed about the design and properties of the MDIs they prescribe, as well as about the way these MDIs are used by their patients in order to estimate the risk of incorrect medicine delivery. For correct use of a suspension MDI, good shaking of the canister prior to dose activation is necessary in order to homogenise the suspension. Some patients tend to use their MDI upside down which could lead to incorrect refilling of the metering chamber, depending on its design.

6.5.2.6 Valved Holding Chambers (VHCs)

VHCs are storage chambers for the aerosols from MDIs with a valve in the mouthpiece. The one-way valve, which is meant to prevent exhalation through the VHC, should also remain closed during firing of an aerosol into the chamber and open when the patient inhales through the mouthpiece. Different types of VHCs exist with different volumes, made of different construction materials. VHCs reduce the oropharyngeal deposition from MDIs with a high plume velocity, but they also reduce the inhaled dose as the result of losses into the chamber which may be the result of inertial impaction against the end with the valve, electrostatic interactions with the chamber walls and sedimentation. To reduce the losses by electrostatic interactions, it is recommended to wash the spacer before use with a highly diluted solution of household detergent and dry it to the air (dip and dry method). This method is equally effective as priming with doses, which is a loss of medication. Also after coating with detergent or priming, losses in a VHC can be substantial, however, and they increase with decreasing relative air humidity (RH). For corticosteroids the dose from a well prepared VHC at low RH (30 %) may be reduced to 20–40 % of the dose directly from the MDI. At higher RH (75 %) the reduction may still be 40–70 % of the MDI dose, depending on the type of VHC and medicine formulation used. Metal VHCs or antistatic VHCs do not need priming or washing, but losses in antistatic plastic VHCs are influenced by the RH too. Losses due to sedimentation are less extreme and limited to approximately 30 % after 20 s (compared to the delivered dose immediately after firing into the VHC). Special attention should be given to VHCs used in combination with a face mask for very young children. When the mask does not fit closely to the child's face, unmedicated air is inhaled. A small leakage of approximately 0.5 cm^2 may result in near-complete bypassing of the VHC which has the consequence that only a fraction of the dose is delivered to the respiratory tract [32].

Because patients may accidentally exhale through their VHCs depending on the design or performance of the valve system, contamination with micro-organisms is possible. In VHCs used over a period of 4 months by children with asthma and recurrent cough, species of *Bacillus* and *Staphylococcus* could be detected. In a total of 64 VHCs only one was infected with *Pseudomonas aeruginosa* and no other pathogenic organisms could be found. The presence of *Bacillus* and *Staphylococcus* appeared to be independent of the type of VHC used and the cleaning procedure [33].

6.5.3 Nebulisers

Nebulisers are less frequently used than DPIs and MDIs and their application is mainly confined to active substances that are not available in registered inhalation devices (which can for instance be high dose medicines) or to the administration of medication to ventilated patients.

Basically three different types of nebulisers exist:

1. Jet nebulisers, which consist of a two-fluid nozzle connected to a reservoir cup for the medicine solution and a compressor or a compressed air system
2. Ultrasonic nebulisers
3. (Vibrating) membrane inhalers with a high output rate based on different aerosol generation principles, designs and performances

Jet nebulisers in the home situation are increasingly replaced by (vibrating) membrane inhalers which give better control over the medicine delivery to the respiratory tract than the classic jet and ultrasonic nebulisers, and may increase the adherence to the therapy.

In contrast to DPIs and MDIs, nebulisers do not contain a medicine formulation. Nebulisers receive market clearance in the USA via a 510(k) premarket notification (CDRH Guideline 784) and by CE marking in Europe. They can either be developed for the administration of a particular type of a solution or suspension of an active substance, or a medicine may be licensed for the administration with a particular type of nebuliser. An example is tobramycin solution (TOBI®, Novartis) which is licensed in the USA for use with the Pari LC Plus® nebuliser in combination with the DeVilbiss Pulmo-Aide® compressor. In Europe, a 'suitable' compressor is allowed, which for TOBI® for the LC Plus® nebuliser is specified as a compressor with a jet pressure between 110 and 217 kPa or a jet flow between 4 and 6 L/min. In practice, suitable compressors are not always used and the LC Plus® is also frequently exchanged with vibrating mesh devices, like the Pari eFlow rapid®. This is a consequence of the fact that in most countries the purchase of nebulisers is not regulated as tightly as the purchase of medication and patients can get hold of nebuliser equipment without medical advice. This situation has not really changed since the European Respiratory Society (ERS) issued their guidelines on the use of nebulisers in 2001 [34]. In fact, many nebuliser systems are still sold without or with no printed information regarding their use and the

hope of the ERS task force that their guidelines would improve clinical practice in the use of nebulised therapy throughout Europe has not come true.

6.5.3.1 Basic Design of Jet Nebulisers

The basic design of a jet nebuliser is shown in Fig. 6.9. A jet nebuliser has a reservoir cup for the solution (suspension) of the active substance and a nozzle. The nozzle starts at the bottom of the medicine reservoir and consists of two co-axial tubes ending on the same level above the medicine solution. One of the co-axial tubes is connected to a supply system for compressed air, the other tube is open on its lower side to allow medicine solution to enter this tube. For reasons of design, mostly the inner tube is for compressed air, whereas the outer tube is for the medicine solution. The air jet leaving the nozzle exit entrains liquid from the outer tube by momentum transfer. The liquid jet disrupts by shear forces into droplets with a size distribution that is too wide for inhalation. For that reason, a baffle is placed at a short distance above the nozzle. Droplets that are too large to reach the site of action in the lungs impact against this baffle according to the same principle as described for medicine particle deposition in the oropharynx and return to the liquid reservoir. Only the smallest droplets can pass the baffle and mix with the inhaled air stream.

Many different types of jet nebulisers exist and they differ not only in the properties of the delivered aerosol regarding the size distribution and output rate, but also in the efficiency with which the aerosol is delivered to the patient. They can be distinguished in:

- Nebulisers without valves
- Nebulisers with open valves
- Nebulisers with breath assisted valves
- Breath actuated nebulisers (BAN)

Most basic nebulisers (e.g. Hudson T Updraft®) have no valves. They continuously produce the aerosol which is released into a chamber connected with a T-shaped mouthpiece. One of the branches of this mouthpiece delivers the aerosol to the patient's respiratory tract during inhalation. Aerosol losses to the environment are relatively high because the patient also exhales through the same T-shaped mouthpiece and the approximate ratio for exhalation to inhalation time during normal breathing is 2:1. Exhaled air may entrain aerosol from the nebulisation cup too and release it to the environment. For that reason, different valve systems have been developed to increase the aerosol mass delivered to the patient. The most simple example is an open valve (e.g. Respironics Sidestream®) which directs (part of the) inhaled air through the aerosol chamber to flush this chamber, thereby increasing the aerosol output. Open valve systems have further evolved into breath assisted open valve nebulisers (e.g. Repironics Sidestream Plus® and Pari LC Plus®). Such nebulisers have inlet and outlet valves which open and close in an alternating way during the inhalation cycle. Upon inhalation, the inlet valve opens to enable the inhaled air to entrain the aerosol from the aerosol chamber. Meanwhile the outlet valve, which is in an elongated mouthpiece, is closed. During exhalation, the inlet valve closes to prevent aerosol escaping from the nebuliser whereas the outlet valve opens to bypass the exhaled air. In the meanwhile, the aerosol produced accumulates in the aerosol chamber and elongated mouthpiece. The outlet valve may be connected with a filter to collect exhaled aerosol particles. With such a double valve (with filter) system, the aerosol losses to the environment can be minimised. Inlet valves may be complex to reduce the range of attainable flow rates in favour of central and deep lung deposition (e.g. Pari LC Sprint® with PIF control). Such valves have an increased resistance when the flow rate becomes too high and limit the flow rate to approximately 25 L/min. Mechanical breath actuated nebulisers (e.g. Trudell AeroEclipse®) interrupt aerosol production during periods of exhalation. They have a diaphragm which moves down an actuator piston to start the nebulisation process when the flow rate has reached a threshold value of approximately 8–15 L/min [35]. During exhalation, the actuator piston moves up again to stop the aerosol production and to eliminate waste to the environment. Some modern liquid inhalers have an electronic instead of a mechanical breath actuation system, but they will be discussed separately.

6.5.3.2 Jet Nebuliser Use, Performance and Maintenance

The performance of a jet nebuliser depends on many different parameters. The jet pressure, or jet flow rate, is one of the primary determinants for the droplet size distribution of the delivered aerosol [36]. A higher jet flow rate results in smaller particles and because the size distribution of an aerosol affects the site of deposition in the respiratory tract, replacing the compressor by another type may change the efficacy of the therapy if the jet pressures of both compressors are not the same. The jet flow rate furthermore determines the nebulisation time. Additionally, the physical properties of the solution of the active substance may influence the size distribution of the aerosol and the output rate of a nebuliser [37]. These properties, of which the surface tension, viscosity and density are the most relevant, depend not only on the type of active substance in solution, but also on the concentration of the active substance [36–39]. Furthermore, the flow rate may influence the size distribution of the aerosol from a jet nebuliser and the influence increases with decreasing jet flow rate [36]. Finally, good maintenance of a nebuliser is important. Nebuliser cups are used over longer periods, varying from several months to years, and particularly when antibiotics are nebulised, good cleaning

and disinfection on a regular basis are of utmost importance. Disinfection may prevent bacterial resistance development in the medicine administration device and re-infection of the patient by medicine-resistant strains. During cleaning and disinfection, nebulisers are frequently disassembled and patients should take care that re-assembling occurs precisely as prescribed. Small variations in the distance between the nozzle exit and the baffle considerably influence the size distribution of the aerosol and so does a minor change in the diameter of the nozzle exit. Clogged nozzle exits should therefore never be opened with a sharp pin, but by submersion in warm water with some household detergent and using the compressed air from the compressor to remove the plug if it does not completely dissolve.

Major disadvantages of jet nebulisers are their long preparation, cleaning and nebulisation times and their low lung deposition efficiency. Total administration times can cumulate to more than 30 min, whereas estimated mean lung doses in well controlled clinical studies vary between only 9–20 % for breath enhanced and breath-actuated nebulisers [40]. The lung deposition in real life may even be considerably lower as patients are tempted to combine nebulisation with other activities. This may for instance result in keeping the nebulisation cup not in the prescribed position. It has been shown that controlling the inspiratory flow manoeuvre significantly increases the lung dose and reduces the variability in lung deposition from jet nebulisers. Flow and volume regulated inhalation technology with the Akita Jet® (Activaero) has shown that 60 mg nebulised tobramycin with this system and the LC Star® nebuliser can result in the same serum level after 1 h as 240 mg nebulised tobramycin with an LC Plus®/PariBoy® N combination in less than half the administration time [41]. The Akita system is voluminous however and reduces the mobility of the patient. Finally, and in contrast, the delivered lung dose may considerably deteriorate from using long, tortuous and/or corrugated tubings as in the treatment of mechanically ventilated patients. Total lung deposition in such patients from jet nebulisers may be as low as 2.3 % [42]. Successful administration of inhaled medication to mechanically ventilated patients requires special equipment and arrangements which is not further discussed in this chapter.

6.5.3.3 Basic Design of Ultrasonic Nebulisers

Ultrasonic nebulisers make use of piezo technology to create an aerosol from a solution of active substance. In such nebulisers the high frequency mechanical vibration of a piezoelectric element is transmitted to a solution of the medicine which creates standing capillary waves on the surface of that solution. Small droplets break free from the crests of these waves and constitute the aerosol. The mean droplet diameter is a function of the frequency of the acoustic signal, the surface tension, density and viscosity of the medicine solution [43]. Basically two different classes of ultrasonic nebulisers exist: those in which the ultrasonic vibration is directly transmitted to the medicine solution and those in which the oscillation is transmitted indirectly via an outer bath. A third type of ultrasonic nebulisers making use of perforated membranes (vibrating membrane technology) will be discussed in Sect. 6.5.4.

6.5.3.4 Ultrasonic Nebuliser Use and Performance

As for jet nebulisers, a great variety of different designs exists for ultrasonic nebulisers. Which type to select primarily depends on the desired droplet size distribution. The design, in particular the operating frequency, is a major determinant for the aerosol characteristics but also incorrect use may influence the aerosol properties. Particularly the filling degree of the outer bath of jacketed nebulisers proves to be very critical for performance. Ultrasonic devices may also have a baffle to return large droplets to the medicine reservoir and a fan to assist the fine particle output. The size of the droplets is often larger and the aerosol output rate higher compared to jet nebulisers. Evaporation is less extreme in ultrasonic nebulisers however, and therefore the increase in concentration of the active substance with aerosolisation time is lower. Residual volumes in ultrasonic nebulisers are higher. Solutions of high viscosity and suspensions of active substance (e.g. budesonide) cannot efficiently be atomised by ultrasonic nebulisers. In contrast to jet nebulisers, where a drop in temperature can be observed due to evaporation, the temperature of solutions in the reservoir of ultrasonic nebulisers increases during the atomisation process. This may result in partial degradation of heat sensitive substances, such as proteins. Liposomal formulations have successfully been delivered with ultrasonic nebulisers, although some disruption of vesicles has been observed and increasing the vesicle stability by use of substances such as cholesterol is recommended [44]. Ultrasonic nebulisers do not require compressors and are generally much smaller and less heavy than jet nebulisers. In addition, they are almost silent, but these advantages have not made them very popular in most European countries [34]. Therefore, they are not discussed further (see also novel liquid inhalers).

6.5.3.5 The Choice of Device and Instructions for Use

A great variety of jet and ultrasonic nebulisers is available for a wide range of size distributions and different output rates [45]. If an inhaler is approved for the administration of a particular type of medicine formulation, it should be the first choice for that application. If the nebuliser or compressor (for jet nebulisers) is not available, as for instance

(in Europe) the DeVilbiss Pulmo-Aide® compressor for TOBI®with the LC Plus®, an alternative with the same specifications should be selected. For a compressor, this is the jet flow through the nebuliser cup. Also when a jet nebuliser is connected to a compressed air system (as is mostly the case in hospitals and nursing institutes) it should be controlled such that the pressure regulator is set to the correct value for the type of nebuliser cup used. This must be checked when the nebuliser is operated. Only when patient adherence to the therapy is very low, for instance due to very long nebulisation times, a change of device may be considered, as a (slightly) different lung deposition pattern could be less bad for the patient than omitting the medication on a regular basis.

6.5.4 Novel Liquid Inhalers

In addition to classic jet and ultrasonic nebulisers a new class of high-performance novel liquid aerosol delivery devices has become available. They have a high aerosol output rate in common (yielding a dense mist) and most of them have a perforated vibrating membrane (mesh) as aerosol generator. The oscillations are obtained with piezo technology which in combination with the membrane is referred to as vibrating membrane technology (VMT). Basically two slightly different principles can be distinguished: those in which the membrane is oscillated (e.g. Pari eFlow rapid®) and those in which a horn transducer adjacent to the membrane is vibrated (e.g. Philips Respironics I-neb®). The perforated membrane makes contact with the medicine solution and the pressure pulses of the liquid against the membrane force the medicine solution (or suspension) through the tiny holes which determine the size of the droplets. Principles based on Rayleigh break-up of liquid jets forced through the perforated membrane under a constant pressure are still in development (e.g. Aradigm AERx Essence®). Only one alternative principle is currently available on the market: the Respimat® soft mist inhaler (Boehringer Ingelheim). Although the Respimat® has a different design, it will also briefly be explained in this paragraph. A good review of novel liquid nebulisers based on different aerosolisation principles has been given by Knoch and Keller (2005) [46].

Compared to classic jet and ultrasonic nebulisers, most novel liquid inhalers have the advantages of:

- Much shorter nebulisation times
- Delivering narrower size distributions
- Being small and portable
- Being battery operated, which eliminates the need for mains
- Being less noisy
- Having lower fill and residual volumes
- (Optional) Breath controlled or adaptive medicine delivery
- (Optional) Patient monitoring and feedback

Reduction of the nebulisation time and a greater convenience in handling may increase the patient's acceptance and this can reflect positively on the adherence to the therapy. Many novel liquid inhalers are electronic devices. This offers possibilities for patient monitoring and feedback, but also for so-called adaptive aerosol delivery (AAD), a principle of medicine delivery which has been described elsewhere [46]. In brief, a flow sensor in the inhaler measures the patient's breathing pattern and the system's software computes the mean of a few breathing cycles. The average breathing cycle is the basis for pulsed aerosol delivery only during periods of inhalation, thereby avoiding waste during exhalation. It is believed that the narrow size distributions of the aerosols from membrane nebulisers contribute to better targeting, but there is no evidence yet for that from deposition studies.

Different novel liquid inhalers are on the market for different applications and only some representative examples are described in more detail in this section.

6.5.4.1 Respimat®, Boehringer Ingelheim

The working principle of the Respimat® has been described before by Zierenberg [47]. In the Respimat®, a medicine reservoir is connected to a capillary tube with a one-way valve. During preparation of the device, a spring is loaded and medicine solution is drawn through the capillary into a metering chamber. When the patient presses the dose release button, the metered volume of medicine solution is pressed through a so-called uniblock with a nozzle by mechanical power of the preloaded spring. The nozzle releases two converging jets at precisely controlled angles which collide with each other at a short distance from the nozzle exits. This creates a slow-moving fine mist. The inhaler is re-usable but the medicine reservoir is replaceable. When a new cartridge is inserted, the inhaler has to be primed to expel air from its inner parts. The Respimat® is available with tiotropium bromide (Spiriva®) and ipratropium bromide with salbutamol (Combivent®). The inhalation technique is similar to that for an MDI and requires a good hand-lung coordination. The emission time is longer (approximately 1.5 s) and the exit velocity is lower (approximately 0.8 m/s) compared to MDIs, however. The fine particle dose from the Respimat® strongly depends on the inspiratory flow rate, which due to the low resistance can be very high (2 kPa corresponds with 125 L/min). Measured with a cooled Next Generation Impactor to minimise droplet evaporation, FPF 1–5 μm from the Spiriva Respimat® decreases from over 40 down to 28 % when the flow rate is increased from 30 to 90 L/min. The reason is a strong reduction of

particularly the larger particle fractions (from 35 % at 30 L/min to 20 % at 90 L/min for the fraction 3–6 μm). As a consequence, the fraction < 3 μm remains more or less constant (18 % at 30 L/min versus 22 % at 90 L/min), but this is partly the result of a much higher fraction < 1 μm at the higher flow rate (8.0 % versus 1.8 %). Therefore, it should be recommended not to inhale with much greater effort as during tidal breathing through the Respimat®.

6.5.4.2 eFlow (Rapid)®, Pari

The Pari eFlow rapid® is an example of a vibrating mesh nebuliser [48]. The eFlow® platform makes use of the TouchSpray™ (piezoelectric) technology [49] and the rapid®, as one of the members of the eFlow® family, is designed to deliver nebulised medicines used in CF therapy. It reached the European market in 2005 and according to the manufacturer, this device has already reached approximately 75 % market share amongst European CF patients. The eFlow rapid® consists of a controller and a handset. The handset comprises the medication reservoir with an aerosol chamber, the vibrating membrane in contact with the medicine solution and the mouthpiece. The membrane has a large number of tapered holes that narrow towards the aerosol release side. During vibration, sound pressure is build up in the vicinity of the membrane thus ejecting the fluid through the holes. Because all holes have the same size, the droplet size distribution in the aerosol is rather narrow. According to Pari, the hole diameters can be adjusted from 2 μm upwards to meet the requirements for different therapeutic applications. Also according to the manufacturer, the mass median aerodynamic diameter of TOBI® (tobramycin), measured at 28.3 L/min, is 3.95 μm from the eFlow rapid® versus 3.5 μm for the Pari LC Plus® jet nebuliser with PariBoy N® compressor. The difference has to be confirmed in several independent studies and it can increase when a more powerful compressor (with higher jet pressure) is used for the LC Plus®. On the basis of the differences in MMAD and the span of the size distribution, it must be expected that both nebulisation devices result in different distributions of active substance over the lung and therefore, they cannot be considered completely equivalent in this respect. The average nebulisation time with the eFlow rapid® is considerably shorter than with classic jet nebulisers and the reduction can be more than 50 %. CF patients do use their eFlow rapid® also for the administration of other medication, like salbutamol, ipratropium bromide, terbutaline, colistimethate sodium, rhDNase and acetylcysteine. This has the risk of membrane pollution, as patients do not always clean their nebuliser equipment properly after use. It can result in clogging of holes in the perforated membrane, which does not result in a change in particle size, but in a reduced output rate [50]. This leads to longer nebulisation times and may be at the cost of the patient's adherence to the therapy. Pari has developed a function test for the membrane and a cleaning device (easycare), but after a number of cleanings the membrane should be replaced.

6.5.4.3 I-neb®, Philips Respironics

The I-neb® is a membrane (mesh) nebuliser with an AAD system which is approved for the delivery of iloprost in the USA and in Europe as a multipurpose nebuliser for special applications included in the medicine license [51]. The I-neb® consists of a mouthpiece, a medication chamber and a handpiece. The medication chamber comprises a horn with the mesh plate which has 5,000–6,000 holes of 3 μm in diameter. The piezo crystal imposes a high frequency upward and downward movement upon the horn and this pushes the liquid through the holes in the plate. The I-neb® is operated with discs that are programmed for delivery of specific medicine formulations. These discs have microchips that correspond with the I-neb® handpiece about the dose, the dosing frequency, the number of doses and other variables related to the medicine administered. The I-neb® AAD system has two different modes of operation: the tidal breathing mode (TBM) and the target inhalation mode (TIM) which is for slow and deep inhalation. The TBM mode is suitable for most adults and children of 2 years and older; for optimal use of the TIM mode, patients need to have a forced vital capacity > 1.75 L. Breathing with TIM increases lung deposition and reduces total treatment time. It is claimed that the majority of medicine in the aerosol from the I-neb® (60–80 %) is within the size fraction < 5 μm. Due to its higher efficiency compared to classic jet nebulisers, a threefold reduction in medicine volume and up to a fivefold reduction in nominal dose may be possible with the I-neb® with the AAD system [51].

Similar portable mesh nebulisers are available from Omron (MicroAir NE-U22®) and Aerogen (Aeroneb Go®). The Aeroneb Go® is based on the OnQ™ vibrating mesh technology which comprises a dome-shaped aperture plate containing over 1,000 precision-formed tapered holes, surrounded by a vibrational element. The aperture plate is caused to vibrate at over 128,000 times per second. Aerogen also have a multidose vibrating mesh nebuliser (Aerodose®) [52] and two VMT devices for hospital use (Aeroneb Pro® and Aeroneb Solo®). The Aeroneb Pro® is a reusable, multi-patient use nebuliser which is suitable for hospital environments where the appropriate sanitisation facilities are available. This autoclavable nebuliser provides effective dose delivery of physician-prescribed inhalation solutions for infants through

(continued)

adults in both on and off ventilator applications. The Aeroneb Solo® is a single-patient use nebuliser for continuous and/or intermittent nebulisation, ensuring targeted delivery of active substance to the smallest airways in the lungs. The silent operation of the Aeroneb Solo® allows it to be used in paediatric ICUs where noise levels are critical. The Solo® has a low residual volume (<0.1 mL for 3 mL dose). The Omron MicroAir NE-U22® has a vibrating horn within the liquid reservoir that pushes the liquid through the membrane. The frequency of oscillation of this horn is 180 kHz and the particle diameter claimed for the MicroAir is 5 μm. For the MicroAir it is recommended that the vibrating mesh cap is replaced every 6 months to maintain its peak performance.

The novel liquid inhalers have several specific pros and cons. An attractive feature is the potential for a single platform to deliver multiple inhaled medicines in complex treatment regimens, like in CF [51]. However, it has to be recommended that patients and physicians do not decide to change from an approved (medicine-nebuliser) combination to a novel liquid inhaler when the medicine formulation has not yet been tested first in the VMT device. Neither should patients decide to use their inhaler for other medication than the medicine for which their mesh nebuliser was prescribed. Different solutions of active substance may result in aerosols with different size distributions due to differences in physico-chemical properties and this can lead to poor targeting of the site of action (poor efficacy of the therapy) compared to delivery with the approved nebuliser. Another advantage of the new class of nebulisers is the wide range of doses that can be delivered with these devices. Pari claim a range from a few micrograms up to several grams. Also the possibility to store data about the use of the inhaler and to give immediate feedback to the patient about the inhalation performance may be an advantage. Synchronising aerosol delivery with the breathing manoeuvre (as with AAD) may furthermore considerably improve the efficacy of the delivery of active substance to the lungs. Reduced nebulisation time, smaller and mostly battery operated devices and a more silent operation are likely to increase patients' adherence to the therapy compared to classic jet and ultrasonic devices, but whether a better adherence is really achieved has still to be proven. The high price of most novel liquid inhalers is a serious drawback and could become a reason for healh funders to deny reimbursement when improved adherence is not shown. Vibrating meshes are also vulnerable to pollution and the need for good cleaning must be emphasised. Patients should clean their inhaler thoroughly and immediately after use according to the instructions in order to prevent clogging of the apertures in the membrane. In practice, patients are not always compliant with the instructions, however, and it has been shown that off-clinic use may result in a significant change in performance within a period of 6 months [50]. Finally, also the most recently developed systems require at least 2–4 min for the administration of a dose and this excludes the time needed for preparation and cleaning of the equipment. For patients with multiple medicine therapies, this is still burdensome. For a number of applications, dry powder inhalation may be a better alternative, also because dry powders are more stable than medicine solutions. Therefore, they need no cold chain storage.

6.6 Medicine Formulations for Nebulisation

Many marketed medicine formulations for nebulisation are available, but in contrast to preparations for dry powder inhalers and metered-dose inhalers, solutions and suspensions for nebulisation are also prepared in pharmacies. Marketed formulations may furthermore have to be diluted, depending on the type of inhaler used. Many nebulisers have a residual volume between 1 and 2 ml and the fill volume has to compensate for these losses. Compensation is also needed for the amount of medicine in the residual volume. Diluted formulations must be used within 24 h after preparation because of poor stability. Most nebulised medicines fall into two physico-chemical categories: solutions and suspensions [34]. For solutions it is assumed that the medicine is homogeneously distributed throughout all droplets. Suspensions are inherently more complicated as their density may be less homogeneous and individual droplets may contain different amounts of the active substance. This could lead to a droplet size dependent concentration of the active substance or a considerable change in concentration with nebulisation time. Below some of the most relevant aspects regarding the preparation of medicine solutions and suspensions for nebulisation are summarised; additional general recommendations for preparation, labelling, testing and packaging can be found elsewhere in this book.

6.6.1 Medicine Solutions

Medicine solutions for nebulisation may contain several additives such as co-solvents, solubilising and stabilising agents, antimicrobial preservatives, salts and pH-regulators to adjust the acidity and tonicity of the solution. Additives may contribute to the osmotic value. Both high and low osmotic values can produce cough and bronchoconstriction

(or both). If the patient shows signs and symptoms of bronchospasm, baseline spirometry before dose administration is recommended, followed by spirometry at 15 and 30 min post-dose. Active substances such as salbutamol, terbutaline and ipratropium are mostly dissolved in isotonic saline (0.9 % sodium chloride). Sodium chloride strengths between 3 % and 7 % are also used for nebulisation, but they may not be mixed with other medicines. To enhance the solubility of active substance in water or saline, the addition of a co-solvent may be needed and surfactants can be added. Also controlling the acidity may lead to a better solubility and the European Pharmacopoeia allows to vary the pH within the range between 3 and 8. However, it is known that aerosols with a pH below 4.5 can cause cough and bronchoconstriction, particularly in asthmatic patients, and some caution is therefore required. The medicine in solution may also change the pH of the solvent and pH-regulators such as sulphuric acid and sodium hydroxide are frequently added to keep the acidity within the desired range. If the solubility of active substance and stability allow for it, it is best to keep the acidity close to neutral as the pH in healthy lungs ranges between 7 and 8.

6.6.2 Medicine Suspensions

Currently, suspensions prepared from micronised active substances are the only marketed delivery system for nebulisation of poorly water soluble substances such as steroids and cyclosporine [53]. Several problems are inherent in nebulising micro-suspensions and they vary from non-optimised lung deposition for the active substance to heterodispersity of the active substance concentration in the aerosol droplets and poor compatibility with different types of nebulisers, particularly ultrasonic devices. Suspensions may also have poor stability and the two components (solid and liquid) tend to separate with time within the formulation by sedimentation or flocculation, depending on the particle density relative to that of the liquid. Several jet nebulisers can deliver suspensions quite effectively, even independently of the primary particle size [54], but ultrasonic devices may convert primarily the continuous phase into aerosol whereas vibrating mesh inhalers can be blocked by particles being larger than the pore diameter of the membrane.

In addition to solutions and suspensions, liposomal formulations of active substances are used and various nanoemulsion-based formulations and micellar solutions are explored for nebulisation [55]. Currently, no marketed inhaled liposomal products are available [56], but liposomal amphotericin B for injection or infusion is frequently used for nebulisation against invasive fungal pulmonary infections. Compared to amphotericin B, which is relatively instable and therefore commercially available as a complex with sodium desoxycholate, the liposomal formulation has a higher tolerability profile. Most liposomal formulations are currently developed for sustained release however, and two liposomal antibiotics for nebulisation (Arikace®, Insmed, for amikacin and Lipoquin® and Pulmaquin®, Aradigm, for ciprofloxacin) have received orphan drug designation to treat lung infections caused by nontuberculosis mycobacterial (by the European Medicines Agency) and for inhalation in bronchiectasis (by the US Food and Drug Administration (FDA)) respectively. Which type of nebuliser to use best for liposomal formulations may not only depend on the desired particle size distribution of the aerosol and aerosol output rate, but also on relevant physico-chemical properties of the formulation. Both jet and ultrasonic nebulisers damage the liposome structures and the smaller the droplet size, the greater the damage may be. The degree of disruption also depends on the excipients used, and the inclusion of cholesterol or DPPC increases the resistance to disruptive forces [44]. The liposomal ciprofloxacin Pulmaquin® is developed for Aradigm's AERx® pulmonary medicine delivery platform (with perforated mesh).

6.6.3 Stability of Formulations for Nebulisation

Most ready-to-use liquid preparations for nebulisation are supplied in single-dose vials and according to the European Pharmacopoeia, they have to be sterile and preservative-free. When they are supplied in multidose containers, they have to be sterile if they do not contain an antimicrobial preservative or when the preparation does not have adequate antimicrobial properties itself. The multidose containers have to be designed to prevent microbial contamination of their contents during storage and use. A wide variety of preservatives is available but some of them, like phenol, bisulfites, edetate and benzalkonium chloride can cause airway irritation and result in bronchoconstriction or reduce the efficacy of the medicine [57]. Other compounds such as chlorobutanol, methyl- and propyl-parahydroxybenzoate and also benzalkonium chloride are ciliotoxic at

concentrations equal to or lower than those in use for preserving aqueous formulations [58, 59]. Ciliotoxicity, reduced medicine efficacy and airway irritation resulting in cough and chest tightness are the reasons why many bactericidal agents have been removed now from marketed medicine formulations. Some alternatives have been presented as less harmful, like chlorocresol and chlorbutanol [60] but generally it may be safer to supply sterile preservative-free liquid formulations for nebulisation in unit dose vials.

In formulations for nebulisation also the stability of the active substance itself in solution must be taken into consideration. For instance, colistimethate sodium (CMS), increasingly used to treat multi-resistant gram negative infections by nebulisation, spontaneously hydrolyses in aqueous solution to form colistin A (polymyxin E1) and colistin B (polymyxin E2/B). High levels of these decomposition products have been associated with nephrotoxicity and even death and in 2007 the FDA issued an alert after a patient died following the inhalation of a solution of CMS. CMS is supplied as a lyophilised powder and current recommendations state that CMS should be reconstituted no more than 24 h prior to the administration by nebulisation [61]. It is important to note that sterile water is the diluent recommended by the major manufacturers because reconstituted CMS in saline is significantly less stable [62]. Recently, the stability of reconstituted CMS for injection in sterile water was investigated at different storage temperatures and it was found that total colistin A and B formation at room temperature in 24 h is less than 1 % [61].

6.6.4 Mixing of Formulations for Nebulisation

Most product information leaflets for nebulised medicine formulations discourage mixing of marketed formulations but in practice different formulations are frequently mixed to increase patient comfort. Particularly CF patients tend to combine medicines in order to save time as well as to overcome adverse effects (e.g. bronchoconstriction) of one active substance (antibiotic) by another (salbutamol). They also tend to refill their nebuliser with a new medicine without emptying and cleaning the nebuliser between the administrations. Relatively little has been reported in the literature about the compatibility of medicine mixtures, however, and interactions may be expected with respect to chemical and physical stability, droplet size distribution of the aerosol, nebuliser output rate and therapeutic effect. From a survey of studies on chemical stability, it is known that particularly dornase alpha (Pulmozyme®) is incompatible with many other nebulised medicine formulations due to inactivation of the protein [63]. Additives, like stabilisers that work well in some medicine formulations, may be incompatible with other preparations and induce cloudiness or precipitation. For instance, benzalkonium chloride may form an oily, non-crystalline complex with cromolyn, depending upon its concentration [64]. Benzalkonium chloride is also incompatible with colistin, whereas edetate is known to increase the activity of azithromycin [65] and colistimethate sodium [66] by chelating divalent cations such as calcium. The effect of mixing medicine solutions or suspensions on nebulisation performance is studied even less although for a few combinations data can be found in the literature. For instance, it has been shown that inhalation solutions of Pulmozyme® can be mixed with tobramycin (Bramitob® or TOBI®) as one of the few examples of compatibility for dornase alpha without changing the stability of these products and their aerosolisation performance [67]. In contrast, mixing salbutamol with other medicine solutions may change the mass median aerodynamic diameter in either direction, depending on the combination and the type of nebuliser used [68]. The changes in median diameter can be as high as 50 % and also the span of the size distribution and the delivered respirable mass are influenced. This may have a considerable effect on the dose delivered to the site of action and thus the efficacy of the therapy. For these reasons, mixing medicine formulations for nebulisation should preferably be avoided unless they are needed to obtain good adherence to the therapy. In the latter case, desired combinations need not only to be tested on chemical and physical stability, but also on their aerosolisation performance in the nebuliser used for the administration. Furthermore, mixtures should be made from preservative free solutions and suspensions to avoid incompatibilities with these additives.

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Oropharynx

7

Suzy Dreijer - van der Glas

Contents

Abstract

Preparations for the oropharynx form a wide range, from the classical gargles and lozenges up to modern muco-adhesive forms, based on polymer technology. This chapter deals with dosage forms intended for administration to the oral cavity and the throat, or both, to obtain a local effect. These dosage forms can be solutions such as mouthwashes and gingival solutions, or buccal tablets or semisolid preparations such as oromucosal pastes and dental gels. In this chapter the use, the design of formulation and preparation method will be discussed.

In the formulation of preparations for the oropharynx, taste and texture are features that are important for the acceptance by the patient. Pharmacy preparation can play an important role, because of the advantage that preparations can be tailor made according to the specific situation or taste of the patient. For instance, chemotherapy and several other active substances, may cause dry mouth and stomatitis, and mouthwashes or gels can relieve these problems. However, they should not cause irritation and must be accepted by the patient. This has to be kept in mind when choosing a vehicle, or the pH or the osmotic value of a preparation.

Keywords

Dental gel • Mouthwash • Oropharynx • Formulation • Preparation • Muco-adhesive

7.1 Orientation

Medicines that are meant for the oral mucosa are often applied as a mouthwash, gingival solution or a semisolid mouthpaste. A mouthpaste will theoretically stay on the mucosa for the longest time and it is useful in formulating poorly water soluble ingredients. However viscous mouthwashes and suspensions in water are easier to apply to those parts of the oral cavity that are difficult to reach with a (stiffer) mouthpaste [1]. Especially in the case of a painful ailment prescribers and patients mostly prefer a mouthwash. An example of this is the local application of corticosteroids in oral lichen planus [2]. In such cases a (viscous) suspension could be preferred to a solution in water to obtain the intended effect [1].

In patients undergoing chemotherapy or radiation therapy in the head and neck area saliva production is diminished, and the immune system is weakened. For these reasons

Based upon the chapter Mond en keel by Suzy Dreijer and Annick Ludwig in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_7,

mouthwashes are prescribed to prevent caries and sores or infections of the oral mucosa. For example chlorhexidine or hexetidine mouthwash or spray can be used instead of toothpaste. Sometimes nystatin is added to the mouthwash, to prevent Candida infections. Different forms of fluoride are used to prevent dental decay.

Not only chemotherapy, but some other medicines can diminish saliva production. In these patients saliva substitutes are very popular to reduce mouth dryness. These are Over The Counter (OTC)-preparations with mucine or viscous solutions with electrolytes [3]. Examples are Xialine® and Saliveze®. The result of these preparations is often no better than (sugar free) chewing gum.

Fluoride mouthwashes are examples of preparations for dental use. Dental solutions in general have the advantage that mouthwashes are easy to use by the patient. Semisolid dental gels can be applied to specific places on the teeth. Normally this is done by the dentist or dental hygienist. An example is a hydrogel with phosphoric acid, used in etching teeth enamel to facilitate composite restoration.

Oromucosal and gingival solutions are applied to local ailments in the oral cavity. They are administered with a brush, a spatula or a cotton swab.

The pharmacy preparation of dosage forms for the oropharynx can be customised by changing the strength, taste, viscosity or volume according to the patient's needs. Some examples are shown below.

Solutions that are less concentrated than the licensed preparation reduce the risk of intoxications or adverse reactions if the product is accidentally swallowed.

OTC mouthwashes with chlorhexidine or fluoride often contain (red) dyes, which could be a problem in case of an allergy.

Many cancer patients have disorders in the oral cavity after radiation or chemotherapy. They form a typical group that could benefit by care, attention and customised pharmacy preparations. Optimal oral hygiene can help to prevent problems in these patients.

Dental fluoride gels are normally acidic in order to obtain a better effect. However, when the salivary glands are damaged by radiation or chemotherapy, the acidic licensed preparations are often not tolerated, as they will be too irritant on the mucosa. A neutral dental fluoride gel, prepared in the pharmacy, would be the medicine of choice. Formulations containing ethanol can also irritate a damaged oral mucosa.

Tranexamic acid is used in dentistry as a 5 % mouth rinse after extractions or surgery in patients on oral anticoagulant therapy to prevent postoperative bleeding [4].

Decontamination of the oropharynx plays an important role in the prevention of hospital infections. In a large trial, selective decontamination of the oropharynx and the digestive tract, combined with intravenous antibiotics, reduced the rate of infections only slightly more than just decontamination of the oropharynx [5]. For the oropharyngeal application the antibiotics were formulated in an adhesive paste. Other trials showed that prophylactic application of chlorhexidine in the mouth reduces the risk of ventilation associated pneumonia [6–8]. In these trials chlorhexidine mouthwash was replaced by a hydrophobic mouth paste, since intubated patients are not able to rinse their mouth.

Gargles with disinfecting active substances are still prescribed to soothe an irritated throat. But the tonsils, at the rear of the throat, are hardly reached by gargles. Lozenges, or gargling with salted water are less irrational as an alternative and may be relieving. The effect of lozenges in the treatment of sore throats is possibly due to a mechanical effect, related to saliva production from sucking movements. Local anaesthetics, antiseptics and astringents do not add much to this effect. There is a wide variety in OTC lozenges for sore throat on the market.

Because of the risk of swallowing, mouthwashes and gargles should only be used by adults and children older than 6 years. Gingival solutions and oral gels or pastes can – with caution- be used in young children. These dosage forms can be applied at specific locations.

The advantages of preparations for the oropharynx are: local application directly to the lesions, which can be done by the patient. Adverse effects however may occur as well: irritation, undesirable systemic effects after accidentally swallowing and allergic reactions.

7.2 Definitions

The Ph. Eur. describes mouthwashes and gargles in the monograph on Oromucosal Preparations (Praeparationes buccales).

Mouthwashes are aqueous solutions intended for use in contact with the mucous membrane of the oral cavity. They are not to be swallowed. Mouthwashes may contain excipients to adjust the pH which, as far as possible, are neutral. Apart from these oromucosal solutions the Ph. Eur. lists oromucosal suspensions, drops and sprays.

The Ph. Eur. specifies that gargles are aqueous solutions intended for gargling to obtain a local effect and not to be swallowed. They may contain excipients to adjust the pH which should be neutral.

Mouthwashes and gargles are supplied either as ready-to-use or as concentrated solutions to be diluted. A well-known example is hydrogen peroxide 3 %, which is normally diluted before use to 1,5 %. They may also be prepared from powders or tablets to be dissolved in water before use, for instance powders with sodium perborate.

Semisolid preparations are hydrophilic gels or pastes intended for application in the oral cavity or a specific location like the gums (gingival) or the teeth (dental). According to the Ph. Eur. these semisolid oromucosal preparations comply with the requirements for semisolid preparations for cutaneous use.

Lozenges and pastilles are solid, single-dose preparations intended to be sucked to obtain a local effect in the oral cavity and the throat. They contain one or more active substances, usually in a flavoured and sweetened base. They are intended to dissolve or disintegrate slowly in the mouth when sucked. They have to comply with most of the requirements for tablets. Lozenges are hard preparations, pastilles are soft.

Buccal mucoadhesive tablets are mostly intended for systemic use, but adhesive tablets and semisolid forms can also be used to obtain a local effect.

An example is a mucoadhesive tablet with miconazole. With this dosage form higher saliva concentrations are obtained compared to an oral gel, whilst no miconazole is detectable in blood plasma [9]. Other examples are buccal films, in use for the treatment of herpes labialis [10].

7.3 Biopharmaceutics and Side Effects

The oropharynx serves three purposes. In the first place food is taken in through this route, after chewing if needed. Secondly the oropharynx is one of the routes for air in- and exhalation. Third it plays an important role in speaking.

The side effects of preparations for this route of administration are already mentioned in Sect. 7.1. Accidentally swallowing is one of the main causes of side effects in mouthwashes and gargles. As swallowing cannot be excluded (especially in children), doses for local administration in the oropharynx have to be checked in the same way as oral doses.

Excessive use of dental sodium fluoride solutions may cause coloured stains on the enamel.

Chlorhexidine causes a reversible yellow discolouration of the teeth and the tongue, and sometimes taste disorders.

Too violent gargling may cause irritation of the pharyngeal mucosa. Gargling with hydrogen peroxide may irritate because of the itching effect of the active ingredient. Excessive use of 3 % hydrogen peroxide as a gingival solution may cause painful blisters [11].

Extensive use of local anaesthetics in the oropharynx can be hazardous because of impaired swallowing as long as the mucosa is numbed by the anaesthesia.

7.4 Product Formulation

This section focuses on the design of the formulation of oromucosal preparations. Design and excipients are described, in liquid, semisolid and solid dosage forms respectively.

7.4.1 Liquid Preparations (Mouthwashes, Gingival Solutions and Gargles)

7.4.1.1 Physico-chemical Properties of the Active Substance

Mouthwashes usually are solutions of active substances in water or aqueous solvents; so the water soluble form of the active substance is chosen. For corticosteroids this would mean an aqueous solution of a phosphate ester. When rinsing with such a solution the contact time would be too short to obtain a sufficient therapeutic effect of the corticosteroid [1]. As a viscous suspension sticks to the oral mucosa, the active substance can work for a longer period of time. Therefore a (viscous) suspension is to be preferred. In addition such a suspension has the advantage that the bitter taste of the corticosteroid is less pronounced. An example is a suspension with hydrocortisone acetate, lidocaine and dexpanthenol (Table 7.1).

7.4.1.2 Vehicle

Purified water is the first choice as a basis in mouthwashes and gargles. Aqueous solutions of glycerine or sorbitol are good alternatives. The use of high concentrations of glycerine in mouthwashes is controversial. By dehydrating the mucosa these solutions would have the opposite effect to that which they are meant to have [13].

Gingival solutions with antiseptics or local anaesthetics may also be formulated in mixtures of water and glycerine. In this case glycerine serves the purpose of raising the viscosity of the vehicle and improving adherence to the mucosa. This is relevant because gingival solutions are used on local ailments in the oral cavity.

When saliva production is insufficient, many different liquids can be used. They vary from glycerol with citric acid to the saliva substitutes already mentioned in Sect. 7.1. Citric acid stimulates the saliva production in the salivary glands, and therefore raises the amount of saliva in the mouth. If there is damage to the oral mucosa, it is best to avoid ethanol and propylene glycol, because these solvents may cause irritation, A German hospital developed an

Table 7.1 Hydrocortisone Acetate Oral Suspension 0.5 % with Lidocaine Hydrochloride and Dexpanthenol [12]

Hydrocortisone acetate	0.5 g
Lidocaine hydrochloride	1 g
Dexpanthenol	5 g
Disodium phosphate dodecahydrate	0.05 g
Macrogolglycerol hydroxystearate	0.2 g
Peppermint oil	0.15 g
Propylene glycol	40 g
Water, purified	53.1 g
Total	100 g

Table 7.2 Lidocaine Hydrochloride Oral Gel 20 mg/ml [15]

Lidocaine hydrochloride	2 g
Disodium phosphate dodecahydrate	0.1 g
Glycerol (85 %)	20 g
Hypromellose 4,000 mPa.s	1.5 g
Methyl parahydroxybenzoate	0.0875 g
Peppermint oil	0.02 g
Propyl parahydroxybenzoate	0.0125 g
Saccharin sodium	0.1 g
Water, purified	81.2 g
Total	105 g (= 100 mL)

Table 7.3 Chlorhexidine Digluconate Mouthwash 0.2 % [16]

	FNA	Adapted for mouth lesions
Chlorhexidine digluconate solution	10.65 g	10.65 g
Ethanol (96 % V/V)	70 g	–
Peppermint oil	3 dr	3 dr
Sorbitol liquid, crystallising	535 g	–
Water, purified	493 g	986 g
Total	1,109 g (= 1,000 mL)	996.95 g (= 1,000 mL)

alcohol free formulation with benzydamine, especially for patients on chemotherapy or radiation treatment [14]. Benzydamine is a NSAID with local anaesthetic and antiseptic properties.

It is clear that surface tension and the viscosity of the vehicle will influence the effect of a mouthwash, but there is still little investigated in this area.

7.4.1.3 pH

For reasons of taste mouth preparations should be slightly acid or neutral. Instability or ineffectiveness of the active ingredient can make deviations in pH necessary. In Lidocaine hydrochloride oral gel 20 mg/ml FNA the pH is adjusted to 6.8, because at that pH part of the lidocaine will be in the base form (Table 7.2). Therefore, at that pH the numbing effect will be much better than in an acid solution.

More information about the influence of pH on chemical and physical stability of solutions and suspensions can be found in Sect. 22.2.

7.4.1.4 Osmotic Value

Mouthwashes need not be made iso-osmotic. But strongly hyperosmotic solutions may hurt in case of lesions in the mouth. Sorbitol solution, because of its viscosity sometimes used as vehicle for suspensions, is strongly hyperosmotic. For patients with lesions a formulation sometimes has to be adapted. For instance many chlorhexidine mouthwashes contain sorbitol as a flavouring and ethanol as preservative. In the following adapted version both are omitted (Table 7.3).

7.4.1.5 Viscosity

In the preparation of viscous mouthwashes common viscosity enhancers are used. Mostly cellulose derivatives are used, such as hypromellose, but sometimes tragacanth is preferred. Nowadays tragacanth with a good microbiological quality can be purchased. The main advantage of tragacanth gels is their resemblance to oral mucus, which makes flavouring easier. An example is Tetracycline mouthwash 5 % FNA (Table 7.4).

Table 7.4 Tetracycline Hydrochloride Mouthwash 5 % [17]

Tetracycline hydrochloride	5 g
Methyl parahydroxybenzoate	0.1 g
Propylene glycol	0.6 g
Sodium citrate	6.5 g
Sorbitol liquid, crystallising	65.5 g
Tragacant	0.5 g
Water, purified	40 g
Total	118.2 (= 100 mL)

Table 7.5 Citric Acid-Glycerol 1 % [18]

Citric acid, anhydrous	1 g
Glycerol (85 %)	84 g
Orange essence (local standard)	0.01 g
Water, purified	14.99 g
Total	100 g

7.4.1.6 Microbiological Stability (Preservation)

As most preparations for the oropharynx are aqueous solutions, growth of micro-organisms is possible. Therefore, the addition of a preservative is generally needed, except for those preparations that have intrinsic preservative properties. In this category there are many preparations with glycerol, propylene glycol or ethanol, provided that these are present in a sufficiently high concentration. See also Sect. 23.8. An example is glycerol with citric acid, see Table 7.5

This solution contains so much glycerol that addition of a preservative is not necessary. Zinc chloride and alumen gargle FNA does not need preservation due to the low pH (2.3–2.7) and the presence of salicylic acid Table 7.6.

7.4.1.7 Preservatives

If a preservative is needed in a preparation for the oropharynx the following considerations are important:

- Methyl parahydroxybenzoate and propyl parahydroxybenzoate may cause an itching sensation on the tongue in some people.

Table 7.6 Zinc Chloride-Alumen Gargle [19]

Alumen	3.3 g
Zinc chloride	3.3 g
Peppermint oil	7 dr
Salicylic acid	1 g
Water, purified	995 g
Total	1,003 g (= 1,000 mL)

- Sorbic acid is only effective in acid solutions.
- Chlorhexidine digluconate has an unpleasant taste and with excessive use it may stain the teeth.

In general methyl parahydroxybenzoate (sometimes combined with propyl parahydroxybenzoate) or sorbic acid are chosen. For stability reasons the pH is adjusted to 5 by the addition of potassium sorbate. If these substances cannot be used, the organic solvents mentioned earlier (ethanol or glycerine) are an alternative to a preparation less susceptible to microbial growth.

7.4.1.8 Taste, Smell and Colour

Naturally taste and smell are very important in preparations for the oral cavity. Flavouring is frequently needed. To mask the unpleasant taste of chlorhexidine, sorbitol with peppermint oil or raspberry essence are eligible. Lemon essence can be added to preparations with citric acid.

Simple syrup is inappropriate for mouth preparations because it lowers the pH in the mouth and thus may cause caries. Polyols like sorbitol or xylitol and glycerine are considered safe for the teeth, as they do not lower the pH of the dental plaque. Xylitol would be the choice if sweetness is most important, because it is as sweet as saccharose. Saccharin is not useful because of its bitter after taste. An overview of flavourings can be found in Sect. 5.4.10.

7.4.2 Semisolid Preparations

7.4.2.1 Active Substance

The aqueous solubility of the active substance is important when choosing between an aqueous gel or a fatty mouth paste or ointment. Lidocaine is used as the hydrochloride in lidocaine gels (see Table 7.2). Tretinoin may be formulated in a hypromellose 20 % (adhesive) ointment, see Table 7.7.

7.4.2.2 Ointment Base

An ointment base containing 20 % hypromellose is often used in mouth pastes. The hypromellose, formulated in white soft paraffin, has the purpose of making the paste adhere to the mucosa. Even better adherence can be obtained by preparations in a hydrocarbon gel ointment (Plastibase®, Hydrophobe basisgel DAC). Plastibase® is a proprietary mixture of 5 % polyethylene in liquid paraffin. The preparation is difficult, and Plastibase® is on the market in Germany, but not in many other European countries. A combination of Plastibase® with pectine, glycerine and carmellose sodium is marketed as Orabase® Although this preparation is originally meant for use on peristomal skin, it is often used in mouth disorders.

Table 7.7 Tretinoine Oromucosal Paste 0.1 % [20]

Tretinoin	0.1 g
Ethanol (96 %)	16 g
Hypromellose 4,000 mPa.s	16.78 g
Paraffin, white soft	67.12 g
Paraffin, white soft	q.s. for supplementing the evaporated ethanol
Total	100 g

Table 7.8 Metronidazole-Dental Gel 25 % [22]

Metronidazole	25 g
Citric acid, anhydrous	0.07 g
Poloxamer 407	20 g
Potassium sorbate	0.14 g
Water for injections	54.79 g
Total	100 g

7.4.2.3 Hydrogel Base

Gels can be meant for application on the oral mucosa or on the teeth. When the active ingredient is intended for the teeth the following points are important:

- The pH should be rather low to improve penetration of the active ingredient in the enamel (for instance pH 4 in OTC products with fluoride).
- Surface tension and viscosity should be low for the same reasons [21].
- Because of the low pH carbopols are not suitable as viscosity enhancers (see Sect. 23.7.3.5). Cellulose derivatives are a better choice.

When the gel is intended mainly for the gums or the teeth pockets, a low pH is not needed. In this case poloxamers are an alternative to cellulose derivatives. The thermoreversible viscosity of poloxamer gels can be used in the preparation and administration of a dental gel with metronidazole (Table 7.8).

A special case is the use of an inorganic thickening agent in a 35 (or 50) % phosphoric acid dental etching gel (Table 7.9). In the strongly acidic environment of 35 % phosphoric acid only colloidal anhydrous silica can be used as a viscosity enhancer.

Table 7.9 Phosphoric Acid Dental Gel for Etching [23]

Phosphoric acid (85 %)	41.2 g
Glycerol (85 %)	15 g
Methylthioninium chloride solution 10 mg/mL DAC	1 g
Silica, colloidal anhydrous, compressed	7 g
Water, purified	35.8 g
Total	100 g

7.4.2.4 Microbiological Stability (Preservation)

The microbiological aspects of hydrogels are comparable with those of aqueous solutions. So the same principles as for mouthwashes hold in mouth gels.

7.4.2.5 Scent and Colour

Dental gels often contain a taste correction. An overview of flavourings can be found in Sect. 5.4.10.

In many dental gels a colouring agent is needed to obtain a contrast between gel and teeth. For instance methylene blue (methylthionine) is used in phosphoric acid gel [23]. For an overview of water soluble dyes see Sect. 23.11.

7.4.3 Solid Preparations

As many aspects of solid preparations for the oropharynx are similar to those of solid preparations for oral use, at first reference is made to Chap. 4. Sweetening and flavouring agents are important ingredients in lozenges. The active substances may be formulated in hydrophilic bases with gelatin in glycerine, or a mixture of acacia gum (Arabic gum) and sugar.

Lozenges are not to be swallowed. During the time that they stay in the mouth the active substance is released in a certain period of time, to have a local effect. These lozenges may contain antiseptics, local anaesthetics or antimycotics (for instance Amphotericin B in Fungizone® lozenges).

Lozenges should not disintegrate in contact with saliva: so they have to be formulated differently from tablets for oral use. They may not contain disintegrants, but always contain flavouring agents, especially sweeteners. Tragacanth (0.5–1 %) is a strong binder that is used in lozenges. It delays the disintegration of the tablet. Dextrose solutions are also used as a binder to obtain firm tablets. Stearic acid delays disintegration because of its hydrophobic properties; therefore, it is a good lubricant for lozenges.

Mucoadhesive tablets are prepared by compression of mono or multilayers. Usually they contain hydrophilic polymers, that form a flexible hydrogel after wetting by the saliva.

Table 7.10 Glycerated Gelatine Suppositories [24]

Gelatin	2 g
Glycerol (85 %)	5 g
Water, purified	4 g

7.5 Method of Preparation

7.5.1 Liquid Preparations

For the preparation of oromucosal solutions and gargles the active ingredients and the excipients are dissolved in the (mixture of) solvent(s) (see Sect. 5.5.2).

Oromucosal suspensions are prepared in the same way as suspensions for cutaneous use (see Sect. 12.7.3). So also for in-process controls reference is made to those chapters.

7.5.2 Semisolid Preparations

The preparation of semisolid oromucosal preparations is the same as that of cutaneous preparations (see Sect. 12.6). The same is true for the in process controls.

When preparing phosphoric acid gel, metallic utensils or homogenisers are not to be used, because they would be tarnished/corroded by the acid.

7.5.3 Solid Preparations

The preparation of tablets in general is dealt with in Sect. 4.9.3. The preparation of lozenges with a gelatin base can be found in Sect. 11.4.3 and other references about gelatin suppositories. An example of such a base is in Table 7.10.

7.6 Container, Label, Dosage Delivery Devices

Mouthwashes and gargles are packed in glass or plastic bottles, with a screw cap and a dosing cup.

For dental sodium fluoride solutions a plastic bottle is preferable as sodium fluoride reacts with glass, the solutions may therefore be stored longer in plastic. Gingival solutions are best supplied in a bottle with a brush or a spatula (see Sect. 24.4.19.1).

Fluoride dental gel may be packed in a coated aluminium tube (see Sect. 24.4.8) or in a plastic bottle with a dosing pump or spraying device. For phosphoric acid gel a plastic bottle with a dosing device or a syringe with a cap is the

packaging of choice. Viscous gels should be avoided in babies, as they give a risk of suffocating even if the gel is applied on the nipple of the mother.

A dental syringe (with a hooked end) may help to apply liquids in cavities in the mouth that are hard to reach. An alternative is chewing on a piece of cotton gauze, wetted with the liquid to be applied, e.g. hydrogen peroxide solution. Cotton swabs can be used to clean the tongue and oral mucosa when a tooth brush hurts too much.

Dosage forms that are not to be swallowed by the consumer (mouthwashes, solutions for dental or oromucosal use, gargles and dental gels) have to be labelled accordingly. Preferably the label should bear the text 'mouthwash', 'solution for dental use', 'gargle', 'dental gel', or 'solution for oromucosal use'. When these labels are not available, a strip in a contrasting colour with the words 'Not to be taken' would also be acceptable. In this case additional information about the dosage form and the manner of use will be necessary.

7.7 Release Control and Quality Requirements

Mouthwashes and gargles have to be checked before dispensing at the following points:

appearance, colour, packaging and labelling. Solutions should be clear and should not contain a precipitate, sediment or (dust) particles. Gels for dental or oromucosal use should be checked before dispensing for appearance, texture, packaging and labelling. In a gel with suspended ingredients a check for coarse particles or agglomerates is also needed. Here the same requirements are valid as in gels for cutaneous use (see Sect. 12.7.11).

All preparations for oropharyngeal administration have to be analysed for identity, content, pH, purity etcetera. See Table 32.2.

7.8 Storage and Stability

For chemically stable, standardised formulas for the oropharynx, packed in multiple-dose containers a maximum shelf life assigned at 2 years at 2–30 °C (see Sect. 22.7 for the way of thinking) is generally acceptable. In standard formulas that are not chemically stable, the maximum shelf life should be indicated in the relevant monograph in the formulary. The maximum shelf life is to be used only for the unopened storage container. Once opened, the usage period in the pharmacy of storage containers with preserved mouthwashes and gargles is 12 months (at 2–30 °C) after opening, provided that this date does not lie after the expiration date. For patients the usage period will be 6 months at most (see Sect. 22.7), because of the risk of contamination by frequent opening of the package and possibly unhygienic handling.

For non-standardised formulas storage conditions, shelf life (of the unopened package) and usage period (after opening) have to be assigned at the design phase of the product. If not enough is known about the chemical, physical or microbiological stability, a beyond-use date of 1 month after preparation arbitrarily is maintained for preserved liquid dosage forms (see Sect. 22.7).

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Nose

8

Suzy Dreijer - van der Glas and Anita Hafner

Contents

Abstract

This chapter deals with preparations for nasal administration, with a local or a systemic effect. Classical nasal preparations were always associated with local ailments, but nowadays the interest in the nasal route for systemically acting substances and direct nose to brain delivery is increasing. Fast absorption, the possibility of high blood levels and a patient friendly dosage form are the reasons. Nasal administration of medicines with local effect is the first choice for the treatment of topical nasal disorders. It is also an attractive route for low dose active substances with a systemic effect, such as peptides or benzodiazepines (e.g. midazolam). When compared to parenteral administration nasal administration is more easily applied and causes less risk of infection.

Nasal preparations can be formulated as liquid, semisolid or solid preparations and can contain one or more active substances. Whether intended for local or systemic action, the mucociliary function of the nose should be disturbed as little as possible by the preparation However, it is well known that active substances as well as excipients may have a negative influence on the mucociliary clearance, in other words may be ciliotoxic. In the formulation of nasal preparations one should take into consideration the possible damage to the cilia in relation to the indication and the period of use.

Within this chapter the emphasis is on dosage forms that are prepared in the pharmacy and on forms that are supplied by the pharmacy.

Keywords

Ciliotoxic • Mucociliary clearance • Nasal preparation • Local effect • Systemic effect • Preparation • Formulation

Based upon the chapter Neus by Annick Ludwig and Suzy Dreijer in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_8,

8.1 Orientation

8.1.1 Local Action

Active substances formulated as nasal preparations are traditionally used in the treatment of local ailments such as allergy, congestion and infections. Nasal preparations that are prepared in the pharmacy are mainly intended for the inner part of the nose. In addition nasal drops are often applied in diseases of the middle ear, in order to keep the Eustachian tube open (see Sect. 9.1).

In the treatment of local impairments mainly aqueous solutions of decongestants or sodium chloride are used, or (micro)suspensions of poorly water-soluble active substances (levocabastine hydrochloride or beclomethasone dipropionate) [1].

Aqueous nasal drops as well as sprays are suitable for self administration. Viscous solutions are best avoided, as they make less contact with the nasal mucosa. To clear a congested nose the patient can also sniff a salt solution (half a teaspoon of salt in a glass of lukewarm water) four to six times a day. The benefit of the addition of sodium hydrogen carbonate for a so-called alkaline nasal wash has not been demonstrated [2].

Nasal sticks and so called inhalation ointments with volatile ingredients such as menthol and eucalyptol are mainly used in self-care. The same is true for vapours.

Nasal powders for insufflation (i.e. with corticosteroids) are on the market as an alternative to sprays, but powders seem to give more risk of irritation and bleeding [3].

In general, retention of the product within the nasal cavity will be attained if the vast majority of the particles or droplets are larger than 10 μm. The deposition site of the formulation is important and therefore also the container and dosing device and the way of administration. When using a spray the solution is finely distributed in the anterior part of the nose and mucociliary clearance causes the formulation to be transferred throughout the nasal cavity, whereas nasal drops spread at the posterior part of the nose. Deposition of the formulation in the anterior part of the nose provides longer residence time and a longer period of contact between active substance and mucosa. When the medicine is deposited in the posterior part of the nose, mucociliary clearance is faster [4]. The permeability of the nasal mucosa however is better at the posterior part of the nasal cavity. Thus, active substances that are slowly absorbed should best be applied in the anterior part, while substances that are intended to act fast should be applied in the posterior part of the nose. This should be kept in mind when choosing a dosage form (nasal drops, spray or gel) [3, 5, 6]. In allergic rhinitis nasal sprays with corticosteroids are the most widely used. In the treatment of nasal polyps, which are mostly located at the posterior part of the nose, nasal drops would give a better contact with the mucosa than nasal sprays. In some countries nasal drops with fluticasone propionate are authorised especially for nasal polyps, the spray for allergic rhinitis.

The ciliary epithelium cannot perform its transport function if it is covered by lipophilic vehicles (e.g. liquid paraffin). The use of soft fatty nasal ointments or creams is only appropriate in disorders of the vestibulum nasi, because in the anterior part of the nose, cilia are absent (see Sect. 8.3.1).

Nasal gels are normally hydrogels, and as such less toxic for the cilia than nasal ointments, more efficient in applying, and they remain longer on the mucosa [3]. However, the cellulose thickening agents in these hydrogels form a crusty layer (xerogel) on drying, that may irritate. The addition of a humectant (glycerine, sorbitol) should prevent drying out and irritation, but generally patients do not appreciate nasal gels. As a consequence, very few nasal gels with a local action are on the market. A nasal gel can however be a good choice for short term use. Chlorhexidine nasal gel is used in the prevention of ventilation associated pneumonia in Intensive Care patients [7].

Examples of nasal preparations with local action are given in Table 8.1.

Table 8.1 Nasal preparations with local action (examples)

Active substance	Physical form	Indication/therapeutic class	Preparation
Azelastine HCl	Solution	Allergic rhinitis/antihistamine	Allergodil®, Allergocrom®, Cromohexal®
Levocabastine HCl	Microsuspension	Allergic rhinitis/antihistamine	Livocab®, Livostin®
Oxymetazoline HCl	Solution	Nasal decongestion/vasoconstrictor	Afrin®, Dristan®, Nasivin®, VicksSinex®
Beclomethasone diproprionate	Suspension	Allergic rhinitis/corticosteroid	Beconase®, Nasobec®,Qnasl® and generics
Fluticasone propionate	Suspension	Allergic rhinitis and nasal polyps/corticosteroid	Nasofan®, Flixonase®, Flonase® and generics
Momethasone furoate	Suspension	Allergic rhinitis and nasal polyps/ corticosteroid	Nasonex®, Mommox®
Budesonide	Suspension	Allergic rhinitis, rhinitis and nasal polyps/ corticosteroid	Rhinocort® spray
	Powder		Rhinocort® turbuhaler

Table 8.2 Nasal preparations for systemic purpose (examples)

Active substance	Physical form	Indication/therapeutic class	Preparation
Desmopressin	Solution	Central diabetes insipidus/derivative of the antidiuretic hormone	DDAVP, Minrin®
Nafarelin acetate	Solution	Endometriosis/agonist of gonadotropin-releasing hormone	Synarel®
Oxytocin	Solution	Gynaecological hormone (uterotonic, uterostiptic)	Syntocinon®
Sumatriptan	Solution	Migraine/antimigraine agent	Imigran®, Imitrex®, Rosemig®
Fentanyl citrate	Solution	Chronic pain/opioid analgesic	Instanyl®[a], PecFent®[a]

[a]Approved for use in the European Union

8.1.2 Systemic Action

Nasal administration of medicines is an effective way of systemic delivery of active substance, alternative to oral and intravascular delivery. Advantages of nasal systemic delivery include relatively large surface area available for absorption, rapid onset of therapeutic action, avoidance of first-pass metabolism (see Sect. 16.2.6), non-invasiveness of application of the active substance, resulting in patient comfort and compliance [8].

Generally speaking active substances with a systemic therapeutic action can be formulated as nasal preparations under the following conditions: high water-solubility (required dose must fit in 25–150 microlitres vehicle), sufficient chemical stability, no unpleasant smell or taste, favourable nasal absorption parameters, minimal nasal irritation and clinically important properties such as fast onset of therapeutic action, low dosage (normally less than 25 mg per dose), and no toxic metabolites [3, 8].

In preparations intended to obtain a systemic effect a spray solution is the favourite dosage form, because it enables accurate dosing. Examples of nasal preparations for systemic purpose are listed in Table 8.2. Examples of licensed preparations are nasal sprays with buserelin, fentanyl and vaccines (e.g. against airway infections) [8].

8.1.3 Advantages and Disadvantages of Nasal Preparations

The advantages and disadvantages of nasal preparations are summarised in Table 8.3.

8.2 Definitions

The European Pharmacopoeia (Ph. Eur.) defines nasal preparations as a liquid, semisolid or solid preparations intended for administration to the nasal cavities to obtain a local or systemic effect. They contain one or more active substances. Nasal preparations are as far as possible non-irritating and do not adversely affect the functions of the nasal mucosa and its cilia. Aqueous nasal preparations are usually iso-osmotic and may contain excipients, for example, to adjust the viscosity, to adjust or stabilise the pH, to increase the solubility of the active substance or to stabilise the preparation.

Nasal preparations are supplied in multidose or single-dose containers, provided, if necessary, with a suitable administration device, which may be designed to avoid contamination.

The Ph. Eur. lists

- Nasal drops and liquid nasal sprays
- Nasal powders
- Semisolid nasal preparations (nasal ointments and gels)
- Nasal washes
- Nasal sticks

Nasal drops and liquid nasal sprays are solutions, emulsions or suspensions intended for instillation or spraying into the nasal cavities. Nasal powders or nasal insufflation powders are intended for insufflation into the nasal cavity by means of a suitable device. The size of the particles are such as to localise their deposition in the nasal cavity. In nasal sticks and so-called inhalation ointments mostly volatile active substances are formulated in a fatty base. Nasal washes are generally aqueous iso-osmotic solutions intended to cleanse the nasal cavity. If they are intended for application on injured parts of the mucosa, or prior to a surgical operation, they have to be sterile. Nasal powders and nasal sticks are not very common in pharmacy practice. Therefore they are not discussed in this chapter.

8.3 Biopharmaceutics

8.3.1 Anatomy and Function of the Nose

The nostril, the vestibulum nasi, is covered by hairy skin for 1–1.5 cm inward. The nose skin is not different from the rest of the skin, and can suffer from the same disorders. Further inward the skin is replaced by the nasal mucosa, which is covered by cilia (see Fig. 8.1).

The nasal epithelium contains cells with or without cilia, mucous cells and basal cells. The submucosa contains glands that produce mucus and an aqueous secretion. Nasal mucus consists of 95 % of water and contains 2 % mucine, 1 %

Table 8.3 Advantages and disadvantages of nasal preparations. + the advantage applies for this type of preparation, × the disadvantage applies for this type of preparation

	Nasal preparations with local effect	Nasal preparations with systemic effect
Advantages		
Administration by patient, at home	+	+
Good adherence	+	+
Accurate dosing possible	+ (only for sprays)	+
Little risk of overdosing	+ (except for sprays in young children)	+
High absorption, pharmacokinetic profile comparable with intravenous injection	–	+ (for lipophilic substances)
Fast absorption, onset of therapeutic effect within 30 min	–	+ (for lipophilic substances)
Possible direct pathways to the CNS, bypassing the blood–brain barrier [5, 8, 9]	–	+
Possible alternative for active substances with low biological availability caused by insufficient absorption or extensive first-pass metabolism	–	+
Possible induction of systemic or local immune response without injection (vaccines)	–	+
Disadvantages		
Ciliotoxicity and nasal irritation by active substances or excipients	×	×
Fast clearance (15–20 min) of liquids and powders due to activity of mucociliary apparatus	×	×
Variablility in mucociliary clearance related to patient condition and environmental factors (moisture, temperature)	×	×
Variability in absorption and therapeutic effect related to the nature of the active substance and condition of the patient		×
Nasal absorption of systemically acting substances resulting in a profile with ups and downs	–	× (when an even profile is needed)
Limited volume that can be administered per nostril (25–200 microlitres)	(×)	×
Accurate dosing not possible	× (nasal drops)	–
Low biological availability of hydrophilic substances, such as peptides with a high (>1,000 Da) molecular weight	–	×
Enzymatic degradation or metabolism on the mucosa	–	×

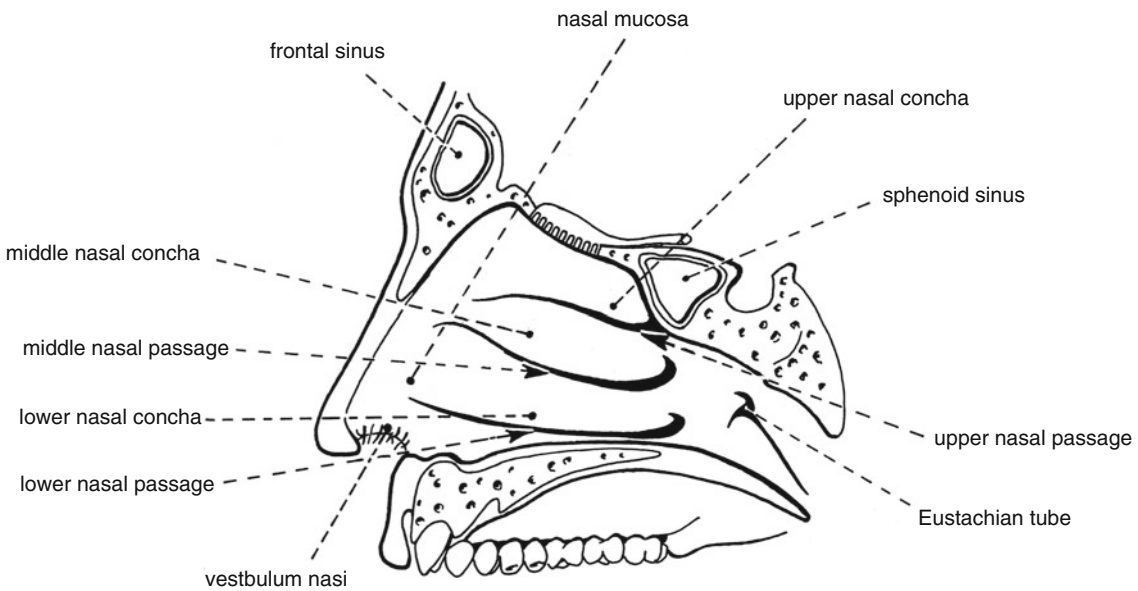

Fig. 8.1 Schematic cross section of the nose. Source: Recepteerkunde 2009, ©KNMP

inorganic salts, 1 % proteins (albumin, immunoglobulines, lysozyme) and less than 1 % of lipids. Mucus comes from the chalice-shaped mucous cells and the submucosal glands. The mucus layer (thickness 5 μm) actually consists of two layers. The lower part is a aqueous layer, in which cilia move. The upper layer is a discontinuous viscous mucus layer resting on the cilia, which is passed on by the cilia in the direction of the pharynx. The viscosity of this aqueous layer (sol layer) and gel layer, respectively, has influence on the mucociliary clearance. In the case of rhinitis the sol layer is so thick that the cilia cannot reach the upper layer (gel layer) to transport it to the pharynx. If the upper layer becomes too viscous due to dehydration, the cilia do not have sufficient power to move and clear it. The mucus layer has several different functions: it covers and protects the mucosa physically and by the action of enzymes, it has a capacity for water retention, allows the transfer of warmth and moves particles down to the nasopharynx [10, 11].

The thin, porous and highly vascularised nasal epithelium has a high total blood flow, which facilitates fast absorption of substances. Direct transport to the systemic circulation or the central nervous system makes it possible to obtain a rapid therapeutic effect. The intranasal absorption depends on the mucociliary clearance, pathological conditions such as infections, allergy and obstruction, mucus secretion, moisture content, enzymatic degradation, and blood flow. It should be remembered that the blood flow can be affected by either locally or systemically active substances. These phenomena can determine the nasal absorption of substances. Oxymetazoline and clonidine reduce the blood flow, while phenylephrine and salbutamol raise it.

8.3.1.1 Mucociliary Clearance

The function of the nose is, besides being the olfactory organ, to prepare the air in such a way that the airways and the lungs will not be damaged. In the nasal cavity the air is warmed up and moisturised before reaching the lungs. Coarse dust particles are held back by the hairs at the entrance of the nose, while smaller particles and microorganisms can pass this first barrier, but are retained in the mucus layer. The cilia show a coordinated movement in wave-like patterns. By these movements the mucus with all the retained particles (dust, bacteria, powders, oil droplets) is drained to the pharynx, where the soft palate conducts it to the oesophagus by the swallowing movement. The coordinated movement (phase and frequency) is necessary for an efficient mucociliary clearance [11, 12].

More detailed information about the anatomy of the nose and the properties and functions of the nasal mucosa can be found in the literature [3, 8, 11–15].

8.3.1.2 Ciliary Beat

A well operating ciliary epithelium is important in prevention as well as cure of many diseases of the airways. The activity of the cilia depends on a number of factors, including temperature and humidity of the air, pH and viscosity of the mucus layer. Besides pathological conditions (allergic diseases, sinusitis, measles) also chemical influence may inhibit the action or even destroy the ciliary epithelium. This is called ciliotoxicity. Ciliotoxicity is an important reason to restrict the period of use of nasal preparations.

The inhibiting effect of anaesthetics on the ciliary epithelium is supposed to be an important cause of respiratory infections following surgery [12].

The rate of mucociliary clearance differs between individuals (fast and slow movers), but it does not depend on gender or age [11].

8.3.2 Biopharmaceutical Aspects of Nasal Preparations

Section 16.2.6 discusses biopharmaceutics of nasal preparations from a general biopharmaceutics viewpoint. This subsection adds some more specific details, first on the nasal absorption and then on the many investigations on absorption enhancing substances. The interest for nasal absorption is predominantly raised by the desire to find an alternative administration route for systemically acting active substances.

8.3.2.1 Intranasal Absorption

The mucociliary clearance rate may influence the intranasal absorption of systemically active substances. Pathological conditions and an accelerated rate of mucociliary clearance shorten the contact time between active substance and the absorbing mucosa. A delayed mucociliary clearance will have the opposite effect. Nasal hypersecretion dilutes the medicine solution and delays passive absorption. In addition it may lead to a local loss of some of the medicine due to a washout effect. A change in pH of the mucus layer may have consequences on the ionisation of some substances, and thus on their absorption [11].

8.3.2.2 Absorption Enhancers

Three ways exist to improve limited nasal absorption of systemically acting substances:

- Using substances enhancing absorption through the mucosa
- Using enzyme inhibitors to reduce degradation of active substances
- Using mucoadhesive polymers, to make the preparation stay in the nasal cavity for a longer time

Any substance added to improve absorption should be pharmacologically inert, with no taste or smell, non-allergenic, non-irritating, non-toxic, affecting the structure of the mucosa and the mucociliary clearance only in a reversible way [11, 12]. Examples of mucoadhesive polymers are carbomers, chitosan and carmellose. They lengthen the residence time of nasal powders or suspensions in the nasal cavity [13, 16–18]. In addition to that carbomers bind in a reversible way with the tight junctions of the epithelium, thus facilitating paracellular transport [11, 12, 19–21]. Using cell culture and animal models, the mechanism of absorption enhancement of chitosan was also shown to be the transient opening of the epithelial tight junctions combined with the mucoadhesion [22]. However, more research has to be done on the effects of chronic use of mucoadhesive polymers in nasal preparations.

Absorption enhancers such as cyclodextrins can enhance the biological availability of intranasally administered medicines [23]. Research has mainly been focused on the influence of these excipients on systemic availability, but an enhanced local effect seems possible as well.

In short term studies cyclodextrins caused less histological changes of the nasal epithelium in rats than for instance benzalkonium chloride [24]. Other studies in rats showed that dimethyl betacyclodextrin, methylated betacyclodextrin and hydroxypropylbetacyclodextrin are safe and efficient enhancers of nasal absorption [8, 25, 26]. These results suggest that cyclodextrins (see also Sect. 18.1.4) can be used in nasal preparations, but more research is still needed.

Surfactants are also used to promote penetration of ingredients with systemic activity through the nasal mucosa. Their mechanism of action is based on a change of the permeability by disturbing (reversibly or irreversibly) the structural integrity of the mucosa. Polysorbate 80, for instance, has a strong negative effect on the cilia, which is however reversible.

More information about absorption enhancers is to be found in literature [3, 11, 12, 27, 28].

A range of nasal peptides such as desmopressin, buserelin, nafarelin and oxytocin, have been formulated into licensed nasal products. However, none of them contains a nasal absorption enhancer. Even though these nasal products are characterised by low peptide bioavailability they are efficacious, as low systemic levels are needed to exert a therapeutic effect. However, developing of novel safe and efficient nasal absorption enhancers is of great interest to improve bioavailability of presently marketed peptides and to provide sufficient nasal permeability of less potent biologicals [22].

Several novel nasal absorption enhancer systems with promising preclinical or clinical data or both are now being commercially developed (i.e. cyclopentadecalactone, alkylsaccharides, chitosan, low methoxylpectin, hydroxyl fatty acid ester of polyethylene glycol) and have been reviewed in the literature [22]. Low methoxylpectin is already used in PecFent®, an intranasal preparation with fentanyl (Table 8.2). It contains the PecSys® delivery system, an in situ gelling system that gels due to interaction with calcium ions in the nasal fluid [29].

8.3.2.3 Local Effect

Not much is known about the biopharmaceutics of nasal preparations with a local effect. Dosing is done on a therapeutic result basis. What is known is that bioavailability and residence time are influenced by:

- The position of the head during administration
- The droplet size, which depends on different factors, including the interfacial tension of the solution and the dropper
- The pattern of atomisation, that depends on the properties of the nozzle
- The viscosity of the solution
- The administered volume (number of drops or spray volume)
- The site of deposition (anterior or posterior part of the nasal cavity)
- Pathological situations and the condition of the mucosa (cold or flu, nose congestion, runny nose, nasal polyps, etc.), which affect absorption and mucociliary clearance

8.4 Adverse Effects and Toxicity of Nasal Drops and Sprays

As the mucosa is highly sensitive to irritation, nasal toxicity of active substances and excipients is an important issue in formulating nasal preparations, especially when they are intended for treatment of chronic diseases [11]. Nearly all substances used in nasal preparations have a negative influence on the ciliary beat, and are therefore ciliotoxic. The influence may vary from a temporary (reversible) effect up to an irreversible inhibition of the ciliary beat [30]. In many nasal drops and nasal sprays preservatives cause the toxic effect on cilia [31], but the active substance itself may also have a negative influence on the ciliary epithelium. Nasal drops with decongestants have been shown to exhibit relatively low ciliotoxicity (e.g. Xylometazoline nasal drops 0.025 %, 0.05 % and 0.1 % (see Table 8.4) as well as a number of licensed preparations) [32].

A review of the ciliotoxicity of other active substances that are used in nasal preparations, including local anaesthetics, antibiotics, antihistamines and corticosteroids can be found in the literature [12].

Table 8.4 Xylometazoline Nasal Drops/Spray, Solution 0.025 % [33]

Xylometazoline hydrochloride	0.025 g
Benzalkonium chloride	0.01 g
Disodium edetate	0.1 g
Disodium phosphate dodecahydrate	0.1 g
Sodium chloride	0.8 g
Sodium dihydrogen phosphate dihydrate	0.15 g
Water, purified	ad 100 mL

The administration of nasal drops or sprays may sometimes cause temporary irritation of the nasal mucosa. Systemic (side) effects, e.g. of decongestants, may be seen as a result of absorption by the nasal mucosa and the gastrointestinal tract. Problems of this kind can be avoided, if the patient carefully follows the instructions for use, the quantity to be administered and the duration of the therapy.

Especially in young children the use of nasal drops or sprays should be restricted. An overdose administered in the nose (e.g. by too high concentration) will more quickly lead to intoxication in young children than in adults, as the absorption surface of the mucosa compared to body weight in children is larger than in adults. In using nasal sprays, the contact absorption surface is larger than for nasal drops, so overdosing is more likely to occur. Due to the ease with which nasal sprays can be administered there is a real risk of overdosing in children. This risk led to the removal of the indication of primary nocturnal enuresis (PNE) in 2007 from all desmopressin nasal spray products, due to increased risk of hyponatremia and other adverse effects compared with the oral formulation [34].

In children under about 2 years of age there is the risk of a life-threatening laryngospasm. The nasal mucosa after a mechanical stimulus or a stinging smell can show a reflex apnoea or a spasm of the vocal cords. Menthol is a notorious example, but other volatile substances might cause the same reflex action.

In this section focus lies on the design of the formulation of nasal preparations, first for liquids and then for semisolid forms.

In addition to the active substance, nasal preparations often contain a number of excipients, including vehicles, buffers, preservatives, tonicity adjusting agents, solubilising agents, humectants, viscosity enhancing substances and possibly antioxidants. In the design of a nasal preparation, great care is needed when choosing a vehicle and other excipients. The integrity of the mucosal epithelium, the overall ciliary function and the mucus production should be retained as much as possible after administration. Otherwise the physiological function, and thus the protective action, of the nose will be disturbed. In many cases there will be a need to compromise between physiological requirements and restrictions with regard to the stability and pharmacological activity of the active substances.

8.5 Product Formulation

8.5.1 Liquid Preparations (Nasal Drops and Nasal Sprays)

8.5.1.1 Physico-chemical Properties of the Active Substance

A water soluble form of the active substance is preferred. This may bring about oxidation or hydrolysis reactions (see Sect. 22.2). Common sympathomimetics such as naphazoline, oxymetazoline and xylometazoline may hydrolyse in aqueous solution, but this happens only at a pH higher than what is normal for nasal preparations, or at a higher temperature than what is normal for the storage of these preparations.

In preparations for intranasal administration for systemic purposes, the aqueous solubility of the substance must be sufficient to make administration of the desired dose in a small volume possible. The volume that can be administered per nostril is 25–150 microlitres at the time, with a maximum of 200 microlitres.

Lipophilic substances are absorbed better, but the water solubility may be the limiting factor. For insoluble active substances, such as many corticosteroids, a suspension is the most suitable form. In that case the particle size of the raw material should be less than 90 μm. Beside particle size, polymorphism is another influencing factor [3, 8]. See also Sect. 18.4.2.4.

For the formulation of a homogeneous, readily dispersible suspension reference is made to Sect. 5.4.6 about oral suspensions.

Tables 8.1 and 8.2 give some examples of nasal preparations, solutions as well as suspensions. Note that all licensed preparations for systemic therapy are solutions, as shown in the second column of Table 8.2.

8.5.1.2 Vehicle

Properties of the vehicle which influence the effectiveness of a nasal solution include pH, buffer capacity, osmolarity, stability, influence on normal mucus viscosity, compatibility with active substance and compatibility with ciliary function. Water is chosen as the solvent, because most other solvents will have a negative influence on the ciliary function. A buffer solution may be needed for stability reasons.

Propylene glycol is strongly ciliotoxic, as it causes immediate paralysis of the cilia, it is also hypertonic and it dehydrates the mucosa. It may also change the rheological properties of the mucus. However propylene glycol may be necessary to bring an active substance into solution, e.g. midazolam nasal spray [35]. In a preparation for incidental use, e.g. as an emergency medication in people

suffering from epilepsy, ciliotoxicity could be acceptable, more than in a nasal spray against chronic rhinitis.

Fatty vehicles, such as (vegetable) oils, have the disadvantage that they do not mix with the mucus layer. In that situation there would be little contact of an oil soluble active substance with the nasal mucosa and that oily substances would rapidly pass on to the nasopharynx.

8.5.1.3 pH and Buffer Capacity

The pH of the nasal formulation is a very important parameter which can be set to avoid irritation of the nasal mucosa and influence on physiological ciliary movement, to ensure active substance solubility or availability in unionised form suitable for absorption, to prevent growth of pathogenic bacteria or to maintain functionality of preservatives [36]. The pH of physiological normal nasal liquid is 6–8 [37]. The health condition of the patient is one of the factors that influence the pH. A physiological pH is necessary for a normal mucociliary clearance and minimal nasal irritation. A pH outside these limits will have a negative influence on the activity of the cilia. Deviations in the alkaline region are better tolerated than acid solutions. After the introduction of a solution of pH 5.8, the mucosa will react by increasing the production of bicarbonate containing mucus [37]. For this reason the pH of nasal drops and sprays should be not far below the physiological value. The Ph. Eur. does not set limits for the pH of nasal preparations, but requires they will not have a negative influence on the functioning of the nasal mucosa and the cilia. A pH between 6.2 and 8.3 is generally considered safe for the cilia. (A pH $>$ 8.3 and $<$10 would perhaps not affect the cilia much, but may cause an unpleasant taste after administration). The safe range for the pH of nasal drops is narrower than for eye drops, because the buffering and diluting effect of the nasal liquid is less than that of tears. This means that a formulation for eye drops cannot always simply be used for nasal drops.

The ciliotoxicity of some substances depends on the pH of the solution. For instance when benzalkonium chloride is used as preservative, the pH of the preparation should be $>$5 to reduce the ciliotoxicity. Preservative efficacy can also be dependent on pH of the formulation. For instance, antimicrobial activity of benzalkonium chloride occurs between pH 4 and 10, and methyl parahydroxybenzoate exhibits antimicrobial activity over the pH range of 4–8 [38, 39]. See also Sect. 23.8.2.

In other cases the stability or solubility of the active substance requires a pH deviating from the physiological one. Midazolam nasal spray has pH 4, in order to keep the active substance in solution [35].

Buffers are included to maintain a desired pH throughout the shelf life of the preparation. As the nasal liquid has only limited buffering effect, it is important for the buffer capacity of the preparation to be as low as possible. When a buffer is needed, phosphate (pH 6.8–8.5) and trometamol (pH 7.2–8.5) buffers are suitable. Citrate buffers should be avoided because of their ciliotoxic effect and possible irritation of the nasal mucosa. Borate buffers are ciliotoxic and badly tolerated [10]. The nasal drops in the Dutch formulary are (weakly) buffered with a mixture of sodium mono hydrogen phosphate and sodium dihydrogen phosphate, see Table 8.4.

In medicines with intended systemic action a certain pH may be necessary to guarantee sufficient absorption of the active substance. In that case a buffer with high capacity is chosen, although it will have a negative effect on cilia. The more pH deviates from the physiological value, the more irritation will be felt. An example is a licensed nasal spray with the peptide buserelin in a citrate buffer (pH 5.5–6). Its Summary of product characteristics (SPC) says nasal irritation may occur, sometimes leading to epistaxis or hoarseness, as well as changes in taste and smell.

8.5.1.4 Osmotic Value

Nose drops and sprays that are not iso-osmotic have a negative influence on the ciliary epithelium. Hypo-osmotic solutions however are more ciliotoxic than hyper-osmotic ones [32]. Again the requirements should be more strict than for eye drops, because the diluting effect of the nasal liquid is much smaller than that of tears. Nasal drops are made iso-osmotic with sodium chloride, or in case of incompatibilities with glucose or mannitol. More information about osmotic pressure and tonicity, and the calculation of the osmotic value of solutions, is given in Sect. 18.5.

8.5.1.5 Viscosity

In many licensed medicines viscosity enhancers and surfactants are added to stabilise suspensions. In such cases it is important to avoid too high concentrations of these excipients, in order to avoid too much negative influence on the mucociliary clearance.

Also solutions are sometimes made viscous to prevent them from flowing out of the nose, for example nasal drops with 0.9 % or 1.5 % sodium chloride (Table 8.5), but there are doubts whether this will help.

Opinions on the use of viscosity enhancers in nasal sprays are not uniform. Firstly, the residence time of viscous nasal

Table 8.5 Sodium Chloride Nasal Drops, Viscous Solution 0.9 % [40]

Sodium chloride	0.9 g
Benzalkonium chloride	0.01 g
Disodium phosphate dodecahydrate	0.025 g
Hydroxyethylcellulose 400 mPa.s	0.5 g
Water, purified	88.35 g
Total	100 g

sprays within the nasal mucosa is somewhat longer. Secondly, non-viscous sprays may be nebulised to smaller drops, which enlarges the contact surface. In addition, during its residence time a viscous liquid will stay on top of the viscous mucus, and therefore be passed on easily. A non-viscous solution will have better contact with the nasal epithelium.

When surface-active viscosity enhancers are used, the surface tension will influence the droplet size of the nebulised solution. A lower surface tension will lead to smaller drops, and thus a larger contact surface. For instance nasal sprays with corticosteroids often contain carmellose.

When a nasal spray is supplied in a squeeze bottle instead of one with a pump atomizer, a viscous spray might be difficult to nebulise. So, in the design of a spray formulation, viscosity has to be considered together with the intended type of container and atomising device.

Nasal suspensions can be characterised by thixotropic properties [41]. Nasal sprays containing triamcinolone acetonide or mometasone furoate showed time-dependent, reversible loss of viscosity under shear (shaking or spraying,) flowing more freely. Recovery of viscosity after application is likely to inhibit suspension flowing out from the nasal cavity [42, 43].

8.5.1.6 Preservation

Aqueous nasal drops and nasal sprays are preserved when they are supplied in multidose containers. In order to get a low level of microbiological contamination at the start, the use of sterilised water or sterilised solutions of preservatives as primary materials is recommended.

Benzalkonium chloride is so far the most widely used preservative, but thiomersal, chlorobutanol, phenylethanol, and parabens can also be found in nasal formulations.

Mercury compounds, such as phenylmercuric borate and thiomersal, can lower the ciliary beat frequency fast and irreversibly and, therefore, should be avoided, if their use is not already limited because of environmental reasons [44]. See also Sect. 23.8.4. Chlorobutanol inhibits the ciliary beat very fast, but provided the contact time is short, the ciliary movement will recover after some time. Parabens also have proved to be able to inhibit the ciliary movement (*in vitro* studies) [45].

Benzalkonium chloride *in vitro* has a ciliotoxic effect, which develops slowly, but is irreversible. Benzalkonium chloride slows down the ciliary movement and disorganises the mucus layer. This structure change is supposed to be the result of an interaction of anionic substances in the mucus with the cationic benzalkonium. The ciliotoxic effect of benzalkonium chloride increases when pH is lowered from 7 to 5. Therefore nasal drops preserved with benzalkonium chloride should preferably have a pH around 7. *In vivo* however, long-term use of benzalkonium chloride 0.02 % did not change the rate of mucociliary clearance and the morphology of the mucosa [24]. In addition, benzalkonium chloride safety has been reviewed on the basis of 14 *in vivo* and 4 *in vitro* studies [46]. It has been concluded that intranasal products containing preservative benzalkonium chloride appear to be safe and well tolerated for both long- and short-term clinical use.

Disodium edetate, normally the second component in preserving solutions with benzalkonium chloride, has limited intrinsic antimicrobial efficacy and a relatively small effect on the cilia.

Balancing advantages and disadvantages the combination of benzalkonium chloride 0.01 % and disodium edetate 0.1 % is the preferred preservative for nasal drops and sprays. Second choice would be methyl parahydroxybenzoate 0.1 %. Detailed information about the efficacy of preservatives in nasal preparations can be found in [47].

8.5.1.7 Appearance, Smell and Taste

When used correctly, nasal drops and sprays will not come into contact with the taste buds, but nevertheless they can give a sensation of taste [23]. This is easy to understand, as the olfactory organ plays an important role in the experience of taste. The clearance through the nasopharynx can be another cause, as a bitter taste is mainly observed at the rear of the tongue. Usually nasal preparations do not contain any flavouring agents. A side effect of especially nasal sprays may be a change in the users sensation of smell and taste. Examples are nasal sprays with fluticasone and with buserelin (Suprefact®).

8.5.2 Semisolid Preparations (Nasal Ointments and Gels)

8.5.2.1 Active Substance

Active substances may be incorporated as a solution or as a suspension. More information about this choice can be found in Sect. 5.4.2.

8.5.2.2 Ointment Base

The choice of an ointment base depends on the site of application. In the anterior part of the nose, where cilia are absent, and in rhinitis sicca or in atrophic rhinitis, a fatty ointment base is used. An example is Menthol-paraffin nasal ointment 0.6 % (Table 8.6). When the nasal mucosa does not function, as in atrophic rhinitis, possible ciliotoxicity of the

Table 8.6 Menthol-Paraffin Nasal Ointment 0.6 % [48]

Menthol, racemic	0.6 g
Paraffin, liquid	49.4 g
Paraffin, white soft	50 g
Total	100 g

ointment base is less relevant. The same applies to the treatment of vestibulitis nasi, because of the absence of cilia in that part of the nose (see also Sect. 8.1).

In diseases of the vestibulum nasi soft ointment or emulsion bases are often used. Examples of ointments are Hydrophobes Basis gel DAC (see Sect. 12.7.6), with added wool fat or a similar w/o emulsifier. Sometimes part of the white soft paraffin in these ointments is replaced by liquid paraffin or triglycerides, to make them softer and easier to apply in the nose.

Alternatively w/o emulsion bases are used in practice, such as hydrophobic creams:

1. Glycerol 85 % – White soft paraffin – Water – Wool fat (33.3 % - 33.3 % - 8.3 % - 25 %)
2. Anhydrous Eucerinum® – Propylene glycol – Sodium chloride – Water – Refined Olive oil (23 % - 10 % - 1 % - 46 % - 20 %)

None of them has been officially published however.

8.5.2.3 Hydrogel Base

Theoretically a hydrogel is safer for the cilia than a nasal ointment with fatty components. Compared to nasal drops the application of a hydrogel is more efficient, and it stays longer on the mucosa, thus raising the chances for absorption of the active substance. Gels containing humectants (glycerol, sorbitol and mannitol) are supposed to diminish the irritation caused by some active substances.

There are however a number of restrictions to the formulation of a nasal gel. Carbomer gel is not acceptable, because of the incompatibility with substances such as sodium chloride, chlorhexidine digluconate and other ionogenic substances that are often incorporated in this dosage form. A hydrogel with a cellulose derivative leaves a crusty layer after drying, which may irritate. This effect is more obvious for high molecular derivatives than for those with lower molecular weight. Uncharged cellulose derivatives show least ciliotoxicity. Suitable cellulose derivatives for nasal preparations are hypromellose 4,000 mPa.s (2–6 %) and hydroxyethylcellulose 300–560 mPa.s (3–6 %). The addition of a humectant (e.g. glycerol 85 %) is necessary in order to soften the crusty layer that will be left, thus lessening irritation. The addition of such a humectant will however cause hyperosmosis, which is not desirable regarding the ciliary function. A suitable hydrophilic gel base might be the formula given in Table 8.7 that has been used clinically according to [7]. It is based upon the formula of Hydroxyethylcellulose gel DAB [49], but with the combination of benzalkonium and disodium edetate as preservative.

Table 8.7 Base for Hydrophilic Nasal Gel [7]

Benzalkonium chloride	0.01 g
Disodium edetate	0.1 g
Glycerol (85 %)	10 g
Hydroxyethylcellulose 400 mPa.s	4 g
Water, purified	85.89 g
Total	100 g

8.5.2.4 pH

In nasal gels pH should be in the range 6.2–8.3, as in nasal drops. Values outside these limits may be necessary for reasons of solubility, stability or efficacy of the active substance. Preferably nasal gels are not buffered, but when for instance the stability of the active substance demands a certain pH, phosphate or trometamol buffers are used.

8.5.2.5 Preservation

When preservation of a nasal gel is needed, like in nasal drops the combination of benzalkonium chloride and disodium edetate (0.01 % and 0.1 % respectively) is preferred. According to the NRF the concentration of benzalkonium chloride should preferably be doubled to 0.02 %, because the antimicrobial action is not always sufficient in the presence of viscosity enhancers [50]. Methyl parahydroxybenzoate is the second choice.

8.6 Method of Preparation

8.6.1 Nasal Drops and Liquid Nasal Sprays

8.6.1.1 Sterile Vehicles

In order to get a low degree of microbiological contamination at the start, the use of sterilised water or sterilised solutions of preservatives as primary materials is recommended. A Dutch example is Benzalkonium Sterile base solution 0.1 mg/ml (Table 8.8).

For nasal drops as a suspension, or when viscous nasal drops are needed, the combination of equal parts of hypromellose-benzalkonium solution (Table 8.9) and benzalkonium base solution 0.1 mg/ml (Table 8.8) may be used.

Both preservative solutions can be sterilised by steam and stored in bottles of borosilicate glass (Type I glass see Sect. 24.2.1).

8.6.1.2 Preparation Method

In the preparation of nasal drops and liquid nasal sprays the active substances are dissolved or suspended and the excipients are dissolved in the preservative solution or sterilised water. For viscous nasal drops the components

Table 8.8 Benzalkonium Sterile Base Solution 0.1 mg/ml [51]

Benzalkonium chloride	0.01 g
Disodium edetate	0.1 g
Water, purified	ad 100 mL

Table 8.9 Hypromellose-benzalkonium Sterile Base Solution [52]

Benzalkonium chloride	0.01 g
Hypromellose 4,000 mPa.s	1 g
Disodium edetate	0.1 g
Water, purified	ad 100 mL

may be dissolved or suspended in a standard base solution such as the benzalkonium base solution 0.1 mg/ml of Table 8.8. This solution or suspension is then diluted with hypromellose-benzalkonium base solution (Table 8.9).

8.6.1.3 In-process Controls

In the preparation of nasal drops and nasal sprays the following in-process controls are important:

- Writing down the tare or calibrating utensils in case a final addition to weight or volume is required
- Measuring of temperature, for instance during dissolving under heating of thermolabile substances, and after cooling down
- pH
- Clarity after each dissolution step
- Absence of particles in solutions by visual inspection
- Homogeneity and absence of lumps in suspensions
- Total weight or total volume or the yield.

8.6.2 Nasal Ointments and Nasal Gels

8.6.2.1 In-process Controls

The In-process controls of nasal ointments are the same as those of similar cutaneous preparations (see Sect. 12.6.4).

For the preparation and in-process controls of nasal gels see Sect. 12.7.11.

8.7 Containers and Labelling

8.7.1 Packaging of Nasal Drops

Containers for nasal drops usually should protect their content from light, as many nasal preparations show degradation on exposure to light. Dropper bottles are therefore made of brown glass. Also an opaque white plastic bottle (high density polyethylene bottle) generally gives sufficient protection from light.

Nasal drops can be supplied in a multidose bottle with an integral dropper or with a dropper applicator. From a microbiological point of view an integral dropper may offer better protection, but for practical reasons a dropper applicator is often preferred. It makes dosing easier for the patient and so prevents overdosing (see Sect. 24.4.19.9). The disadvantage of a separate dropper for the administration of nasal drops is that mucus with bacteria from the nose can get into the liquid. This can be avoided if patients are instructed to keep squeezing the rubber balloon until the dropper tip has been removed from the nostril. In any case the dropper should be cleaned with warm water each time it has been used.

Preservative free nasal drops should be supplied in single-dose containers (see Sect. 24.4.14).

8.7.2 Packaging of Nasal Sprays

Nasal sprays can be supplied in containers with some form of atomiser. There are two possibilities: plastic (high density polyethylene) squeeze bottles with an atomiser and glass bottles with a pump atomiser (see Fig. 24.14 in Sect. 24.4.19.9). In the first type, dosing is done by squeezing the bottle; in a pump atomiser, by pumping. Dosing with a pump atomiser is more accurate than by squeezing, which makes the pump atomiser more suitable for highly active substances, such as corticosteroids [7].

To avoid contamination with nasal liquid, the squeeze bottle should be kept pressed in until it is removed from the nose. This is not needed with the pump atomiser. Both devices have to be cleaned by rinsing or wiping.

In some licensed nasal sprays dosage delivery devices are used that make it possible to deliver doses free from micro-organisms and at the same time maintain sterility of preservative free solutions. The manner of construction is claimed to prevent environmental air coming into contact with the (sterile) content in the reservoir. Examples are the COMOD® system and the Freepod® pump system. These systems are not available for pharmacy preparations.

8.7.3 Packaging of Nasal Ointments and Gels

Nasal ointments and gels are supplied in tubes. Eye ointment tubes are often chosen, not only for their application tip, but also because, usually, small quantities are dispensed, for short term treatments (see Sect. 24.4.9).

8.7.4 Labelling and Patient Counselling

Nasal drops should be dispensed in a container with a label saying “nasal drops” or “for nasal use”. Nasal sprays and nasal gels and ointments can be labelled as such. When labels with that specific indication are lacking, the label should at least make clear that the medicine is not for oral use. When the container is dispensed in a secondary packaging, this should be labelled also. The label should comply with the requirements mentioned in Sect. 37.3.

For suspension nasal drops the label should bear the warning “Shake well before use”. This applies also to the many licensed suspension nasal sprays that are on the market. For these preparations it is important to shake first and only then start pumping. Doing this in the right order prevents clogging of the tube of the atomiser. Thixotropic suspension nasal sprays should be shaken vigorously in order to transform a thick suspension into liquid as it will spray only when it becomes liquid.

When dispensing nasal preparations the patient should receive all relevant information, oral as well as written.

In using nasal drops, the method of instillation is important to obtain the required effect [5, 6]. After blowing the nose nasal drops are usually instilled with the head tilted forward or backward. A disadvantage of a backward tilted head is that the nasal drops will flow across the bottom of the nose to the nasopharynx, and hardly come into contact with the mucosa where they are to act. For this reason several different positions of the head have been suggested, but the identification of a single ‘best technique’ appears not to be realistic. Lying head back (with the head just off the bed) or lateral head low (bent down forward and at the same time sideward, see Fig. 8.2) gave slightly better results than head bent down forward (so called Moffat position) [53].

An individual approach seems more appropriate. During the administration, the drops should be gently inhaled, keeping the other nostril closed. The teat should remain pressed until it has been removed from the nostril. Rinse and wipe the dropper after use.

When using a nasal spray, the position of the body is much less important. After blowing each nostril, the spray can be nebulised with the head in upright position. Plastic squeeze bottles demand short and firmly squeezing, and keeping the bottle pressed until it is drawn back. When using a pump atomiser for the first time, pumping several times (‘priming’) is needed, until an even mist is produced. Priming is needed to displace air that might be present in the dip tube. Only then the desired dose will reach the nose [54]. In addition, preparing the spray for use should not include shaking it unless specified by the manufacturer, as this can affect the dose. Patients can also be advised to keep the bottle upright to reduce the risk of air bubbles getting into the dip tube. If the spray has not been used for a certain period (usually 7 days or more), ‘re-priming (pumping the spray several times) is needed until a fine mist is produced. The number of priming and re-priming actuations is usually recommended in the labelling.

Fig. 8.2 Position of the head during the administration of nasal drops. Source: Recepteerkunde 2009, ©KNMP

When using a nasal spray, the tip of the atomiser is brought into each nostril respectively, while pumping once and inhaling through the nose. The nozzle of the squeeze bottle or the pump atomiser should be cleaned by rinsing and wiping, taking care that water is not sucked up.

Patients should be advised that nasal products are for one patient only and should not be passed around since the risk of inter patient contamination by nasally administered products is very high.

8.8 Release Control and Quality Requirements

Nasal drops and sprays are to be checked before release on appearance, packaging and labelling. Solutions should be clear and free from (dust) particles. Suspensions should be checked on homogeneity and resuspendability.

Specifications for nasal drops are (see Table 32.2):

- Identity
- Appearance (clarity, no precipitate, sediment or dust particles)
- Content (of active substances)
- pH
- Microbiological quality

- For preparations in single-dose containers: uniformity of mass (solutions) or uniformity of content)
- In some cases: uniformity of dosage units

Nasal sprays with a declared amount of active substance for each puff (so called metered-dose sprays), should comply with the requirements on the variation in this amount. In practice, this is only seen in licensed medicines. For solutions the test for uniformity of mass is sufficient. Suspensions should comply with the test for uniformity of dosage units (see Sect. 32.7.2.4), or, where justified and authorised, with the test for uniformity of delivered dose. In this test, specially meant for metered-dose sprays, the allowed range of variation is much broader than for oral preparations.

Release controls for nasal ointments and gels are similar to those on the corresponding cutaneous preparations, i.e. gels and creams (see Sect. 12.6.5).

8.9 Storage and Stability

Generally, nasal preparations should be stored at either room or refrigerated temperatures and should not be frozen.

For chemically stable, preserved nasal drops, sprays and hydrophilic nasal gels, a maximum shelf life of 2–3 years at $\leq$ 25 °C (not in a freezer) is acceptable (see Sect. 22.7). Once opened by the patient, the usage period is arbitrarily set at 1–3 months, at $\leq$ 25 °C (not in a freezer). The allowed maximum length of this period varies from one country to another, and it depends also on the type of preparation and package. A period of 1 month is often chosen for nasal decongestants, as these preparations are particularly liable to contamination during use. In a hospital a usage period of a week is more usual, as decongestants should not be used much longer for pharmacotherapeutic reasons as well. Corticosteroid sprays, used for longer periods in allergic rhinitis, may have usage period of 2–3 months after opening. In some licensed nasal sprays a beyond-use date after opening is not mentioned at all. Nasal solutions of peptides should be stored in a refrigerator (2–8 °C) before first opening. Once opened such solutions should be kept at 25 °C and can be used within 1 month after opening.

For standard nasal preparations that are not chemically stable, the maximum shelf life must be indicated in the formulary. For chemically and physically stable fatty nasal ointments that contain water, the maximum shelf life is set at 3 years at $\leq$ 25 °C, (not in a freezer). The usage period after opening the container may be 3 months (see Sect. 22.7.1).

For non-standard extemporaneous pharmacy preparations, the design must include attention to the way of storage, and the maximum shelf life and beyond-use period after opening. For preparations with uncertain or unknown chemical, physical or microbiological stability, arbitrarily a shelf life of 1 month at $\leq$ 25 °C (not in a freezer) is advised (Sect. 22.7.1). For preservative free nasal drops, sprays and hydrophilic nasal gels a shelf life of 2 weeks refrigerated (2–8 °C) is recommended. In containers with the special systems COMOD® or Freepod® preservative free preparations the Companies give a shelf life of 2–3 years and a beyond-use after opening date of several months.

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Ear

9

Suzy Dreijer - van der Glas and Monja Gantumur

Contents

Abstract

This chapter deals with formulation and preparation of ear drops for application to the external auditory canal as well as those intended for the middle ear. Creams and ointments for the ear are similar to semisolid preparations for cutaneous use.

The most used ear drops prepared in pharmacies are discussed for their formulation (solvent, pH, osmotic value, preservation), method of preparation, packaging, storage and methods of administration.

The formulation of ear drops, especially the choice of the vehicle, depends on the site of action: the external auditory canal or the middle ear. When ear drops get to the middle ear, they may come into contact with the inner ear and so cause ototoxicity. Because of the ototoxicity of active substances, non-aqueous vehicles and many other excipients, special precautions are needed in formulations that should, or may accidentally, come into contact with the middle ear. Preparations intended for the middle ear are aqueous, sterile and preferably iso-osmotic. When non-aqueous vehicles are used in ear drops for the external auditory canal, it depends on the state of the patient's ear drum whether they will reach the middle ear.

Keywords

Formulation • Preparation • Ear drops • Ototoxicity • Vehicles

9.1 Orientation

For the treatment of diseases of the external auditory canal and the auricle non-sterile ear drops or semisolid bases are normally used. In the case of ear drops non-aqueous preparations are preferred, due to the possibility of microbial growth in a moist environment caused by aqueous vehicles. Therefore in external otitis non-aqueous vehicles are the

Based upon the chapter Oor by Annick Ludwig and Suzy Dreijer in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_9,

ones of choice, except for those situations where the skin would be excessively irritated.

Ear drops that have to act in the middle ear have to be sterile, aqueous and preferably iso-osmotic. They are applied to the auditory canal and reach the middle ear via the eardrum, which, in the diseased state, is usually permeable by perforation.

The requirements for sterility, aqueous vehicle and osmotic value also apply to eardrops that are placed directly in the middle ear during surgery, and to eardrops that are used for the external auditory canal, but can easily reach the middle ear. This is the case for a "clean" perforated eardrum because if not clean the debris will normally block the entrance to the middle ear anyway. Most non-aqueous solvents and many active substances are ototoxic (see Sect. 9.4). Thus the choice of the vehicle depends on the type of treatment and the site of application. For the auditory canal glycols (such as propylene glycol or glycerol) are preferred, provided they do not irritate. Ear drops for the treatment of infections in the external auditory canal usually contain antibiotics or corticosteroids or both, in a non-aqueous vehicle. For example eardrops with acetic acid and hydrocortisone (Table 9.1) have propylene glycol as the solvent. They have the purpose of reducing the swelling of the auditory canal in acute external otitis.

In the case of an acute weeping otitis the cooling effect of water can be advantageous as in eardrops with aluminium acetate and tartrate (Table 9.2). They are applied on a piece of gauze or an ear tampon, which should be changed at least every 24 h. In the acute phase the ear tampon often is chosen. The treatment is then continued with acid ear drops combined with a corticosteroid.

In the case of a perforated eardrum propylene glycol should not be used because of the possible ototoxicity. In the aqueous ear drops (Table 9.2) the concentration of aluminium acetate or acetotartrate may be too high. Therefore a tenfold dilution is normally used as a matter of precaution.

The antibacterial action of acetic acid in these preparations is due to a specific effect of acetic acid as well as the lowering of the pH. There are two benefits, namely that acetic acid is bactericidal to *Pseudomonas aeruginosa*, the major pathogen isolated from otorrhoea, and that it also suppresses several fungi [3–5]. In chronic suppurative otitis media (CSOM), the most common organism is *P. aeruginosa*, followed by *Staphylococcus aureus*.

Table 9.1 Acetic Acid with Hydrocortisone 1 % Ear Drops, Solution [1]

Hydrocortisone (micronised)	1.0 g
Acetic Acid (30 %) DAC	2.4 g
Propylene glycol	96.6 g
Total	100 g

Table 9.2 Aluminium Acetate Ear Drops, Solution [2]

Aluminium sulfate	22.5 g
Acetic acid (30 %) DAC	25 mL
Calcium carbonate	10 g
Tartaric acid	4.5 g
Water, purified	75 mL

These bacteria usually originate from the external ear canal and contaminate the middle ear [6].

For ear drops that are given to reduce pressure in the middle ear, as is often the case in inflammations, glycerol is used as the solvent, provided the eardrum is not perforated. A disadvantage of this kind of ear drops is that they make it difficult for the physician to clearly view the eardrum.

There are many different treatments for cleaning the external auditory canal or softening hard plugs of earwax. Some of them may be prescribed as a pharmacy preparation. These remedies vary from peanut oil or almond oil (of pharmacopoeia quality, not ordinary vegetable oil) to solutions of sodium carbonate in mixtures of glycerol and water. There are different opinions on the best way to soften earwax. Good research on the rationality of the different remedies is lacking. According to a Cochrane review, it is uncertain if one type of drop is better than another, although the use of any kind of drop is better than no treatment [7].

Theoretically, preparations with a fatty base are the first choice in dry external otitis. But because of practical problems in applying ointments and creams in the ear, ear drops are often preferred. Some guidelines recommend applying the ear drops, cream or ointment on an ear tampon that can be placed in the external auditory canal [8].

In the NRF ear drops with the antimycotic clotrimazol in peanut oil are included [Table 9.3]. This vehicle could be an alternative when propylene glycol would excessively irritate.

Chronic as well as acute inflammations of the middle ear are treated with sterile, aqueous ear drops with antibiotics, sometimes in combination with a corticosteroid. Normally these are short-time treatments. Many medicines of this kind are commercially available.

Ear drops have the following advantages and disadvantages:

Advantages:

- Simple application

Table 9.3 Clotrimazole Ear Drops, Solution 1 % [9]

Clotrimazole	1 g
Arachis oil, refined	99 g
Total	100 g

- Local application enables much higher tissue concentrations than would be possible with systemically administered medicines.
- Low risk of systemic adverse effects.
- Due to the higher tissue concentrations development of resistance against antibiotics is (at least theoretically) less likely [10]

Disadvantages:

- Ototoxicity of many active substances, non-aqueous vehicles and other excipients.
- For short term use only.
- Risk of contact allergy.
- Assessment of the eardrum may be difficult due to residues from ear drops.

Ear drops are not the only dosage form for treatment of diseases of the ear. Nose drops with decongestants are used to keep the Eustachian tube open to relieve the pressure and pain in otitis media, although the effect is not proven. In diseases of the middle ear nasal drops can be used

For the local administration of medicines in the inner ear and the cochlea highly sophisticated systems are used, like microcatheters, osmotic and peristaltic pumps. Current research on repairing patients hearing includes gene therapy, administration of neutrophins and stem cells [11, 12].

9.2 Definitions

The Ph. Eur. states that Ear preparations (Auricularia) are "liquid, semisolid or solid preparations intended for instillation, for spraying, for insufflation, or application to the auditory canal or as an ear wash. Ear preparations usually contain 1 or more active substances in a suitable vehicle. They may contain excipients to adjust tonicity or viscosity, to adjust or stabilise the pH, to increase the solubility of the active substances, to stabilise the preparation or to provide adequate antimicrobial properties. The excipients do not adversely affect the intended medicinal action of the preparation, or, at the concentrations used, cause toxicity or local irritation.

Preparations for application to the injured ear, particularly when the eardrum is perforated, or prior to surgery are sterile, free from antimicrobial preservatives and supplied in single-dose containers.

Ear preparations are supplied in multidose or single-dose containers provided, if necessary, with a suitable administration device which may be designed to avoid the introduction of contaminants.

Unless otherwise justified, aqueous ear preparations supplied in multidose containers contain a suitable antimicrobial preservative at a suitable concentration, except where the preparation itself has adequate antimicrobial properties."

An example of this is Bacicoline B®. These ear drops contain a borate buffer, but no preservative. This was accepted by the licensing authorities because borate buffers have some antimicrobial properties and because the beyond-use date is 10 days after opening.

In the monograph Ear Preparations of the Ph. Eur. the following categories are distinguished:

- Ear drops and sprays
- Semisolid ear preparations
- Ear powders
- Ear washes
- Ear tampons

9.3 Biopharmaceutics

9.3.1 Anatomy of the Ear

Looking from the outside to the inside the ear consists of the auricle, the external auditory canal, the middle ear and the inner ear (Fig. 9.1).

The middle ear is connected to the nasal pharynx by the Eustachian tube and to the inner ear via the oval and the round window.

The inner ear consists of the cochlea and the labyrinth, organs for hearing and balance respectively, with the eighth cranial nerve. This nerve has an auditory and a vestibular portion. The inner ear is filled with liquid. When sound waves strike the eardrum, between the external canal and the middle ear, this causes movements of the ear bones (hammer, anvil and stirrup). These movements are transferred into vibrations of the liquid in the inner ear, where the hair cells convert the movements to nerve impulses. The signals are sent to the brain through the auditory nerve.

More information about the anatomy and the physiology of the inner ear can be found in [11].

9.3.2 Passing the Eardrum

In external otitis, and, less often, for diseases of the middle ear, local application of medicines – i.e. in ear drops, may be necessary. Pharmacokinetic data of substances after administration to the middle ear have been reported in the literature [11].

Administration of preparations in the external auditory canal means that (theoretically) there is a chance that some

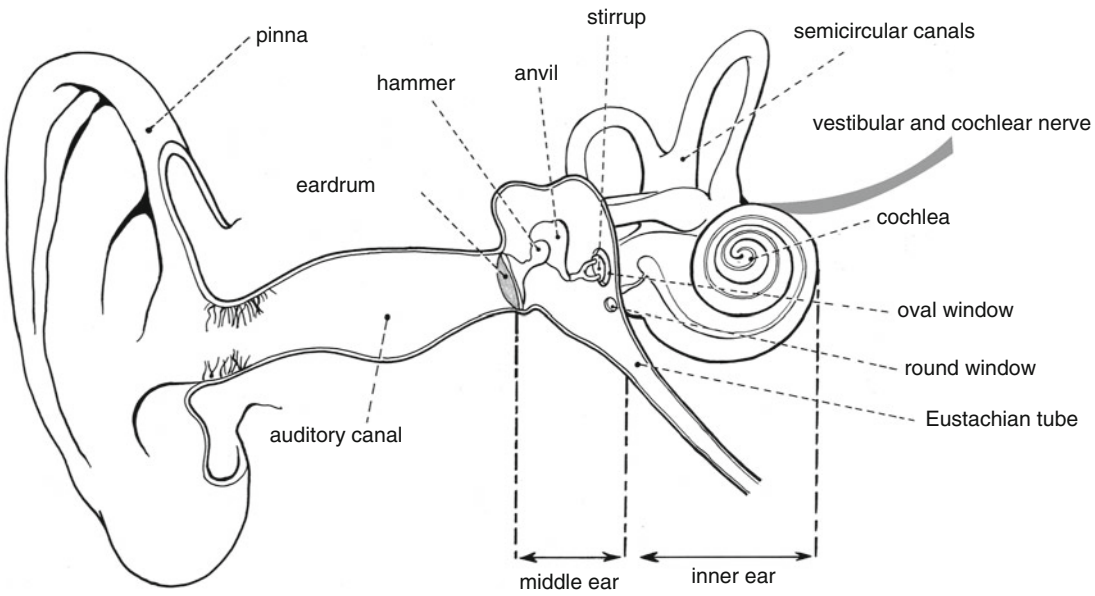

Fig. 9.1 Anatomy of the ear. Source: Recepteerkunde 2009, ©KNMP

substances will pass the eardrum and thus may damage the hearing organ. To be ototoxic a substance has to reach the inner ear. To do this from the external canal, first the eardrum has to be passed, and secondly from the middle ear the round or oval window. All of these membranes appear to be more or less permeable for the ingredients of ear drops [13]. Factors affecting permeability include the thickness of the membrane, concentration of the solution, electrical charge, and facilitating agents (prostaglandins, leukotrienes, staphylococcal and streptococcal exotoxins) [14, 15].

Factors that make the passage more difficult are contaminating substances in the external canal, and a swollen mucosa or purulence in the middle ear.

Especially in the case of a perforated eardrum preparations for the external auditory canal could accidentally reach the middle ear and thus the inner ear. Still, in acute situations treatment can be necessary, even when the condition of the eardrum is not known. Use of ear drops should then be restricted to a couple of days.

Preparations intended for the middle ear are aqueous and sterile. They are mostly used in middle ear infections, because in that condition the drops will be unlikely to reach the inner ear.

9.4 Ototoxicity

Ototoxicity may be caused by the active substance, the excipients or the solvent [11, 13, 16]. The risk of ototoxicity as a result of the use of ear drops can be limited by not giving ear drops when the middle ear (and thus also the inner ear) is easily accessible. A traumatic eardrum perforation, the presence of a tympanostomy tube without inflammation, or other ailments where the middle ear is accessible, but not affected, are examples of this situation. In infections of the middle ear the inner ear cannot easily be reached, and eardrops may be used. Aqueous preparations are then preferred, and the period of use should preferably not exceed 10 days.

It has been explained (Sect. 9.3.2) that the chance of passage of substances to the hearing organ is at the greatest when the middle ear is 'clean and healthy'. Theoretically all active substances and excipients that can reach the middle ear and subsequently diffuse into the inner ear may be ototoxic. There are a few exceptions, like azole antimycotics that show no ototoxicity [13, 17].

There is discussion in literature [13, 18] on the seriousness of the ototoxicity of aminoglycosides (e.g. neomycin, gentamycin). In clinical practice ototoxicity is seldom seen [18], but loss of hearing has been reported [11]. In the treatment of some forms of external, otitis, omitting aminoglycosides may be more harmful than a short term treatment with this kind of antibiotic, as secretion of puss may also be ototoxic [18]. Fluoquinolones, mostly considered as a standby medication, are less ototoxic than aminoglycosides. In some parts of the world (USA, Australia) ear drops with fluoquinolones are commercially available. Where this is not the case, as in many European countries, eye drops with ofloxacin or ciprofloxacin are prescribed for use as ear drops.

Vehicles such as propylene glycol and macrogol (polyethylene glycol) not only are ototoxic, but they can also enhance the passage of their solutes through membranes. The longer substances are in contact with the middle or

inner ear, the greater is the chance of damage. Shortening the period of contact may thus limit the risk.

9.5 Product Formulation

9.5.1 Active Substance

Ear drops are usually solutions of active substances in water or non-aqueous solvents, depending on the kind of treatment. Solutions are to be preferred to suspensions, as it is easier to control their homogeneity. In Acetic acid with hydrocortisone ear drops, solution (Table 9.1) hydrocortisone is present as such, so not as the more common hydrocortisone acetate, because the acetate is insoluble in propylene glycol. For the same reason of solubility miconazole base instead of the nitrate is chosen for miconazole ear drops 2 % in Table 9.4.

When a (water) soluble form of the active substance is lacking, a suspension has to be prepared.

9.5.2 Chemical Stability

Chemical stability (in general) is discussed in Chap. 22 and storage in Sect. 9.9.1. For formulation of ear drops it is relevant to consider hydrolysis reactions as being likely with phosphate esters of corticosteroids, such as prednisolone sodium phosphate or dexamethasone sodium phosphate. These hydrolysis reactions are catalysed by hydrogen ions. Therefore the vehicle should be neutral or slightly alkaline. Oxidation of dexamethasone sodium phosphate can be prevented by adding disodium edetate, which binds the catalysing metal ions.

In Acetic acid with hydrocortisone 1 % ear drops, solution (Table 9.1) the acetic acid content decreases by esterification with propylene glycol. Degradation of hydrocortisone occurs by a non-oxidative reaction. Also triamcinolone acetonide shows degradation in the acetic acid –propylene glycol vehicle. For these reasons these ear drops are kept refrigerated and the storage period is limited. When reasons of stability make it necessary to keep ear drops refrigerated, the solubility of the active substance in the chosen vehicle must be sufficient in order to prevent crystallisation at this storage temperature.

Table 9.4 Miconazole Ear Drops, Solution 2 % [19]

Miconazole	2 g
Propylene glycol	98 g
Total	100 g

9.5.3 Solvents

The choice between an aqueous or non-aqueous solvent has already been explained in Sect. 9.1. Glycerol, propylene glycol and macrogol 400 are used as non-aqueous solvents. Propylene glycol is the most used. It is less hygroscopic than glycerol and less easily oxidised compared to macrogol 400. It has preservative properties in concentrations >15 %.

The application of glycerol is based on the hygroscopic properties. The suggested pharmacotherapeutic action is by the lowering of the pressure in the middle ear by dehydration. Glycerol has preservative properties at concentrations >30 %.

Hypromellose 0.5 % is a suitable viscosity enhancer when a viscous aqueous vehicle is required, for instance in the formulation of a suspension of slightly soluble corticosteroids.

9.5.4 pH

A change of pH in the external auditory canal can be very important for the pathogenesis of both acute and chronic external otitis [20].

Drops with an acidic pH have the theoretical advantage of restoring the external auditory canal environment to normal and may contribute to the treatment of external otitis.

Aqueous ear drops intended for the middle ear should have a pH between 6 and 8. However a different pH may be needed because of stability, efficacy or tolerability of the active substances. When the pH of the vehicle is not 7.4, the buffer capacity should be as low as possible. These requirements are similar to those for eye drops, but they are more strict, as there is no physiological correction by tears. Thus, formulations of eye drops are not always suitable for the middle ear.

Strongly acidic or alkaline solutions may be unpleasant or irritate. This applies in the external auditory canal as well, as this is comparable with the skin. The acceptable range for the pH is much broader than for the middle ear however, see the examples of ear drops with acetic acid or sodium carbonate in Sect. 9.1. Again, care should be taken when such ear drops are used in situations where the middle ear is easily accessible.

9.5.5 Osmotic Value

Ear drops for the middle ear should preferably be iso-osmotic, or at least between the osmotic value of 260 milliosmols and 460 milliosmols (a 0.8 % and a 1.4 % solution of sodium chloride). Substances used to adjust the pH or the osmolarity are the same as those used in eye drops.

These excipients are dealt with in Sect. 10.6.1. To adjust pH boric acid or sodium tetraborate can be used, or dilute hydrochloric acid or sodium hydroxide solution. The systemic exposure to boric acid by the use of ear drops will not be relevant, because of the low concentration and the short period of use [21].

9.5.6 Viscosity

Viscosity is to be considered when using topical agents [10]. Theoretically, the more viscous a preparation, the more difficult it will pass through a tympanostomy tube or a drum perforation and enter the middle ear. A higher viscosity could also help to prevent ear drops flowing from the auditory canal.

9.5.7 Preservation

Ear drops for the external canal in non-aqueous vehicles (glycerol, propylene glycol or macrogol) do not need to be sterile. As the water activity in these solvents is very low, the addition of a preservative is unnecessary. Water is the solvent in the ear drops with aluminium acetate or acetotartrate (Table 9.2). The active substance in this concentration has such strong antimicrobial properties, that the formulation complies with the test on the efficacy of microbial preservation of the Ph. Eur. without an additional preservative [22]. However in the tenfold diluted ear drops (used if physicians want to avoid the risk of ototoxicity at all) the preservative properties are insufficient, due to the low concentration. Therefore the shelf life as well as the usage period are much shorter than for the undiluted preparation [23].

Ear drops that may, or should reach the middle ear are sterile aqueous solutions, with a preservative added when they are supplied in multidose containers. The monograph Ear Preparations of the Ph. Eur. states that ear drops that may or should reach the middle ear, should be sterile and free from antimicrobial preservatives. That sterility is required seems clear, as the solvent in ear drops intended for the middle ear is water, and the middle ear has little defence because of its low blood flow. When preservatives are not to be used, such ear drops should be supplied in single-dose containers, unless otherwise justified.

There is little chance that the sterile ear drops that are normally used, will actually reach the middle ear. These ear drops are applied for indications where the drops only theoretically may reach the middle ear, such as (impending) chronic otitis media with effusion, or when a glue ear develops in a patient with grommet. A swollen middle ear mucosa or a glue ear greatly reduces the chance of penetration of the ear drops into the middle ear. Besides, the period of use should be restricted to a maximum of 2 weeks. Taking into account the short period of use and the low concentrations, the risk of possible side effects of preservatives is considered acceptable. This applies even more when the active substances of the ear drops are ototoxic themselves. In practice sterile ear drops are packed in multidose containers, and preserved.

9.5.8 Preservatives

In aqueous solutions intended for the external auditory canal or the middle ear, where the active substance has no preservative properties, the combination of benzalkonium chloride 0.01 % and disodium edetate 0.1 % is the first choice; the second choice is methyl parahydroxybenzoate 0.1 %. They are dealt with in Sect. 23.8. Phenylmercuric salts are not used in ear drops anymore, as the use of mercury and its salts is discouraged for reasons of protection of the environment and possible toxic effects.

9.5.9 Method of Sterilisation

Aqueous ear drops can be sterilised in the same ways as eye drops (see Sect. 10.7.1). Sterilisation in the (final) container for 15 min at 121 °C is to be preferred. Preparation in a controlled, clean environment combined with a heat treatment of 30 min at 100 °C (in streaming steam) is an alternative for preserved ear drops, when steam sterilisation is not possible due to instability. In formulations with substances that cannot tolerate heating at all, aseptic preparation is the only possibility left.

9.6 Method of Preparation

9.6.1 Non-sterile Ear Drops

The active substances and the excipients are dissolved in the vehicle (see Sect. 29.5).

When glycerol is used as the solvent, care should be taken that it attracts as little moisture as possible, for instance by working in a closed vessel. For non-sterile ear drops the following in-process controls are important:

- Writing down the tare or calibrating utensils in case a final addition to weight or volume is required
- Measuring of temperature, for instance during dissolving under heating of thermolabile substances, and after cooling down
- pH in aqueous ear drops
- Clarity after each step of dissolution

- Homogeneity after mixing of liquids
- Absence of particles in solutions by visual inspection
- Total weight or total volume or the yield

9.6.2 Sterile Ear Drops

For the preparation of sterile ear drops sterilised and preserved base solutions for eye drops (for instance those of Table 10.9) should preferably be used. When a preservative free preparation is needed, sterilised water is the alternative. The active substance is dissolved in the eye drop base solution or the sterilised water. Details about the preparation process can be found in Sect. 10.7.

The in-process controls for sterile ear drops are the same as for non-sterile ear drops, with extra controls for the microbiological quality. These could be the bubble point test on filters and parameters of the sterilisation process.

9.7 Containers and Labelling

9.7.1 Containers

According to the Ph. Eur. ear drops are usually supplied in multidose containers of glass or suitable plastic material that are fitted with an integral dropper, or with a screw cap of suitable materials incorporating a dropper and a rubber or plastic teat. Alternatively, such a cap is supplied separately.

Non-sterile ear drops are dispensed in a bottle of 10 or 20 mL with an integral dropper or with a dropper applicator (see Sects. 24.4.2 and 24.4.19.4). The bottle with screw cap and dropper applicator is preferred, because it is easier for the patient in measuring the prescribed quantity before administration.

The requirements for the packaging of sterile ear drops are the same as for eye drops. That is why they are supplied in similar bottles (see Sect. 24.4.2). These may contain at most 10 mL. Sterile aqueous ear drops may also be supplied in a single-dose container. Plastic materials should, preferably, be polyolefins, that means, polyethylene (PE) or polypropylene (PP) because these are free from harmful phthalates.

9.7.2 Labelling

Ear drops should be dispensed in a container with a label that says ‘ear drops’. The same applies to a secondary packaging. The label should comply with the requirements mentioned in Sect. 37.3.

For ear drops that are kept refrigerated by the patient, the label should mention a warning to warm the drops to at least to room temperature (with the hand) before use (see Sect. 9.10).

9.8 Release Control and Quality Requirements

Ear drops are to be checked before dispensing for appearance, packaging and labelling.

Solutions should be clear and free from (dust) particles. Suspensions should be checked on homogeneity and resuspendability.

Specifications for ear drops are (see Table 32.2):

- Identity
- Appearance (clarity, no precipitate, sediment or dust particles)
- Content (of active substances)
- pH
- Microbiological quality
- Sterility if applicable

And for ear drops in single dose containers:

- Uniformity of content of single-dose preparations or
- Uniformity of mass of single-dose preparations

9.9 Storage and Stability

Ear drops are best stored at room temperature, provided the chemical and microbiological stability permit this. The reason is that administration of cold drops may cause dizziness (see Sect. 9.10). Ear preparations should only be stored refrigerated when this is absolutely necessary.

9.9.1 Non-sterile Ear Drops

For chemically stable ear drops a maximum shelf life of 2 years at ≤25 °C, not refrigerated, is generally considered acceptable (see Sect. 22.7). For standard ear drops that are not chemically stable, the maximum shelf life is specific and validated, and should be indicated in the relevant monograph in the formulary. The maximum shelf life is to be used only for the unopened container. Once opened, the usage period for patients may be arbitrarily set at 6 months at ≤25 °C, not refrigerated, provided that the end of this period is not beyond the expiry date.

Aqueous solutions for the external canal that do not contain a preservative are an exception. They get a shelf life of 2 weeks at 2–8 °C (refrigerated). An example is tenfold diluted Aluminium-acetate or -acetotartrate ear drops (see also Sect. 9.5.7).

9.9.2 Sterile Ear Drops

Sterile ear drops may also have a shelf life of 2 years (see Sect. 22.7), but only if they have been sterilised by steam sterilisation (15 min at 121 °C). Ear drops that are only subjected to a heat treatment at 100 °C are best stored refrigerated (2–8 °C), and for aseptically prepared ear drops an additional security against any microbial growth may be obtained by freezing at least −15 °C, for a maximum of 6 months, provided the closure/container security at this temperature has been suitably validated.

Ear drops that have been stored in a freezer should be swirled until clear during thawing.

For sterile aqueous preserved ear drops the usage period is set at maximum 1 month after opening.

For preservative free preparations intended for the middle ear the in-use expiry date is 24 h after opening; possibly longer if the solution is known to have preservative properties. An example is Bacicoline B® (see Sect. 9.2).

For preparations with uncertain or unknown chemical or physical stability, arbitrarily a shelf life of 1 month at ≤25 °C, not refrigerated, is advised. For preparations liable to degradation a shorter period and refrigeration may be necessary. See Sect. 22.7 for more information.

As many preparations will show degradation under the influence of (day) light, most ear drops should be kept away from light. In some cases the protection against light by a brown bottle will not be enough, for instance for chloramphenicol.

> The stability of some ear drops may be such that they have a more practical shelf life when stored refrigerated than at 25 °C. So the pharmacy stock will be refrigerated and that will be indicated on the label. It is preferable for the patient to store such ear drops at room temperature, as the period of use will normally be much shorter than the shelf life. This must be remembered when dispensing the ear drops, so the patient label will not mention the warning “keep refrigerated”.

9.10 Administration and Dosage Delivery Devices

Ear drops should be slightly warmed in the hand before administration, to avoid dizziness after instillation of a cold liquid. Dizziness can develop as a result of a thermic effect on the organ of balance.

The patient should lie down after the administration, with the treated ear upside, to make the drops go down the auditory canal. Ear drops are used for 2–5 days, depending on how serious is the disease. For antimycotic drops a longer treatment may be needed. Sometimes the advice is to continue use for 3 days after disappearance of the symptoms.

In external otitis the physician can reduce the swelling in the external canal by placing an ear tampon or a gauze, which is drenched in aqueous Aluminium acetate or -acetotartrate ear drops or Acetic acid ear drops (in propylene glycol) with a corticosteroid (Tables 9.2 and 9.1). The gauze or tampon should be kept moist by repeated instillation of the ear drops 6–8 times a day. For aqueous Aluminium acetate or -acetotartrate ear drops application on a tampon or gauze is absolutely necessary, because otherwise crystals can be formed on the eardrum. When the ear tampon has been removed, mostly after 24 h, the patient has to continue treatment with non-aqueous Acetic acid ear drops (often with a corticosteroid).

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Eye

10

Annick Ludwig and Holger Reimann

Contents

Abstract

In this chapter several aspects of ocular dosage forms are discussed with emphasis on eye drops, eye lotions and eye ointments prepared in pharmacies. Their formulation, method of preparation, packaging, storage and methods of administration are also discussed.

The availability of medicines in ocular dosage forms is low due to the efficient barrier function of the cornea, lachrymation, tear turn over and drainage. Formulations should take into account these constraints. The vehicle and excipients selected should improve the permeation of the active substances in the eye or the residence in the conjunctival sac and consequently the therapeutic effects, but also minimise irritation. Tolerance of the preparation is of utmost importance.

When formulating aqueous ophthalmic preparations attention should be given to osmolality, pH, solubility, chemical interactions, stability of the active substance, together with viscosity and the choice of a preservative. Sterility is of critical importance and therefore the most appropriate sterilisation method must be chosen.

Besides pharmaceutical factors, the correct administration of the eye drops is an important factor. Therefore, clear instructions to the patients about eye drop instillation and correct storage of the medicine is essential. It will add to the success of pharmaceutical care and patient compliance.

Keywords

Eye • Eye drops • Eye ointment • Eye lotion • Eye cream • Formulation • Preparation • Tear film • Biopharmaceutics • Osmotic value • Lachrymal secretion

Based upon the chapter Oog by Adriaan van Sorge en Annick Ludwig in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_10,

10.1 Orientation

Eye medication is intended for local use on or into the eye. Eye drops and semisolid preparations are usually applied topically, in the lower conjunctival sac. Absorption of active substances into the ocular blood vessels and also into the systemic circulation occurs at the conjunctiva and nasal mucosae. Due to absorption, systemic side effects could appear after instillation.

After permeation through the cornea, active substances reach the anterior chamber and afterwards the posterior chamber and vitreous. With cases of external infections absorption should not happen, because the active substance needs to be present in therapeutic concentrations at the cornea and conjunctiva. An example of a targeted local eye preparation are erodible inserts, the active substances diffuse slowly from the matrix at the ocular surface.

Some ocular diseases require specific treatment given via intravitreal or periocular injection into the eye.

The sensitivity of the eye requires that the formulation and sterility of ocular medication are of critical importance. An inappropriate formulation can cause irritation or disruption of the mechanisms responsible for the protection of the eye. Contaminated ophthalmic preparations could, especially in the case of an injured eye, cause infections or exacerbate the infection.

The preferred route of administration depends on the location of the disease (Table 10.1; [1, 2]).

Eye preparations are also employed for diagnostic purpose or in connexion with surgery. Combinations of fluorescein with oxybuprocaine, proxymethacaine or lidocaine are applied for the measurement of intra-ocular pressure with tonometry, diagnosis of corneal defects and choice of size and control of hard contact lenses. Strips with fluorescein are used to examine the integrity of the tear film. In some countries they are considered medical devices. Sodium hyaluronate eye drops, other eye drops which relieve the symptoms of dry eyes by increasing the viscosity of the tear film or eye preparations in the context of contact lenses are generally regarded as medical devices.

In order to improve bioavailability, active substance targeting and patient compliance new dosage forms with controlled release have been developed: colloidal carriers, implants, inserts, plugs, active substance eluting contact lenses and iontophoresis [3–6].

In community pharmacies contact lens solutions are delivered to customers as medical devices. It is noteworthy to mention that many contact lens wearers do not clean their lenses properly. The careless use of their lenses can result in eye infections. During application of medicated eye preparations contact lenses should not be worn.

In some countries eye preparations are prepared in pharmacies for the special needs of animals. E.g. some breeds of dogs frequently suffer from dry eyes or vascular keratitis. Formulas for veterinary use generally do not differ from those designated for human use.

10.2 Definitions

The description of eye preparations to be used as medicinal products is similar in the European, British, Japanese and US-American Pharmacopoeias. Several categories may be distinguished:

- Eye drops
- Eye lotions
- Powders for eye drops and powders for eye lotions
- Semisolid eye preparations (ointments, creams and gels)
- Ophthalmic inserts

Eye drops are sterile aqueous or oily solutions, emulsions or suspensions of one or more active substances intended for administration upon the eyeball or instillation into the conjunctival sac.

Eye lotions are sterile aqueous solutions intended for use in rinsing or bathing the eye or for impregnating eye dressings in order to cover the eye.

Semisolid eye preparations are sterile ointments, creams or gels intended for application to the conjunctiva or to the eyelids. They contain one or more active substances dissolved or dispersed in a suitable base. They have a homogeneous appearance.

Table 10.1 Location and preferred routes of administration

Location	Route of administration				
Conjunctiva					External
Cornea					External
Internal eye	Intravitreal			Subconjunctival	External
	Intracameral				
Eyelids					External
Orbita		Oral	Parenteral	Retrobulbar	
Retina	Intravitreal	Oral	Parenteral		
Lachrymal apparatus		Oral	Parenteral		External

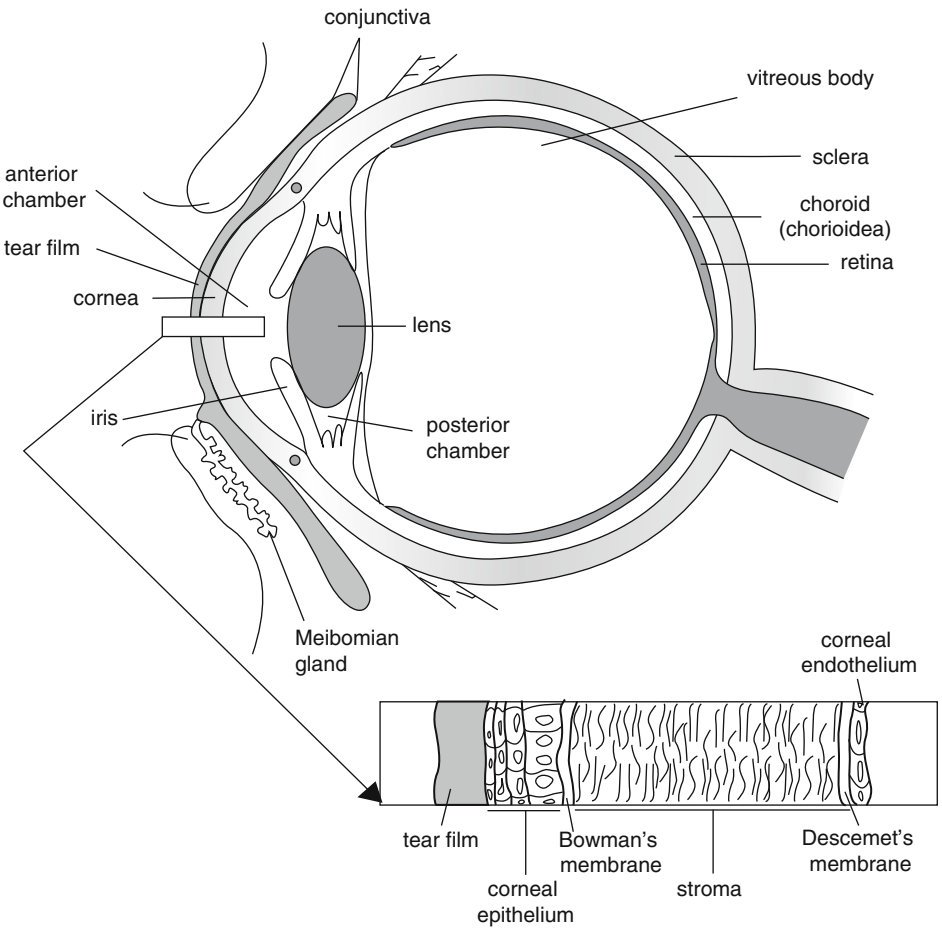

Fig. 10.1 Schematic representation the human eye and the structure of the cornea [77]

Ophthalmic inserts are sterile, solid or semisolid preparations of suitable size and shape, designed to be inserted in the conjunctival sac, to produce an ocular effect. They generally consist of a reservoir of active substances embedded in a matrix or bounded by a rate-controlling membrane. The active substance, which is more or less soluble in the lachrymal liquid, is released over a determined period of time. Ophthalmic inserts are individually distributed into sterile containers.

These pharmacopoeial general monographs on eye preparations do not comprise parenteral preparations to be administered in the eye.

10.3 Anatomy and Physiology

Anatomical characteristics and physiological mechanisms protect the eye against toxic external effects. These mechanisms include the specific structure of the cornea, blinking, baseline and reflex lachrymation, drainage, tear film composition and the corneal sensitivity. The combination of all mechanistic, anatomical and physiological characteristics maintains the integrity of the eye, together with immunological and antimicrobial properties of the lachrymal fluid [5, 7–10].

10.3.1 Structure of the Eye

Figure 10.1 shows schematically the structure of the human eye. In detail the structure of the cornea is given. The cornea separates the aqueous humour from the lachrymal fluid and protects the delicate internal structures of the eye from external influences. The cornea is a clear, avascular tissue to which nutrients and oxygen are supplied by the lachrymal fluid and the aqueous humour. It is composed of five layers: a lipophilic multilayered epithelium, Bowman's membrane, a hydrophilic stroma, Descemet's membrane and a lipophilic endothelium.

The epithelial cells are closely packed together like a pavement, forming not only an effective barrier to most micro-organisms, but also for active substance absorption. The low permeability of the cornea is due to the presence of tight junctions between the epithelial cells. The superficial corneal epithelial cells are exfoliated from the ocular surface, their average life is 4–8 days.

The cornea is highly innervated with sensory nerves, which serves important sensory and reflex functions.

The eyeball has a wall consisting of three layers: the outer coat or the sclera and cornea, a middle layer or uveal coat and the inner coat or retina.

The cornea has no blood vessels and the sclera only a few, consequently the supply of immunoglobulins to these tissues is limited. Therefore the treatment of infections is difficult.

The conjunctiva is a thin transparent membrane, which lines the inner surface of the eyelids and is reflected onto the globe. The conjunctiva consists of three parts: bulbar on the eye surface (sclera), fornix or conjunctival sac and palpebral on the inner side of the eyelids. The bulbar conjunctiva lies upon the sclera and only attaches to the sclera on the limbus. The structure resembles a palisade and is more permeable than the cornea.

The high corneal sensitivity is due to the specific innervation of the eye. The corneal surface possesses the highest nerve density of all organs in the human body: about circa 7,000 nociceptors per mm^2. The nerve endings are located only one layer below the corneal surface. Consequently they are very sensitive and active substances elicit reflex blinking. Three types of stimuli are responsible for pain perception: mechanical, physico-chemical and temperature gradient dependent. The distribution of the various kinds of nerves and receptor is functional heterogeneous: 20 % mechanical, 70 % physico-chemical and 10 % temperature (cold) sensitive. The sensitivity of the cornea and conjunctiva seems to be dependent on the colour of the iris, age and gender [11, 12]. Pathophysiological processes, long term use of ocular medication could influence the corneal sensitivity [13, 14].

The high corneal sensitivity serves to protect the eye. Reducing pain perception is dangerous. Patients should be warned of the danger of anaesthesia dolorosa due to repeatedly instillation of local anaesthetic eye drops. Welding without protection or snow blindness due to excessive exposure to UV light can cause photoelectrical keratitis, which is a very painful condition [15]. Administration of local anaesthetics will be recommended. It is true that local anaesthetics reduce corneal sensitivity but they delay the renewal of corneal epithelium layers with nerve endings. Repeated instillations of anaesthetics result in the duration of action being shortened resulting in pain breakthrough and are responsible for the serious condition where the stroma melts away [16]. Therefore, local anaesthetics should only be delivered in single-dose containers and their use should be limited.

10.3.2 Tear Film and Lachrymal Secretion

The lachrymal glands secrete lachrymal fluid, which spreads on the exposed part of the eye forming the precorneal tear film. An intact film protects the ocular surface from desiccation. The tear film results from the lachrymal functional unit [8] which consists of the:

- Lachrymal glands
- Ocular surface
- Sensory nerves involved

The tear film is a mixture of several excretion products:

- Aqueous fluid (95 % of water, salts, glucose, urea, proteins) secreted by the lachrymal glands
- Soluble mucins produced by the goblet cells present in the conjunctiva
- Lipids from the Meibomian glands embedded in the tarsal plate of the eyelids

The lipid composition is kept within physiological limits by androgens [17]. The decrease of their secretion in elderly people is one of the reasons for development of dry eye syndrome. Patients with Meibomian gland dysfunction show a high tear film evaporation rate and a high tear osmolality [18, 19].

The structure of the tear film

According to the "three layers theory" the tear film consists of a superficial lipid layer, the central aqueous layer and an inner mucus layer.

No clear separation exists between the aqueous layer and the mucus layer because mucins are dissolved in the aqueous layer (see Fig. 10.2).

To maintain the integrity of the tear film is of utmost importance during the administration of eye drops. The role of the glycocalyx is essential. The glycocalyx consists of anionic membrane-spanning or membrane-associated mucins secreted by corneal and conjunctival epithelial cells [20, 21]. Due to its moisture binding characteristics it stabilises the tear film (see Fig. 10.2). Moreover the superficial lipid layer prevents evaporation of the central viscous aqueous layer.

About 1.2 microlitres of lachrymal fluid is secreted per minute. The functions of the lachrymal fluid are:

- Improvement or maintenance of the optical quality of vision (homeostasis)
- Lubrication of the eyeball
- Elimination of foreign bodies
- Supply of nutrition to the ocular surface
- Defence against infection (viral and bacterial)
- Oxygen transport to the avascular corneal epithelium

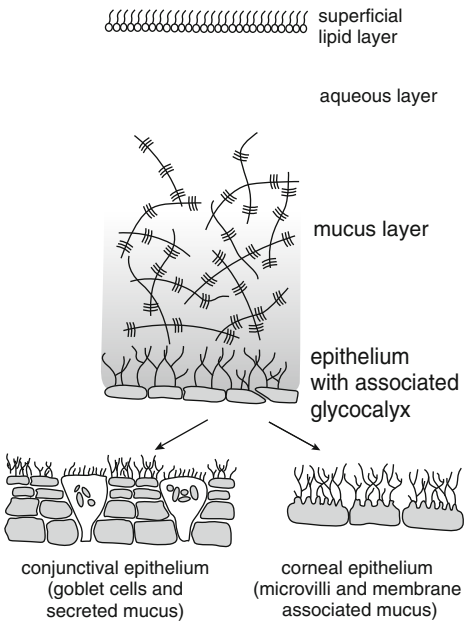

Fig. 10.2 Schematic representation of the tear film structure [77]

The secreted lachrymal fluid is spread over the ocular surface by the eyelids (precorneal tear film) and distributed to the conjunctival sac during blinking. Meanwhile the tears are swept to the medial canthus and drained through puncta, canaliculi, lachrymal sac and nasolachrymal duct which opens into the inferior nasal passage. The volume of the precorneal tear film amounts to about 7 microlitres. The conjunctival sac can accommodate about 30 microlitres, but in some persons only 20 microlitres or even less [22]. The tear film evaporates at a rate of 6–12 microlitres per hour [23].

Immunological and Antibacterial Mechanisms of the Eye

The ocular surface is the domain of the mucosa-bonded immune system [24]. This system plays an important role in combating infections by killing micro-organisms. It consists of the lachrymal gland, conjunctiva and related structures. Besides immunoglobulins, enzymes and bactericidal components are present: IgA, lysozyme, lactoferrin, lipocalins, cathelicidine and probably beta-defensins [25]. Lipocalin is considered the most important component in eliminating toxic (phospho)lipids and fatty acids from the ocular surface [26]. Elimination is necessary, otherwise only partial hydration of the corneal epithelium will occur, which could result in ulceration [27].

10.3.2.1 Tear Film Stability

The tear film is only temporarily stable. The time period of stability of an intact tear film is named the tear film break up time (TFBUT) [28]. TFBUT is measured using fluorometry [29]. Tear film stability is reduced by tensioactive preservatives, which solubilise the superficial lipid layer. The example is the preservative benzalkonium chloride. Reduction of stability causes an increase in blinking frequency [30]. The tear film breaks up after 10–20 s and dry spots form on the corneal surface (dewetting of the cornea). These dry spots irritate the corneal nerve endings and activate the lachrymal functional unit, which triggers the blink reflex. During eyelid opening a new protective film spreads over the ocular surface. Patients suffering from dry eye syndrome exhibit formation of dry spots even when eye drops without benzalkonium chloride are instilled. The reduced film stability can be due to lower lipid-, tear- or mucin production [31].

Improvement of the Diagnosis of Dry Eye Syndrome

The Ocular Protection Index (OPI) was proposed to get a better insight into the uncomfortable condition, dry eye syndrome [32]. To obtain an optimal hydration of the corneal epithelium the ratio between the time period of an intact tear film and the time between two reflex blinks must be greater or equal to 1 (OPI $\geq$ 1). Investigation of tear film stability using sodium fluorescein improves the diagnosis of dry eye syndrome when 1–5 microlitres solution is used instead of larger volumes [33]. As a result the certainty of diagnosis is increased. However, the use of small drop volumes has not yet been introduced, as this technique is insufficiently developed.

Improvement of Tear Film Stability

Patients suffering from dry eye syndrome complain about tear film instability. Stability can be improved by increasing the viscosity of the tear film (see also Sect. 10.4.4) [34]. Viscoelastic polymers increase viscosity but also possess elastic properties. During blinking sodium hyaluronate (Na-HA) exhibits a kind of cushioning action and induces improved protection of the ocular surface compared to classical pseudoplastic viscosity enhancing polymers.

(continued)

Consequently the movement of the eyelids during blinking is smoother. Na-HA is effective in providing relief to dry eyes.

Other viscosity enhancing polymers are natural anionic polysaccharides such as gellan gum (E-418) and xanthan gum (E-415). These macromolecules are used as gelling agents. Artificial tears may contain dextran, hypromellose and carbomer sometimes with or without polyvinylalcohol and povidone. Unfortunately the ideal non crust forming and stability improving gelling agent has not yet been developed. It seems that hydroxypropyl-guar possess more specific adhesive properties to injured ocular surfaces [35–37].

10.4 Biopharmaceutics

After administration active substances should reach their target tissue. Therefore eye drops should fulfil certain requirements. The following properties are important:

- The lipophilicity of the active pharmaceutical ingredient (active substance)
- Active substance concentration
- Dilution by the lachrymal fluid and drainage
- Viscosity of the tear film
- pH value and buffer capacity of the preparation
- Osmotic value of the preparation

First the absorption of the active substances through the cornea is discussed and afterwards how the previously mentioned factors will influence the absorption.

10.4.1 Lipophilicity and Ionisation of Active Substance

As shown in Fig. 10.2 the cornea consists of various layers. The permeation of the active substances occurs transcellular or paracellular. Lipophilic, non-ionised molecules will diffuse via the transcellular pathway, while ionised, hydrophilic molecules pass through the paracellular space (tight junctions). The pore size at the corneal surface is about 6 nm (60 Å). The lipophilic epithelium prevents the passage of 90 % of the hydrophilic active substance dose, but only 10 % in the case of a lipophilic active substance [38]. Most ophthalmic active substances are salts of weak bases, which are completely dissociated at a low pH value. The contrary is true in the case of most NSAIDs. The permeation of pilocarpine [39] and some mydriatics [40] is higher when the molecule is not dissociated, resulting in a higher therapeutic effect compared to the protonated molecule (see Fig. 10.3).

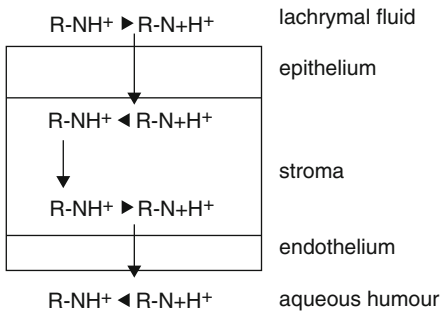

Fig. 10.3 Transport of dissociated active substances through the cornea. Source: Recepteerkunde 2009, ©KNMP

The degree of lipophilicity and ionisation of the active substance determines the extent of corneal permeation. Many examples are reported in the literature [41, 42].

However, recent research proved the presence of a number of transporters in the cornea and conjunctiva such as amino acid/peptide, nucleoside, organic anionic and organic cationic. These systems will influence the absorption of active molecules. Moreover active substance efflux pumps at the cell surface could restrict active substance penetration into ocular tissues [5].

10.4.2 Active Substance Concentration, Drop Size, Surface Tension

The amount of active substance applied to the eye depends not only on the concentration but also on the drop size, which is influenced by the surface tension of the solution. The design, dimensions of the dropper tip, the cross-sectional surface area on which the drop is formed and the dispensing angle at which the patient manipulates the bottle influence the drop volume instilled [43].

Drop size Variation
Research performed in the eighties in the USA showed that most dropper containers delivered drop volumes between 25 and 75 microlitres [44]. A similar study performed about 10 years later demonstrated that drop volume of products on the market had decreased [45]. This trend will continue as production techniques of dropper tips became more precise.

Active substances such as antazoline and tetracaine reduce the surface tension. Eye drops with a surface tension below 35 mN/m (normal surface tension of lachrymal fluid is 40–46 mN/m) are painful and uncomfortable [30].

10.4.3 Dilution and Drainage

The maximum volume of solution the lower conjunctival sac can accommodate is about 30 microlitres. After instillation the normal volume of the precorneal tear film (7–10 microlitres) is established again due to drainage of the extra volume of fluid present. The drainage rate is directly proportional to the volume of ophthalmic solution instilled. A high percentage of hydrophilic active substances are eliminated and lost to the eye. The drained active substance reaches, via the nasolachrymal duct, the nasal mucosae and after absorption enters the systemic circulation. As lipophilic substances are absorbed much more rapidly, these systemic effects are less prominent.

If the decision is taken to administer very small volumes (1–10 microlitres) of concentrated active substance solutions in order to compensate for dilution in the tear film, irritation becomes a problem. Consequently excessive lachrymation, drainage and wash out will occur, resulting in low active substance availability. To avoid irritation the surface tension, osmolality, pH and buffer capacity should be within certain limits (see Sects. 10.4.5 and 10.4.6).

Tolerance and availability of ophthalmic preparations are closely related [46]. The condition being treated can also play a role: i.e. the drainage rate in Sjögren's patients is slower than in healthy people [47].

Administration of more than one eye drop makes no sense. The second drop or a drop of double volume will be drained almost immediately. The availability could only be improved by lengthen the residence time of the preparation in the lower conjunctival sac. Closing the puncta by applying pressure with the thumb or fingers, but also closing the eyelids for approximately three minutes, increases the residence time and decreases the drainage of the ophthalmic solution to the nasal mucosae [48].

Animal experiments evaluating drop size and percentage of drained active substance demonstrated that after instillation of a 50 microlitres solution more than 50 % was lost [49]. When three drops of flurbiprofen (0.3 mg/mL) were instilled in rabbits, one drop every 30 min, a 2–3 times higher concentration was measured only in the corneal tissues [50].

10.4.4 Viscosity of the Tear Film

To improve the therapeutic effect of a medicine, one should try to increase the absorption of the active substance. Eye ointments and eye creams stay much longer in the conjunctival sac and on the ocular surface than eye drops. Consequently the active substance is delivered during a longer period of time to the eye. Ointments or creams could be considered as prolonged release dosage forms (depot preparations) for ophthalmic use. Viscous eye drops can increase residence time in the eye but are generally less successful. The use of viscous ophthalmic gels is under discussion. Xerogel forming polymers such as cellulose derivatives are in theory able to block for example puncta on the eyelids and canaliculi when used in high concentration and after desiccation. Carbomer, which does not form xerogels, used in the concentration 2 mg/mL, improves the availability and the prolonged activity of some active substances. No blurred vision was reported [51].

10.4.5 pH Value and Buffer Capacity of the Solution

The pH value of the lachrymal fluid is about 7.4. Due to evaporation of CO_2 from the tear film when the eyes are open, the pH value increases to 8 and even higher values [52]. Three buffer systems are present in tear fluid: bicarbonate-carbonate, mono-dibasic phosphate and amphoteric proteins; the buffer capacity is low [53]. The acid-neutralising capacity of the tear fluid of one eye is equal to about 8–10 microlitres 0.01 M NaOH.

The pH value influences the active substance availability from an ophthalmic preparation in two ways:

- A pH value outside the physiological range causes extra lachrymation and reduces the residence time of the active substance on the ocular surface.
- The pH value influences the permeation of the active substance through the cornea (see Sect. 10.4.1).

Solutions with pH values below 5.0 and above 8.5 are uncomfortable and not well tolerated [54]. The intensity and the duration of pain sensation after instillation are related to the acidity (pH) and buffer capacity of the eye drop.

10.4.6 Osmotic Value of the Preparation

Eye drops should be in principal iso-osmotic with lachrymal fluid, which means the NaCl concentration 9 mg/mL or approximately 0,9 % (280 mosmol/L). This value corresponds to the tear fluid of patients suffering from conjunctivitis. In healthy persons the osmolarity of the lachrymal fluid equals 290–310 mosmol/L, but varies during the day [55]. Tears of keratoconjunctivitis sicca and Sjögren's patients show higher values (343 mosmol/L) [56]. Therefore these patients welcome hypotonic eye drops [57].

Almost no pain sensation occurs within the range 0.5–2 % NaCl [58]. Strong hypo-osmotic solutions could damage the corneal epithelium. This should not happen during normal application of eye drops, because one minute after instillation of distilled water the baseline osmolarity of the tear film is restored.

10.5 Adverse Effects and Toxicity

The irritating properties of substances have been investigated using the Draize irritating test on rabbit eyes [59]. This method was used to test many different substances and resulted in serious consequences for the rabbit eye. Nowadays the test is performed according to contemporary acceptable procedures. The redness and its rate of development are an indication of the irritating potential of the substance examined. No satisfactory alternative method is available. Caution should be taken regarding interpretation of the observations collected. For example the frequency of (reflex) blinking influences the results obtained after application of ophthalmic preparations. The frequency differs between rabbit and human being. The rabbit blinks about every 20 min, while humans every 10 s. This difference in blinking frequency is relevant during investigation of viscous solutions.

Alternative *in vitro* or ex vivo methods have been developed and validated for assessing ocular irritation [60, 61].

Ophthalmic preparations should not contain substances, which could mechanically injure the eye during the blinking of the eyelids (see also Sect. 10.8). The cornea is extremely sensitive to solid particles especially when larger than 50 μm. Particles of 20–25 μm could, depending on their shape, irritate the eye. Due to the induced lachrymation the active substance will be washed away rapidly.

Even if eye drops are applied topically, undesirable systemic side effects could occur after absorption [43, 62]. The effects could be dangerous to life. Administration of scopolamine eye drops in children resulted in a toxic coma [63]. A substantial amount of active substance administered is drained through the nasolachrymal tube, reaches the nasal mucosae and will be absorbed in the systemic circulation. The correct instillation of eye drops reduces the risk of drainage to the nose but this cannot be completely eliminated. The correct methodology for instilling eye drops will be discussed under Sect. 10.9.

A special mention concerns the use of chloramphenicol in ointment and eye drops, see also Sect. 22.2.4. Chloramphenicol is degraded by light. During preparation and storage the degradation product 4-nitrobenzaldehyde is formed by photolysis. This degradation should be avoided because 4-nitrobenzaldehyde is responsible for a non-dose dependent aplastic anaemia, which condition is rare but lethal. This photochemical reaction can also occur on the ocular surface and skin. Therefore it may be better to apply chloramphenicol as eye ointment at night instead of eye drops at daytime. This might be anyway as effective as the general recommendation of 0,5 % eye drops 3 times a day.

After administration of eye drops, chloramphenicol appeared to disappear very rapidly from the tear film and aqueous humour contrary to the prolonged concentration after administration of the ointment [64, 65].

10.6 Product Formulation

A reliable source of information concerning this section can be found under "Codex der Augenarzneistoffe und Hilfsstoffe" published in Ophthalmika [66]. The pharmaceutical, physico-chemical and pharmacological properties of many active substances used for the preparation of eye drops are described.

Initially the formulation of eye drops will be discussed followed by eye lotions, eye ointments and eye creams.

10.6.1 Eye Drops

10.6.1.1 Choice of Active Substance

A soluble active substance is preferred when eye drops are being formulated. When the active substance prescribed is not (or not sufficiently) aqueous soluble, a suspension will be prepared.

Active substances employed in suspension eye drops are usually micronised. Polysorbate 80 or 20 may be used for wetting of the powdered active substances.

Hydrocortisone eye drops (see Table 18.12) is an example of a suspension formulation, where micronised raw material is used. Povidone is used mainly as wetting agent for an effective dispersion of the hydrocortisone acetate. This improves the settling behaviour (see also Sect. 18.4.2.2).

Precipitation or opalescence could occur when the concentration of one of the formulation components is near to its limit of solubility or due to an incompatibility between two formulation components. The appropriate choice of excipients can solve these problems. For example, the addition of citrate to an eye lotion containing zinc sulphate prevents precipitation of zinc hydroxide (see Table 10.2).

Borax in aqueous solution associates to form a 2:1 complex with chloramphenicol. Therefore, chloramphenicol 0.5 % eye drops could be prepared with the pH value of the solution adjusted to 7 (see Table 10.3).

Frequently the active substance is not or not readily available for pharmacy preparation. Then a sterile licensed pharmaceutical preparation must be used as starting material. Usually powder for solution for injection (i.v.) is used, sometimes solution for injection, powder for bladder

Table 10.2 Zinc Sulphate Eye Lotion [67]

Zinc sulfate heptahydrate	0.25 g
Borax	0.53 g
Boric acid	1.15 g
Phenylmercuric borate[a]	0.0045 g
Sodium citrate	0.5 g
Water, purified	ad 100 mL

[a] Phenylmercuric borate is no longer available for pharmacy preparation

Table 10.3 Chloramphenicol Eye Drops, Solution 0.5 % [68]

Chloramphenicol	0.5 g
Borax	0.3 g
Boric acid	1.5 g
Thiomersal	0.002 g
Water for injections	97.7 g
Total	100 g

Table 10.4 Ciclosporin Eye Drops, Oily Solution 1 % [70]

Ciclosporin	1 g
Castor oil, refined	9.9 g
Triglycerides, medium chain	89.1 g
Total	100 g

irrigation or other products. The active substances comprise the range of antifungals (e.g. fluconazole, voriconazole, amphotericin B), antibiotics (e.g. vancomycin hydrochloride, cefuroxime sodium, tobramycin, bacitracin) or others, e.g. mitomycin. Detailed information is necessary about the overage with respect to the labelled value, the quantity of excipients, the resulting pH and osmolality. Suitability of the reconstituted solution for intravenous injection does not necessarily mean suitability for topical ophthalmic use.

10.6.1.2 Vehicle

Usually eye drops are formulated as an aqueous solution. If an oil is employed medium chain triglycerides [69] are suitable as a vehicle along with refined castor oil, refined peanut oil, refined sesame oil or mixtures of triglycerides (see Table 10.4 and Sect. 23.3.5).

10.6.1.3 pH and Buffer Capacity

The buffer capacity (see Sect. 18.1.1) of the tear film is low. Consequently the buffer capacity of eye drops should be as low as possible. The acid neutralising capacity of tear fluid of one eye is about 8–10 microlitres 0.01 M NaOH (see Sect. 10.4.5). In order to avoid eye irritation the following rule of thumb is used. The volume of 0.01 M NaOH necessary to adjust the pH of the tear film to 7.4 should be less than 25 microlitres 0.01 M NaOH per dose. Sometimes even the equivalent of 10–15 microlitres 0.01M NaOH may be uncomfortable.

The volume of 0.01 M NaOH needed depends on the acidic ingredients, including the buffer. In simple cases knowledge of the pK_a value and the molar concentration of the active substance or the buffer substances enables the estimation of the pH of the solution (see Sect. 18.1.1).

Information on the maximum acceptable amount of H^+ ions at a pH $>$ 7.4 is not available and of less relevance.

A drop of 1 % pilocarpine HCl solution has a pH value of about 5.5, which after instillation must be adjusted to 7.4 by the lachrymal functional unit. 2 % and 4 % pilocarpine HCl solutions exhibit a pH value of 5.3 and 4.0 respectively, and more NaOH will be required to compensate for the pH difference. If the amount of NaOH needed is higher than the neutralising capacity of the tear fluid, instillation will be painful. The choice of a different salt of the active substance can potentially reduce the irritation caused by ophthalmic preparations. E.g. epinephrine HCl eye drops are less painful compared to epinephrine bitartrate.

For example, pilocarpine HCl, phenylephrine HCl and lidocaine HCl solutions in concentrations higher than 10 mg/mL possess such a high buffer capacity that during administration substantial pain is experienced resulting in lachrymation and wash out of the eye drop. This is due to their high therapeutic concentrations and their pK_a values in the neutral or slightly acidic range. Therefore, the pH value of these eye drops should be adjusted as near as possible to 7.4.

The pH value of pilocarpine solutions on the market is 4 and is irritating due to the low buffer capacity of the tear fluid. Therefore the LNA formulated pilocarpine eye drops with a pH value of 6.5, this improves the tolerance of the preparation [71].

When the pH value of the eye solution deviates from 7.4, it will take time to get the normal pH restored in the tear fluid. The greater the buffering capacity is, the longer it will take [72]. Therefore, it is advisable not to use buffering solution outside the pH range 6.5–8.5.

In order to obtain well tolerated eye drops, the pH of the active substance solution is measured and if necessary a combination of excipients is added to adjust to the required value (see Table 10.5).

Addition of the excipients mentioned in Table 10.5 increases the osmotic value of the preparation. Due to

Table 10.5 Combination of excipients used to adjust the pH value of eye drops

Decreasing pH	Increasing pH
Boric acid	Borax ($Na_2B_4O_7.10H_2O$)
Sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2H_2O$)	Disodium phosphate dodecahydrate ($Na_2HPO_4.12H_2O$)
Citric acid, anhydrous; citric acid, monohydrate	Sodium citrate
Acetic acid	Sodium acetate trihydrate

incompatibility or a high osmotic value of the active substance solution, the substances cannot be always employed. In these cases a diluted HCl or NaOH solution is recommended. The disadvantage is of course that an amount of solution instead of solid powder must be weighed or measured. A pH increase can also be carried out with trometamol ($pK_a > 8$).

Exact buffer compositions and osmotic values are reported in [66].

It is preferable to use a boric acid-borax buffer, because this buffer system has a very low buffer capacity at the pH value of the tear film and at any lower pH. Boric acid is a weak acid. Boric acid-borax buffer solutions reacts neutral to weakly basic.

Boric acid and borax are regarded as reproductive toxicants. The use of boric acid in eye drops for children younger than 3 years old is not recommended, but it is permitted since a clarification in 2003 [73]. Boric ions do not permeate through the intact corneal epithelium [74].

The EMA's committee for medicinal products for human use (CHMP) considered that the benefits of phosphate-containing eye drops outweigh their risks, but that in very rare cases patients with significant damage to the cornea may develop corneal calcification during treatment with eye drops that contain phosphate [75].

10.6.1.4 Viscosity

The mean viscosity of tear fluid is between 1.3 and 5.9 mPa·s [76]. As expected, increasing the viscosity of eye drops increases the residence time in the conjunctival sac [77]. Not only the viscosity, but also tensioactive properties, adhesion on the ocular surface and interactions with mucins play a role in increasing residence time.

Viscosity enhancing agents intended for use in eye drops must fulfil several requirements. Their chemical and physical characteristics must be stable during and after sterilisation. Sterilisation induces an important viscosity decrease for some polymers. Moreover viscous polymer solutions should be free of particles, colourless, be optically clear and have a refractive index comparable to tear fluid ($\eta_D^{20} = 1.336–1.338$). The concentration used should not cause discomfort and irritation.

10.6.1.5 Viscosity Enhancing Polymers

In Table 10.6 the characteristics of most frequently used viscosity enhancing polymers are reviewed. More information is available in literature [77] and Sect. 23.7.

Apart from the polymers mentioned in Table 10.6 some authorised medicines contain other viscosity enhancing agents such as dextran, hydroxyethylcellulose, hyaluronic acid and hydroxypropylguar gum (HP-guar; Systane®) [36, 37, 57]. Hyaluronic acid possesses good adhesive properties. In situ-gelling systems, such as gellan gum, are used in order to increase the precorneal residence time of the eye drop and to obtain a sustained active substance release [78, 79].

Nowadays interest in poloxamers has increased [77, 80]. Their solution viscosity increases at body temperature, however poloxamers are not added frequently to artificial tears. Excellent overviews of non-ionic poloxamers and surface active substances can be found in literature [81].

10.6.1.6 Preservatives

During the development of an eye preparation whose formulation contains an antimicrobial preservative, the necessity for and the efficacy of the chosen preservative must be demonstrated. The effectiveness of the preservative in the final preparation is tested according to the Ph. Eur. Efficacy of antimicrobial preservation (see Sect. 32.8).

Testing of Antimicrobial Activity

The methodology used to test the antimicrobial activity is still under debate.

A high storage temperature could reduce the antimicrobial activity as seen during the use of a new contact lens solution ReNu with moistureLoc® formulated with a new preservative alexidine [85]. The use of this commercial product caused a Fusarium keratitis epidemic worldwide. Research at room temperature and at high temperature (60 °C) has shown, contrary to other preservatives, that alexidine loses its antimicrobial activity at higher temperature. The cold supply chain of the product is of primary importance. The possible contribution to the development of the biofilm on the contact lens surface was also investigated, but was not considered to have contributed to the problem [86]. The researchers concluded that temperature control during production, storage and transport is of utmost importance. Examination of possible biofilm formation was relevant, because other studies investigated this phenomenon as possible origin of infections. In general, attention is drawn during antimicrobial efficacy tests to planktonic free moving bacteria contrary to microorganisms fixed in biofilm structures. Nowadays interest in biofilm formation (see also Sect. 19.3.5) has increased, because bacteria associated with such systems are more difficult to kill [87].

Table 10.6 Overview of viscosity enhancing agents used in eye drops preparations (see also 23.7)

Carbomer	Carbomer is a viscosity enhancing polymer used in eye gels. Its activity is based on an interaction with mucins. The interaction is the most effective when flexible and mobile polymer chains entangle and interact with mucins present at the conjunctiva [20, 77]
Hyprolose (hydroxypropylcellulose, HPC)	Hyprolose is used in the production of inserts, such as Lacrisert®. The macromolecules can adhere to the eyelashes, they glue them together
Hypromellose (hydroxypropylmethylcellulose, HPMC) 4,000 mPa·s; 0.125–0.5 % or 1.25–5 mg/mL	Hypromellose is a non-ionic cellulose polymer. Hypromellose is a component of the viscous vehicle hypromellose-benzalkonium solution (see Table 10.10). The concentration is % (10 mg/mL), but as it will be diluted 1:1 during preparation of viscous eye drops, the final concentration will be 0.5 % (5 mg/mL). Hypromellose solutions are not always well tolerated because of surface tension reduction of the tear film [30]. The antimicrobial activity of benzalkonium chloride is only slightly influenced by hypromellose [82]
Methylcellulose (MC) 4,000 mPa·s; 0.5–1.25 % or 5–12.5 mg/mL	Methylcellulose is a non-ionic cellulose polymer. The high viscosity types of methylcellulose are employed, because at low concentration solutions are viscous enough and the refractive index is only slightly changed
	As with all cellulose ethers, methylcellulose increases the residence time of the preparation. In addition, methylcellulose possesses wound healing properties. Therefore the polymer is suitable as a tear substitute for dry eye especially for those with punctate lesions. A disadvantage are irritating insoluble cellulose particles present in methylcellulose. The amount of insoluble particles depends on the quality of the product
Carmellose (carboxymethylcellulose sodium, Na CMC)	The adhesion of carmellose to the ocular mucosa is less than carbomer. The solubility of the polymer depends on the degree of substitution. The viscosity decreases during heating and at a pH value lower than 5
Poly(vinyl alcohol) (PVA) 1.4 % or 14 mg/mL	The viscosity and surface tension depend on the degree of polymerisation of the PVA selected. PVA is often a component of artificial tears and contact lens solutions. PVA solutions (viscosity = 25 mPa·s) sometimes irritate, because of its inherent surface active properties [30]
Povidone (polyvidone, PVP) K 30	Povidone is used in the preparation of suspensions in order to facilitate resuspendability of the sediment on shaking. Complex formation between PVP and methyl parahydroxybenzoate or propyl parahydroxybenzoate is possible

If eye drops do not contain antimicrobial preservatives (Tables 10.7 and 10.8) they are supplied in single-dose containers or in multidose bottles preventing microbial contamination of the content after opening.

Antimicrobial preservatives should be omitted in eye drops intended for use in surgical procedures. Tetracaine hydrochloride eye drops (Table 10.7) comply with the Ph. Eur. efficacy of antimicrobial preservation.

The use of preservatives is not possible when the patient is sensitive or allergic to the preservative or if eye drops will be administered just before, during or after surgery, because of its toxicity. Commercial ophthalmic products without preservatives are popular because of their better tolerance and lower irritancy potential [88–90].

The preference is given to the combination of benzalkonium chloride and sodium edetate (EDTA). Edetate is added in order to improve the activity of benzalkonium chloride against *Pseudomonas aeruginosa*.

Table 10.7 Tetracaine hydrochloride Eye Drops, Solution 1 % [83]

Tetracaine hydrochloride	1 g
Borax	0.01 g
Sodium chloride	0.7 g
Water for injections	ad 100 g

Table 10.8 Indometacine Eye Drops, Solution 0.1 % [84]

	With thiomersal	Without a preservative
Indometacin	0.1 g	0.1 g
Borax	0.3	0.3 g
Disodium phosphate dodecahydrate	3 g	3 g
Sodium dihydrogen phosphate dihydrate	0.25 g	0.25 g
Mannitol	1.6 g	1.6 g
Thiomersal	0.002 g	–
Water for injections	94.75 g	94.75 g
Total	100 g	100 g

Benzalkonium Chloride / Edetate and Active Substance Effect

Could the combination of benzalkonium chloride and edetate present in so many ophthalmic solutions influence the therapeutic activity of the active substance? In the case of an intact cornea a higher active substance availability is assumed because benzalkonium chloride acts as a penetration and solubility enhancer increasing passive diffusion of the active substances through the corneal epithelial cells (transcellular pathway). Additionally, edetate is a penetration enhancer, active at the tight junctions between cells, and has an effect on intercellular passive diffusion. Research performed using ketorolac eye drops on rabbits with intact and de-epithelialized corneas [91] demonstrated that the availability of ketorolac in the case of intact corneal epithelium was similar after application of drops with or without benzalkonium chloride and edetate, whilst in the case of the injured cornea a lower availability was measured in the presence of benzalkonium chloride. The researchers speculate that the non-irritating ketorolac formed an irritating combination with benzalkonium chloride resulting in lachrymation (active substance wash out) and lower availability. Combination of edetate with boric acid and an experimental active substance in an ophthalmic solution seems to exhibit permeation increasing properties ex vivo on intact rabbit cornea [92]. The results of both studies do not provide sufficient information to draw a meaningful conclusion as to whether benzalkonium chloride and edetate influence the availability of ophthalmic medicines.

When the combination of benzalkonium chloride and edetate cannot be used because of incompatibilities, thiomersal sodium can be used. Phenylmercuric borate is not available anymore because of toxicological problems to the environment.

A third preservative is chlorhexidine in the form of chlorhexidine acetate or chlorhexidine digluconate at a concentration of 0.1 mg/mL. However, chlorhexidine induces many chemical incompatibilities (see Sect. 23.8).

The preservative selected reduces the choice of other excipients required to adjust pH and osmotic values. Table 10.9 shows the possible combinations of preservatives, pH modifiers and excipients that can add up to the right osmotic value. Table 10.10 shows how these possibilities have led to standard basic solutions (vehicles) for eye drops and concentrates for further dilution.

Table 10.9 Possible combinations of excipients for basic ophthalmic solutions

Preservative	pH-modifying excipient	osmotic active excipient
Benzalkonium chloride 0.1 g/L + Na edetate 1 g/L	Boric acid/borax; (citric acid/citrate; phosphates; HCl, NaOH)	Boric acid/borax (NaCl, KNO_3, mannitol, glycerol)
Chlorhexidine digluconate 0.1 g/L or Chlorhexidine diacetate 0.1 g/L	Acetic acid/acetate; boric acid/borax	Mannitol; boric acid/borax
Thiomersal 0.2 g/L	Borax; phosphates	Mannitol

Table 10.10 Preserved base solutions and concentrates of FNA and NRF

Preservatives and concentrations	Properties	pH
Benzalkonium chloride solution 0.1 g/L + Na edetate 1 g/L (FNA)	Non iso-osmotic; vehicle	4.9
Benzalkonium chloride solution 1 g/L + Na edetate 10 g/L (NRF)	Non iso-osmotic; concentrate	4.8
Boric acid – Benzalkonium chloride solution 0.1 g/L + Na edetate 1 g/L (FNA)	Iso-osmotic; vehicle	4.6
Hypromellose – Benzalkonium chloride solution 0.1 g/L + Na edetate 1 g/L (FNA)	Non iso-osmotic, viscous; vehicle	5.1
Chlorhexidine diacetate solution 1 g/L (NRF)	Non iso-osmotic; concentrate	≈7
Thiomersal solution 0.2 g/L (NRF)	Non iso-osmotic; concentrate	≈7
Hypromellose 4,000 mPa.s is used in the concentration 10 g/L if added for increasing viscosity		

An overview of preservatives is given in Sect. 23.8. More information concerning specific preservatives suitable for ophthalmic preparations can be found in the literature [66, 72, 88, 93, 94]. Benzalkonium chloride is the most frequently used preservative in ophthalmic products. However its use is under discussion, because of its toxicity in chronic treatment [95, 96]. Therefore new preservatives are used in the development of licensed products [94, 97–100].

The efficacy of a preservative is pH dependent. Therefore the pH value of the ophthalmic solution determines the choice of the preservative. Sorbic acid and benzoic acid present in other dosage forms are active at a pH value lower than 5, and therefore unsuitable in most ophthalmic solutions.

Phenylethanol alone is not routinely used as preservative in eye drops due to too low an antimicrobial activity especially against gram-positive bacteria. Moreover phenylethanol cannot be combined with other preservatives because of its potential to irritate the eye [101]. Hydroxybenzoic esters are also reported to cause a high incidence of eye irritation. Thiomersal is not routinely used due to low antimicrobial activity, allergic reactions and penetration of mercury into the eye. The same is also true but to a much lesser extent for phenylmercuric salts [102–104] (see also Sect. 23.8.4).

The preservative should remain effective throughout the period of use by the patient. The substance should be chemical stable, even after heat sterilisation. Moreover the preservative should be physically stable during preparation and storage. The preservative should be compatible with the other ingredients of the preparation, filters and packaging. Significant adsorption can reduce the antimicrobial efficacy partially or completely [105, 106].

Organic phenylmercuric derivates and thiomersal are known for their strong adsorption onto rubber and various plastics such as low density polyethylene (LDPE).

Benzalkonium chloride and chlorhexidine are also adsorbed onto plastics and rubber, but to a lesser extent.

Chlorobutanol is not recommended because of the relative strong adsorption on and permeation through the packaging material, degradation by heat, relative low dissolution rate and the chemical instability of the raw material.

Chlorhexidine degrades during heating but not to such an extent that autoclaving is impossible. The degradation product 4-chloraniline and related substances are formed. The degradation is strongly dependent on the pH of the solution. The lower the pH the lower the decomposition, with maximum stability at pH 5–6. During autoclaving the concentration of 4-chloraniline is less than 0.125 % (pH range 5–8). According to the Ph. Eur. monograph the maximum tolerable values are 0.25 % chloraniline and 3 % related substances for the chlorhexidine raw material (see also Sect. 23.8.7).

As already mentioned for contact lens solutions (see box Testing of Microbial Activity in Sect. 10.6.1.6) storage temperature also influences the preservation of eye drops. At room temperature a solution of borax, boric acid and edetate exhibit an effective antimicrobial activity but not at 4 °C. Non preserved pilocarpine-hypromellose eye drops can be used for a longer period of time when stored at room temperature compared to storage in the refrigerator.

10.6.1.7 Sterility

Sterility is the most important requirement concerning ophthalmic preparations. A diseased or injured eye is extremely sensitive to infections with catastrophic consequences. *Pseudomonas aeruginosa* is the most feared organism due to the organism causing serious and difficult to treat corneal ulceration, which can result in rapid loss of vision. Other bacteria such as *Bacillus subtilis*, *Staphylococcus aureus* and *Haemophilis influenzae* as well as yeasts and moulds such as *Aspergillus fumigatus*, *Fusarium* species and *Candida albicans* (or non-albicans) are responsible for serious eye infections.

Therefore ophthalmic preparations must be sterile when dispensed to the patient, and this sterility must be guaranteed throughout storage. When using single-dose packaging for eye drops, no issues with sterility should occur. When multidose packaging is chosen, the risk of contamination should be reduced by the following measures:

- Preservation
- Adequate design of primary packaging
- Adequate instructions to the patient concerning correct application technique and hygiene
- Limited storage time once the container is opened
- Refrigeration once the container is opened

The probability of eventual growth of bacteria contaminating the preparation depends on:

- Presence of a preservative
- pH value of the preparation
- Adequate antimicrobial properties of the active substance or the excipients
- Presence of water and water activity (see Sect. 19.2.2)
- Temperature

Literature reports are published on a regular basis concerning ophthalmic preparations which have been contaminated during use, even when the solution complies with the criteria of the antimicrobial efficacy test of the Ph. Eur. After 4 weeks of use caps, dropper tips or even solutions can be contaminated. The reasons are: careless administration, transfer of tear fluid into the dropper tip at instillation, cross-contamination in hospitals and nursing homes and resistance of (gram-negative) bacteria against preservatives [107–109]. This phenomenon is underestimated and is one of the reasons why after opening the contents of the container must not be used for longer than 4 weeks (unless otherwise justified). To reduce cross-contamination patients should be instructed how to correctly instil eye drops (see Sect. 10.9) and snap-cap containers (see Sect. 24.4.2.3) should be selected.

10.6.1.8 Osmotic Value

The osmotic value (see Sect. 18.5) of ophthalmic solutions should be in the range equivalent to 0.5–2 % sodium chloride solution in order to avoid pain sensation. However, in practice the upper limit should be set to 1.6 % NaCl to make sure the eye drops are well tolerated by all patients.

Isotonicity of eye drops is obtained by adding boric acid, borax or a combination thereof. If their use is not possible due to chemical incompatibilities, sodium chloride solution can be employed. Other tonicity substances are mentioned in Table 10.9.

10.6.1.9 Container and Labelling

A review of ophthalmic dropper packaging is given under Sect. 24.4.2. In community pharmacies glass containers with dropper tips are usually used to dispense multidose preparations. Polyethylene containers are becoming more popular. Chloro-or bromobutyl rubber teats should not be used with oily eye drops and with iodinated povidone only if previously tested, well defined and standardised cases. The dropper tip and the cap should be made of polypropylene. Packaging should protect the eye drops against exposure to light. If impossible the preparation must be placed into a protecting secondary packaging, e.g. a carton.

The label (see also Sect. 37.3) should mention the storage conditions, shelf life of unopened containers and for multidose bottles and the in-use shelf life after which the contents must be discarded. This period must not exceed 4 weeks. In order to guarantee sterility during use, the Ph. Eur. requires that multidose preparations are supplied in containers containing at most 10 mL solution.

The use of tamper-evident packaging makes it clear to the patient that he is the first person to open the container.

Non preserved ophthalmic solutions are preferably delivered in single-dose packaging such as Redipac® plastic tubes. In pharmacy preparation alternatives may be:

- 1 mL syringes (Luer) with stopper
- 10 mL polyethylene dropper bottles filled to only 250 microlitres or maximum 1 mL

Multidose containers could be used if sterility during storage and in use has been proven and guaranteed. Research on the storage of non-preserved eye drops delivered in Gemo-type containers with snap-cap (see Sect. 24.4.2.2) has been undertaken. In the case of acetylcysteine 5 % eye drops integrity during storage of the containers was guaranteed from a microbiological point of view, even after freezing and thawing [110]. Whether non-preserved eye drops supplied in this packaging could be administered for longer than 24 h, was not investigated.

10.6.1.10 Storage and Stability

A general discussion concerning stability and assignation of storage times is provided in Sect. 22.7.

Hydrolysis and oxidation play an important role in the stability of ophthalmic preparations. Degradation can be maintained within acceptable limits when an appropriate pH is selected and by addition of antioxidants if necessary. Degradation is also reduced by a lower sterilisation temperature, a lower storage temperature or a shorter shelf life.

Non-preserved aqueous eye drops sterilised by autoclaving may be stored in unopened containers for a maximum of 1 year in Redipac plastic tubes and 2 years in dropper bottles. After opening of the container storage should not exceed 28 days in the case of preserved solutions, eye drops with adequate antimicrobial properties imparted by the active substance, and oily eye drops. But for use on wards, 1 week is considered more appropriate.

The storage of aseptically prepared eye drops without preservative may be at maximum 6 months at –15 °C. If no freezer is available, the preparation should only be stored for 1 week in the refrigerator. After opening of the container there is no storage in the narrower sense, because non-preserved eye drops must be packaged in single-use containers. This must be strictly observed without exception when application to different patients cannot be excluded or with immunosuppressive eye drops. In practice storage and application on one and the same patient within some hours after opening of the container occurs frequently and is widely accepted. When justified the period of use after opening is always a maximum of 24 h and the volume of the preparation should be adjusted. When the patient‘s eye is injured or infected a shorter time limit should be considered. Research has demonstrated that some non-preserved preparations are not easily contaminated. If this is the case, a period after opening of longer than 24 h may be acceptable.

10.6.2 Eye Lotions

Eye lotions are defined as aqueous solutions. Thus active substances must be soluble at the concentration needed. Eye lotions must be sterile. According to Ph. Eur. eye lotions intended for use in surgical procedures or in first-aid treatment do not contain an antimicrobial preservative and are supplied in single-dose containers, see for example an eye lotion with iodinated povidone (Table 10.11).

Table 10.11 Iodinated Povidone Eye Lotion 1.25 % [111]

Povidone, iodinated	1.25 g
Disodium phosphate dodecahydrate	0.25 g
Sodium chloride	0.8 g
Water for injections	97.7 g
Total	100 g

Table 10.12 Disodium Edetate Eye Lotion 2 % [115]

Disodium edetate	2 g
Benzalkonium chloride	0.01 g
Borax	0.95 g
Sodium chloride	0.15 g
Purified Water	ad 100 mL

Antiseptic eye lotions frequently used pre-, intra- and postoperatively at eye surgery may contain polihexanide (PHMB), iodinated povidone or chlorhexidine salts.

If a preservative is required for multidose containers, sterile and preserved vehicles can be used (see Table 10.10). The same considerations regarding the use of preservatives in eye drops apply to eye lotions.

Compared to eye drops a higher volume of eye lotion will be in contact with the eye. Therefore the pH value should be adjusted very close to 7.4. If this is not possible, the buffer capacity of the solution must be low in order not to cause discomfort and pain. Irritation is a great challenge in the case of eye lotions. The results of a German study evaluating eye lotions are surprising and showed that about 16 % of the commercial products showed a pH value outside the range 6.4–8.0 [112].

10.6.2.1 Osmotic Value

As high volumes of eye lotions are applied, the product must be isotonic to avoid irritation. However, eye lotions intended to treat ocular oedema should be hypertonic. As discussed under Sect. 10.6.1 the tonicity of eye drops is frequently adjusted with boric acid, borax or a combination thereof. The same is valid for eye lotions. If these excipients are chemically incompatible, or as an alternative, sodium chloride can be used (see Tables 10.11 and 10.12). Suitable excipients adjusting tonicity are summarised in Table 10.9.

Hypertonic Eye Lotions to Prevent Oedema

Research on the use of eye lotions to treat chemical burns noted the importance of hypertonicity. *In vitro* and ex vivo (rabbit and pigs eyes) a 2 M NaOH solution was applied resulting in tissue damage. The pH value of the aqueous humour increased by 5 pH units, the increase being quickest in eyes that were not rinsed. The rinsing solutions examined were: tap water (hypotonic), phosphate buffered saline solution (PBS, isotonic), physiological saline solution (0.9 % NaCl, isotonic), saline in hypertonic borate buffer solution and a hypertonic saline solution with an amphoteric chelator. Immediately after chemical burning, intensive rinsing for 15 min was carried out, according to American guidelines. PBS induces calcium phosphate precipitation at the ocular surface due to complexation of calcium ions released from the damaged cells with phosphate ions. Physiological saline solution exhibits the same effect as tap water. Without debate, the hypertonic eye lotions showed the best results. The use of hypertonic rinsing solutions prevents the development of corneal oedema. The amphoteric molecule diphoterine neutralises acids and bases and prevents chemical wounds. If only tap water is available, it should be used immediately but there is the risk of corneal swelling. The dilution of the chemical substance by tap water will reduce pain until a more suitable eye lotion is available, but rinsing as soon as possible is of utmost importance [113, 114].

10.6.2.2 Packaging and Labelling

High volume eye lotions prepared in pharmacies may be packed in sterile, clean polypropylene bottles with an appropriate closure. Also type I glass bottles can be used. The volume is a maximum of 200 mL, except if the solution is intended for first-aid treatment where a dispensed volume of 1,000 mL is more appropriate. Aseptically prepared eye lotions should be packed in sterilised containers.

An example of an eye lotion prepared in pharmacies is a low volume antiseptic solution for eye surgery. The lotion is filled in sterile injection vials, polyethylene dropper bottles or other suitable single-dose containers. If eye lotions do not contain antimicrobial preservatives they must be supplied in single-dose containers too.

The label states:

- Where applicable, that the contents are to be used on one occasion only
- For multidose containers - the period after opening after which the contents must be used or discarded: this period should not exceed 4 weeks

According to national legislation the label mentions the dosage form (eye lotion), the route of administration (ocular use), the patient information for the intended use. If necessary an eye cup should be supplied. The patient should be instructed as to the proper use of the eye lotion and eye cup, the contact time of bathing the eye and cleaning of the eye cup. The device should be thoroughly rinsed and cleaned before and after use.

10.6.3 Eye Ointments and Eye Creams

Apart from eye ointments and eye creams also eye gels could be seen as semisolid eye preparations. But many of the so

Table 10.13 Erythromycin Eye Ointment 0.5 % [116]

Erythromycin, anhydrous	0.5 g
Cetostearyl alcohol	2.5 g
Paraffin, liquid	39.8 g
Paraffin, white soft	51.2 g
Wool fat	6 g
Total	100 g

Table 10.14 Sodium Chloride Eye Ointment 5 % [117]

Sodium chloride	5 g
Cetostearyl alcohol	1.9 g
Paraffin, liquid	30 g
Paraffin, white soft	38.6 g
Wool fat	4.5 g
Water, purified sterile	20 g
Total	100 g

called eye gels are not actually semisolid but they are high-viscous liquids (see Sect. 10.6.1).

10.6.3.1 Choice of the Dosage Form

The choice of the type of dosage form will depend on the salt form, particle size and solubility of the substance. In principal there are three categories of semisolid eye preparations:

- The active substance is dissolved in a lipophilic ointment base.
- The aqueous active substance solution is emulsified in the lipophilic ointment base (resulting in an eye cream).
- The active substance is dispersed in the ointment base.

The first ointment type is applicable for only a few active substances dissolved in the non-aqueous ointment bases. To date, almost only paraffin-based lipophilic ointments are used for semisolid ophthalmic products. An example of this type of preparation is eye ointment with 0.5 % erythromycin (Table 10.13). Suitable triglyceride-based vehicles may lead to more solution-type eye ointments (see Sect. 10.7.3).

The second category of semisolid eye preparations is a lipophilic cream: the active substance is dissolved in water or a (preserved) aqueous vehicle and emulsified in the ointment base. An example to mention is a sodium chloride 5 % eye cream (Table 10.14).

The most common category of semisolid eye preparations is a suspension ointment as in chloramphenicol 1 % eye ointment (see Table 10.15). A microfine powdered chloramphenicol substance is used as starting material. The particle size of the powder to be dispersed must comply with Ph. Eur. requirements (see Sect. 10.8).

Table 10.15 Chloramphenicol Eye Ointment 1 % [118]

Chloramphenicol microcrystalline	1 g
Eye ointment base FNA[a]	99 g
Total	100 g

[a]For eye ointment base FNA see Table 10.16

Table 10.16 Eye ointment base [119]

Cetostearyl alcohol	2.5 g
Paraffin, liquid	40 g
Paraffin, white soft	51.5 g
Wool fat	6 g
Total	100 g

Table 10.17 Emulsifying Eye Ointment [120]

Cholesterol	1 g
Paraffin, liquid	42.5 g
Paraffin, white soft	56.5 g
Total	100 g

10.6.3.2 Vehicle

The base must be non-irritant to the conjunctiva. Non-aqueous lipophilic ointment bases consist of a mixture of white or yellow soft paraffin, liquid paraffin and lipophilic surfactants, such as cholesterol or wool fat.

Triglyceride-based vehicles may also be suitable and advantageous in respect to their dissolving power for active substances (see also Sect. 10.7.3).

Wool fat or cholesterol in an eye ointment emulsify with lachrymal fluid resulting in a water-in-oil emulsion-type cream. Cetostearyl alcohol is not a muco- or bioadhesive substance.

Common eye ointment bases are given in Tables 10.16 and 10.17.

10.6.3.3 Preservatives

Micro-organisms are not able to grow in ointments, as no water is present. Therefore, the addition of a lipophilic preservative to a non-aqueous ointment makes little sense. However for lipophilic eye creams the addition of a preservative to the aqueous phase is recommended.

The strong hypertonic aqueous phase of sodium chloride 5 % eye ointment FNA (Table 10.14) prevents bacterial growth.

10.6.3.4 Packaging and Labelling

Eye ointments are packed in small, clean, sterilised collapsible tubes fitted or provided with a sterilised cannula (see

Sect. 24.4.9). According to Ph. Eur. the tube contains a maximum of 10 g of the preparation.

Eye ointments and eye creams are applied in the same manner as eye drops: in the lower conjunctival sac and after administration the eyelid is pulled forward. Due to body temperature the ointment melts and is spread by the eyelids over the ocular surface during blinking. When the eye is injured the ointment is applied on the eyelid rim, not in the conjunctival sac. Ointments and creams are not well tolerated, because they produce a film over the eye and thereby blur vision [121]. Therefore, application in the evening is preferred.

Patients should be instructed to the proper use and administration of eye ointments and eye creams. It is important to avoid contamination by contact with the skin or surface of the eye. Consequently, one preparation should be used only by one patient. The same tube can eventually be used by care providers for several persons, however, nursing home staff should be aware of the contamination risk.

According to national legislation the label mentions the dosage form (eye cream or eye ointment), the route of administration (ocular use), the intended use, the storage conditions, the expiry date and, for multidose containers, the beyond-use date after which the opened preparation must not be used. This period should not exceed 4 weeks. If necessary the label also bears warnings and mentions that the contents should be brought to room temperature before administration if the tube is stored in the refrigerator.

10.7 Method of Preparation

The preparation process for eye drops, eye lotions, eye creams and eye ointments will be described subsequently.

10.7.1 Eye Drops

Eye drops are prepared using materials and methods designed to ensure sterility and to avoid the introduction of contaminants and the growth of micro-organisms as also stated by the various Pharmacopoeias. The preparation method consists of several steps: dissolution of the ingredients, (sterile) filtration, filling and packaging and (when possible) heat sterilisation.

10.7.1.1 Dissolution of the Ingredients

For the dissolution process see Sect. 29.5. For small-scale preparation of preserved eye drops the use of autoclaved stock solutions may be convenient. They contain a preservative and often boric acid and borax (see Table 10.5). The other ingredients will be dissolved in these vehicles. When viscous eye drops are prepared, the viscous hypromellose stock solution containing the preservative (see Table 10.10) is always diluted 1:1 with a stock solution containing the same preservative. Vehicles for eye drops prepared on stock often show a weak acidic reaction. Benzalkonium chloride solutions with high pH values, containing alkaline substances such as borax, attack glass material, i.e. the borosilicate glass (type I) of Schott Duran bottles (see also Sect. 24.2.1).

In-process control of the dissolution of the active substances may include pH measurement of the bulk solution immediately before filtration to confirm that the correct ingredients and vehicles have been used.

10.7.1.2 Filtration

Foreign particles can be removed by (pre)filtration over a membrane filter ($\leq$1.2 µm pore size). The use of this filter reduces the initial viable contamination as well. When autoclaving or steam sterilisation is not suitable for the product in order to remove viable contamination, i.e. bacteria, the solution is passed through 0.2 µm membrane which will retain all bacteria. In practice a one-step procedure is preferred using only one membrane filter with a nominal pore size of 0.2 µm. For use in pharmacies this type is readily available.

> Polyethersulfone (PES) material for the membrane filter is preferred because of low active substance adsorption and superior filtration. It is unclear whether PES filters are suitable for oily eye drops. Usually fluoropolymer filters are used in these cases.
>
> A viscous benzalkonium chloride solution, for instance with 0,5 % hypromellose 4,000 mPa·s, is filtered through a membrane with pore size $\leq$ 1.2 µm to eliminate non dissolved hypromellose fibres. The solution is too viscous to be forced through a 0.2 µm membrane filter. When eye drops are prepared by dissolving a dry powder in a container with the supplied vehicle, the solution obtained should be withdrawn using a 5 µm filter needle to remove any undissolved powder particles [122].

The integrity of membrane filters with a pore size of 0.2 and 1.2 µm should be verified using a bubble-point test after use as an in-process control. During this test a 0.2 µm membrane filter should resist the air pressure produced by moving the plunger over 80–85 % of the total syringe volume and in the case of a 1.2 µm membrane filter over 50–60 % without continuous bubble formation on the opposite of the membrane (see also Sect. 30.6.5).

Table 10.18 Conditions for the preparation of *preserved* aqueous eye drops

Method	Filtration	Other characteristics
Steam sterilisation 15 min 121 °C	Membrane filtration ≤ 1.2 µm	Terminal sterilisation
Heating 30 min 100 °C (over boiling water) + membrane filtration + preservative	Membrane filtration ≤1.2 µm	Sterile vehicle
		Class A workbench
		Sterile container
Filtration	Membrane filtration ≤0.2 µm	Sterile vehicle (recommended)
		Class A workbench (recommended)
		Sterile container
		Filtration into final container
Aseptic handling	–	Sterile vehicle
		Sterile products
		Sterile equipment
		Class A workbench
		Sterile container

10.7.1.3 Sterilisation

Sterilisation is generally dealt with in Chap. 30. The preferred method is a 15 min steam sterilisation at 121 °C of the active substance solution filled into the final container. Sterilisation in the final container is however not always feasible because the container is not heat resistant or the active substance degrades at elevated temperatures. In order to keep the risk of non-sterile eye drops as low as possible a combination of measures must in that case be taken. The possible measures are:

- Use of sterile vehicles (sterile stock solutions, sterile purified water or water for injections)
- Addition of preservatives
- Heating 30 min 100 °C over boiling water
- Filtration through bacterial-retentive membrane with the nominal pore size of 0.2 µm
- Use of sterile final container
- Aseptic preparation in a Class A laminar flow workbench
- Storage in a refrigerator
- Deep-freeze storage

These measures reduce microbial contamination or prevent an increase in contamination during preparation and storage. For extemporaneous preparation of eye drops in pharmacies the responsible pharmacist must select the most adequate sterilisation technique after performing a risk assessment.

Tables 10.18 and 10.19 summarise for preserved and non-preserved eye drops respectively the range of obvious combinations of methods, procedures, utensils and containers for small scale preparation for obtaining a sterile product. The presence of a preservative in the formulation makes heating at 100 °C during 30 min (over boiling water) much more effective (see Sect. 30.7) and is therefore an important parameter in the risk analysis.

10.7.1.4 Aseptic Handling

Aseptic handling in clinical practice often occurs when licensed parenteral medicines are used off-label for eye disorders, i.e. amphotericin B, fluconazole, mitomycin, and voriconazole [123–126]. A sterile product with the active substance (i.e. a powder for solution for infusion, a concentrate for solution for infusion, a solution for infusion or these dosage forms for injection) has to be adapted into eye drops. The first preparation step involves dissolution of the powder in the vial, thus resembling the reconstitution for the designated use. The sterile vehicle used may contain a preservative [123] or may be water for injections [124, 125], saline or buffer solution [126]. Sometimes dilution to a larger volume is necessary before finally filling the eye drops into the container. It depends on the outcome of a risk assessment of each individual case, if filling should include filtration [123–125] or not (see Table 10.19). Aseptic handling, outside a Class A environment, may be achieved by preparing in a 'nearly closed system', by filling the sterile dropper bottle by piercing the package wrapped around it, after suitable disinfection of the packaging surface (see Fig. 10.4). This technique can include filtration or just mixing of sterile solutions. The conditions for the preparation are best described by the term 'aseptic handling', see Sect. 31.3.

10.7.1.5 Handling Containers

During heating at 100 °C (over boiling water), the caps of the dropper bottles should be closed or open depending on the kind of container (see Sect. 24.4.2). If the closure is open, the dropper bottles should be placed immediately after heat treatment in a Class A laminar flow workbench. After cooling down the cap has to be closed.

After filling, sealing and sterilisation of single-dose containers (for example Redipac plastic tubes, see Sect. 24.4.2.6), the integrity of the container should be confirmed by

Table 10.19 Conditions for the preparation of *non-preserved* aqueous eye drops

Method	Filtration	Other characteristics (depending on type of container)		
		Redipac plastic tubes	Dropper bottles	Syringes
Steam sterilisation 15 min 121 °C	Membrane filtration ≤1.2 µm	Terminal sterilisation	Terminal sterilisation	–
Heating 30 min 100 °C (over boiling water) + membrane filtration	Membrane filtration ≤0.2 µm	Sterile solution of excipients	Sterile solution of excipients	–
		Class A workbench	Class A workbench	
		Sterile containers	Sterile containers	
		Storage in freezer	Storage in freezer	
Aseptic handling	Membrane filtration ≤0.2 µm, if possible	Sterile solution of excipients	Sterile solution of excipients	Sterile solution of excipients
		Class A workbench	Class A workbench	Class A workbench
		Sterilised Redipac plastic tubes	Sterile dropper bottles	Sterile syringes
		Storage in freezer	Storage in freezer	Storage in freezer

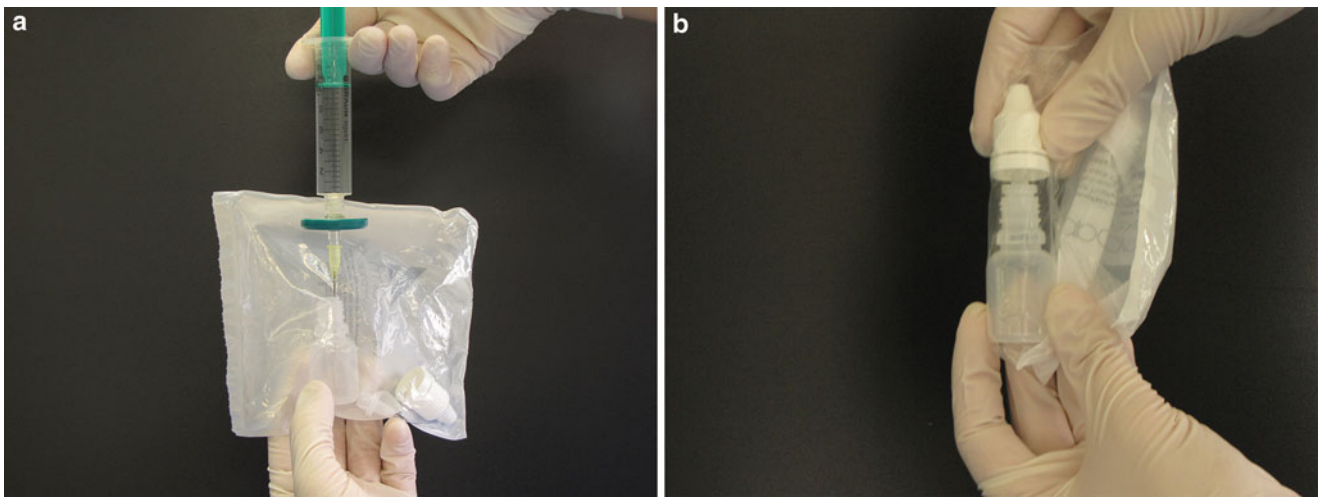

Fig. 10.4 (**a** and **b**). Aseptic handling of eye drops preparation (see text under Sect. 10.7.1.3)

squeezing and inspecting for leakage. For prevention of water evaporation during storage, Redipac tubes should be wrapped individually in foil, already before sterilisation. This makes drying after sterilisation necessary: approximately 10 min at 80 °C in an oven has showed to be sufficient.

When heating at 100 °C (over boiling water) during 30 min in combination with membrane filtration sterile containers (dropper bottle or Redipac) and sterile solutions of excipients are required. The preparation will be performed in a Class A laminar flow workbench. After sterilisation the containers must be stored in the freezer.

When only aseptic preparation is possible Redipac plastic tubes, dropper bottles and syringes could be used as containers. The same requirements such as sterile container, sterile solution of excipients, aseptic preparation in a Class A laminar flow workbench and storage in a freezer are valid to ensure sterility.

10.7.2 Eye Lotions

The preparation of eye lotions is similar to eye drops (see Sect. 10.7.1). As in most cases non-preserved stock vehicles are used, eye lotions should be sterilised by autoclaving for 15 min at 121 °C in the final container. If not possible, several measures may be combined in order to keep the risk of contamination as low as possible, analogously to Tables 10.18 and 10.19.

Low-volume eye lotions with antiseptics (iodinated povidone, polihexanide or chlorhexidine salts) for use in eye surgery must not contain preservatives. They are usually prepared aseptically in pharmacies using water for injection and sterile excipients, analogously to Table 10.18. Iodinated povidone eye lotion is thermally unstable and membrane filtration (≤0.2 µm) has to be applied.

10.7.3 Eye Ointments and Eye Creams

An ointment base is prepared by melting the ingredients together. Sterilisation can be performed by dry heating (see Sect. 30.5.2) or membrane filtration (see Sect. 30.6.1). Heat sterilisation requires a validated heat steriliser, which may be expensive. In addition, a disadvantage of dry heat sterilisation is the partial decomposition of the fat components. The degradation products could negatively influence the stability of the active substance and probably cause irritation of the eye.

Some types of tubes can resist 3 h at 140 °C (see Sect. 24.4.9). Although this is not exactly the Ph. Eur. requirement for dry heat sterilisation, the use of this method has the advantage of a much easier and thereby safer aseptic preparation of the medicine. Heat sterilisation of an eye ointment can only be performed if the active substance is dissolved in the base and is stable to elevated temperatures.

Sterilisation in the final container obviously is not possible for eye creams. It is practical to distinguish solution-type preparations from suspension-type preparations.

10.7.3.1 Solution-Type Preparations

Preparation of a solution-type eye ointment starts with the melting and mixing all ingredients as described above.

Preparation of an eye cream (see Sect. 10.6.3) includes the preparation and sterilisation of the aqueous phase in a similar manner to eye drops. The aqueous phase is then incorporated into the sterile ointment base by aseptic processing. Using an oily solution of the active ingredient instead results in an eye ointment.

A semisolid triglyceride (Softisan 378®) that meets the monograph Hard fat Ph. Eur. may establish the option to prepare not only eye creams with water-soluble active substances but also solution-type eye ointments and eye creams with active substances soluble in fatty oils (i.e. clotrimazole, ciclosporin). Softisan 378® shows delayed solidification when molten and drawn into a syringe, thus making membrane filtration (≤0.2 µm pore size) possible at about 30 °C. However, specific formulas of triglyceride-based eye ointments and creams have not been fully developed yet. For example the ratio Softisan 378®)/ refined peanut oil or the optimum cholesterol concentration as an emulsifier still has to be investigated.

For reading the temperature as an in-process control a non-contact laser infrared digital thermometer is used. The consistency could be measured using two glass plates as a simple extensometer.

Mixing Technique with Connected Syringes

For extemporaneous preparation an aseptic procedure is suitable for the preparation of eye ointments and eye creams in pharmacies. It requires 2 or more Luer-Lock-syringes consecutively conjoined by a sterile Luer-Lock-connector [127]. By pushing liquid and semisolid intermediate product from one syringe to the other and back through the connector, homogeneous ointments or creams can be prepared (see Fig. 10.5b, c). With the help of additional syringes, connectors and a membrane filter (≤0.2 µm pore size) aqueous or triglyceride-based solutions and certain types of molten ointment bases can be filtrated (see Fig. 10a) and kept into sterile syringes prior to mixing. Molten sterile ointment base can also be drawn into a syringe directly. Mixing in the 'nearly closed system' reduces the risk of microbial contamination. This method has of course to be validated for each formulation, especially with suspension-type ointments if agglomerates have to be broken up.

Fig. 10.5 (**a–c**) Preparation of a solution-type eye ointment or eye cream by the mixing technique with connected syringes.

10.7.3.2 Suspension-Type Preparations

Sterilisation in the final container is not possible for suspension-type eye ointments. During heating the ointment base melts and the dispersed powder particles will settle. Active substances intended for use in suspension ointments must be purchased sterile or sterilised by dry heat prior to use if their thermal stability is sufficient. The container with the raw material should only be used for the preparation of eye ointments.

The substance must comply with Ph. Eur. requirements concerning particle size (see Sect. 10.8). During incorporation agglomerates should be broken down. This best may be performed using a stone or porcelain mortar and pestle. The use of plastic mortar and pestle or glass plate and flexible spatula is usually not sufficient to break down the agglomerates.

The laminar flow is disturbed more by operating with the open product as happens with the preparation of suspension-type eye ointments, than with eye drop preparation or by the mixing technique with connected syringes for semisolid eye preparations (see Fig. 10.5). Consequently, a higher risk of contamination exists (see Sect. 31.3.2), which has to be accounted for in the risk assessment.

As an in-process control the presence of agglomerates and the homogeneity shall be carried out visually after placing a sample of the preparation between two glass slides. No particles or agglomerates should be visible. The control of the particle size is performed using a microscope. For temperature and consistency measurement as in-process controls see Sect. 10.7.3.1.

The preparation of tetracycline eye ointment can be problematic and it is preferable to use micronised active substance to overcome particle size issues, knowing at the same time that the raw material must comply with chemical purity specification. The microcrystalline raw material as described in USP meets both requirements. Another way to solve the problem is the preparation of a semi-finished product using tetracycline base, dissolved in semisolid base which significantly reduces the decomposition rate [66, 128, 129].

10.8 Release Control and Quality Requirements

For ophthalmic preparations following quality requirements apply (see also Table 32.2):

- Identity
- Appearance (homogeneity, for eye drops: clarity and no precipitation)
- Content of active substance(s) and preservative
- pH (for eye drops)
- Sterility
- Foreign particles
- Uniformity of dosage units

Solution-type eye drops must be practically free from particles. Eye drops that are suspensions may show a sediment that is readily resuspended on shaking to give a suspension which remains sufficiently stable to enable the correct dose to be delivered.

Suspension eye ointments should be prepared with powder as fine as possible, because large particles could mechanically injure the eye. Even small needle-shaped crystals (smaller than 50 µm) could damage the corneal surface.

Suspension-type eye drops and eye ointments must, according to the Ph. Eur. comply with following test: For each 10 microgram of solid active substance, not more than 20 particles have a maximum dimension greater than 25 µm and not more of two of these particles have a maximum dimension greater than 50 µm. None of the particles has a maximum dimension greater than 90 µm. The investigation is carried out using a microscope.

The Ph. Eur. has no test for metal particles originating from poor quality metal ointment tubes. The Japanese Pharmacopoeia has a specification for the presence of metal particles, number and dimensions. In 10 samples no more than 50 particles of 50 µm or greater should be present, the shape is not specified. In addition, in 1 sample not more than 8 particles should be found.

10.9 Administration of Ophthalmic Preparations

Each type of ophthalmic dosage form has advantages and drawbacks. The administration of aqueous eye drops appears to be the most practical and comfortable dosage form for an ocular medication. However, the residence time on the eye is very short. Viscous eye drops and eye ointments adhere better to and stay longer on the ocular surface.

The patient, carer or nurse should apply each type of ophthalmic preparation in the correct and reproducible way. Table 10.20 describes the best instillation technique [130, 131] for eye drops.

Many patients, especially the elderly, experience difficulties in administrating eye drops. It has been demonstrated that standardisation of administration instructions and the use of mechanical aids can improve patient compliance. Certain commercial products are supplied with devices to facilitate instillation such as Xal-Ease and Eyot, and also Autosqueeze developed by the British Royal National Institute for the Blind [133]. An overview of the various mechanical aids can be found in Sect. 24.4.19.

Table 10.20 The instillation of eye drops – how to proceed. Example of a patient instruction for the administration of eye drops [130]

1. Wash your hands using soap and water; dry with a tissue – preferably not with a towel which has been used several times. Your eyes and eye drops are very sensitive to bacterial contamination
2. Unscrew the cap of the dropper bottle and place the cap on its side on a horizontal surface. This will reduce the risk of the ophthalmic solution being contaminated
3. Check if the dropper tip is damaged
4. Do not touch the tip, either with the eye, eye lashes or anything else
5. If necessary, remove your contact lenses
6. Hold the bottle like a pencil
7. Tilt your head back and look up to your eyebrows
8. Place your index finger of the other hand under the eye concerned. With your finger pull your lower eyelid gently away from the eye creating an open conjunctival sac to drop the medication into
9. Invert the bottle and hold the dropper bottle vertically above your eye, but be careful not to touch your eye or eyelashes
10. Use the other fingers of this hand to stabilise your head to avoid unexpected contact with the dropper tip
11. Squeeze the bottle and instil one drop into the open conjunctival sac
12. Sit upright
13. Keep your eyelids closed but without forcibly blinking. Firmly press your free index finger into the inner corner (near the nose) of the closed eyelids. This will ensure that the eye drop solution remains in the eye and does not drain away immediately into the nose
14. Press for between 1 and 3 min
15. Do not blink or forcefully close your eyelids
16. Wipe away any excess (overflow of eye drop solution) from the cheeks
17. If you have to administer eye drops in both eyes, or two drops in the same eye, repeat procedure from 4 to 16
18. Please wait 5 min before instilling a second drop of medication in the same eye
19. Recap the dropper bottle without touching the dropper tip or wiping the dropper tip
20. Store the bottle according to the instructions on the bottle
21. Finally wash your hands again

For patients on an intensive care ward following procedures were developed: in principle they should be applied conscientiously at each hospital ward and nursing home [132]:

- Avoid ocular contact with dropper(tip) and tip of the ointment tube.
- Do not use the same dropper tip or tube for both eyes of the patient. This prevents the possible spread of infection from one eye to the other. This implies that a separate preparation for each eye is preferable.
- Do not forget to remove contact lenses prior to administering the ophthalmic preparation.
- Do not use an eye covering wound dressing in cases of secreting ocular wounds.
- Do not perform pulmonary suction over patient's head without a procedure involving protection of his eyes against infection.
- Do not use swabs imbibed with ethanol when patient is in coma.

Arthritic patients, elderly people and children all experience difficulties with administering eye drops [43, 134–137]. In the group of elderly persons studied less than 33 % were able to instil eye drops or even to squeeze the dropper bottle. Only 50 % of the persons, who were able to administer their eye drops could apply the eye drops into the conjunctival sac. This illustrates that clear and practical instructions are required. For children clear instructions were described for an alternative method of administration. The technique was initially tested on volunteers (20–33 year old). The patients should lay down and close their eyes. The caregiver instils a drop on the inner canthus (near the nose), the patient then slowly opens their eye lids and the drop runs into the tear film. The pharmacological effect of pilocarpine nitrate 0.25 % and 0.5 % applied using the above described technique, exhibits an effect between that of pilocarpine nitrate 0.25 % and 0.5 % with nasolachrymal occlusion. The 'closed eye' technique is thus an effective and easy to use alternative for reluctant children.

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Rectal and Vaginal

11

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Contents

Based upon the chapter 'Rectaal en Vaginaal' by Stineke Haas and Christien Oussoren in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_11,

Abstract

This chapter is on dosage forms for rectal and vaginal use, with the main focus on suppositories and small-scale preparation methods. The position of rectal and vaginal administration in therapy and research is discussed as well as the main biopharmaceutical issues followed by the design of the formulation and preparation method. The suspension suppository is the most used form and the qualities of the active substance as well as of the excipients largely influence the therapeutic action. Therefore the chemical form of the active substance, its particle size and the suppository base get the most attention. The method of preparation is presented in detail, i.e. dispersing, mixing and pouring.

The onset of action with enemas is often faster than with suppositories and a larger part of the rectum and colon can be used for absorption. The latter is relevant for a local action. The chemical form of the active substance, the choice of the solvent and the pH of the preparation are important criteria.

Vaginal pessaries resemble rectal suppositories in many aspects. Differences from rectal suppositories are discussed. Vaginal solutions are mentioned briefly. They are not frequently used and largely resemble irrigation solutions and solutions for cutaneous use.

Finally, semisolid preparations for rectal and vaginal administration are focused on. Little difference exists from the corresponding cutaneous preparations and they are only discussed as far as there are specific requirements.

Keywords

Suppositories • Enemas • Pessaries • Vaginal solutions • Biopharmaceutics • Formulation • Preparation • Hard fat • Content uniformity

11.1 Orientation

Rectal dosage forms may be applied for systemic as well as for local action. Vaginal dosage forms are almost exclusively used for local action. Rectal administration of an active substance for systemic action is sometimes a good alternative to oral administration, especially in the following situations:

- Swallowing problems
- Nausea and vomiting
- Impaired consciousness
- Severe gastro-intestinal complaints after oral administration
- An unpleasant taste, especially in children
- A non-cooperative patient, e.g. a small child and the mentally disabled
- When abuse of the medication is suspected or may be life threatening (to take a rectal overdose is difficult)

For rectal administration an active substance can be formulated into a suppository (solid dosage form) or in an enema (liquid dosage form). The desired onset of action is important for the choice. For a rapid onset an enema is preferable, because a suppository base has to melt or to dissolve first. A suppository may be preferred because its use is easier and more patient-friendly. An enema is the best choice when a local effect over a large surface is desired, for instance in the treatment of ulcerative colitis. From a practical viewpoint an enema can be prepared faster, but is more sensitive to chemical degradation, due to the presence of water.

Examples of rectal administration of active substances for systemic effect are:

- Treatment of epileptic seizures in children where a rapid onset of action is very important , e.g. by rectal administration of a diazepam enema (diazepam solution) at home.
- Many active substances for pain control, such as paracetamol, diclofenac and opioids such as tramadol and morphine, administered as suppositories.
- Migraine headaches accompanied with nausea and vomiting can be controlled by starting with a prokinetic such as metoclopramide or domperidone in a suppository, followed by an analgesic in a second suppository.
- Morphine and oxycodone suppositories might be useful in terminal patients when oral therapy is difficult, but this therapy is often replaced by transdermal fentanyl.
- When nausea and vomiting occur in patients with any illness, a chronic oral medication may be temporarily replaced by the same active substance in a rectal dosage form: so a hydrocortisone suppository may replace hydrocortisone in tablet or capsule; a carbamazepine suppository may replace carbamazepine and a valproic acid suppository sodium valproate in syrup, tablet or capsule.

Even so many active substances may be given rectally to obtain local action. Some examples are:

- Laxatives such as bisacodyl in a suppository; docusate sodium and sodium phosphate in an enema.

- Anti-hemorrhoid medication as hydrocortisone acetate, lidocaine and zinc sulphate in a fatty cream or ointment and zinc oxide in suppositories.
- Chronic inflammatory bowel conditions (ulcerative colitis, Crohn's disease) treated by mesalazine, beclometasone and budesonide given as a suppository or enema for a local action, but only if the disease is limited to the rectum (suppository) and the distal part of the colon (enema).
- A contrast medium like barium sulphate may be given as a suspension by a large volume enema for colon diagnostics.

Vaginal preparations may especially be used for a local antifungal or antimicrobial therapy, or for a local treatment with sex hormones. Butoconazole is used in vaginal suppositories (pessaries or ovules) or in a vaginal cream, clindamycin in a cream, clotrimazole in a vaginal tablet or pessary and in a cream, miconazole in a vaginal capsule and in a cream, nystatin in a cream and metronidazole in a vaginal tablet or pessary and in a cream or gel. Iodinated povidone (povidone iodine) may be applied in the form of a vaginal solution.

A new development is the incorporation of antiretroviral substances, such as dapivirine and tenofovir, into an intravaginal ring for HIV prophylaxis. A ring can stay *in situ* for 1 (to 3) month(s) and delivers controlled doses of the active substance(s). The antiretroviral substance may be combined with a contraceptive such as levonorgestrel [1]. These vaginal rings are in various phases of clinical trial. A similar vaginal ring with only contraceptive action has been available for 10 years as NuvaRing® with etonogestrel and ethinylestradiol. Traditional examples of sex hormones for vaginal application are estradiol in a vaginal tablet and estriol in vaginal cream and pessaries. Finally, lubricants and spermicidals are applied vaginally.

In clinical practice various oral dosage forms are also used for rectal administration. There is often little scientific support for such use, nevertheless it may be effective. Evidence exists for rectal administration of an oral controlled release morphine tablet (MS-Contin®) [2, 3]. Rectal use of temazepam oral capsules is not effective. There is a broad variation in time to reach the maximum plasma concentration and in the biological availability. Better outcomes are obtained with temazepam dissolved in glycofurol:ethanol:water = 5:1:4 and given rectally as an enema [4].

11.2 Definitions

Rectal preparations are intended for rectal use in order to obtain a systemic or local effect, or they may be intended for diagnostic purposes.

The Ph. Eur. lists under Rectal preparations or Rectalia the following dosage forms:

- Suppositories
- Rectal capsules
- Rectal solutions, emulsions and suspensions (enema)
- Powders and tablets for rectal solutions and suspensions
- Semisolid rectal preparations (ointments, creams and gels)
- Rectal foams
- Rectal tampons

Vaginal preparations are liquid, semisolid or solid preparations intended for administration to the vagina usually in order to obtain a local effect. They contain one or more active substances in a suitable basis.

Under Vaginal preparations or Vaginalia the Ph. Eur. lists:

- Pessaries
- Vaginal tablets
- Vaginal capsules
- Vaginal solutions, emulsions and suspensions
- Tablets for vaginal solutions and suspensions
- Semisolid vaginal preparations (ointments, creams, gels)
- Vaginal foams
- Medicated vaginal tampons

From the rectal dosage forms the suppositories, enemas, ointments and creams are important as extemporaneous pharmacy preparations; from the vaginal dosage forms these are the vaginal suppositories (pessaries), solutions, creams and gels.

Suppositories are solid, single-dose preparations. Their shape, volume and consistency make them suitable for rectal administration. They contain one or more active substances dispersed or dissolved in a suitable basis that may be soluble or dispersible in water or may melt at body temperature. Excipients such as diluents, adsorbents, surface-active agents, lubricants, antimicrobial preservatives and colouring matter, authorised by the competent authority, may be added if necessary (Ph. Eur.).

Rectal solutions, emulsions and suspensions are liquid preparations intended for rectal use in order to obtain a systemic or local effect, or they may be intended for diagnostic purposes. Rectal solutions, emulsions and suspensions are supplied in single-dose containers and contain one or more active substances dissolved or dispersed in water, glycerol or macrogols or other suitable solvents. Rectal solutions, emulsions and suspensions may contain excipients, for example to adjust the viscosity of the preparation, to adjust or stabilise the pH, to increase the solubility of the active substance(s) or to stabilise the preparation. These substances do not adversely affect the intended medical action or, at the concentrations used, cause undue local irritation (Ph. Eur.).

Pessaries are solid, single-dose preparations. They have various shapes, usually ovoid, with a volume and

consistency suitable for insertion into the vagina. They contain one or more active substances dispersed or dissolved in a suitable basis that may be soluble or dispersible in water or may melt at body temperature. Excipients such as diluents, adsorbents, surface-active agents, lubricants, antimicrobial preservatives and colouring matter, authorised by the competent authority, may be added if necessary (Ph. Eur.).

11.3 Biopharmaceutics

An active substance is rectally administered for either a systemic or a local effect. The biopharmaceutics of the systemic effects have been studied quite well. The outcomes of these studies support recommendations for the formulation of rectal dosage forms, see Fig. 11.1. See also Sect. 16.2.4.

In contrast, very little is known about the biopharmaceutics of vaginal dosage forms. The vagina has good absorbing properties, but this is seldom used for a systemic effect. Vaginal dosage forms are administered for a local effect only.

Rectal and vaginal dosage forms aimed to obtain a local effect are, from a biopharmaceutical viewpoint, comparable with dermal preparations. However it should be known that after rectal and vaginal application a greater part of the active substance may reach the general circulation than after cutaneous application. This may result in significant blood levels and unwanted systemic effects.

Rectal administration of an active substance can be justified only if adequate data are available about the release from the dosage form and the absorption from the rectum. Without such a support rectal administration of an active substance should be discouraged. Tables with data from biopharmaceutical and pharmacokinetic research on rectally administered active substances are available from literature [5a].

11.3.1 Specific Problems of Rectal Administration

Compared to oral administration, rectal administration encounters some specific problems. Degree and rate of absorption of the active substance are more difficult to predict and depend largely on the never predictable residence time in the rectum. Both irritation of the rectal mucosa by the active substance or the excipients and a large (liquid) volume in the rectum may cause a defecation reflex terminating the absorption process of the active substance. Also the degree of filling of the colon and sometimes the rectum influences the release and the absorption of the active substance. In favour of rectal administration would be bypassing of the hepatic portal circulation and thereby the first-pass effect. However, clinical studies in men do not support this argument, see also Sect. 16.2.4.

Rectal absorption of an active substance proceeds, usually, more slowly and less completely than oral absorption. The active substance can only be absorbed after melting or dissolution of the base and dissolution of the active substance in the rectum fluid. These processes take time. Additionally, the surface for rectal absorption is much smaller than for oral absorption. Literature often advises higher standard dosages for rectal administration. The rectal dose of carbamazepine, for example, is for children 125 % of the oral dose [6]. No universal guidance could be found for the dose correction for rectal administration. When a rectal dosage cannot be found in literature the safest approach is to use the oral dosage.

11.3.2 Release and Absorption Rate

Contemporary research focuses on the development of dosage forms with a better and faster release of the active substance and on dosage forms with a delayed or controlled release. The addition of surfactants to the suppository often enhances the rate and extent of release and even the absorption of an active substance, but there are many exceptions. For a delayed or controlled release an increased viscosity of the suppository mass appears to be relevant. Most research has not yet yielded a licensed medicine.

Absorption Enhancers

Many studies have been published on the use of various enhancers for the rectal absorption. They increase the absorption of an active substance by enhancing the membrane permeation, rather than increasing the solubility. Published examples of absorption enhancers are capric acid and sodium caprate, lauric acid and sodium laurate, sodium salicylate and sodium cholate. These enhancers however give an unpredictable and strongly variable improvement of the biological availability [5b]. Nevertheless they sometimes lead to a licensed medicine: sodium caprate is already in use in a suppository product available in Japan [7].

Non-ionic surfactants can be added to a fatty suppository base to enhance the release of poor water-soluble active substances [5b]. The results of studies on this subject, however, vary considerably. Often the *in vitro* release is improved, whereas the *in vivo* results are disappointing [8a]. This is partly caused by the formation of micelles in the rectal fluid and partly by the influence of the surfactant

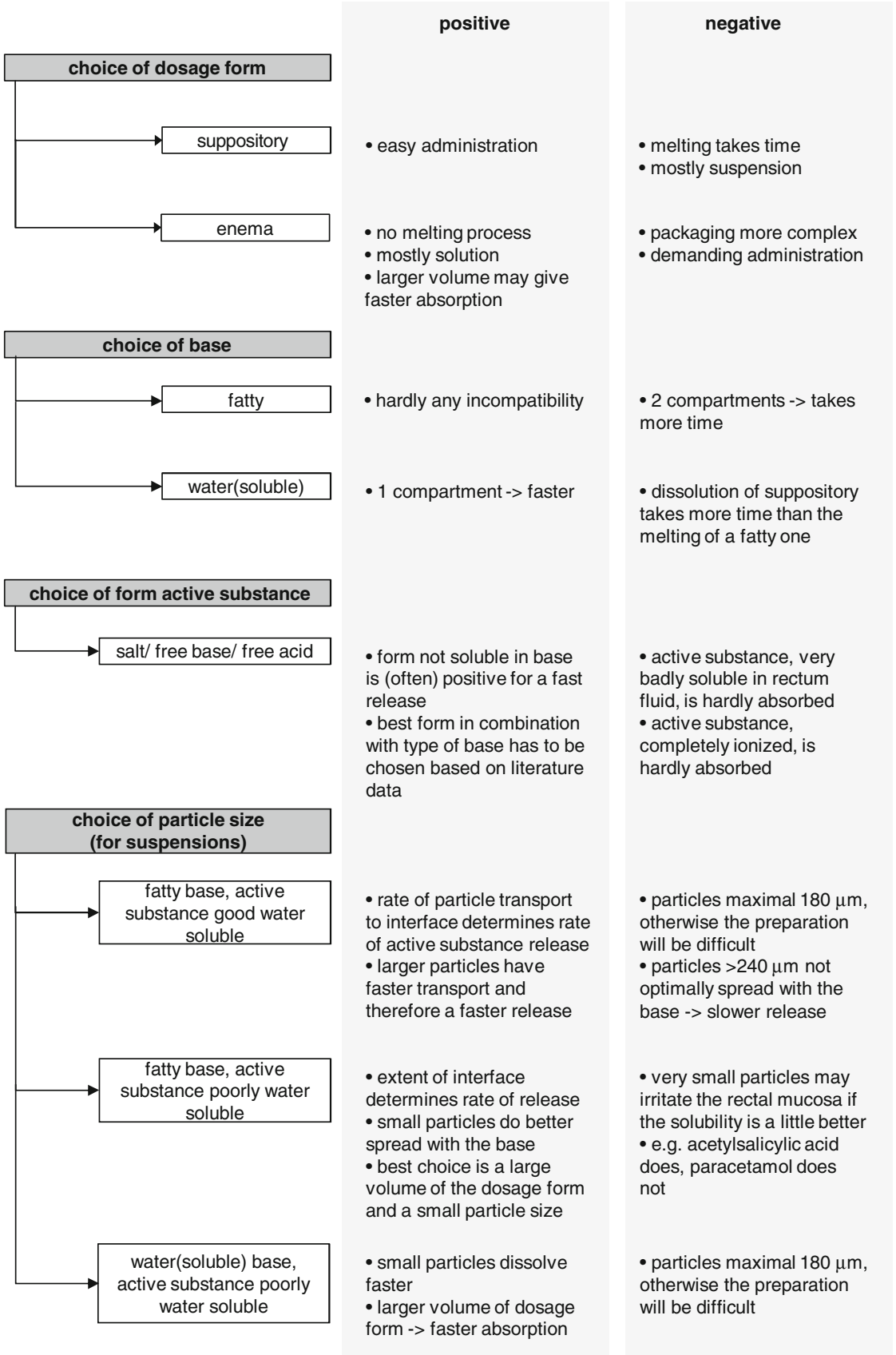


Fig. 11.1 Rectal dosage forms for systemic action: biopharmaceutical considerations

on the rectum wall. In fat-based suspension-type suppositories the release rate is determined by the particle transport to the surface of the fatty phase and by the dissolution rate in the aqueous rectum fluid. For active substances with a moderate to poor solubility in water the rate-determining step is the dissolution of the active substance in the rectal fluid, see also Sect. 16.2.4. This dissolution may be accelerated by a better wetting of the active substance particles. This can be achieved by adding a surfactant [8b]. In general, the rate of release *in vitro* increases with an increasing amount of surfactant [8a]. However, *in vivo* there is a critical concentration. It appears that at higher concentrations of surfactant the absorption of active substance decreases again. The critical concentration of surfactant seems to be 1–3 % of the suppository weight. Probably the active substance gets enclosed in micelles in the rectal fluid. This may reduce or even impair the absorption [8a]. Surfactants may also change the membrane permeability. These changes depend on surfactant concentration and will alter the absorption. Because of such large and varying influences on the absorption of active substance, surfactants may only be added based on *in vivo* research, such as has been done with the influence of lecithin on absorption from indometacin suppositories. The influence of different concentrations of surfactant on release and absorption is illustrated with indometacin suppositories. Witepsol® H15 was used as suppository base and increasing amounts of lecithin were added. The addition of 1 % lecithin (about 25 mg per suppository) gave a distinctly higher blood concentration. The dissolution rate of indometacin was increased and, as a result of the decreased viscosity of the suppository mass by the surfactant, the suppository spread better *in vivo*, giving a larger area for indometacin release. In this way the surfactant increased dissolution over a larger area and hence increased the blood concentration [8a]. However, increasing the quantity of lecithin to over 300 mg per suppository produced slow release profiles and sustained plasma levels of indometacin when administered to rabbits. Consequently, a sustained release (controlled release) indometacin suppository was created [5c].

Controlled Release

Controlled release by increasing the viscosity of the suppository base has been studied with morphine.

A fatty base such as Witepsol® H15 is miscible with polyglycerol esters of fatty acids with a relatively high melting point, such as decaglycerol heptabehenate (HB750®) [9]. The increased viscosity of the melted mixture, results in a slower *in vitro* release of morphine sulphate compared to Witepsol H15 alone. *In vivo* the morphine level initially increases slowly and remains on a relatively high level for a longer time.

Morphine sulphate in a matrix of a fatty base (Witepsol® W25) with colloidal anhydrous silica (Aerosil® R 972) and hydroxypropylmethylcellulose (HPMC 4000) [10] showed an absorption rate and a biological availability equivalent to orally given morphine sulphate retard tablets (MS Contin®). Such suppositories can be made as a regular pharmacy preparation [11] but in our opinion this requires more convincing evidence that morphine release is sufficiently reproducible. MS-Contin® suppositories (not available in all countries) have a fatty base with sodium alginate and calcium phosphate [12].

Metoclopramide hydrochloride controlled release suppositories were prepared by mixing Witepsol® W35 with 30 % lecithin [13]. The metoclopramide is incorporated in this base in a (solid) reversed micellar solution. The diffusion rate of the active substance from the melted suppository in contact with the aqueous rectum fluid was very low. Compared to licensed normal metoclopramide suppositories a five times longer mean residence time was found *in vivo* for the lecithin suppositories.

A survey of research on special formulations of suppositories, such as hollow type suppositories, can be found in [5d].

Unconventional (Suppository) Bases and (Vaginal) Delivery Systems

Other rectal dosage forms may be used other than fat-based suppositories. One study describes a liquid ‘suppository’ that immediately after administration forms a gel with strong adhesion to the rectal mucosa [14]. The gelling at body temperature is caused by a poloxamer. Adhesion to the rectal mucosa is provided by carbomers and cellulose derivates. Compared to a fatty suppository, this delivery system is expected to spread less far into rectum and colon, thereby avoiding the hepatic portal system (see also Sect. 11.3).

The vaginal delivery system for dinoprostone (Propess® 10 mg) is even more different from the classical dosage forms for rectal or vaginal use. It is a thin, flat polymeric matrix of crosslinked macrogols forming a hydrogel in the vagina. Dinoprostone is

(continued)

released from the matrix in a controlled way: about 0.3 mg per hour during 24 h. A knitted polyester retrieval system envelopes the matrix and facilitates removal from the vagina at the time the cervical ripening has completed as decided by the gynaecologist [15].

Another intravaginal device is the vaginal ring see also Sect. 11.1. Already available is the NuvaRing®, used as contraceptive. It is a polymeric vaginal ring containing etonogestrel and ethinylestradiol. The ring has to be placed high in the vagina and should stay there for 3 weeks. After a 1-week break the next ring is inserted. Vaginal rings containing antiretroviral medicines for HIV prevention have been developed, but are not yet available for use. They show a sustained and controlled active substance release over 28 days, sometimes over 90 days. Polymers used for the rings are, for example, polysiloxanes and polyurethanes. For the NuvaRing® 2 different ethylene vinyl acetates are used.

11.4 Product Formulation, Suppositories

This section discusses the active substance (particle size and solubility), the bases and the excipients to obtain optimal release and absorption. Obviously these three components are closely interrelated. The active substance must be used in a chemical form, ionised or not, and with a particle size that are optimal for release and rectal absorption. In addition a base has to be chosen that optimises release, see also Fig. 11.1. Excipients can be added to improve dissolution and absorption or for technological reasons. However, excipients aimed at technological improvement may also influence the release of active substance. Whatever choice is made for active substance, base and excipients, their impact on the preparation process, the stability of the product and the shelf life must also be considered.

11.4.1 Particle Size of Active Substance

Usually the active substance does not dissolve in the base. Even lipophilic substances are often poorly soluble in fatty bases, so most suppositories are suspensions of the active substance in a (solid) vehicle, the suppository base. For these suspension suppositories the particle size of a dispersed active substance is important because it influences:

- The pharmaceutical availability of the active substance
- The physical stability of the suspension
- The irritation of the rectal mucosa
- The chemical stability of the active substance

The particle size is preferably chosen based on published data. If these are not available it has to be chosen in accordance with the physico-chemical properties of the active substance. Section 16.2.4 gives guidance for such a choice, summarised as follows:

- For a fatty base with a good water soluble active substance, a particle size as large as possible should be taken, but not above 180 µm.
- For a fatty base with a slightly water soluble active substance that is very slightly or practically insoluble in the fatty phase as well, a particle size as small as possible should be taken, for instance 45 µm for paracetamol.
- For a fatty base with a slightly water soluble active substance that is sparingly to freely soluble in the fatty phase, the particle size of the active substance has hardly any influence.
- For a water soluble base with a slightly water soluble active substance, small particles are chosen because they dissolve more readily; usually a particle size not exceeding 180 µm satisfies.

A stable suspension of active substance in the base is important during the preparation process, especially when the melted mass is poured into the molds and during subsequent cooling and solidification. The smaller the particles, the more stable the suspension (see also Sect. 18.4.2). In practice, a particle size not exceeding 180 µm meets all demands. Any agglomerates should be carefully fragmented.

Irritation of the rectal mucosa occurs when large particles are used. A particle size of 180 µm should therefore be the maximum. Irritation of the mucosa may also occur when small particles of an irritating active substance dissolve (too) quickly. This happens for instance when acetylsalicylic acid with a particle size of 45 µm is used in suppositories. It has a fast release of the active substance from the suppository and it dissolves rapidly, but as a result it irritates the mucosa. Therefore acetylsalicylic acid should be used with a particle size of 180 µm.

Chemical degradation occurs faster when the total surface of the particles is larger. Therefore a larger particle size enhances chemical stability, for instance particles of 90–180 µm.

11.4.2 Solubility of Active Substance

If an active substance is practically insoluble in water (and therefore in the rectal fluid), the suppository will be ineffective. Certain excipients may increase the water solubility and, as a result, the absorption. A surfactant can be added

for a better wetting of the particles and thereby increasing dissolution rate. A macrogol (polyethylene glycol) suppository base may increase the solubility of the active substance by acting as a co-solvent. As the suppository dissolves in the rectal fluid, a mixture of macrogol and rectal fluid develops, in which the active substance may dissolve better.

The active substance should have certain lipophilicity as well. If not, it will not pass the rectal lipoid membranes. On the other hand, a too high lipophilicity causes the active substance to be hardly released from a fatty base. For a systemic effect a good water-soluble active substance is preferred with sufficient lipophilicity at the pH of the rectal fluid to allow passage of the rectal membranes for absorption [8c].

Which form of the active substance should be chosen, more hydrophilic or more lipophilic, is related to the choice of the suppository base, fatty or water soluble. These choices can only be based on published data about release and absorption.

Form of Active Substance and Type of Base in Relation to Efficacy

Glafenine has a solubility in water of 1 in 60,000 at pH 7. The rectal absorption of glafenine from an aqueous micro-enema, and of glafenine hydrochloride from a fatty suppository is extremely slow and incomplete, due to the low solubility of glafenine at the pH in the rectum [16]. Therefore this active substance is not effective after rectal administration, although glafenine suppositories were commercially available in the past century. On the contrary, for example, the solubility of phenobarbital in water of 1 in 1,000 is sufficient for rectal administration.

Hydrocortisone (soluble in water 1 in 3,500) is better soluble than hydrocortisone acetate (practically insoluble in water). Therefore, in a suppository given for a systemic effect, hydrocortisone is used, but in a suppository given for local problems such as haemorrhoids, hydrocortisone acetate is preferred, in order to avoid unwanted systemic effects.

Phenobarbital sodium can be processed in a fatty base and the release of this salt is faster than that of the corresponding acid, phenobarbital. The bioavailability of both substances is almost equal, but for the rapid increase of plasma concentrations the salt is the better choice [17, 18].

Sodium valproate is released well from a fatty base, but absorption is better with the free acid in a fatty base [17]. Moreover, the processing of valproic acid is much easier than that of the strongly hygroscopic sodium salt. For both reasons the acid is preferred.

Methadone is best incorporated in a macrogol base in the form of its hydrochloride salt, to obtain a good efficacy. Methadone hydrochloride (pK_a 8.25) will be released from a fatty base, but at the rectal membrane methadone is converted to its unionised form. This lipophilic substance is so poorly soluble in the aqueous rectal fluid that it is not absorbed. By using a macrogol base (macrogol 1500 or PEG 1500), the solubility of the unionised methadone in the rectal fluid (now containing the macrogol as co-solvent) is improved [19, 20].

11.4.3 Types of Suppository Base

The common suppository bases can be classified into two main categories: the lipophilic and the hydrophilic bases. See Sect. 11.3 and Fig. 11.1 for the choice between these types from a bioavailability viewpoint. Usually a fatty base will comply but a lipophilic active substance may not be released well enough, because the partition coefficient lipid/water is unfavourably high. The consultation of published data about active substance release and absorption is recommended. When published data are not available, the solubility of the active substance (Sect. 11.4.2) should be considered, but without *in vivo* test the therapeutic action is not assured. This section considers some general characteristic points of the bases and gives some information on the less usual bases cocoa butter and glycerinated gelatin. The most used bases, hard fat and macrogol, are dealt with in Sects. 11.4.4 and 11.4.5.

A suppository base should not irritate the rectum and be harmless in case of absorption. Chemically and physically, the base should have a good shelf life and not decrease the stability of the active substance.

With regard to the preparation process the following requirements are set:

- Upon solidification, the base must not form unstable modifications with a solidification point below room temperature, as is seen for cocoa butter.
- Upon solidification, the suppository mass (base + active substance(s) + excipient(s)) preferably contracts slightly, facilitating removal from the mold.
- At the pouring temperature, the suppository mass should be sufficiently viscous to prevent the settling of dispersed particles during the filling process.
- At room temperature, the suppository mass must be solid and must keep its shape.

Seldom will a suppository base meet all these qualities. The properties of a base may be improved by the addition of a substance that influences the melting point. For instance,

Table 11.1 Chloral Hydrate Suppositories 500 mg [21]

For a suppository mold 2.3 mL[a]:	
Chloral hydrate	0.5 g
Macrogol 1500	2 g
Macrogol 6000	0.17 g

[a]In case of a different volume of the mold, the ratio between chloral hydrate, macrogol 1500 and macrogol 6000 has to be reinvestigated

Table 11.2 Zinc Oxide Suppositories 10 % [23]

For a suppository mold of any volume:	
Zinc oxide (90)	10 g
Triglycerides, medium-chain	20 g
Hard fat	70 g
Total	100 g

the use of a macrogol (polyethylene glycol or PEG) combination with a higher melting point than the usual macrogol base gives chloral hydrate suppositories a sufficient consistency (Table 11.1).

A low melting point may be necessary when the body temperature of the patient is below normal. A low body temperature may occur at terminal illness. From a standard suppository base, the release of the active substance will be insufficient. For a low melting point, 20 % of the fatty base is replaced by a liquid triglyceride such as Miglyol®, such as is done for morphine suppositories in clinical practice [22]. A low melting point may also be needed to obtain a better local effect, for example in 10 % zinc oxide suppositories (Table 11.2) that are used to soothe haemorrhoidal pain. In this formulation 20 % of the total weight consists of Miglyol® 812. As a result of the low melting point, the suppository melts superficially at insertion, creating a protective layer in the anal canal.

Increasing the melting point of a fatty suppository above a normal body temperature is not an option. Not even in suppositories for tropical use if melting during storage and transport has to be prevented. With a higher melting point the in-patient melting time and therefore the time to the release of the active substance will be unacceptably long.

11.4.3.1 Cocoa Butter

Cocoa butter (Cacao oleum) is a solid fat, pressed from the roasted seeds of *Theobroma cacao*. Since the middle of the eighteenth century it is used as a suppository base. Cocoa butter melts at body temperature. At room temperature it is a solid mass. But cocoa butter has a number of undesirable properties: it soon becomes rancid on storage and it exhibits marked polymorphism. It has four polymorphic forms: alfa, beta, beta-accent and gamma. The melting points are 22 °C, 34–35 °C, 28 °C, and 18 °C respectively. The beta-form is the most stable one.

Cocoa butter suppositories can be extemporaneously prepared by hand rolling (the oldest, historical method), compression molding (compressing cold mass into the molds) and fusion molding (filling the molds from a melt). The first and the second method have the advantage of avoiding heating and melting of the cocoa butter. Problems on solidification of the mass, caused by the polymorphism, are bypassed in this way. In both methods grated cocoa butter is mixed with the active substance in a mortar, using a plastic card. In hand rolling the mass from the mortar is pressed in the palm of a hand into an elastic mass that is cut into an appropriate number of portions and subsequently rolled by hand on a flat surface to obtain a cylindrical shape, conical at one end. Plastic gloves should be worn when forming the suppositories. Hand-operated compression molds facilitate different shapes and sizes of the suppositories, so there is little need for shaping by hand anymore [5e].

In compression molding, the mixture in the mortar is transferred to special pressing equipment, holding the proper compression mold (see Fig. 11.2). The method requires a replacement factor (see Sect. 11.5.1) specifically valid for this compression method. In both 'cold' methods the quality of mixing active substance and grated base is very critical for sufficient content uniformity of the suppositories. Although no investigations are available, it is obvious that this process is most critical with low-dosed active substances and definitely has to be validated.

Fusion molding involves mixing the active substance with molten cocoa butter and pouring the mixture into the mold. Because of the polymorphism, great care is needed to melt the base properly. When cocoa butter is melted too fast and too far above 36 °C is kept too long too warm or is cooled down too quickly, the result is the metastable alfa-modification. This modification has a substantially lower melting point giving rise to difficulties in solidification. In fact, the melting point may become so low that the cocoa butter will not solidify at room temperature any more. However there is a slow transition from the alfa-form to the more stable beta-form (with higher melting point), which may take several days [5f]. An ongoing transition of unstable to stable modifications during storage may affect the melting properties of the suppository and therefore the release of the active substance.

As opposed to these disadvantages of cocoa butter in fusion molding, there is the advantage that in compression molding (cold preparation) no settling of particles will occur, thus eliminating a main cause for content uniformity problems.

Hard fat, the alternative for cocoa butter, is less sensitive to rancidity and shows substantially less modifications.

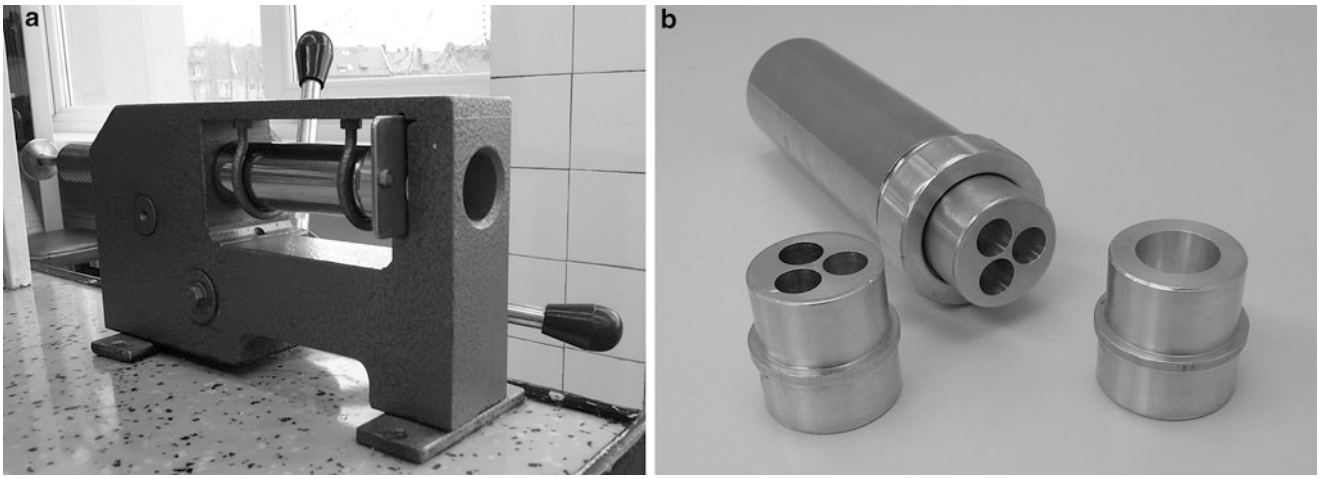


Fig. 11.2 Hand press (**a**) and molds (**b**), used in compression molding. Source: Department of Pharmaceutical Technology GUMed Gdansk, with permission

Therefore it has replaced the cocoa butter as a suppository base in Dutch pharmacies, although the disadvantage of particle settling during pouring has to be overcome instead. Hard fat is the main suppository base in many countries. Cocoa butter has until now a place in suppository preparation in some other countries.

11.4.3.2 Glycerinated Gelatin

The oldest water-soluble suppository base is a mixture of gelatin, glycerol and water. The ratio differs from country to country. The Dutch pharmacopoeia (Ph. Ned. VI) specified Suppositoria Gelatinosa as containing 2 parts of gelatin, 5 parts of glycerol 85 % and 4 parts of water. BP and USP describe this type of base as well. The glycerinated gelatin base has long been used in pessaries (vaginal suppositories) for its good adhesion properties to the vaginal mucosa and its patient friendly softness. However, a glycerinated gelatin base may give microbiological problems on storage. Using a natural starting material (gelatin) enhances the chance of microbiological contamination. Water can condense at the package and microorganisms may then grow. Physical problems related to storage are loss of water in dry circumstances and a tendency to absorb moisture under damp conditions. For these reasons and from the authors' viewpoint, the use of glycerinated gelatin base for rectal and vaginal dosage forms is obsolete. Nevertheless, in many countries this base is used for pessaries. Such pessaries must be kept in well-closed containers and in a cool place. For an extended shelf life a preservative should be added, such as methyl parahydroxybenzoate or propyl parahydroxybenzoate or both (see Sect. 23.8.5). Otherwise the shelf life should be limited to 1 or 2 weeks.

11.4.4 Hard Fat (Adeps Solidus)

Hard fat is a collective name for (semi-)synthetic mixtures of mono-, di- and triglycerides of the fatty acids C10 - C18 with a melting range between 33 and 36 °C. It is marketed in many varieties and under various brand names. An elaborate survey with the composition, melting and solidification range, hydroxyl value, acid value, saponification value, peroxide value and iodine value can be found in [5g]. Table 11.3 shows the characterisation parameters of common fats used as suppository bases. Some of these properties will be described.

11.4.4.1 Hydroxyl Value

By varying the ratio of mono-, di- and triglycerides, different hydroxyl values are obtained. A higher hydroxyl value is, among others, associated with more tendency to further hardening after preparation and a higher elasticity and viscosity of the (molten) base [8d]. Higher elasticity diminishes the risk of fracturing at rapid cooling. A higher viscosity is advantageous for the suspension stability of the active substance in the molten base, but may also reduce the availability of the active substance [24]. Otherwise, a very low hydroxyl value may have an unexpected influence on the active substance release. Therefore bases with very different hydroxyl values should not be exchanged without further investigation.

11.4.4.2 Acid Value

A low acid value is desirable because irritation of the mucous membrane and chemical reactivity increase with a higher content of free fatty acids. According to the Ph. Eur., the maximum acid value is 0.5.

Table 11.3 Characterisation parameters of commonly used lipophilic suppository bases

Suppository base	Melting range (°C)	Solidification range (°C)	Hydroxyl value[a]	Iodine value[b]	Acid value[c]
Adeps solidus (hard fat)[d]	30-45	–	≤50	≤3	≤0,5
Novata B	33.5–35.5	31–33	20–30	≤3	≤0.3
Suppocire AM	35.0–36.5	–	5	–	–
Witepsol H15	33.5–35.5	32.5–34.5	5–15	≤3	≤0.2
Witepsol W25	33.5–35.5	29–33	20–30	≤3	≤0.3
Witepsol W35	33.5–35.5	–	40–50	≤3	≤0.3
Witepsol E75	approx. 38	–	≤15	≤3	≤0.3
Cocoa butter	31–34	–	approx. 0	31–38	<5

[a]Milligrams of potassium hydroxide required to neutralise the acid that is bound by acylation of 1 g of the substance
[b]Grams of halogen, calculated as iodine, that can be bound by 100 g of the substance
[c]Milligrams of potassium hydroxide required to neutralise the free acids in 1 g of the substance
[d]According to the Ph. Eur.

11.4.4.3 Iodine Value

The iodine value is a measure of the number of double bonds in an oil or a fat. A low iodine value in the base is achieved by using esters from saturated fatty acids. A large number of double bonds increases the tendency to oxidation and rancidity.

11.4.4.4 Peroxide Value

The peroxide value is a measure of the amount of reactive oxygen in the fat. A low peroxide value decreases oxidation of the active substance by the base which enables processing of easily oxidisable active substances, such as ergotamine and chlorpromazine.

11.4.4.5 Saponification Value

The saponification value is directly related to the molecular weight of the fats, and thus to the chain length of their fatty acids and to the melting point. Hard fat with a melting point (actually a melting range) between 33 and 36 °C meets the requirements of the Ph. Eur. regarding the saponification value of 210–260.

The requirements set by the Ph. Eur. to hard fat are relatively broad; all mentioned brands meet them. To limit formulation variation, it is recommended to use only one or two types of fatty suppository bases. Commonly used are Witepsol ® H15, Suppocire ® AM, Novata ® B and Witepsol W25. Witepsol H15 is the most commonly used suppository base in the Netherlands and many other countries. Suppocire AM is useful for acidic ingredients. Its low hydroxyl value may diminish interaction between free hydroxyl groups and acidic active substances. The last two bases may withstand forced cooling, as they have a higher hydroxyl value and consequently a larger elasticity [25].

11.4.4.6 Solidification Point or Solidification Range

The Ph. Eur. sets no requirements for the solidification point or range of hard fat. Hard fat types which meet the requirements of Ph. Eur. and have the same melting range, may still have different solidification ranges due to a different composition.

A short interval between melting point and solidification point seems to be advantageous as it shortens the time that particles can settle after the suppository mass has been poured into the molds. This settling may lead to a brittle tip. This is however not necessarily true, because often supercooling occurs before the mass starts to solidify [8e]. Forced cooling will shorten the solidification time but it cannot be applied to each type of hard fat; fractures easily occur in the suppository.

A different composition of hard fat also influences the solidification behaviour and may cause a (welcome) increase of viscosity before the mass solidifies completely. The viscosity increase may decrease settling during the filling process and thereby improve content uniformity. Often however, during cooling, no increase of viscosity is seen but suddenly a fast solidification occurs. This solidification behaviour complicates manual preparation of suppositories. The lack of gradually increasing viscosity is a quality aspect of hard fat that usually gets too little attention.

As for cocoa butter various modifications exist for hard fat, but their consequences are much less pronounced [8f]. Therefore, control of temperature during melting and cooling comes far less precise than in cocoa butter. Nevertheless, the polymorphism of hard fat is responsible for some physical processes including the process of secondary hardening (ageing) as described in Sect. 11.4.8. It is hardly possible yet to trace back this process to certain phase transitions.

11.4.4.7 Compatibility

Hard fat is compatible with the majority of active substances. However, active substances with free acid groups can react with the free hydroxyl groups of the mono- and diglycerides. For such active substances a base with a low hydroxyl value should be used.

Active substances can also react with the free fatty acids in the base. To avoid this, a base with a low acid value can be chosen, so with few free fatty acids.

Reactions of an active substance with free hydroxyl groups or free fatty acids of the base changes the melting behaviour and thereby may affect the release of the active substance.

Reactions of an active substance with peroxides in the base can be prevented by choosing a base with a low peroxide value. When formulating ergotamine or chlorpromazine, the peroxide value of the base must not exceed 0.5.

11.4.5 Macrogol

Macrogols are polymers of ethylene oxide, see Sect. 23.3.4. Usually mixtures of macrogols are used as suppository base. The desired hardness can be adjusted by choosing the molecular weight and suitable ratios. Even macrogol 1500 is too soft if used as such [8g]. The most commonly used base in Dutch pharmacies is 1 part of macrogol 1500 plus 2 parts of macrogol 4000. If suppositories with this base become too soft, a macrogol with a higher molecular weight should be used, see the example in Table 11.1.

11.4.5.1 Advantages and Disadvantages

A macrogol base will mostly be chosen based on published data showing better release or absorption, or both. The advantage of water solubility and thus avoidance of the melting time is somewhat overestimated because the dissolution of macrogol in the rectal fluid takes time as well. Once the macrogol has been dissolved the active substance release is faster than from a fatty base because in the latter transport of the active substance from the fatty to the aqueous phase still has to take place. Moreover the active substance can dissolve in the rectal fluid simultaneously with the base. The base has considerable disadvantages however: chemical incompatibilities and irritation.

11.4.5.2 Incompatibilities

Macrogols are incompatible with many more active substances, compared to hard fat. Upon storage, macrogols can form peroxides and therefore they are not suitable for the processing of easily oxidisable substances such as ergotamine and chlorpromazine (Sect. 22.2.2). Incompatibilities may also be caused by complex formation and transesterification. Acetylsalicylic acid decomposes rapidly in a macrogol base, yielding salicylic acid while macrogol is acetylated. A list of incompatibilities with macrogols can be found in [26]. Because of its high melting point, a macrogol base is often recommended for use in tropical circumstances. Its usability is however restricted by the chemical incompatibilities and the hygroscopic character.

11.4.5.3 Irritation

From a macrogol base the active substance is released not only by melting of the base, but primarily by dissolving of the base in the rectal fluid. Due to the high osmotic value of the dissolved macrogol, water is withdrawn from the surrounding tissue. This may cause irritation [8g]. Moistening the suppository with water before insertion is suggested to avoid irritation [5h]. It will help insertion but the effect on irritation is questionable because much more water will be attracted when the suppository dissolves.

11.4.6 Excipients

In suppositories all excipients should be used with care. The addition of excipients often negatively influences active substance release. This applies for instance when tablets are used as starting material because of costliness or unavailability of the active substance as such or when the quantity needed is too small to be weighed with sufficient accuracy (see Sect. 29.1.8). The very nature and the amount of excipients in tablets is usually unknown and may have unexpected effects on active substance release. Especially talc and magnesium stearate, common excipients in tablets and insoluble both in fat and in water, may strongly impair the release by accumulating in the interface between fat and water [24].

11.4.6.1 Lactose

In suspension suppositories, the active substance is processed as small particles that are prone to form agglomerates. The effective dispersion of the agglomerates (see Sect. 29.3) is a prerequisite for a sufficient content uniformity. Lactose may be used in pharmacy preparations to disperse the agglomerates and to maintain separation of the primary particles. This is most important with low dosed active substances, which do not easily lead to a good content uniformity. If 50 mg or less of active substance(s) is used per suppository, as a standard 100 mg lactose may be added to each suppository, as illustrated by chlorpromazine suppositories in Table 11.4. The added lactose should not be considered as a filler only as it is in tablets or capsules, but its main function in suppositories is the dispersing of the active substance.

Table 11.4 Chlorpromazine Hydrochloride Suppositories 25 mg [27]

Chlorpromazine hydrochloride	0.025 g
Lactose monohydrate (180)	0.1 g
Hard fat with peroxide value $\leq$ 0.5	q.s.

Table 11.5 Paracetamol and Codeine Suppositories 1000 mg/60 mg [29]

For a suppository mold of at least 2.8 mL:	
Paracetamol (45)	1 g
Codeine phosphate hemihydrate (90)	0.06 g
Silica, colloidal anhydrous (compressed)	0.005 g
Lecithin (NF)	0.06 g
Hard fat	At least 1.8 g

In large-scale preparations of suppositories lactose may be added for another purpose. Sometimes a high dose analgesic suppository has a good structure, while a low dose suppository is brittle. In such case another suppository base may be used. More easily, the volume of the suspended active substance may be increased by adding lactose. This provides a good suppository too. In this case the lactose only acts as filler. Other fillers used in suppositories are sucrose and microcrystalline cellulose [8h].

11.4.6.2 Colloidal Anhydrous Silica

Dispersing of agglomerates may also be achieved by using colloidal anhydrous silica (colloidal silicon dioxide use Aerosil® 200V, the compressed quality). For example, colloidal anhydrous silica facilitates the dispersing of agglomerates in a mixture of paracetamol and codeine phosphate. It should be added in an amount of 0.5 % of the amount of paracetamol, as in suppositories with high doses of paracetamol and codeine (Table 11.5). In general, colloidal anhydrous silica can be added up to a maximum of 1 % of the weight of the active substance.

When silica is used, it should be considered that the release of aqueous soluble to very soluble active substances may be reduced. Silica increases the viscosity of the base which may impair the transport of the active substance to the interface between water and fat, thereby impairing active substance release. For water-soluble active substances, crossing the interface is rate determining (Sect. 16.2.4). For this reason the amount of silica has to be limited to 1 % of the weight of the active substance. A negative influence of anhydrous colloidal silica on active substance release is evident for amounts above 1.5–2 % of the suppository base [8i]. Concentrations above 1.5–2 % are used only for suppositories with an intentionally delayed release profile.

Table 11.6 Suppository Molds

Volume	Application
1.15 mL	Children up to about 4 years
2.3 mL	Standard
2.8 mL	Larger quantities of active substance

11.4.6.3 Lecithin

When large amounts of active substance are incorporated in a suppository, especially when the active substance particles are very small, the viscosity of the melted mass may become so high that it cannot be poured out into the mold. This happens in the preparation of suppositories containing 1,000 mg paracetamol with a particle size of 45 µm and Witepsol H15 as the base (Table 11.5). Adding a small quantity of soya lecithin renders the mass more fluid. In general, 1–2 % of soya lecithin, calculated on the suppository weight, is sufficient [8h], see Table 11.5. A disadvantage of adding soya lecithin is that air gets beaten into the suppository mass more easily [28]. Larger amounts of lecithin may delay the absorption of the active substance (see Sect. 11.3.2).

11.4.6.4 Antioxidants

In pharmacy preparations of suppositories antioxidants are seldom used. If needed, butylhydroxytoluene (BHT) and butylhydroxyanisole (BHA) may be the right choice in fatty suppositories, but see Sect. 22.2.2. These antioxidants are lipophilic and dissolve easily in a fatty base. The usual concentration in fats is 0.02 % [30], see also Sect. 23.9.

11.4.7 Shape and Size of Suppository Molds

Suppositories may appear in various shapes, including a cylindrical, a conical and a torpedo form. The torpedo shape is generally used in pharmacy preparations, see Fig. 11.6. Suppository size varies from 1 to 4 mL. Commonly a size of 2–3 mL is used, for young children usually a size of 1 mL is taken, see Table 11.6.

From a biopharmaceutical viewpoint, a large sized suppository may be advantageous. In principal, a larger volume spreads over a larger intestinal surface. As a result more active substance is released from the base, more active substance dissolves in the rectal fluid and the absorption is faster. This is especially important for substances that are poorly soluble in both fat and water, such as paracetamol. The release of active substance from the base in this case strongly depends on the extent of the interface between fat and rectal fluid available for active substance release. From a technological point of view a large size suppository must be

Table 11.7 Ergotamine and Caffeine Suppositories 1 mg/100 mg [31]

Caffeine	0.1 g
Ergotamine tartrate	0.00105 g
Tartaric acid	0.002 g
Hard fat with peroxide value ≤0.5	q.s.

chosen if a large amount of active substance, such as 1,000 mg paracetamol, has to be incorporated. Even using a 2.8 mL mold, the viscosity of the suppository melt is so high that the addition of lecithin is necessary to allow pouring of the melt into the molds (see Table 11.5).

11.4.8 Stability

Chemical and physical processes may limit the stability of active substance, base and excipients in suppositories. Also the packaging and the conditions and times of storage need attention. Suppositories with a fatty or a macrogol base do not contain water. Therefore bacterial growth is unlikely and preservation is not needed.

11.4.8.1 Chemical Stability

Modern suppository bases usually do not contain water. Hydrolysis of an active substance will therefore seldom be an issue. Oxidation, in contrast, occurs. Oxidative reactions occur in the presence of oxygen and peroxides, under the influence of light and heat and are catalysed by traces of heavy metals, see Sect. 22.2.2. Macrogols (see Sect. 11.4.4) and some types of hard fat may form peroxides under influence of light, air and heat. These peroxides may readily oxidise oxidisable substances such as ergotamine and chlorpromazine which should, therefore, be incorporated in a hard fat (with a low peroxide value). Storage in the refrigerator (2–8 °C) will increase storage times, for example of suppositories with ergotamine and chlorpromazine hydrochloride (see Tables 11.7 and 11.4). Both active substances have to be protected from light as well by choosing an appropriate packaging. Chemical degradation by oxidation increases proportionally with the particle surface area in contact with the base. Smaller particles of an active substance will therefore oxidise more rapidly.

Isomerisation and esterification may be other causes of degradation of an active substance. Ergotamine tartrate, for instance, is very sensitive to isomerisation which in a fatty suppository base, can be limited by adding tartaric acid (see Table 11.7). For esterification effects see Sect. 11.4.4.

Table 11.8 Valproic Acid Suppositories 500 mg [32]

For a suppository mold of at least 2.8 mL:	
Valproic acid	0.5 g
Hard fat	q.s.

11.4.8.2 Physical Stability: Crystallisation of the Active substance

Active substances, and especially those that are partially soluble in the fatty suppository base, may crystallise during storage. Heating the suppository mass before or in the filling process may lead to a partial dissolution of the active substance in the base. A supersaturated solution will be formed on cooling down, with, as a consequence, re-crystallisation and crystal growth during storage (see Sect. 18.4.2.3). This makes particle size uncontrollable. In a macrogol suppository base partially dissolved indometacin may recrystallise at storage, which becomes visible as a spotted appearance. In a fatty base an active substance such as valproic acid dissolves into a higher amount at the preparation process than at storage at room temperature. It is recommended to add this kind of substances to the molten base immediately before the filling process, meaning at the lowest temperature of the melt. The rate of solidification also may influence the physical stability. The longer the solidification process of fatty valproic acid suppositories, the more the valproic acid separates from the solution in visible structures. This may even lead to a 'wet' and grainy suppository tip. Therefore the valproic acid suppositories (Table 11.8) are placed in the refrigerator immediately after the filling process.

In most other suppositories rapid solidification, due to placement of the suppositories into the refrigerator, leads to faults and fractures in the suppositories and should therefore be avoided.

Control of Chemical and Physical Stability, an Example

Indometacin is often formulated in a macrogol base to get a good biological availability [33]. In that base discoloration and esterification may easily occur. Furthermore, the indometacin slowly crystallises giving the suppository a spotted appearance. The antioxidants butyl hydroxytoluene (BHT), butyl hydroxyanisole (BHA) and disodium edetate are added to improve the stability as well as glycerol to limit crystallisation, for instance in Indocid® suppositories (Aspen, UK) [34]. Nevertheless, a fatty base must be preferred. Indometacin is released almost equally from a fatty base as from a macrogol base [8a, 35, 36] and the

(continued)

chemical and physical stability is better in fat. For instance indometacin suppositories (Centrafarm, Netherlands) [37] and indometacin suppositories BP (Actavis, UK) are manufactured with hard fat without additives [34].

11.4.8.3 Physical Stability: Hardening

Further hardening of suppositories on storage (secondary hardening or ageing) may change the crush strength (resistance to crushing) and the melting behaviour. This may be relevant for the therapeutic effect [38, 39]. The secondary hardening process of the suppository base is caused by a further conversion from the liquid phase to the solid phase and by a slow transition into modifications with a higher melting point. These changes usually cause crush strength to increase. They also lengthen the melting time, resulting in a slower release of the active substance. Secondary hardening of suppositories may be limited by cool storage, after sufficient initial hardening. Therefore, suppositories should generally be stored in a cool place.

11.4.9 Packaging

For the packaging of suppositories the chemical and physical properties of the active substance and the base have to be considered. This should be done with respect to sensitivity to oxygen and light, compatibility with the (plastic) package, material evaporation (chloral hydrate) and hygroscopicity (macrogol and different active substances).

Suppositories are preferably dispensed in the plastic disposable molds in which they have been filled (see Sect. 24.4.10). The molds are placed in a carton. An alternative is a well-closed container, a glass or plastic jar, protecting the content against the influence of light and air (see Sect. 24.4.7). Such a jar is needed for instance for suppositories with a macrogol base, such as those with chloral hydrate (Table 11.1). These hygroscopic suppositories remain dry in the plastic strip (mold) placed in a glass jar, while in the plastic strip placed in a carton they become wet. Even with no plastic strip and placed in a glass jar these suppositories become wet and stick together. The upper surface of the plastic strip with macrogol suppositories may be taped before they are placed in a carton, but this is not always sufficient to prevent the suppositories getting wet. Suppositories that are not molded in a plastic strip should always be packed in a light and air resistant jar. For arthritic patients it is impossible to open plastic strips, which makes dispensing the suppositories out of the strip in a glass or plastic jar necessary.

11.4.10 Storage

Shelf life of pharmacy preparations depends on the character and stability of the preparation and has a maximum of 3 years as is explained in Sect. 22.7.1. Generally, physically and chemically stable suppositories have an expiry date of 3 years after preparation, both in strips in a carton or without strip in a jar. It may be convenient to split up this period in 24 months in the pharmacy and 12 months for use by the patient.

Suppositories prepared as extemporaneous preparations following a non-standardised formula, having an unknown chemical or physical stability, should immediately be dispensed to the patient who gets a maximal usage period of 1 month only (see Sect. 22.7.2) if classified as semisolid preparation. If the patient only takes a suppository ‘on demand’ a usage period of 1 month is very short and it may be justified to consider them to be comparable to a dry dosage form with an arbitrarily chosen maximum usage period of 6 months.

For standard preparations the storage conditions and the maximum shelf life are determined in the design phase and stated in the formulary.

11.4.11 Labelling

Section 37.3 gives the general requirements for labelling. There should be a clear indication how to use the dosage form, for instance ‘for rectal use’ or ‘(rectal) suppositories’ as well as how to take a suppository out of the plastic strip. This requires some expertise and strong hands as well.

The correct way to use and insert the suppository should be explained in a patient information leaflet. A Dutch leaflet advises the patient to insert the suppository while lying in a lateral position with the upper knee flexed. After the suppository has been inserted the patient should stay in the horizontal position for 5–10 min, if possible. Another position is bending forward or squatting (sitting on the heels) while inserting the suppository. The patient should insert the suppository (torpedo) tip into the anus and then push the suppository with his finger until that finger is about 2 cm in the anus (for children 1 cm). However, insertion of the suppository with the blunt side forward is reported to have real advantages [40]. There is no need to introduce a finger into the anal canal. The external anal sphincter constricts physiologically better around the tip of the suppository and following this method the patient will better retain the suppository. It is also not necessary to stay horizontal after insertion.

Whatever the method of insertion, the instruction should mention that the rectum is better empty before insertion and thus free from stool. The patient should go to the toilet first if necessary.

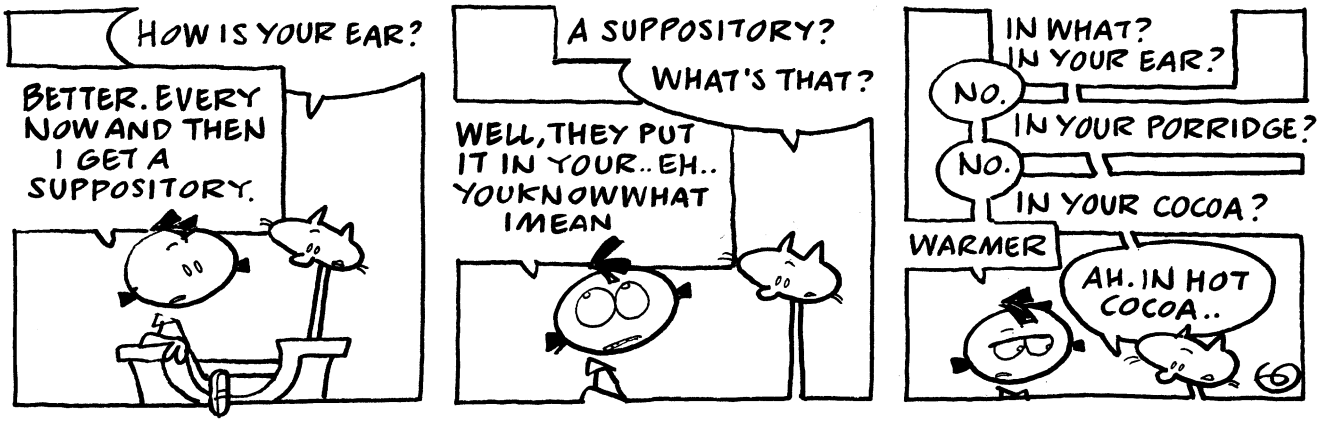


Fig. 11.3 Patient information should be bright and clear. Copyright Gerrit de Jager [41]

To minimise the burning sensation of macrogol suppositories it is often suggested to moisten the suppository prior to insertion. The authors do not expect this will prevent irritation of the mucosa, because the macrogol attracts much more water after being inserted than supplied by moistening. But it might facilitate insertion of the suppository (Sect. 11.4.5).

When dispensing suppositories to the patient he or she should be fully informed about the use. Frequently, patients are insufficiently aware of how to handle a suppository (Fig. 11.3).

11.5 Method of Preparation, Fat-Based Suspension Suppositories

The method of preparation particularly depends on the physico-chemical form of the suppository: a solution or a suspension of the active substance in the base. The nature of the base is of less importance for the preparation method. The most frequently occurring suppository is the fat-based suspension-suppository. The preparation of a suspension suppository is more critical than a solution suppository and therefore requires special attention.

First the calculation of the required quantity of base and the necessary excess is dealt with. Next the preparation steps, dispersing, mixing and pouring, are discussed. These steps are important for a homogeneous distribution of the active substance over the suppositories, its content uniformity (see Sect. 32.7.2). For a homogeneous distribution the so-called squeeze bottle method, has proven to be more effective than more well-known methods. In this method a plastic bottle with a straight nozzle is used, called squeeze bottle. Figure 11.4 surveys suitable combinations of dispersing and pouring methods for small batches of suppositories [42]. The last processing step includes cooling and finishing the suppositories.

11.5.1 Calculation of the Required Base

Most active substances possess a higher density than the suppository base. As a result, if dispersed in the base a weight quantity of active substance occupies less volume than the same weight quantity of base. The ratio between both densities is designated as the dosage replacement factor f:

$$f = \frac{\text{density of suppository base}}{\text{density of active substance}} \qquad (11.1)$$

The density of Witepsol H15, as determined after processing the base as in the preparation process of suppositories, is 0.92 and differs from the density of 0.96 as specified by the manufacturer [8k]. In many cases the density of active substances is unknown. When a dosage replacement factor is calculated, it is important that the active substance is insoluble in the base and perfectly wetted by the base. In practice the base is not only replaced by the active substance but also by the air stuck to the active substance. Therefore a dosage replacement factor should be determined experimentally. Generally however, for low concentrations of active substances in hard fat suppositories, a replacement factor of 0.65 can be taken for most organic active substances. Similarly a factor of 0.85 is valid for a macrogol base. The estimated replacement factors cannot be used with high concentrations: in the case where the quantity of active substance exceeds 125 mg in a 1.15 mL suppository, 240 mg in a 2.3 mL suppository and 300 mg in a 2.8 mL suppository. These amounts are based on calculation of the possible deviation in active substance content. For those high concentrations the actual replacement factor has to be determined experimentally [28]. Inorganic active substances have strongly deviating replacement factors that should be determined as well for each individual substance. The determination of replacement factors shows much variation if

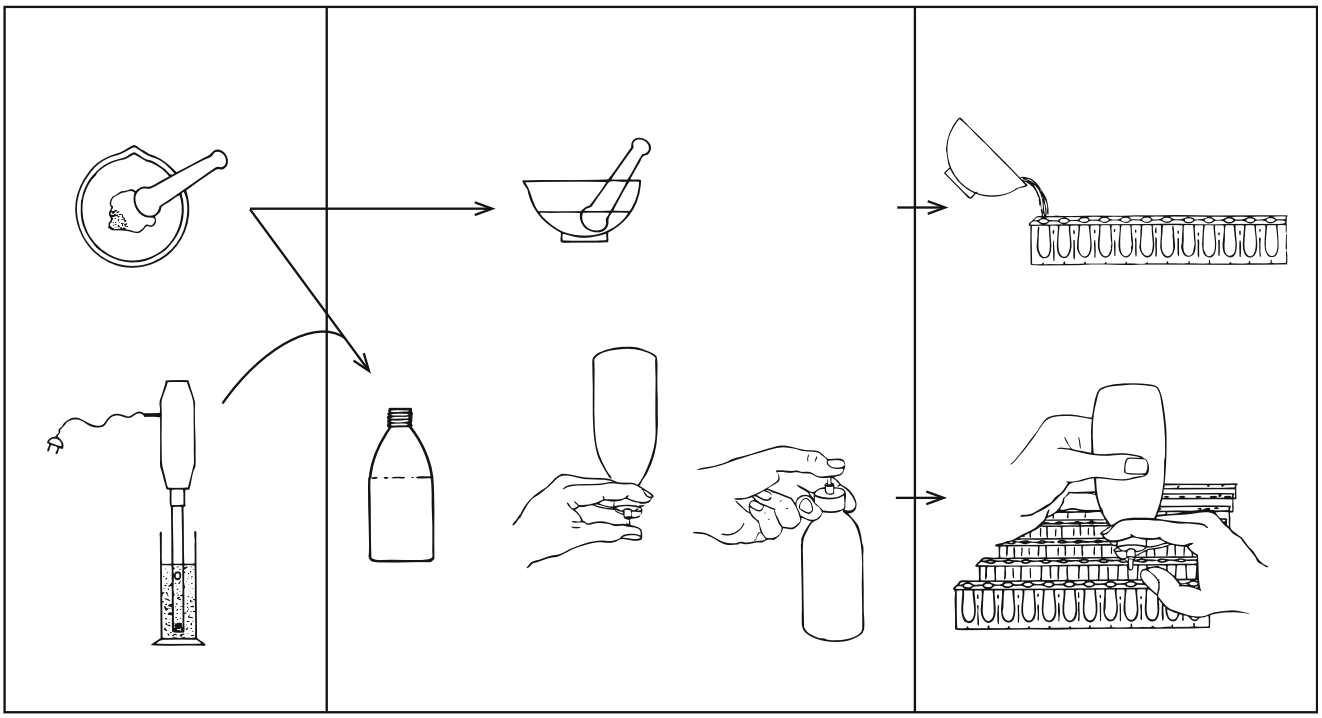


Fig. 11.4 Combinations of dispersing, mixing and pouring methods in the preparation of small batches of suppositories. The bottle used for pouring is a plastic bottle with a straight nozzle (Sect. 11.5.5), called squeeze bottle. Source: Recepteerkunde 2009, ©KNMP

Table 11.9 Replacement factors in Hard Fat

Active substance	Replacement factor
Acetylsalicylic acid (180)	0.65
Atropine sulphate	0.65
Bisacodyl	0.65
Bismuth compounds	0.3
Caffeine	0.60
Chlorpromazine hydrochloride	0.65
Codeine phosphate hemihydrate (90)	0.65
Cyclizine hydrochloride	0.70
Ergotamine tartrate	0.65
Lactose monohydrate (180)	0.60
Lidocaine	1.0
Mesalazine	0.55
Morphine hydrochloride	0.65
Paracetamol (45)	0.65
Pethidine hydrochloride	0.65
Progesterone	0.85
Silica, colloidal anhydrous, compressed	0.65
Soya lecithin (NF XVII)	0.9
Tartaric acid	0.65
Valproic acid	1.0
Zinc oxide	0.25

there is little experience with this method. In that case a replacement factor taken from literature is preferred. Replacement factors of some organic and inorganic substances in hard fat are given in Table 11.9.

If a dosage replacement factor cannot be found in literature it has to be determined. This may be done as follows:

- Prepare a suppository mass using a large proportion of active substance, for instance 1 (mass) part of active substance and 2 parts of base. The amount of mass must be sufficient to fill 10 mold cavities of 2.3 mL for about three-quarters. Beforehand, the weight of the used (stainless steel) mortar, pestle and ointment cards (scrapers) is recorded.
- Fill every mold three-quarters full, the tenth one for as far as there is suppository mass left. Then weigh again mortar, pestle and scrapers.
  Prepared mass – loss of mass on utensils = mass in 10 molds.
- Amount of active substance present in 10 molds = mass in 10 molds × 1/3 (= A).
  Average amount of active substance per suppository = A/10 (= a).

- Next, just before the mass solidifies, top up the 10 partially filled molds to completion with pure base (melted in a clean stainless steel mortar) with a slight excess. After solidification scrape off the excess of mass.
- Weigh the 10 suppositories together (= B).
  Amount of suppository base in 10 molds = B – A; per suppository = (B – A) /10 (= c).
- Compare c with the average blank weight of this base in this mold (= d).
- The amount of base displaced by the active substance (per suppository) = d – c (replacement value).
- The dosage replacement factor f is the displaced amount of base per gram of the active substance, so f = (d – c)/a.

The amount of base required for suppositories with active substances and excipients can be calculated as follows:

$$\text{required base} = n\,x\,[(\text{blank weight mold}) - (f_1\,x\,AS_1) - (f_2\,x\,AS_2) - (f_{e1}\,x\,E_1) - (f_{e2}\,x\,E_2)] \quad (11.2)$$

About Dosage Replacement Factor, Density Displacement Factor and Displacement Value

In textbooks about suppository preparation not only dosage replacement factors are used but there are also tables with density factors and displacement values. The relation between these terms needs to be clarified.

The dosage replacement factor (f) of an active substance is the number of parts by weight of hard fat displaced by one part of the active substance.

The density displacement factor (DDF) of an active substance is the number of parts by weight of the active substance that displaces one part of hard fat [43] and is therefore equal to 1/f.

Regularly, for the dosage replacement factor (f) other terms are used, for example replacement factor, dose-replacement factor and even displacement factor. The density displacement factor (DDF) is frequently called displacement value; the terms displacement factor and density factor are used too. To recognise what authors mean, it is good to realise that mostly $f \leq 1$ and $DDF = 1/f \geq 1$.

Sometimes *the replacement value* is used. This is the weight of base displaced by the active substance (per suppository). Used is also the term displacement value. The replacement value is calculated by multiplying the weight of active substance per suppository by the dosage replacement factor or by dividing the weight of active substance per suppository by the density displacement factor [44].

This seems a real labyrinth of terms, but frequently the right term may be distilled from the context.

In this equation the weight of active substances (AS) and excipients (E) is given per suppository and n is the number of suppositories to be prepared.

For this calculation the blank weight for the suppository mold used should be known. This is the weight of a suppository processed in the given mold consisting of the designated base only and given in terms of gram of base. It is obtained by filling the mold with the particular suppository base, cooling down, scraping off the excess of base, and then weighing the suppositories and calculating the average weight. The blank weight obtained with one type of hard fat may be used for all types of hard fat. The blank weights of standard suppository molds (FNA) in the Netherlands are given in Table 11.10 for hard fat and for macrogol.

11.5.2 Excess

For extemporaneous preparation of a fixed number of suppositories, each containing the right amount of active substance, a sufficient excess of the suppository mass has to be prepared. An excess of mass is not required if the suppositories are filled serially for stock preparation, because there is no need to deliver a precise number of suppositories. In that case it is only necessary to know how many of the first or finally filled suppositories are to be rejected because of unreliability of the content of these suppositories.

The excess of mass is needed for the following reasons:

- There is a loss off mass during the preparation. This is due to the fact that the mass can never be transferred quantitatively, because it sticks to the utensils and because the molds are filled with a slight excess.
- During the serial filling procedure the suspended active substance will easily settle. Optimal stirring or mixing is difficult, because appropriate utensils and a sufficient mass is necessary for effective stirring. Therefore, despite frequent stirring or mixing, a content gradient will easily occur within a single batch. Extent and character of the gradient are determined by the pouring method (from a mortar, squeeze bottle (Sect. 11.5.5), or suppository molding machine), by the particle size of the active substance, the effectiveness of dispersion, the size of the batch, the mixing method before and especially during

Table 11.10 Volume and Blank Weight of FNA Suppository Molds

Volume (mL)	Blank weight (g) hard fat [28]	Blank weight (g) macrogol[a]
1.15	1.07	1.32
2.3	2.07	2.54
2.8	2.61	3.16

[a]1 part macrogol 1500 and 2 parts macrogol 4000

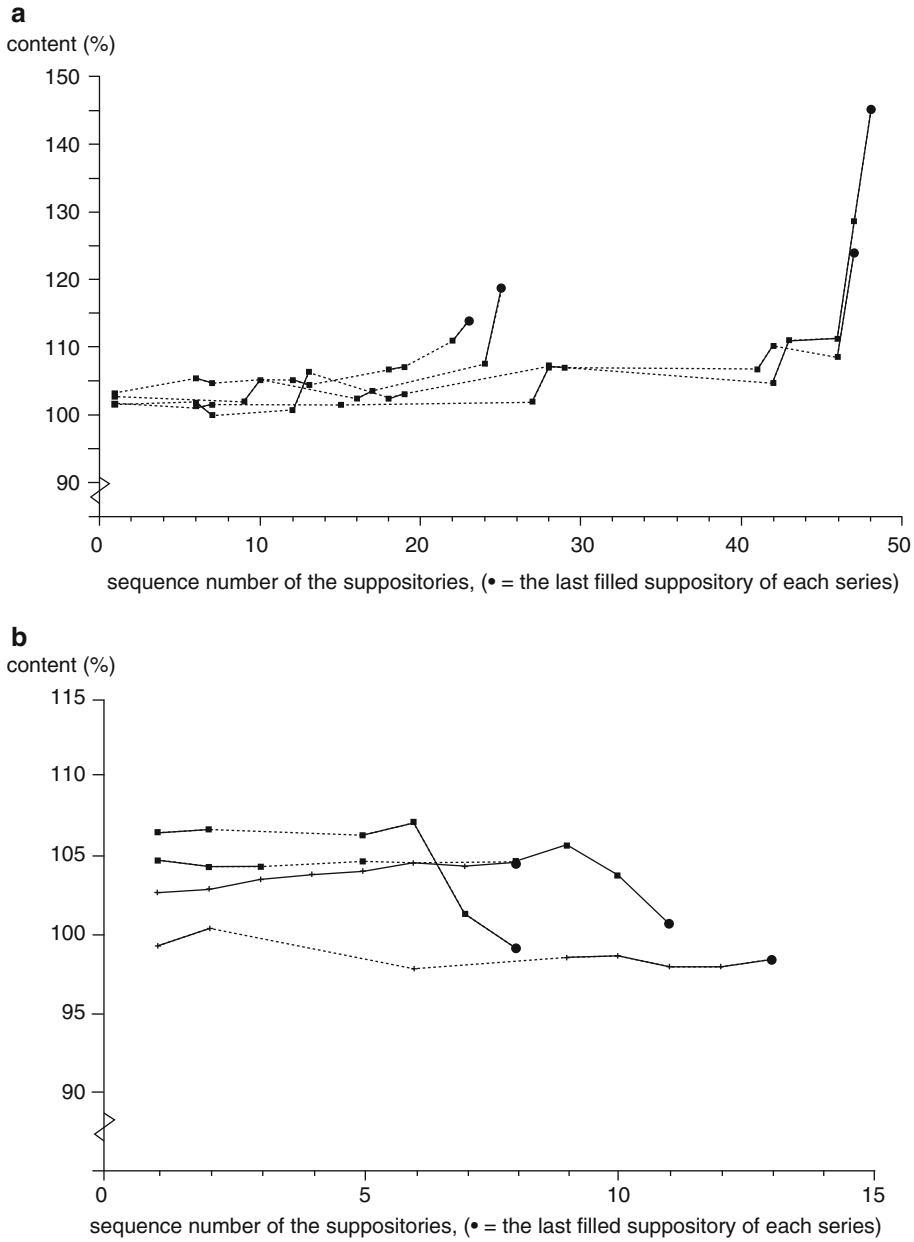


Fig. 11.5 Course of content during filling processes. (**a**) Course of content in suppositories with Acetylsalicylic acid (180) 200 mg, when pouring from a mortar under frequent stirring, following on dispersing with mortar and pestle (suppository mass for 26, 28, 52 and once more 52 suppositories, volume 2.3 mL, no excess of mass) [45]. (**b**) Course of content in suppositories with (■) Acetylsalicylic acid (180) 100 mg or (+) Paracetamol (45) 100 mg, when pouring from a squeeze bottle under frequent homogenising, following on dispersing with mortar and pestle (suppository mass for 10 and 14 suppositories with acetylsalicylic acid and for 10 and 15 suppositories with paracetamol, volume of both suppositories 1.15 mL, no excess of mass) [45]. X-axis: number of the suppositories, (●) is the last filled suppository of each series; Y-axis: content as %. Source: Recepteerkunde 2009, ©KNMP

the filling process, and by the filling ratio[1] of the squeeze bottle. Some examples of the content variation in the filling process are given in Fig. 11.5. When pouring from a mortar or, less obviously, from a squeeze bottle, a sudden, large deviation is observed in the content of the last-filled one or two suppositories. This in spite of pouring the mass only as long as it flows freely, so without scraping the mass out of the mortar. Therefore a number of suppositories has to be rejected, which has to be fixed when validating the preparation method [45].

- When suspension suppositories are molded in a composite metal mold with cadre, the entire mass is poured out over the mold at once. An excess of mass is needed to be able to divide the mass quickly enough over all cavities before the active substance settles.
- With all methods of preparation some suppositories may have to be rejected because of insufficient appearance or breaking.

Taking into account the mentioned loss of mass and possible content variation, Table 11.11 presents the required excess of suppositories for increasing batch sizes. This table is based on relatively fast settling substances such as acetylsalicylic acid (180) and cyclizine hydrochloride (180). For instance in paracetamol (45) the content variation

[1] Filling ratio means the ratio between the used volume of suppository mass and the nominal volume of the bottle.

Table 11.11 Excess for small batches of Suppositories

Volume	Number to be dispensed	Batch size (number to be dispensed plus excess)		Advised methods	
				Dispersing	Pouring
1.15 mL	6	11	(6 + 5)[a]	Hand	Mortar
	10	16	(10 + 6)[a]	Hand	Mortar and squeeze bottle
	20	28	(20 + 8)	Hand	Squeeze bottle
	≥30	≥41	(30 + 11)	Hand and rotor-stator	Squeeze bottle
2.3 mL	6	10	(6 + 4)	Hand	Mortar
2.8 mL	10	15	(10 + 5)	Hand	Mortar and squeeze bottle
	20	26	(20 + 6)	Hand	Squeeze bottle
	30	40	(30 + 10)	Hand and rotor-stator	Squeeze bottle
	40	49	(40 + 9)	Hand and rotor-stator	Squeeze bottle

[a]These batches are too small for suppository molds of 1.15 mL. Without adjustment of the preparation method, a minimum batch size of 20 must be taken

as a result of sedimentation could hardly be observed (Fig. 11.5). For non-standardised preparations this 'worst case' table is a good guideline. For standard preparations it might be worthwhile to investigate, for each preparation, whether a smaller excess will do just as well. If less than 20 suppositories of 1.15 mL are prepared the loss of melted base is relatively high, caused by transference of the melted base to the active substance in the mortar. As a result, the suppositories obtained do have a too high content of active substance. Therefore it is necessary either to maintain a minimal batch size of 20 or to adjust the preparation method. In the latter case an excess of suppository base should be melted and transferred to the active substance in the mortar until the right weight of mass in the mortar is obtained.

11.5.3 Dispersing Methods

In the preparation of suspension suppositories it is important that the used particles of the active substance are small and remain small (don't reagglomerate). Small particles being essential for a correct content and a sufficient content uniformity of the suppositories, dispersion of the active substance in the suppository base will usually be preceded by or combined with particle size reduction, see Sects. 29.2 and 29.3). Large primary particles should be ground and agglomerates should be broken up. If an active substance is not available in the required particle size, the coarse powder must be ground in a rough stone or porcelain mortar. Active substances kept in stock in the required primary particle size commonly contain agglomerates. Usually the agglomerates are pulverised by rubbing the active substance with an almost equal volume of some other substance. This might be a solid, such as another active substance, colloidal anhydrous silica or lactose monohydrate (see Sect. 11.4.6). This 'dry' technique is called trituration. More often a semisolid substance or a liquid is used, generally a small quantity of the molten base. Only when rubbed into the smallest possible quantity of molten base the lateral shearing forces are sufficient to break up the agglomerates effectively. This 'wet' technique is frequently called levigation, but the term trituration is more common. In these techniques, with another solid or with some molten base, the primary particles remain separated, dispersed in the mixture. The agglomerates should not be reduced by rubbing the active substance on its own. This enhances static charging, giving even more agglomerates [42]. Which method should be chosen for particle size reduction and dispersion depends particularly on the batch size.

11.5.3.1 Dispersing with Mortar and Pestle

For small batches it is a good choice to break up the agglomerates in a plastic or stainless steel mortar with a plastic pestle. The agglomerated active substance may be triturated with some other solid substance or with no more than an equal volume of molten base. After trituration with a solid, the mixture is incorporated in the molten base, at first in an equal volume, thereafter the remaining base is added part by part (geometric dilution, see Sect. 29.4.4).

Two or more agglomerated solid substances, not suited for 'dry' trituration, are roughly mixed before trituration with some molten base. Once more a plastic or stainless steel mortar is used, but with a scraper instead of a plastic pestle. Thereafter the mixture is rubbed, with no more than a half to an equal volume of molten base, in the same mortar, but now again with a plastic pestle.

The mass is visually checked for homogeneity. The mortar and pestle method to break up the agglomerates is usually very effective. However, if agglomerates remain once the rest of the suppository base has been added, they cannot be broken up anymore. In that case one has to start again with new amounts of substances. Usually such inadequate break up is caused by using too much molten base or by improper rubbing.

Certain fat based suppositories formulations contain a lipophilic liquid, such as Miglyol 812 in zinc oxide suppositories (see Table 11.2). Such a liquid is very useful for trituration and cannot solidify in the meantime, as a molten suppository base often does.

The suppository base should be warmed on a water bath or heating plate to a maximum temperature of 40–45 °C. Solidifying (and remelting) during dispersion and mixing should be avoided as much as possible by working

sufficiently fast. Choosing a higher temperature for the melt is not a good alternative, regarding the stability of base and active substance.

11.5.3.2 Dispersing with a Rotor-Stator Disperser

For larger batches the agglomerates are more effectively disintegrated with a rotor-stator disperser (see Sect. 28.6.2). A high and narrow vessel must be used, because the distance between liquid surface and dispersing element should be enough to limit air impact. Usually a graduated cylinder will be appropriate. A glass cylinder breaks easily; especially contact with the heating element of the water bath should be prevented. Plastic cylinders are unbreakable, but in plastic the melting and cooling of the fatty base takes more time than in a glass vessel. The effectiveness of the dispersion process is also more difficult to monitor in a plastic vessel. Because melting and dispersing may be done in the same vessel, the rotor-stator method results in a smaller loss of pure suppository base. For small batches the loss of suppository mass is larger with the rotor-stator method. However, unlike loss of pure base, loss of mass does not influence the content of active substance in the suppositories [45]. When dispersing with the rotor-stator method the active substance or the mixture of active substance and excipients is usually added all at once to the entire amount of base. This is followed by pre-blending, by stirring the mass with a spoon. If a squeeze bottle is used, pre-blending may be done by swinging the bottle around gently, to minimise air enclosure. Thereafter the dispersion will be achieved using the rotor-stator disperser. To monitor the effectiveness of the dispersion process (in-process control) the dispersing element is raised from the mass and checked for agglomerates. Alternatively a sample may be taken from the bottom of the dispersion vessel (with a spoon) and checked for agglomerates. Using a squeeze bottle as dispersion vessel the presence or absence of agglomerates is checked by holding the bottle against the light and turning it slowly upside down. The real advantage of the rotor-stator method is that insufficient dispersion can be corrected, at any moment, by continuing the dispersing process. Disadvantages of the rotor-stator method are a greater risk of air enclosure and a disappointing mixing.

11.5.4 Mixing Methods

After dispersing the active substance with mortar and pestle, the remaining suppository base should be added and thoroughly mixed. After dispersing with the rotor-stator disperser all base has already been added, but the mass still needs to be mixed well.

11.5.4.1 Mixing with Mortar and Pestle

A stainless steel or plastic mortar is used, the same in which active substance and excipients, if any, were dispersed. After disintegration of agglomerates with a minimum quantity of molten base, the remaining base should be admixed using the geometric or doubling-up technique (see Sect. 29.4.4). Mixing should be done gently and without entrapping too much air. Entrapment of too much air results in a too low suppository weight thus containing an insufficient quantity of active substance. Mixing with mortar and pestle is not very effective because in a mortar the mixing in a vertical direction is difficult (see Sect. 28.6.4). If the mass, after the mixing, is put into a squeeze bottle for filling the molds, the insufficient mixing does not matter, because the mass can be perfectly mixed by turning the squeeze bottle several times upside down and back again. However, when the mold is filled directly from the mixing mortar, there is a risk of insufficient content uniformity (see Fig. 11.5).

11.5.4.2 Mixing in a Squeeze Bottle

In a squeeze bottle mixing occurs by gently turning the bottle upside down and back again. At the filling of the molds the mass should be mixed at every 2–3 suppositories. Do not shake the bottle because too much air may be entrapped.

11.5.4.3 Mixing in a Suppository Filling Apparatus

In a suppository filling machine the effectiveness of the mixing process depends on the construction of the stirring device (see Sect. 28.7.2).

11.5.5 Pouring the Melt: Methods

After the active substance and excipients have been dispersed in and completely mixed with the suppository base the mass should be poured into the molds. The molds can be filled serially (one by one) or simultaneously (all cavities at once). For serial filling usually plastic strips are used (Fig. 11.3). When using a composite metal mold with cadre or a bearer with a number of strips, 100 cavities can be filled simultaneously. Such metal molds are composed of 10 elements of 10 cavities. Once fixed together a cadre is placed over the mold (Fig. 11.6) and all the mass is poured out at once.

While filling the molds, the suppository mass should be kept homogeneous and at a nearly constant temperature, which requires agility. This is especially important for serial filling and a key issue in the product quality assurance of suspension suppositories. The squeeze bottle is a good help for a fast and homogeneous serial filling. Figure 11.7 pictures the squeeze bottle and other pouring methods that will be dealt with in this section and Table 11.12 compares the suitability of the different pouring methods for different batch sizes.

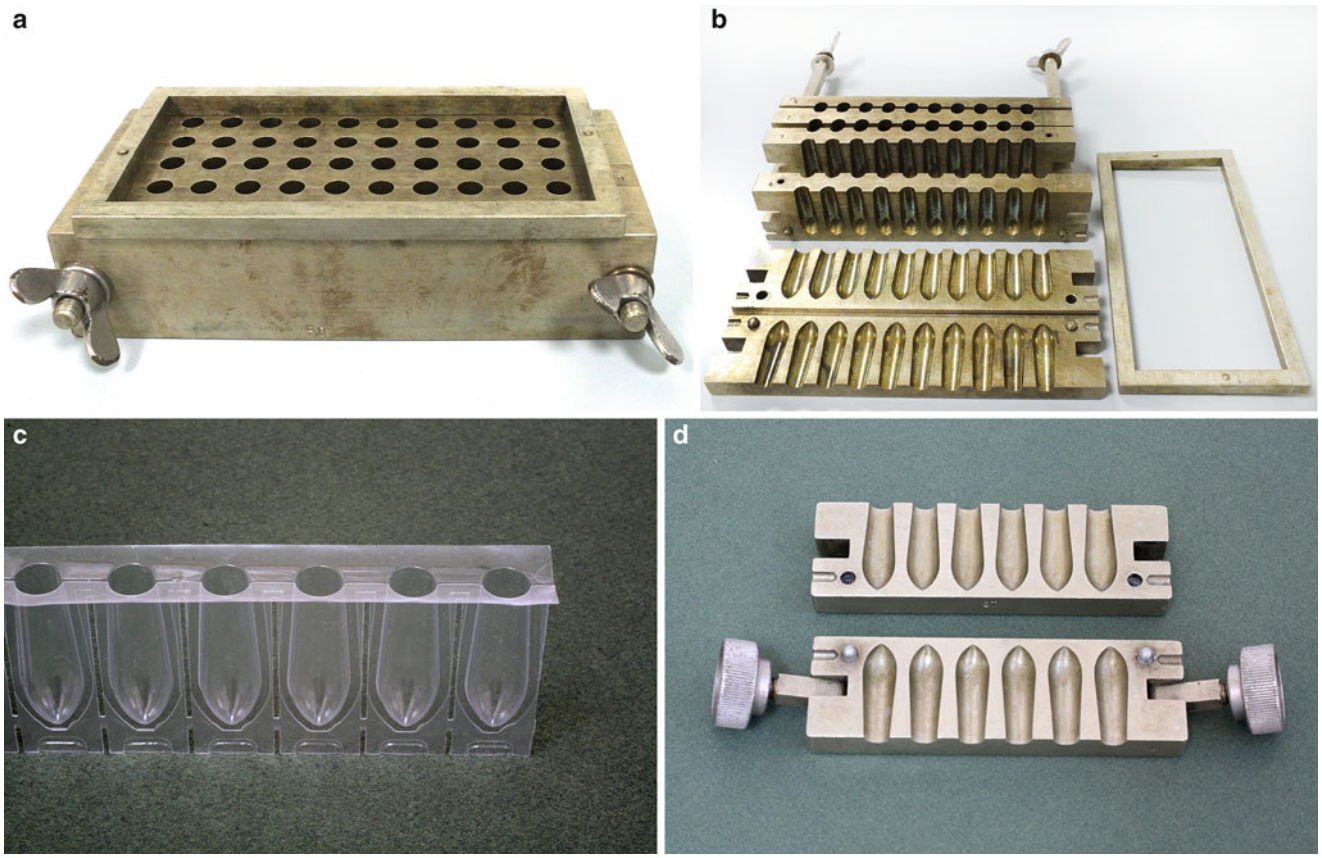


Fig. 11.6 Suppository molds: composite metal mold with cadre for 50 suppositories (**a** and **b**); disposable plastic strip for 12 suppositories of ca 3 g (**c**); single metal mold for 6 suppositories of 3 g (**d**). Copyright Rijksuniversiteit Groningen

Table 11.12 Comparison of Different Pouring methods

Pouring method	Optimal batch size	Reliability	Ease of preparation	Yield
Mortar series	<24	−	±	−
Squeeze bottle series	12–200	+	+	±
Composite mold	20–100	±	+	±
Strips in frame	36–120	±	+	−
Machine, hand	>250	+	±	−
Machine, semi-automatic	>250	+	+	+

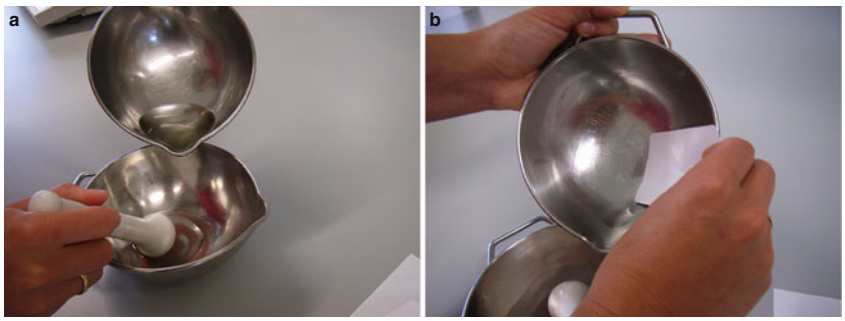
When a filling method is used that is not or less adequate for the batch size, extra attention has to be paid to a proper implementation. Each filling method must be validated. For serially filled suppositories a determination of the active substance content in the first and the last filled suppositories is required, see also Fig. 11.5. In case of serial filling the last filled suppositories have to be rejected. Each cavity must be filled to slightly overflowing because the suppository mass shrinks upon solidification. In simultaneous filling, when the mass is poured out at once as in filling a metal mold with cadre, a sufficient excess of mass has to be prepared to ensure a swift filling of all cavities.

11.5.5.1 Pouring from a Mortar

A stainless steel mortar with a good pouring spout permits convenient pouring of the melt into the cavities of the mold. Using a mortar, frequent stirring is essential but cannot entirely prevent sedimentation of active substance during the filling process. To avoid large deviations in the content, this method must be limited to small batches (up to 24 suppositories) and, as already stated, much attention must be paid to monitoring. If the mass is kept insufficiently homogeneous during filling, the content of active substance will show an increase from the first filled suppository to the last.

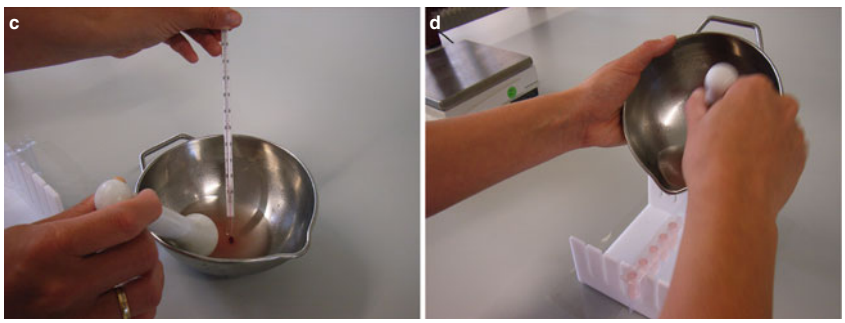
Pouring from a mortar usually follows on dispersing and mixing with mortar and pestle. The recommended pouring (filling) temperature is 33–34 °C. The pouring temperature should not be too low as all cavities must be filled without reheating in between, because a premature solidification of the mass may impair product quality. When the mass solidifies prematurely, it must be reheated until it is completely homogeneous again. This is not easy to monitor and the mass may remain inhomogeneous or the temperature of the mass may become undesirably high. Moreover, not all active substances

Preparing batches, up to about 100 suppositories, by dispersing with mortar and pestle:



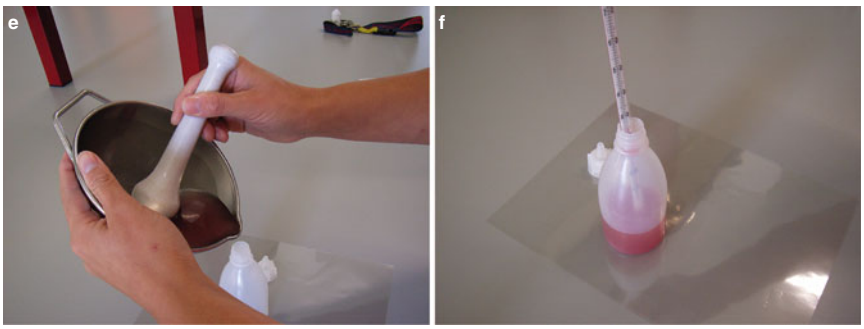
a dispersion of the drug substance(s) by triturating with a half to equal volume of molten base
b addition of the remaining base, followed by thorough mixing of the mass by stirring with the pestle

Preparing small batches, up to 24 suppositories to deliver, by pouring from the mortar:

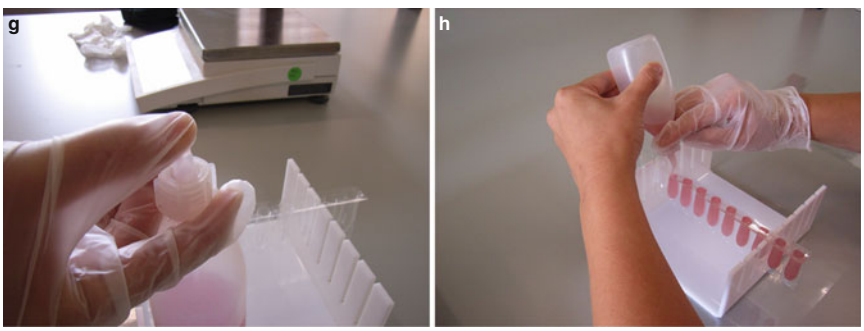


c waiting while stirring until the mass has reached the recommended pouring (filling) temperature (IPC → record)
d filling the mold while stirring frequently, which means stirring after every 2 or 3 suppositories

Preparing larger batches, 12–200 suppositories, by pouring from a squeeze bottle:



e filling the squeeze bottle
f waiting until the mass has reached the recommended pouring (filling) temperature (in-process control (IPC)→ record)



g mixing the mass by keeping the thumb in place while turning the bottle a few times upside down and back again;
h for filling the mold, the thumb is off and the fingers of the other hand squeeze the bottle; to keep the mass homogeneous, mixing is done every 2 or 3 suppositories by replacing the thumb and turning the bottle 2 times upside down and back again

Fig. 11.7 Small scale suppository preparation visualised. Copyright Rijksuniversiteit Groningen

are sufficiently stable if heated again. Pouring from a mortar, the mass meant for the last suppositories will often contain too much active substance, due to sedimentation. Starting with a sufficient excess of mass (see Table 11.11) the filling of the mold can be stopped when the number to be delivered is reached (plus one in excess for each 20 suppositories regarding breaking). The content of active substance in the remaining mass is usually too high, see Sect. 11.5.2. So never use the last drop of the suppository mass!

11.5.5.2 Pouring from a Squeeze Bottle

A flexible plastic bottle with a straight nozzle, a so called squeeze bottle, pointed out, has been shown to be very suitable for the serial filling of suppository molds [45].

After dispersing active substance and excipients in the molten base, the mass is transferred to a lukewarm squeeze bottle. For optimal mixing conditions, the nominal volume of the bottle may only be used for 30–80 %. Adhesion of the active substance to the wall of the squeeze bottle is limited by using a bottle that is not too large for the volume to be poured. However, the bottle should be large enough to allow mixing. After sufficient mixing, by gently turning the bottle a few times upside-down and back again, the suppository mass can be poured into the molds at about 34–35 °C. The bottle is held in one hand, the thumb closing the nozzle and moving away for filling, while the bottle is squeezed with the other hand, see Fig. 11.7. The molds are slightly overfilled. During the pouring process the mass must be kept homogeneous by turning the bottle 2 times upside-down and back again, every 2 or 3 suppositories. The squeeze bottle method is suitable for batches of 12–200 suppositories. When less than 12 suppositories are prepared the loss of mass would be too large.

As with pouring from a mortar the filling of the mold should be stopped when the number of suppositories to be delivered is achieved plus 1 per 20 for loss due to e.g. breaking.

For stock preparations – when no fixed number of suppositories have to be dispensed - pouring may be continued until all mass has been used, but the last filled suppositories will have a low active substance content (see Fig. 11.5). The last 2 suppositories usually do not meet the requirements and in batches of more than 100 even the last 4.

As in pouring from a mortar, also in pouring from a squeeze bottle premature solidification of the mass is a problem. To prevent this problem occurring, the pouring temperature has to be chosen while taking the batch size and the ambient temperature into account. Usually 36 °C is satisfactory for molding a batch of about 100 suppositories without premature solidification and 34–35 °C is high enough for smaller batches.

11.5.5.3 Filling a Composite Metal Mold with Cadre

This method may be used for 20–100 suppositories. Metal molds should be equilibrated at room temperature before they are used, thus preventing the occurrence of fractures and fissures by a too rapid temperature decrease of the suppository mass. Keeping the mass homogeneous while filling the mold, being a critical point in other pouring processes, is very easy to achieve when a composite metal mold with cadre is filled. It is important, however, to fill the mold in one flow. Immediately after having been poured out on the mold all at once, the mass must be distributed as fast as possible over the cavities by the aid of a scraper. When working too slowly, the first filled suppositories will contain too much and the latest ones too little active substance. This is caused by settling of the active substance. To be able to fill the cavities fast enough a sufficient excess of mass should be used.

11.5.5.4 Filling Molds with a Suppository Filling Apparatus

A suppository filling machine enables a serial filling of large quantities of suppositories. The apparatus and its use are described in Sect. 28.7.2. A manually operated machine keeps the mass automatically homogeneous. The tap is operated manually as is the movement of the plastic suppository strips. An automatic machine fills the plastic molds automatically and often transits them too. The filling process of a suppository filling machine always has to be validated. The content of both the first and the last suppositories may not meet requirements.

11.5.6 Choice of Preparation Method

Tables 11.11 and 11.12 give the method of preference of dispersing and pouring in relation to the batch size. Using (stainless steel) mortar and (plastic) pestle for dispersing and pouring gives the least reliable results. This is due to the fact that sufficient homogeneity of the mass is difficult to achieve during the filling of the molds from a mortar. Therefore, if more than 12 suppositories have to be supplied, a squeeze bottle is a good choice for pouring.

The rotor-stator disperser is better reserved for batches of 50 and more suppositories. Smaller batches frequently trigger problems in finding appropriate utensils, in loss of mass and in premature solidification.

11.5.7 Choice of Pouring Temperature

First, a proper pouring temperature has to be chosen to assure that the mass will not solidify during the filling

process (pouring). Moreover the pouring temperature also determines whether the active substances will settle within the suppositories or not.

Choosing the lowest possible temperature for pouring shortens the solidification time and consequently the period in which the active substance may settle. A low temperature would also benefit the homogeneity during the filling process if the suppository base would be more viscous at this lower temperature. In practice this effect on base viscosity is not often seen (see Sect. 11.4.4) and therefore it is not a valid issue in relation to the filling process.

A great risk of a lower pouring temperature is the tendency of the mass to solidify during filling. As said, reheating the mass often leads to an unnecessarily high pouring temperature or – in case of insufficient reheating – to an inhomogeneous mass. Therefore the pouring temperature should be high enough to ensure that all cavities can be filled without reheating. The distribution in the suppositories will probably not be ideal. But content uniformity goes beyond a uniform distribution in the suppositories.

The rate of solidification also depends on the material of the mold. In a metal mold the mass cools down more quickly than in a plastic strip. In plastic strips hanging closely together the mass takes even longer to cool down.

Solidification Range

Choice of pouring temperature also has to do with the behaviour of the suppository base upon cooling. For hard fat the temperature – time relation is shown in Fig. 11.8.

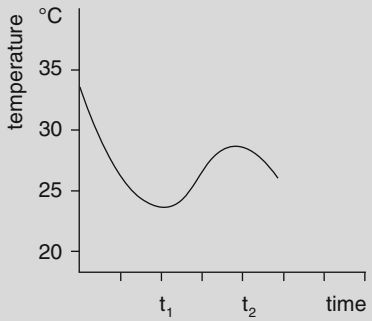


Fig. 11.8 Illustration of the temperature - time relation while cooling a suppository base of the Adeps solidus type. Source: Recepteerkunde 2009, ©KNMP

On cooling down of a suppository mass, the temperature first decreases until it reaches a minimum (time = t_1) while the mass remains liquid, meanwhile supercooled. From that moment the solidification process starts and the viscosity rapidly increases. However since solidification releases heat, the temperature will rise to a maximum (time = t_2). When the operator happens to measure the pouring temperature at this moment, he may suppose that there is ample time for filling and will be surprised by sudden solidification.

In practice the gradient of the curve depends on the way of cooling, the type of base and the incorporated substances. See also Sect. 11.4.4 under Solidification point or range. For hard fat the maximum is determined under standard conditions and defined as solidification point, but in fact it is a solidification range. Melting range and solidification range of different types of hard fat are given in Table 11.3.

The choice of the pouring temperature also depends on the pouring (filling) method:

- During a serial filling process with mortar or squeeze bottle the temperature of the molten mass decreases. The initial temperature should be chosen so that solidification starts just at the time of filling the last suppository. This depends of course on working speed as well. Filling may start at 34–35 °C if using a squeeze bottle and at 33–34 °C if using a mortar.
- Filling a composite metal mold with cadre the pouring temperature is chosen just high enough to prevent solidification before all cavities are filled; 34–35 °C will usually do.
- For filling from a suppository filling machine the pouring temperature is chosen just above the start of the solidification range.

These pouring temperatures should be increased for large batches and when the room temperature is lower than usual. For small batches (required number of suppositories 6–12) the pouring temperature should be taken lower; when using a mortar a pouring temperature of about 30 °C satisfies. Note: if for a low melting point Miglyol is added to the base the solidification point is also significantly lower than normal and pouring temperature and cooling procedure should be adapted.

11.5.8 Cooling and Finishing

Cooling suppositories should start at room temperature. As soon as the mass has set, but before it has hardened completely, the excess of material should be trimmed off. This is easily done with the flat blade of a stainless steel spatula, first been dipped into hot water and wiped dry. Sometimes a razor blade does better. Due to settling the excess of material on top contains little active substance and can never be used for an additional suppository. After removing the excess of material the suppositories have to harden thoroughly. If necessary they can be placed in the refrigerator for a more rapid hardening process,

but only after a period at room temperature of at least 15–30 min. When placed in the refrigerator earlier or poured out into cold metal molds, suppositories may show a greater tendency for fractures and breaking. The rapid cooling of the outer layers of the suppositories compared to the inner layers, causes little cracks. This may happen even if the suppositories are placed in the refrigerator after 1 h at room temperature. The tendency for fractures of fatty bases is stronger when the hydroxyl value of the base is lower and thus the elasticity is less.

Suppositories containing Miglyol solidify slowly. Therefore, in addition to a lower pouring temperature (Sect. 11.5.7) these suppositories should be placed in a refrigerator directly after the filling of the mold. The incorporated substances settle too extensively when the suppositories cool down at room temperature.

11.6 Method of Preparation, Fat-Based Solution-Suppositories

Active substances that are soluble in the suppository base at room temperature, or liquids that are miscible with the suppository base, are incorporated into the base by dissolving in or mixing with the melted base. The calculation of the amount of suppository base is almost the same as with suspension suppositories. In solution-suppositories replacement plays a role if concentrations of active substances are relatively high. If a dosage replacement factor is unknown it has to be determined experimentally. The quantity of excess suppository mass needed may be somewhat smaller than for suspension-suppositories, because the mass can be poured out completely and all the suppositories have the same content. The preparation process steps are almost the same as for fat-based suspension-suppositories, just no dispersion is necessary; in summary (see also Sect. 11.5):

- No dispersion.
- Mixing by adding the active substance to the melted base and continuous mixing until complete dissolution; especially mixing of a liquid with the molten base needs attention; if not done properly the suppository will show a solid part and a liquid layer, mostly underneath.
- Pouring the mass is much easier than with suspension-suppositories because the mass will stay homogeneous at the filling process, so even the last filled cavities will have the correct content and all the mass may be used by scraping out the mortar; the pouring temperature is not important because there are no particles to settle.
- Cooling down and finishing the suppositories is also easier, because of the lack of sedimentation, although attention has to be paid to possible crystallisation or separation. For example in Valproic acid Suppositories (see Table 11.8), fat-based solution-suppositories.

Any dissolved substance lowers the solidification range of the base [8m] and therefore will affect the solidification point of the mass. This may cause a problem when large quantities of lipophilic active substances are added. For example, chloral hydrate in a concentration of 5 % in hard fat lowers the solidification point by more than 5 °C. Sometimes textbooks advise the addition of a substance with a high melting point [5f]. Such an addition bears risks for bioavailability however. The substance, such as beeswax, may separate upon cooling [8m]. Glycerol monostearate does better but increases the viscosity of the mass as well and may therefore retard the release of the active substance. Furthermore the increase of the solidification point may affect the bioavailability as well.

11.7 Method of Preparation, Hydrophilic-Based Suppositories

The preparation of suppositories with a macrogol base corresponds to the preparation of fat-based suppositories. Also suspension-suppositories and solution-suppositories are distinguished. And when preparing hydrophilic-based suspension-suppositories also special attention is needed to keep the mass homogeneous at the filling process. When the required amount of macrogol base is calculated it should be noted that the density of macrogol is higher than the density of hard fat. Therefore the dosage replacement factor is higher too. For most organic active substances incorporated in a macrogol base a dosage replacement factor $f = 0.85$ may be used (see Sect. 11.5.1).

11.7.1 Hydrophilic-Based Suspension-Suppositories

For the preparation of suspension suppositories with a macrogol base the preparation process steps are compared with Sect. 11.5 as follows:

- Melting the base. Mind the higher melting range of macrogol base compared to hard fat. Furthermore because of the hygroscopicity of macrogol a closed vessel should be used; this may be a medicine bottle, or a squeeze bottle if used for dispersing and pouring as well.
- Dispersing the active substance. It is performed similarly to fat-based suspension-suppositories, but when triturating the active substance with a little melted base it should be noted that the macrogol base solidifies sooner than a fatty base and thus it might be helpful to warm up the mortar a little.
- Mixing. To be performed similarly to fat-based suspension-suppositories.

- Pouring the mass is also done in a similar manner, but because of the higher solidification point the pouring temperature needs to be higher. For instance for the chloral hydrate suppositories of Table 11.1 the pouring temperature is 40–45 °C.
- Cooling and finishing is generally similar to the fatty suppositories, with a macrogol base it being even more important to avoid rapid cooling. Trimming off the excess mass is more difficult because fragments break off more easily.

The melting range of a number of macrogols is listed in [5h] and [8n]. Rapid cooling more easily results in cracking than with fatty suppositories. Furthermore, the density after fast cooling of a macrogol base may be lower than after slow cooling due to an abnormal molecular organisation. The consistency is less solid and the dissolution time in water is shorter. The release of active substance may therefore change as well [8p]. Fast cooling and thus facilitating the abnormal molecular organisation must be avoided.

11.7.2 Hydrophilic-Based Solution-Suppositories

For the preparation of a solution suppository the macrogol base is melted, the active substance is dissolved in the melt and the mass is poured, without any additional step. Melting the base in a closed vessel on the water bath (see Sect. 11.7.1) fits better because the dispersion step is lacking. The closed vessel may be a medicine bottle or a squeeze bottle. The medicine bottle is to be preferred because no transfer of molten base is necessary (no loss), it is transparent for controlling the dissolution process and it is suitable for pouring as there is no suspension to be kept homogeneous. The squeeze bottle is less preferred because it is not transparent.

11.8 Release Control and Quality Requirements

For the relevance of in-process controls, especially for extemporaneous preparation, see Sects. 34.14.3 and 21.6.3. Critical steps in the preparation process of suppositories are, for instance, insufficient breaking up of agglomerates, insufficient mixing and too hot or cold pouring, see further Sect. 11.8.1.

The specifications of the Ph. Eur. are the basis of the final controls. Suppositories have to comply with the test for uniformity of dosage units (see Sect. 32.7.2). Furthermore, the Ph. Eur. sets demands on dissolution (dissolution test for lipophilic solid dosage forms) or disintegration and on the softening time of lipophilic suppositories. The disintegration should happen within 30 min for a fatty base and within 60 min for a macrogol base, unless it concerns a suppository with controlled release ('intended for modified release') or for prolonged local action. With the suppository bases recommended in this chapter, the softening time will always be met. And if the preparation instructions, especially about cooling are followed accurately, the breaking resistance will comply. Some of the above-mentioned controls are discussed in the next sections. Additionally a test on the deviation of the average weight from the calculated weight is discussed. This control may be useful for all extemporaneous preparations.

11.8.1 In-process Controls

The preparation steps of dispersing, mixing and pouring determine a homogeneous distribution of the active substance over the suppositories and thus a good content uniformity. The content uniformity is quite laborious to be carried out as final control in pharmacy preparation, which is an extra argument for in-process controls. The dispersion of the active substance as well as homogeneity after mixing has to be controlled visually. The pouring temperature has to be recorded. If the mass is poured from the vessel in which it was dispersed, the vessel has to be checked on agglomerates again after pouring. If another vessel is used for pouring, such as a squeeze bottle, the dispersing vessel (e.g., a mortar), has to be checked for agglomerates when all the mass has been transferred to the pouring vessel. In the preparation of solution suppositories the control on agglomerates is replaced by a control on complete dissolution of the active substance.

11.8.2 Appearance

Above all, suppositories should be checked visually on a uniform appearance. They must show no bursts and cracks, no brittle bottom (brittle blunt end) as a result of incorporated air, and no soft or brittle tip as a result of sedimentation of active substance particles. Furthermore the mold should be filled equally. A brittle or soft tip may be detected by rubbing lightly with a finger over the tip of the suppository.

11.8.3 Average Weight and Average Content

For small scale pharmacy preparations a suitable test for the average weight and content is described as follows. The average weight of suppositories must not deviate more than 3 % from the theoretically calculated weight. This must be controlled for each batch. The theoretical weight is calculated by the summation of the prescribed quantities of all components. If the average weight deviates more than 3 % from the theoretical weight the batch must be rejected. If the average weight marginally exceeds the 3 % limit and it's concerning a large batch, it may be beneficial to check whether the average content meets the requirements of the Ph. Eur.

Whenever the average weight differs more than 3 % from the theoretical weight it is important to determine the cause. Causes may be the use of a wrong sized suppository mold, a miscalculation or too much incorporated air. If the average weight is within the 3 % limit, the average content almost certainly complies with the Ph. Eur. requirements. Table 11.13 shows well-known sources of deviations affecting the average content and also instructions to avoid them [28].

An Example of Large Content Variation Hardly Affecting Weight Variation

Suppose suppositories with 100 mg paracetamol are prepared, incorporated in a fatty base and with a dosage replacement factor f = 0.7 and a suppository weight of 2.00 g. Suppose also that one cavity of the mold has been filled completely, but as a result of separation during pouring contains 200 mg of paracetamol instead of 100 mg.

The 200 mg suppository will have a calculated weight of 2.03 g: [(2.00 + 0.100)–(0.7 × 0.100)]. In this case of a content deviation of 100 % the weight deviation will only be 1.5 %. Also with higher dosages, for instance 500 mg paracetamol per suppository, a content variation may be missed. In the paracetamol case a deviation of 100 mg (20 %) in content results in a weight deviation of only 1.5 %.

11.8.4 Uniformity of Mass

For the Ph. Eur. requirements and tests see Sect. 32.7.1.

For low-dosed suppositories the test on mass variation is hardly relevant because the difference between amounts of active substance will not be reflected in mass difference of the complete suppositories. Only if for instance, in suppositories weighing about 2.0 g, the active substance comprises 500 mg or more, then mass variation will indicate content variation.

However a (visual) release control on equal filling of the molds should be performed, including removing all not entirely filled molds.

Only if the suppository contains 25 mg or more of an active substance, comprising 25 % or more, by mass, of the suppository, the mass variation test is applicable instead of the content uniformity test. For instance, in suppositories weighing about 2.0 g, the active substance should be 500 mg or more for the mass variation test. A determination of the content uniformity will be needed for most suppositories.

11.8.5 Uniformity of Content

To obtain a good uniformity of content is the greatest challenge in the preparation of suspension suppositories and can only be achieved by a proper design of the (batch) preparation instruction and properly following it. So the outcome of determination of content uniformity is very relevant for the monitoring of the preparation process.

Table 11.13 Sources of Error affecting the Average Content of suppositories

Source of error	Measures to limit and to detect deviations
Blank weight	Use suppository molds with constant volume, determine the blank weight accurately, check yield and average weight
Dosage replacement factor	Use standardised batch preparation instruction, use table for dosage replacement factors, determine unknown replacement factors (see 11.5.1)
Loss of molten fat at transfer to dispersing vessel	Use minimum batch sizes;
	or melt excess of fat and fill up to weight in dispersing mortar;
	Disperse with rotor-stator in melting vessel
Inclusion of air	Check average weight
Settling during pouring	Is of little importance for the average content, but of significant importance for the content uniformity of separate suppositories, see 11.5.5
Settling from excess on mold	Pouring should be done carefully

See Sect. 32.7.2 for the performance of the test and the requirements according to the Ph. Eur. These test results don't give maximal information however about the quality of the preparation process, especially of small batches. There are two reasons: the sampling is random and the conclusion of the test is either yes or no meeting the requirements. A specific sampling, especially including the first, middle and last filled suppositories (if a serial filling) or centre and corner filled suppositories (if filled in cadre), would give more information. And a standard deviation of the contents of randomly taken suppositories reflects homogeneity of the mass that has been molded.

The validation of a new suppository formulation will bring about the determination of the content uniformity of a number of batches. Consequently, this determination is also necessary if the preparation method is changed. For a process validation, and probably personnel qualification, of the preparation of suspension suppositories in general, acetylsalicylic acid is a good test substance. Acetylsalicylic acid (180) settles easily and is also easy to analyse in suppositories.

11.8.6 Distribution of Active Substance in Suppositories

A homogeneous distribution of the active substance within one suppository is not important for its therapeutic effect. If the active substance has settled to the tip, it may indicate a too high pouring temperature. If sedimentation is so extensive that the tip has become brittle and breaks, the quality is insufficient.

11.9 Product Formulation, Enemas

Formulation, volume and packaging should make an enema suitable for rectal use. As with suppositories, the form of the active substance, ionised or not, is primarily chosen with regard to optimal effectiveness. Figure 11.1 presents an overview of the choices to be made.

The volume of enemas may vary from a few millilitres (micro-enema) to more than 100 mL, mainly depending on the intended effect: systemic or local. For large-volume enemas water is commonly used and a water-soluble form of the active substance is preferred. The solubility may be increased by addition of co-solvents, to be applied in small volume enemas. If a soluble active substance or an adequate co-solvent cannot be found, a suspension may be prepared. If this is also not an option , a lipophilic vehicle may be chosen. Choice of pH depends on the chosen form of the active substance and is important for the absorption. Excipients may be added to correct the osmotic value, to increase the viscosity, to prevent oxidation or for preservation.

11.9.1 Active Substance: Solubility and Particle Size

Rectal absorption depends on solubility and lipophilicity of the active substance (see further Sect. 16.1.5), and is influenced therefore by volume, pH, and buffering capacity of the enema (see Sects. 11.3 and 16.2.4).

Generally the non-ionised form of an active substance is best absorbed which is in favour of water-insoluble substances. However because of the equilibrium between both forms, the absorbed (non-ionised) form of the active substance will generate a driving force from ionised to non-ionised form. This mechanism enables the use of water-soluble salts, such as dexamethasone sodium phosphate and prednisolone sodium phosphate. They are much easier to be processed than the water-insoluble parent molecule.

A poorly water-soluble active substance such as theophylline becomes soluble by the addition of glycine and sodium hydroxide. In this way a theophylline rectal solution (Table 11.14) can be formulated with theophylline as sodium glycinate.

Table 11.14 Theophylline Rectal Solution 100 mg [46]

Theophylline monohydrate	0.11 g
Glycine	0.042 g
Sodium hydroxide solution 2 M (local standard)	0.3 g
Water, purified	9.55 g
Total	10 g (= 10 mL)

An active substance administered as a suspension must dissolve before it can be absorbed. This may take considerable time which may be a problem due to the termination of rectal retention by defecation. For a systemic effect only a few, if any, suspension enemas are in use. For a local effect a suspension enema is frequently used, for example with mesalazine or beclometasone. The choice between a suspension of the non-dissociated form of an active substance and a solution of the dissociated form can in the end only be based on biopharmaceutical research.

The influence of particle size on the absorption rate from aqueous suspension enemas has probably never been investigated. Dissolution of the active substance is assumed to increase with decreasing particle size (see Sect. 29.2.1). For the requirements on particle size for a stable suspension enema reference is made to Sects. 29.2 and 29.3 as well as to Sect. 5.10 because of similarity with oral suspensions. A particle size of maximal 180 µm generally satisfies. Suspension stability is less important than for oral use since an enema is dispensed in single-dose containers. However,

suspension stability must be sufficient to assure an even distribution of the active substance at filling of the single-dose containers from a bulk suspension. In addition the sediment must be easy resuspendable, in order to avoid active substance remaining in the enema container after administration.

For enemas with an oily vehicle, the considerations regarding solubility of active substance and choice of particle size resemble those for fatty suppositories (see Sect. 11.4.1). The process of release and absorption of the active substance is also largely comparable to that of fatty suppositories; just the melting step is not necessary.

11.9.2 Vehicle

In enemas for a systemic effect, water as a vehicle has the great advantage of presenting only one liquid phase in the rectum, so no transition of the active substance from fat into rectal fluid is needed. The addition of co-solvents (see Sects. 18.1.3 and 23.3) to the aqueous vehicle or the use of another vehicle, such as macrogol, is practised to bring poorly soluble active substances in solution or to increase their absorption. The solubility of an active substance in such mixtures has usually to be tried out. Co-solvents may however irritate. For this reason, co-solvents are used for enemas up to 10 mL only, e.g. diazepam enemas. The use of a fatty vehicle is the next option, which may improve stability as well.

A water-insoluble active substance may be processed into an enema as a suspension. However, the dissolution rate may be insufficient for a systemic effect. If an active substance is too poorly soluble in water and thus in the rectal fluid, it cannot be absorbed at all.

In all enemas having a volume of more than 20 mL, water is used as the single vehicle. These enemas are intended for a local effect. The volume of these enemas usually exceeds 40 mL, see Sect. 11.9.3.

The following are three examples of considerations about the vehicle that had to be made in community and hospital pharmacy practice. Some of them have been confirmed by biopharmaceutical investigations. These investigations are strongly recommended.

11.9.2.1 Choice of the Vehicle for a Chloral Hydrate (Micro) Enema

Chloral hydrate is soluble in water, but the solution irritates the mucous membrane and the active substance is rather unstable in water. The next choice for a vehicle may be macrogol or fatty oil. Chloral hydrate dissolves well in both. The rate and extent of absorption of chloral hydrate from a macrogol base (macrogol 300) is good, but the chemical stability is insufficient. The rate and extent of absorption of chloral hydrate from sesame oil appeared to be sufficient, though less than from the macrogol base. The stability of chloral hydrate in sesame oil is good. Therefore an oily vehicle is preferred. As sesame oil often causes allergic reactions, the chloral hydrate rectal solution of Table 11.15 presents a solution of chloral hydrate in arachis oil [47–49].

Table 11.15 Choral Hydrate Rectal Solution 50 mg/mL en 150 mg/mL [50]

	50 mg/mL	150 mg/mL
Chloral hydrate	5 g	15 g
Arachis oil, refined	88 g	83 g
Total	93 g (= 100 mL)	98 g (= 100 mL)

For an even better bioavailability and easier administration, a chloral hydrate suppository is often preferred. Chloral hydrate suppositories with a macrogol base (see Table 11.1) are chemically stable, this unlike the enema with macrogol 300.

11.9.2.2 Corticosteroids Administered Rectally: Choice of Active Substance and Dosage Form

If a rectal dosage form for the administration of a corticosteroid is prescribed, it is important to know if:

- The physician desires a local or a systemic effect.
- This can be achieved by the prescribed form of the active substance.
- This can be achieved with the dosage form indicated.

If the rectal form follows oral administration a systemic effect may be desired. It must be checked if the particular steroid is suitable for rectal administration, if the oral dosage may have to be adjusted, and if the rectal dosage form is appropriate.

A corticosteroid such as beclometasone acts almost exclusively locally due to a large first-pass effect in the gut wall and the liver and is therefore ideal for local application. Beclometasone dipropionate in a suspension enema of 100 mL is used for chronic intestinal inflammations. A beclometasone suppository may be used to treat proctitis. There is clinical experience with beclometasone dipropionate in an oily base, but literature is still lacking.

Dexamethasone, prednisolone and hydrocortisone are systemically active via the rectal route. The best chemical form of the active substance must be chosen and a dosage form that provides good release of the active substance. A corticosteroid as salt in solution is often optimal for an enema and the preparation is easy. As a solution in water it avoids problems such as release from a fatty base and subsequent dissolution. Dexamethasone and prednisolone for instance are used as sodium phosphate salts. Conversion and factorisation must not be forgotten. For stability reasons

(and to obtain a physiological pH), a phosphate buffer should be added.

Hydrocortisone sodium succinate is the available salt of hydrocortisone. It is not suitable for enemas because it is very unstable in aqueous solution. Alternatives are hydrocortisone or hydrocortisone acetate in a suspension enema or a suppository. For a systemic effect hydrocortisone is preferred because of its better solubility. Administration in a fatty suppository satisfies the requirements [51]. A suspension enema seems the better alternative, but literature does not provide a formula for a stable product. Therefore, in an enema the use of prednisolone or dexamethasone sodium phosphate is preferred. Local effect may be achieved with hydrocortisone acetate, sometimes used in suppositories in the treatment of haemorrhoids. However, for this indication hydrocortisone acetate processed in a fatty cream is preferred. That dosage form minimises absorption as little cream will reach the rectum.

11.9.2.3 Diazepam and Temazepam in an Enema

Two vehicles have been proposed for diazepam enemas. Both are mixtures of water and co-solvents: propylene glycol – ethanol 96 % – water (4 + 1 + 5, parts by volume, pH 4.8) and glycofurol – ethanol 96 % – water (5 + 1 + 4, parts by volume, pH 3.6). No significant difference in irritation score was observed with healthy volunteers [52].

Rectal irritation was studied also for various volumes of both mixtures: 2.5 mL, 5 mL and 10 mL. Only a light irritation was observed in the first 5–10 min after administration, lasting longer at the largest volume. As a control water was administered in the same volumes: all volumes were equally well tolerated. Choosing the smallest volume for enemas with these co-solvents seems best but may be insufficient for dissolution of the active substance. Regarding dissolution and irritation the optimal volume has to be chosen [52].

Both vehicles are also usable for some other benzodiazepines. Temazepam 10 mg in 2 mL of the glycofurol mixture, administrated to healthy volunteers, had a bioavailability equivalent to an orally administered capsule of 10 mg temazepam [4]. In this study the enema was preserved with methyl parahydroxybenzoate (0.15 %). However, a vehicle containing such high percentages of glycofurol and ethanol does not need this supplementary preservation.

11.9.3 Volume

The volume of enemas ranges from 3 to 100 mL. The volume is chosen on therapeutic, biopharmaceutical and technological aspects. Enemas for children are proportionately smaller than for adults.

Volume of Enemas for Neonates

For a baby of 2 months a volume of 5 mL is very suitable for systemic action. For the volume of an enema for local action, e.g., a 0.9 % NaCl solution as a laxative the general rule applies [6]: neonates <1 kg: rectally 5 mL, and neonates >1 kg: rectally 10 mL.

In practice, if a systemic effect is intended, usually a solution enema with a small volume is applied. The lower limit is 3 mL, necessary for a correct administration without unacceptable loss. The upper limit is 20 mL, but usually a volume of 10 mL is not exceeded. Between 3 and 10 mL (eventually 20 mL) the volume is determined by the solubility of the active substance.

For a local effect in the colon, the volume of an enema generally has to be as large as possible. A volume of 100 mL spreads over the distal part of the colon, however with a strong inter-individual variation. An example of an enema for local effect is a mesalazine enema for a distal ulcerative colitis or a distally localised Crohn's disease. The volume can be even larger than 100 mL if the location of the disease and the area to be reached requires it, as for colonoscopy with an X-ray contrasting agent. A smaller volume (40–100 mL) may be preferred for patients highly sensitive to the defecation stimulating effect of an enema,. If the disease is limited to the recto-sigmoidal area 30–60 mL will be enough, and is better retained by some patients [53].

11.9.4 Choice of pH and Buffering

The pH of enemas is important for stability and absorption of the active substance. Regarding irritation, a pH-value between 4 and 10 is acceptable for an enema up to 20 mL [54], but preferably the pH should approach the physiological value (pH 7–8). In particular if the active substance is a weak acid or a weak base the pH may be adjusted to shift the equilibrium to the unionised form. Absorption of an active substance appears to be better from a buffered solution than from an unbuffered solution with equal pH, so adjusting is best done by a buffer [55]. A phosphate buffer is frequently used for this purpose.

11.9.5 Excipients

Excipients may be used to make an enema iso-osmotic, to increase the viscosity and sometimes for the wetting of

solids. Excipients to prevent oxidation and preservatives are discussed under Stability (Sect. 11.9.6).

11.9.5.1 Osmotic Value

For rectal administration, the osmotic value may vary within wide limits. An osmotic value corresponding to a 0–1.8 % sodium chloride solution is tolerated. Adjusting the iso-osmotic value of an enema, by addition of, for example, sodium chloride, offers no advantage regarding activity and irritation, and can be omitted. Strong hyperosmotic solutions must be avoided in enemas, except for those intended as laxative. A strongly hyperosmotic solution, for example a phosphate enema, induces a defecation reflex. The osmotic value of this enema is about seven times higher than that of a normal saline solution.

11.9.5.2 Viscosity

For a suspension enema, the addition of a viscosity enhancer may be necessary. Solutions sometimes have a viscosity enhancer added as well, based on the supposition that a prolonged residence time is beneficial for absorption [56] but published evidence of improved efficacy does not exist. On the contrary, a reduced absorption may be the result of reduced spreading in the gut. But probably the influence of viscosity on spreading is dwarfed by the influence of the intestinal pressure on spreading.

See Sect. 23.7 for the choice of a viscosity enhancer. Cellulose derivatives are often used, for example hypromellose 4,000 mPa.s 0.5–1 %, hydroxyethylcellulose 300–560 mPa·s 1–1.5 % or methylcellulose 400 mPa·s 1–2 %. Also used are a carbomer hydrogel, 0.3 % and sometimes povidone, at a concentration of 2.5 %.

11.9.5.3 Wetting

Wetting of strongly hydrophobic active substances can be so difficult that the solid particles will not get dispersed properly and float on the water. Polysorbate 80 (0.1–0.15 %) can be added to the water to prevent this. Alternatively the solid active substance can be triturated with povidone or colloidal anhydrous silica, see Sect. 29.3. Addition of a surfactant such as polysorbate should be considered carefully, because unless in small amounts it may adversely affect the absorption; comparable with the addition of surfactants to suppositories (see Sect. 11.3.2).

11.9.6 Stability

Chemical stability may be problematic in enemas, especially if the active substance is dissolved in water, hydrolysis may occur. Stability may be improved by a more stable form of the active substance, by a different pH or by a different vehicle (see Sect. 22.2). For the prevention of oxidation see Sect. 22.2.2. The effectiveness of an antioxidant depends on the nature of the active substance and the vehicle, and must be determined experimentally. Sodium metabisulfite appeared to be more active than ascorbic acid in the beclometason-mesalazine enema of Table 11.16.

Table 11.16 Beclometason 3 mg/100 g and Mesalazine 1 g/100 g Rectal Suspension [57]

Beclometasone dipropionate, anhydrous, micronised	0.003 g
Mesalazine	1 g
Carbomer 974P	0.35 g
Disodium edetate	0.1 g
Methyl parahydroxybenzoate	0.15 g
Sodium metabisulfite	0.1 g
Trometamol	0.33 g
Water, purified	97 g
Total	100 g

Physical stability plays a role both for suspensions and solutions. A suspension may settle too fast and the sediment may be poorly resuspendable after standing for some time. Crystal growth too may occur in suspensions (see Sect. 18.4.2.3). In solutions, the active substance may crystallise during storage (Sect. 18.1.6). These physical stability problems resemble those of oral liquid dosage forms, see Sect. 5.4.14.

Microbiological stability may be a problem too. Aqueous enemas are prone to microbiological contamination and growth. The Ph. Eur. sets the same requirements for TAMC and TYMC (see Sect. 19.6.3) to rectal preparations as to oral preparations (10^3 CFU/g or mL, see Sect. 19.6.2). Enemas, like oral mixtures, should also meet with the requirements of preservation efficacy. For preservatives reference is made to Sect. 23.8. Generally methyl parahydroxybenzoate 0.15 % is used.

Prevention of Degradation

The pH of a beclometasone rectal suspension with carbomer as viscosity enhancer has been adjusted to 5–6. That pH is lower than usual for a carbomer hydrogel and is chosen as a compromise for two aspects: the viscosity of the carbomer hydrogel and the stability of beclometasone dipropionate. The same pH is chosen for the beclometasone and mesalazine rectal suspension of Table 11.16. As an additional benefit mesalazine is less soluble at pH 5.5 and hence more stable than at a higher pH. To protect the dissolved fraction of mesalazine against oxidation sodium metabisulfite is added. Adequate storage conditions are important to obtain a reasonable shelf life: protected from light and in the refrigerator.

11.9.7 Containers

See Sect. 24.4.4 for containers for enemas. Enemas are generally dispensed in a single-dose plastic container. Enemas of 3–10 mL, may be packaged in a tube-shaped or bellows-shaped micro-enema bottle. Alternatively, syringes with a rectal cannula may be used for the small volume enemas as well. From a syringe dosing is more exact and may be varied. For optimal dose flexibility at patients, the enema can be supplied as bulk liquid in a glass bottle with a dosage syringe with rectal cannula added (see Sect. 24.4.14).

Enemas of 20–100 mL are supplied in an enema bottle of 100 mL or in an enema bag (both disposable).

These primary packaging provides insufficient light protection. If light protection is desired (for instance with mesalazine) syringes, bottles or bags are wrapped in aluminium foil or delivered in box or bag.

When administering an enema, it is almost impossible to transfer all liquid to the rectum. A small amount will always remain in the bottle or giving tube. Small enema bottles are therefore filled with an excess of liquid. The required excess depends on the model of the micro-enema bottle and on the physical properties of the micro-enema liquid, in particular the viscosity. The residual volume, and thus the required excess, can be determined by weighing a bottle, filling it and emptying it by squeezing, after which it is reweighed.

In enemas for a local effect, usually having a higher volume, the residual volume is neglected.

Preferably a (micro) enema container should be filled completely, which may require adjustment of the active substance concentration. A full container increases stability by reducing the air contact of the content. It also prevents insertion of an undesired amount of air during application.

Packaging and Shelf Life

The type of material of the primary packaging may negatively influence the shelf life of an enema.

Diffusion through the plastic container and degradation of the container may occur during storage of a solution of chloral hydrate in arachis oil packaged in polyethylene enema bottles or in disposable syringes with a rectal cannula. The shelf life of this enema is 24 months, packaged in a glass or a polyethylene terephthalate bottle, 3 months in a micro-enema bottle and 1 month (4 weeks) in a syringe.

During the storage of theophylline rectal solution (Table 11.14) in disposable syringes with a rectal cannula, water evaporates. After 12 months of storage at room temperature, the evaporation rises to 5 %, after 24 months storage to 10 %. This causes an increase in concentration, whereas the administered dose remains (almost) equal. Therefore a shorter shelf life is used: 12 months after filling for the syringe versus 24 months after filling for a micro-enema bottle.

11.9.8 Storage

Enemas (in enema bottles or micro-enema bottles) prepared according to a standardised formula, and which are chemically and physically stable and preserved, may get a shelf life of 12 months in an unopened container. The same type of enemas packaged in a glass bottle with Dose-pac, may be assigned a shelf life of 24 months and 6 months after opening. Preserved enemas with unknown chemical and physical stability cannot be stored in the pharmacy because the usage period – and thereby the shelf life is maximal 1 month and concerns the closed containers. A usage period of 1 month also applies to non-preserved enemas, but until use the patient has to store the closed containers in a refrigerator.

11.9.9 Labelling

Enemas are dispensed with a label preferably bearing the text ‘for rectal use only’. General requirements for labelling are provided in Sect. 37.3. With a suspension enema, “shake well before use” must be stated in the label text and on a separate sticker. If the enema has to be kept in the refrigerator, the label should show the text “Bring to room temperature before use”. Up to 10 mL this can be achieved by holding the bottle for 5 min in a warm hand. Larger enemas should be taken out of the refrigerator 3 h before use. If enemas in micro-enema bottles or syringes are dispensed in a carton as secondary package, the primary package (container) can be provided with a flag label only, showing date, name of preparation and shelf life.

For the application of enemas, the patient is advised to lie down (in a lateral position with the upper knee flexed) and, if possible, not to get up before 5–10 min after administration. The cannula, which is lubricated with soft paraffin, should be brought into the rectum with a rotating movement. Deep breathing facilitates this. A syringe and a micro-enema bottle should be emptied slowly by pressing, an enema bottle and an enema bag by rolling up. Fast insertion may provoke a defecation reflex. When empty, syringe, bottle or bag should be withdrawn, while still compressed [58]. As for suppositories the method of insertion of enemas is not always familiar to the patient. Providing good verbal information and a complete and clear information leaflet as well are important at the moment of dispensing, to avoid an incorrect use.

11.10 Preparation, Release Control and Quality Requirements of Enemas

The process steps dissolving, dispersing and mixing are dealt with in chapter 29. Micro-enema bottles are best filled using a syringe with a needle (but beware of puncturing the bottle). When a bulk suspension is filled into enema bottles homogeneity of the mixture should be maintained to get a good content uniformity.

After preparation and packaging, enemas have to be checked for appearance, labelling and packaging. The final volume or the final weight must also be checked. Solutions must be clear and visually free from particles. For a suspension enema the resuspendability must be evaluated, which may be done following the method for oral suspensions, see Sect. 32.7.2. For other quality requirements see Table 32.2.

11.11 Pessaries

Little is published about the biopharmaceutics of vaginal dosage forms. The vagina is a good absorbing organ, but seldom used for the systemic administration of medicines. The fact that only women can benefit from this route of administration might have limited its use for systemic administration of medicines and further research [59]. Vaginal dosage forms are almost exclusively used for active substances with a local effect on the vaginal mucosa. Product formulation, method of preparation, release control and quality requirements resemble those of suppositories (see Sects. 11.4, 11.5, 11.6, 11.7, and 11.8). Some specific aspects of vaginal application are discussed in the following sections.

11.11.1 Active Substance

High lipid solubility and low molecular weight enhance the absorption through the vaginal mucosa. As for dermal preparations absorption occurs primarily by passive diffusion. Therefore active substances intended for a local effect should have a limited lipophilicity, in order to prevent systemic action [59].

11.11.2 Base

A good adhesion of the base to the vaginal mucosa is needed, because a vaginal dosage form may easily be lost due to the absence of a sphincter. Little is known about the adhesion properties of suppository bases, because for rectal application adhesion is not important. Also little research is done about the biopharmaceutics of suppository bases in case of vaginal application. From a preparation process point of view the same bases can be used for pessaries as for (rectal) suppositories.

In the past a glycerinated gelatin base was often used for pessaries. Glycerinated gelatin pessaries provide at body temperature a good adhesive, softened mass and they are tolerated well. Because of many disadvantages however (see Sect. 11.4.3), this base is not used anymore in Dutch pharmacies.

Hard fat (Adeps solidus) gives little irritation and most active substances can be incorporated without any problem. An important disadvantage of a fatty base is the incompatibility of fat and rubber, the material of condoms and diaphragms. When a fatty base is used, the patient should be warned that the protective effect of a condom or diaphragm is not reliable. A fatty base can also leak out of the vagina, causing problems with regard to clothing.

A macrogol base is often discouraged because it would be irritating to the mucosa. Others report a good acceptance of the base. Irritation is assumed to be caused by the attraction of water from the mucosa. The available amount of water in the vagina varies individually. A slow or incomplete release of the active substance may result in case little liquid is available. Moreover macrogol is incompatible with many active substances, see Sect. 11.4.5.

> In an orientating study on the irritating properties of pessary bases, macrogol (Macrogol 1500 + Macrogol 4000 = 1:2) and hard fat (Witepsol H15) were well tolerated by healthy subjects. The macrogol based pessaries were moistened with water before insertion to prevent irritation. No difference was found between both bases with respect to irritation. For practical reasons the subjects strongly preferred the macrogol base. Leakage of the melted or dissolved base from the vagina, also mentioned in [59], was much more problematic with the fatty base than with the macrogol base, in particular with regard to spotting on clothes.

A choice between hard fat and macrogol should depend on the properties of the active substance. Active substances that are insoluble in water are best incorporated in a hydrophilic base, even when a local effect is desired [8r]. From a lipophilic base these active substances are not or only poorly released. Water soluble active substances can be incorporated in both bases, but macrogol is more comfortable for the patient [5i]. New, strongly adhesive gels as a base for pessaries are likely to be an improvement [59], but too little research is available yet for use in pharmacy practice.

11.11.3 Shape and Size

Pessaries originally are egg-shaped. Other shapes are available as well. In pharmacy practice often suppository type molds are used. Alternatively plastic pessary molds may be used (strips). The volume of these egg-shaped molds is about equal to a suppository of 2.8 mL. Formerly used metal pessary molds had a volume of 5 mL. In literature the size of pessaries varies: weight values between 1.2 and 6.8 g are found [8s]. No studies are available about a desirable volume. For a local effect 2.8 mL seems to be right. For a systemic effect a smaller volume is probably adequate.

11.11.4 Packaging and Labelling

Pessaries can be dispensed in the same way as suppositories. The label should contain a short indication such as 'for vaginal application'. See for general requirements for labelling Sect. 37.3. A clear indication is needed how to use the pessary, for instance 'insert high into the vagina'. Especially when suppository molds were used for the pessaries, it is important to make clear how to use these vaginal suppositories or pessaries. For macrogol based pessaries the label may indicate: 'moisten with water before insertion'. Moistening is advised in literature [60], but the real effect has never been studied and is questionable. In the patient information leaflet, additional information may be needed about use and administration of pessaries, for instance with some figures. It is advised to warn the patient to wear a sanitary napkin or panty liner to prevent spots on clothes or bed linen, especially when a fatty base is used [5k]. For fat based pessaries a warning about the incompatibility with rubber condoms and diaphragms is needed too.

11.12 Product Formulation, Vaginal Solutions

Vaginal solutions usually contain active substances dissolved in water and are intended for a local effect. The Ph. Eur. describes solutions as well as emulsions and suspensions. Only solutions are seen in pharmacy practice and just occasionally such as lactic acid solutions, with or without sodium lactate, iodinated povidone (povidone-iodine) solutions and chlorhexidine digluconate solutions. Accordingly, this chapter discusses the solutions only. Solutions may be prepared either ready-for-use, or as a concentrate to be diluted before use, or as a tablet to be dissolved in water shortly before use.

11.12.1 Vehicle

Water is the only suitable vehicle.

11.12.2 Volume

The volume of a vaginal solution varies from 150 to 200 mL. A concentrate for dilution will be diluted by the patient about ten times, depending on the filling marks of the available irrigator.

11.12.3 Choice of pH and Buffer Capacity

When the physiological pH of the vagina (pH = 3.5–4.5) is not maintained the microbiological balance in the vagina may become disturbed. Therefore the solution should have a physiological pH. Especially when the vaginal solution is intended for correction or support of the pH, for instance a lactic acid solution, a buffered solution is preferred.

11.12.4 Sterility

The Ph. Eur. does not require sterility for vaginal solutions. However, the Ph. Eur. requires for all vaginal dosage forms a preparation ensuring their microbiological quality. These requirements are the same as for cutaneous preparations: not more than 100 CFU/g or mL. For an enema by comparison up to 1,000 CFU/g or mL are allowed. A solution for application on a heavy damaged skin however should be sterile according to Ph. Eur., see under 'Liquid preparations for cutaneous application'. Sterility is also required under 'Preparations for irrigation' for solutions intended for irrigation of body cavities. In (Dutch and German) practice sterile solutions are prepared if they are intended for vaginal use after surgical procedures [8t]. Solutions for use on an intact vaginal mucosa do not need to be sterile, but should have a low bacterial count. This means that starting materials of good microbiological quality should be used and that contamination during the preparation process should be prevented whenever possible.

11.12.5 Excipients

Excipients are added to make a vaginal solution iso-osmotic. Iso-osmosis is especially important for solutions used on a damaged mucosa or after operations. Frequently sodium chloride is added for iso-osmosis. Glycine is used as an

alternative in chlorhexidine digluconate solutions, because of a chemical incompatibility with sodium chloride. For vaginal solutions applied to an intact mucosa iso-osmosis is not strictly required.

11.12.6 Stability

Just as in enemas (see Sect. 11.9.6) chemical stability may be a problem in vaginal solutions. This cannot be avoided by choosing a different pH or another solvent as with enemas. So the active substance should be inherently stable in water. For the microbiological stability of non-sterile vaginal solutions which are often concentrates for multiple dosing, preservation may be necessary if the concentrate doesn't meet the test on preservation effectiveness (see Sect. 32.8). Methyl parahydroxybenzoate can be used as a preservative.

Problems with chemical or microbiological stability may be avoided with a tablet or powder from which the vaginal solution is prepared just before use by dissolving it in water. An example is the Multi-Gyn® effervescent tablet from BioClin® for the preparation of an acidifying vaginal solution. An appropriate irrigator (vaginal douche) is supplied. In addition to sodium hydrogen carbonate (sodium bicarbonate), citric acid, ascorbic acid and lactose, the effervescent tablet contains an extract of Aloe barbadensis, an addition without evident function.

A vaginal solution with iodinated povidone is best delivered as a stable concentrate, for instance Betadine®-solution 100 mg/mL. The patient should dilute the concentrate ten times in an irrigator. The indication is fluor vaginalis with clinically evident inflammation but without a microbiological diagnosis. A bacterial vaginosis during pregnancy can also be treated short term with an iodinated povidone vaginal solution.

11.12.7 Containers

Sterile vaginal solutions are packaged in a single-dose container that can be sterilised, for instance glass (preferably class I, eventually class II) or plastic (polypropylene). Preserved concentrates, intended to be diluted before use, are usually packaged in a container of glass (class III) or plastic (polypropylene, polyethylene) meant for multiple dosing.

11.12.8 Storage

See Sect. 22.7 for the general approach of storage times. Sterile vaginal solutions, prepared according to a standard formula and chemically and physically stable, may have a shelf life of 3 years after preparation if packaged in single-dose containers. If prepared according to a non-standardised formula, a sterile vaginal solution should not be stored in the pharmacy because the maximal shelf life of say 1 month, may be reasonably needed by the patient. After opening, a sterile vaginal solution can be kept in the refrigerator for 24 h.

Non-sterile but preserved vaginal solutions may have a shelf life of 3 years after preparation, if prepared according to a standard formula and chemically and physically stable. Once opened by the patient, such vaginal solutions can be assigned an in-use period of 6 months. A concentrate diluted by the patient should be kept only 24 h after dilution. A non-standardised preserved preparation should not be stored in the pharmacy because the maximal shelf life of say 1 month, may be reasonably needed by the patient. A diluted concentrate may be kept for 24 h after dilution. Unpreserved non-sterile vaginal solutions may have a shelf life of maximal 2 weeks and they have to be stored in a refrigerator.

11.12.9 Labelling

Vaginal solutions are delivered with a label showing 'for vaginal use only'. It is important that the method of administration is clearly indicated. If appropriate, the word ´sterile´ should be written on the package. An irrigator for the administration should be delivered with the product (see Sect. 24.14). The patient has to be instructed how to dilute a concentrate in the irrigator. A mark on the irrigator usually indicates the amount of concentrate to be used. For dilution (fresh) lukewarm tap water can be used. The patient should be fully informed about the administration of the vaginal solution.

11.13 Preparation, Release Control and Quality Requirements of Vaginal Solutions

Method of preparation, release control and quality requirements of sterile vaginal solutions are the same as for irrigation solutions (Preparations for irrigation Ph. Eur., see Sect. 14.7). Preparation method and release controls of non-sterile vaginal solutions are the same as for solutions for cutaneous use (see Sect. 12.6.5).

11.14 Semisolid Dosage Forms, Rectal or Vaginal

For rectal application ointments and creams are common, for vaginal application creams and gels are used. They act locally and the design and preparation hardly differ from corresponding dosage forms for cutaneous use. In the subsequent sections some aspects of semisolid preparations for rectal and vaginal use will be discussed that are not encountered in cutaneous use.

11.14.1 Active Substance

The possibility of absorption and systemic effects should be considered with more attention than with cutaneous use. Most risk of absorption theoretically exists for a lipophilic active substance in a hydrophilic base, but in fact hardly anything is known about this issue. An isosorbide dinitrate soft paraffin cream, for instance, may already cause headache due to systemic absorption although applied on a small anorectal surface. Absorption from a lidocaine soft paraffin cream is found when used for internal haemorrhoids and applied from a tube with a long nozzle (cannula) (see Sect. 24.4.19.12). The cream easily reaches the rectum and the lidocaine can then be absorbed.

Intentional absorption at vaginal administration may be attained by processing a lipophilic active substance in a hydrophilic base: a vaginal gel [61], see also Sects. 11.11.1 and 11.11.2.

11.14.2 Base

Condoms become permeable in contact with a cream or ointment base containing fats or paraffin [62]. This may be a problem for rectal as well as vaginal use. The same problem applies to occlusive diaphragms. For these reasons, a hydrophilic gel is the best possible base if combination with condoms or diaphragms cannot be excluded. An example of a hydrophilic gel is the vaginal gel pH 5 (Table 11.17), used as lubricant in case of vaginal dryness.

Table 11.17 Vaginal gel pH 5 [63]

Lactic acid	0.1 g
Hydroxyethylcellulose 250 mPa.s	7 g
Sodium benzoate	0.15 g
Sodium lactate solution	2 g
Sorbitol, liquid (non crystallising)	5 g
Water, purified	ad 100 g

11.14.3 Additives with a Spermicidal Effect

Sometimes information is needed about the possibility of a (not intended) spermicidal effect of vaginal dosage forms. The viscosity enhancer hydroxyethylcellulose 250, used in the vaginal gel pH 5 (Table 11.17), might act as a barrier for sperm and also a pH 5 (or less) inhibits the mobility of sperm [63]. So this gel should not be used in case of fertility problems. Surfactants and antimicrobial preservatives in a cream or gel are suspected of spermicidal effects. For example, the surfactant nonoxynol-9 is the active substance in most spermicidal creams and gels. The gel lubricant (moisturising gel) Sensilube® that is claimed to be non-spermicidal contains methylparaben, ethylparaben and propylparaben. Therefore these preservatives are likely to be sperm-friendly and usable for vaginal gels. Chlorhexidine digluconate may not be spermicidal in a concentration of 0.1 % and lower and therefore can be used also.

11.14.4 Dosage Delivery Devices

A rectal cannula is adequate for application of ointments and creams in the anus (see Sect. 24.4.19.12). It is about 3.5 cm long and can be screwed onto a tube. Before insertion into the anus the cannula should be lubricated with a little of the product. After insertion of the cannula a small amount of the product can be brought into the anus by squeezing the tube. For vaginal application of a cream or gel a vaginal applicator exists (see Sect. 24.4.19.11). It is a kind of syringe that should be attached to the tube, after which about 5 g of the cream or gel can be expelled. After aspiration of the product the applicator is inserted into the vagina and the piston is pressed to apply the product. For treatment of a vaginal candidiasis during pregnancy (for instance with miconazole) the use of an applicator bears a risk of mechanical injury. The relevance of this risk however is uncertain and the vaginal administration of a cream without an applicator is rather inconvenient.

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Dermal

12

Antje Lein and Christien Oussoren

Contents

Abstract

Preparations for cutaneous (or dermal) application may be used for local treatment as well as for transdermal administration with a systemic effect. The chapter focuses on preparations with a local effect and on design of formulation and method of preparation of those prepared in pharmacies. The interaction between skin, active substance and base, the anatomy of the skin and biopharmaceutical aspects of cutaneous preparations are discussed as well as the therapeutic effect of the base. Because of the important role of the pharmacist in prescription assessment some recommendations for the communication with the physician are given. One aspect is how to proceed with a request for the mixing of two licensed medicines or for the addition of an active substance or an excipient to a licensed product. The formulation design is generally following the several phases of the multicomponent preparations. Based on the

Based on the chapter Dermatica by Christien Oussoren, Gerad Bolhuis en Koen Mutsaerts in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_12,

classification of the European Pharmacopoeia additionally the typical types of cutaneous dosage forms are discussed further, with regard to formulation as well as the way of processing. Extemporaneous preparation mostly involves the addition of active substances to base preparations. Preparations standardised in European formularies are used to illustrate special properties, design of formulation and preparation methods. Preparation processes for large scale require some other methods than small scale preparations.

Keywords

Formulation • Preparation • Base • Semisolid • Cutaneous liquid • Cream • Ointment • Cutaneous gel • Paste • Skin • Cutaneous emulsion • Cutaneous powder • Cutaneous solution • Cutaneous suspension

12.1 Prescription Assessment

12.1.1 Need for Cutaneous Pharmacy Preparations

Licensed products are first choice in the treatment of skin disorders. However, these preparations do not always meet the specific needs of the patient. Therefore patients are often in need for individualised preparations.

Typical situations in which pharmacy preparations may be needed are:

- If no licensed pharmaceutical preparation is available. This may concern less common disorders. Examples are: sodium hypochlorite solution and emulsion for the treatment of ulcers and decubitus, dithranol cream and dithranol ointment in a series of increasing concentrations for psoriasis, levomenthol or lidocaine containing preparations for pruritus, sterile metronidazole gel for foul-smelling wounds and diltiazem hydrochloride creams and gels for the treatment of anal fissures. Many of these are licensed now, although not in every country.
- The patient is allergic to one of the excipients of the licensed product. If the active substance is available the pharmacist may be able to formulate a preparation without the allergenic excipients.
- The physician or patient notifies that an individualised preparation is more effective.
- The physician wants to combine two licensed products in one to ease the application for the patient. For some people instructions for daily application of more than one preparation can be too much of an effort resulting in non-compliance.
- The physician wants to add an extra active substance or excipient to improve the effectiveness of the licensed preparation. For example salicylic acid and urea may be added to corticosteroid containing formulations to improve the penetration of the corticosteroid into the skin, which may increase therapeutic effectiveness. However, it should be reflected whether a stronger corticosteroid may be the better choice.

An example for the early incorporation of new scientific knowledge in dermatological practice by using an extemporaneous preparation is the treatment of chronic anal fissures with diltiazem hydrochloride. The mechanism of action is based on the reduction of the pressure in the anal sphincter. In comparison to organic nitrates diltiazem hydrochloride causes less adverse effects (headache). Based on published experiences with this treatment and the need for a stable preparation, formulations for a gel and a cream were developed (Table 12.1).

Table 12.1 Hydrophilic Diltiazem Hydrochloride Rectal Gel 2 % and Hydrophilic Diltiazem Hydrochloride Rectal Cream 2 % [1]

	Gel	Cream
Diltiazem hydrochloride	2 g	2 g
Hydroxyethylcellulose gel DAB[a]	98 g	–
Cream base DAC[b]	–	98 g
Total	100 g	100 g

[a]Table 12.35
[b]Table 12.6

12.1.2 Adapting Licensed Products

In general adapting licensed preparations is problematic for several reasons:

- Scientific evidence of therapeutic rationality, activity and safety of the adapted product is lacking.
- Additives can change biopharmaceutical properties of the licensed product.
- The combination of two licensed products may decrease concentrations of the active substances too much.
- The duration of the treatment with one or the other active substance may be typically different, causing the patient to be treated inadequate, either too short or too long. For example the combination of antibiotics and corticosteroids can result in bacterial resistance if the antibiotic is applied too long. Upon application of the combination of corticosteroids and antimycotics the patient may be treated too long with the corticosteroid or the treatment with the antimycotic is insufficient.
- The qualitative and quantitative formula of licensed pharmaceutical preparations is often not known. Adding

new active substances or excipients may result in physical and chemical incompatibilities.

12.1.3 Recommendations

The following general recommendations may be helpful for handling prescriptions of cutaneous preparations:

- If suitable licensed medicinal products are available, they should be preferred.
- If a licensed product has to be adapted, the pharmacist should suggest a standard pharmacy preparation with a comparable base and chemical form of the active substance. For example the type of emulsion has to be the same or an anhydrous formulation such as a hydrophilic or hydrophobic ointment should be replaced with a similar anhydrous preparation.
- Is combination or adaptation of licensed products aimed at a better adherence, it is to be preferred that physician and pharmacist give clear advice about the administration of the original products or start from a standard pharmacy formulation. For the instruction of patients where, how, how often and how long to apply cutaneous preparations, a special form with an outline figure may be helpful, see Fig. 2.5.
- Standard formulations in national formularies are to be preferred. The addition of another active substance to standard formulations is possible, but the number of substances has to be limited and incompatibilities must be excluded.
- In case of non-standardised preparations the pharmacist should professionally improve the formulation if necessary, for instance by the addition of buffers and choosing a similar but compatible base.

To ease the communication between pharmacist and physician some defined agreements are useful. The pharmacist has to identify the problems in the prescription and should name alternatives to the formulation if needed. The concept of the treatment has to be considered. The following measures can be agreed upon beforehand:

- Obsolete active substances or excipients should not be processed.
- Preservatives are added if microbial growth is expected. If a formulation should be prepared without a preservative, the physician has to note that on the prescription.
- Overdosing for therapeutic reasons has to be noted on the prescription, for example with an exclamation mark.
- The declaration of the chemical form of steroids for dermal use has to be clear. Some of the steroids have no effect on the skin, for example triamcinolone or betamethasone, but the esters do.

Prescribing extemporaneous cutaneous preparations is a privilege that many physicians appreciate as well as some patients. This may cause a conflict of interest because the physician wants to prescribe a tailor made preparation, but the pharmacist may not be able to formulate and supply a stable and effective product, for example because of incompatibilities, toxicological or quality concerns. In order to agree on which preparations can be prescribed and supplied it has been proven useful if pharmacists and physicians have access to a standardised and rationalised assortment of cutaneous pharmacy preparations, based on literature and multidisciplinary guidelines. Examples are "Dermatica op Recept" in the Netherlands [2] or "Standardisierte Rezepturen – Formelsammlung für Ärzte" in Germany [3]. If the physician needs a non-standardised preparation a full prescription assessment (see Sect. 2.2) should be performed.

12.2 Definitions

12.2.1 Classification of the European Pharmacopoeia

In the eighth edition of the European Pharmacopoeia cutaneous preparations are classified as liquid preparations for cutaneous application, semisolid preparations for cutaneous application and powders for cutaneous application [4].

Liquid preparations for cutaneous application are described as preparations with variable viscosity intended for local or transdermal application. This category comprises solutions, emulsions and suspensions for dermal use containing one or more active substances in a suitable base. As examples for liquid preparations shampoos and cutaneous foams are defined in Ph. Eur.

Semisolid preparations for cutaneous application are subdivided in ointments, creams, gels, pastes, poultices (wet dressings), medicated plasters or patches and cutaneous patches.

Ointments are cutaneous preparations consisting of one phase, hydrophilic or hydrophobic, in which a solid phase may be dispersed. They are subdivided in hydrophobic ointments, water-emulsifying ointments and hydrophilic ointments.

Hydrophobic ointments are ointments that can absorb only small quantities of water. The base of water emulsifying ointments is similar to the base of the hydrophobic ointments but also contains one or a few emulsifying agents, so they can absorb larger quantities of water than hydrophobic ointments and form water-in-oil (w/o) or oil-in-water (o/w) emulsions, depending on the type of the emulsifier. Hydrophilic ointments are ointments which consist of only a hydrophilic phase. They are miscible with water.

Creams are described as preparations comprising a lipophilic and an aqueous phase. Creams with the aqueous phase as

Table 12.2 Definition of cutaneous preparations

Ph. Eur.	Standard terms	Synonyms	Examples
Powders for cutaneous application			
	Cutaneous powder		Base for cutaneous powder (Table 12.18)
Liquid preparations for cutaneous application			
Solution	Cutaneous solution		Salicylic acid cutaneous solution 10 % (Table 12.10), Tretinoin cutaneous solution 0.05 % (Table 12.11)
Suspension	Cutaneous suspension	Mixture, lotion	Zinc oxide cutaneous suspension (Table 12.21)
Emulsion	Cutaneous emulsion	Liniment, milk, lotion	Cetomacrogol cutaneous emulsion (Table 12.24)
Semisolid preparations for cutaneous application			
Lipophilic gel	Gel	Oleogel	Hydrophobic base gel DAC [43]
Hydrophilic gel		Mucilago, hydrogel	Hydroxyethylcellulose gel DAB (Table 12.35)
Lipophilic cream	Cream	W/o cream	Cooling ointment FNA (Table 12.31), Hydrophobic cream base DAC (Table 12.32)
Hydrophilic cream		O/w cream	Nonionic hydrophilic cream SR DAC (Table 12.33), Lanette cream I and II (Table 12.34)
Hydrophobic ointment	Ointment		Coal tar soft paraffin ointment (Table 12.25)
Water-emulsifying ointment			Emulsifying hydrophobic base gel DAC (w/o emulsifying) (Table 12.26), Cetomacrogol ointment base (o/w emulsifying) (Table 12.27)
Hydrophilic ointment			Macrogol ointment DAC (Table 12.29)
Paste	Cutaneous paste		Zinc oxide cutaneous paste DAB (stiff paste) (Table 12.38), Zinc oxide calcium hydroxide weak paste (Table 12.39)

continuous phase are classified as hydrophilic. Lipophilic creams are creams with a lipophilic continuous phase.

Gels are defined as fluids that form a gel because of the presence of a suitable gelling agent. Gels are subdivided in hydrophilic and lipophilic gels.

Pastes are semisolid preparations containing a large amount of solids, dispersed in the base.

Poultices (wet dressings) are hydrophilic heat-retentive bases in which one or more active ingredients, solids or fluids, are dispersed. Generally, they are heated before use and applied on the skin in a thick layer.

Medicated plasters are flexible preparations with one or more active substances that should be slowly absorbed, or they have protective or keratolytic properties.

Cutaneous patches are intended for local effects.

Powders for cutaneous application consist of solid, loose, dry particles with a varying fineness. They may contain one or more active substances and excipients.

12.2.2 Classification in Practice

Official definitions for the different types of cutaneous preparations are given in the European Pharmacopoeia (Ph. Eur.). But in the physicians practice, in licensed preparations and in formularies various terminologies can be found. For example a physician usually associates cream with a hydrophilic base and ointment with a lipophilic one. In the German Pharmacopoeia the Hydrophilic ointment with water (Unguentum emulsificans aquosum) is not an ointment as the Latin term Unguentum suggests. It is on the contrary a hydrophilic cream by Ph. Eur. definition. Emulsions in the sense of liquid preparations with a high amount of water are often named lotions, liniments or milks. As the pharmacist has a lot of different bases for cutaneous preparations it makes sense to communicate the therapeutic goal, the skin conditions and the area of application with the physician to find the right formulation. Knowledge of the characteristics and properties of cutaneous preparations helps to make an appropriate choice. Table 12.2 shows the official terminology in Ph. Eur. EDQM standard terms [5], synonyms used in physicians' practice and European formularies and formulations to be found in this chapter as references for each type of preparation.

12.3 Biopharmaceutics

In cutaneous preparations the base as such has an influence on the therapeutic effectiveness. It also very much influences the therapeutic effect of the active substance by influencing its release and penetration into the skin. To

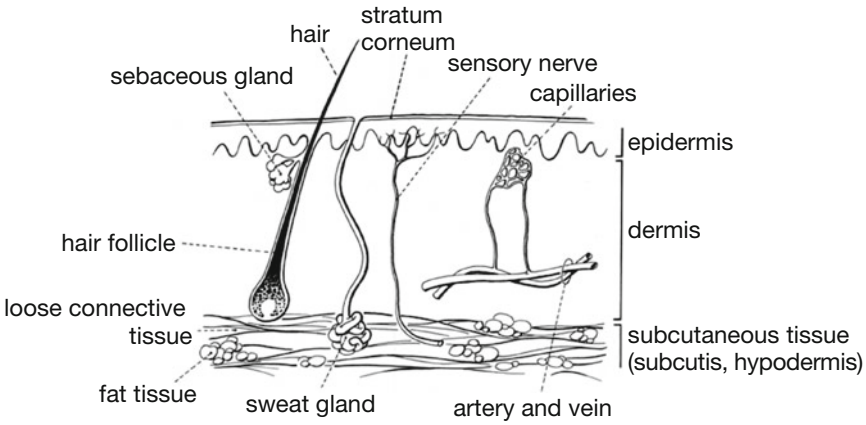

Fig. 12.1 Anatomy of the skin. Source: Recepteerkunde 2009, © KNMP

understand how penetration of active substances and the therapeutic effect are related to the formulation, it is necessary to have knowledge on the anatomy of the skin and skin biopharmaceutics. Release and penetration into the skin is generally described in Sect. 16.2.5. As the therapeutic effectiveness of cutaneous preparations also depends on the frequency of application and the amount to be dispensed, these aspects are also dealt with.

12.3.1 Anatomy of the Skin

From the outside to the inside the skin consists of the following layers (see Fig. 12.1):

- The epidermis, which has mainly a protecting function
- The dermis (corium), which has a supplying and stabilising function
- The subcutis, a layer which has an insulating and protecting function and works as an energy storage

The epidermis consists of a multi-layered epithelium that varies in thickness from 0.03 mm on the eyelids up to 2.0–4.0 mm on the palms of the hands and soles of the feet. The cells are gradually and continuously renewed by being moved from the inside to the outside of the skin. During this outward migration the cells change. They keratinise and disintegrate and become denucleated forming a firm cornified layer. From the outside to the inside the epidermis consists of five layers: the stratum corneum, the stratum lucidum, the stratum granulosum, the stratum spinosum and the stratum germinativum. In the stratum germinativum, the cell division takes place. The interior four layers are called the living epidermis.

The outer layer of the epidermis, the stratum corneum, consists of dead, mainly keratine containing cells that are continuously scaled off. It is considered as a membrane, built from a dense lipid protein matrix. The function of the *stratum corneum* is to form a barrier to protect underlying tissue from infection, dehydration, chemicals, radiation and mechanical stress. During the process of division, migration and death of the epidermis cells the percentage of water decreases from approximately 70 % in the stratum germinativum to 10–20 % in the stratum corneum. However, the stratum corneum can absorb more water (up to 50–75 %), for example under occlusion or while bathing. Hydrated the stratum corneum has a better permeability and the protecting function is decreased. The pH is 7.1–7.3 in the stratum germinativum and 5.4–5.9 in the stratum corneum.

The dermis has a thickness of about 3–5 mm. In contrast to the epidermis it contains blood vessels and nerves. The dermis is divided into two layers. The outer layer, the papillary region contains a network of capillaries and has a supplying function for the epidermis. The inner layer, the reticular region lies under the papillary region and is usually much thicker. Because of the high concentration of collagenous and elastic fibers imbedded in dense connective tissue, it gives the dermis mechanical strength and elasticity.

The subcutaneous tissue mainly contains fat tissue. It has an insulating and buffering function.

Hairs stand loose in hair follicles. Each root of a hair is connected with a sebaceous gland that is secreting sebum into the follicle. Sebum consists of short chain fatty acids, waxes and emulsifiers, such as cholesterol. Sweat glands are coiled tubes that range from the dermis and subcutis into the surface of the skin. The fluid produced by the glands, the sweat, is a hypotonic salt solution with a pH of approximately 5. Beside salts, it contains small quantities of other substances such as lactic acid and urea. The most important function of sweat glands is temperature regulation by loss of water vapour. The mixture of sebum and secreted products of sweat glands and the loose dead cells of the stratum corneum form a greasy layer, which covers the skin. This lipid film can absorb water because of the presence of emulsifying agents. However it remains water resistant and protects the skin against dehydration. The short chain fatty

acids originating from sebum and sweat components and the low pH are responsible for its protecting effect against pathogenic micro-organisms.

12.3.2 Release and Penetration

See Sect. 16.5.1 at first. The rate and extent of penetration of the active substance into the skin mainly depends on the partition of the active substance in the base and the stratum corneum. Other factors such as skin conditions, the area and method of application play a role as well.

Hydrocortisone and the acetate and butyrate esters are often used for cutaneous application. In the skin the esters hydrolyse rapidly and the active substance hydrocortisone is formed. Usually the concentration of hydrocortisone acetate in creams is 10 mg/g. The usual concentration of hydrocortisone butyrate is 1 mg/g, 10 times lower than the hydrocortisone acetate ester.

Glucocorticosteroids for external use are classified by their potency. Two systems of classification exist that must not be mixed up. One is depicted in the WHO Model prescribing information [6]: The steroids for external use are assorted there in four groups with seven classes from class I (ultra high potency) to VII (low potency). The more common and well known system of Niedner [7] has only four categories from class I (low potency) to class IV (very high potency). Criteria for this classification system are the local effect in the vasoconstriction test, the anti-inflammatory and the anti-proliferative effectiveness.

Preparations with hydrocortisone acetate are classified in activity class I, preparations with hydrocortisone butyrate in class II. Although the active substance in both preparations is the same, the therapeutic effectiveness of the butyrate ester is stronger. This is the consequence of the higher lipophilicity of the butyrate ester that leads to better skin penetration.

If substances are in a dissolved state near the skin surface, they will penetrate into the skin rapidly after application. Dissolved molecules in the preparation firstly have to diffuse towards the skin surface. If the rate of diffusion through the base is low, the penetration will be impeded. The rate of diffusion through the base depends on the properties of the active substance and the base.

If the active substance is suspended in the base, it must dissolve first. This process depends on its solubility in the base. A small particle size increases the dissolution rate.

The properties of the active substance influence skin penetration as well. Generally lipophilic molecules penetrate into the skin more rapidly than hydrophilic substances. Additionally, lipophilic substances are released more rapidly from aqueous than from lipophilic bases because of their higher affinity to the stratum corneum.

The base of a cutaneous preparation also influences the rate and extent of absorption. The base can be simple, such as an aqueous solution, but can also be very complex such as an emulsion. The base can alter the skin conditions, for example by hydration. As a result, the penetration of the active substance into the skin may be modified.

Ultimately, the release and penetration of active substances from cutaneous preparations is difficult to predict.

Lidocaine is applied on the skin in its non-ionic form because this form penetrates best. To anaesthesise mucous membranes the hydrochloride salt of lidocaine is more suitable because the charged form dissolves better in the mucous membranes than the base.

Cutaneous preparations for the skin should contain the base as such or the base has to be formed from lidocaine hydrochloride. Three concepts may be followed:

1. Lidocaine hydrochloride is dissolved in an aqueous gel. As only non-dissociated molecules can penetrate into the skin, and lidocaine is slightly soluble in water, the pH is adjusted to 6.5. At this pH only a small amount of lidocaine ($pK_a = 7.9$) is in the lipophilic form, but dissolved anyway.
2. Lidocaine is dissolved in a lipophilic phase by warming. An aqueous phase is added last.
3. Lidocaine is added by deliquescing lidocaine crystals and levomenthol together. The eutectic mixture is than emulsified in an aqueous gel. The biopharmaceutic advantage of this principle is that a molecular dispersion of the lipophilic lidocaine base in a hydrophilic preparation is formulated.

Penetration into the skin can be enhanced by penetration enhancers. These excipients diffuse into the stratum corneum and interact with components of this layer. The barrier function of the skin decreases. The effect of penetration enhancers is based on two mechanisms. The penetration enhancer can change the structure of the stratum corneum or the solubility of the active substance in the skin. Penetration enhancers should not damage the underlying skin layers and should not be toxic or allergenic. Moreover, the effect must be reversible. Because of the different properties and mechanisms of action of penetration enhancers it is difficult to predict which enhancer will be most effective for the penetration of a specific active substance. Substances such as dimethyl sulfoxide (DMSO), salicylic acid, urea, propylene glycol, ethanol, isopropyl alcohol and many acids can act as penetration enhancers.

Table 12.3 Basic preparations for different skin conditions and skin types

Skin	Form	Effect	Base
Wet skin	Water or wet dressing	Drying, astringent	Water, physiological saline solution, black tea as wet dressing
↓			
↓			
↓	Cutaneous suspensions (commonly with zinc oxide)	Drying	Zinc oxide cutaneous suspension (Table 12.21)
	Pastes (commonly with zinc oxide)	Drying	Zinc oxide aqueous paste (Table 12.41)
	Hydrophilic cream	Neutral	Nonionic hydrophilic cream SR DAC (Table 12.33), Lanette cream I/II (Table 12.34)
			Soft paraffin cetomacrogol cream (Table 12.4), Cream base DAC (Table 12.6),
Dry skin	Lipophilic cream	Hydrating	Hydrophobic cream base DAC (Table 12.32)
Strong keratotic disorders	Ointment	Strongly hydrating, occluding	Emulsifying hydrophobic base gel DAC (Table 12.26), White soft paraffin
Greasy (oily) skin	Hydrophilic gel		Hydroxyethylcellulose Gel DAB (Table 12.35)
	Solution		Blends of ethanol/isopropyl alcohol, propylene glycol and water
Scalp (seborrheic)	Hydrophilic gel		Hydroxyethylcellulose Gel DAB (Table 12.35)
	Solution		Blends of ethanol/isopropyl alcohol, propylene glycol and water
Scalp (dry)	Solution (washable, oily)		Vegetable oils, octyldodecanol, triglycerides medium-chain blended with surfactants (for example macrogol lauryl ether)
Open wounds	Solution (sterile)		Physiological saline solution
	Hydrophilic gel (sterile)		Isotonic carbomer gels

To be effective, a locally applied corticosteroid must penetrate into the skin. The rate and extent of penetration is determined for a large extent by the formulation of the base. By adding penetration enhancers such as salicyl acid or urea the penetration of the active substance is enhanced. In this way a class I or II corticosteroid containing preparation becomes more effective.

A particular way to enhance the penetration of substances into the skin is iontophoresis, see also Sects. 12.7.11 and 16.2.5.

12.3.3 Choice of the Base

The base of cutaneous preparations does not only influence the release of the active substance, it can contribute to the therapeutic effectiveness of the preparation itself. In some cases the base alone may sufficiently influence healing, by which the addition of an active substance is unnecessary. In such cases the physical properties of the base are utilised, such as: cooling; dehydration or protection by indifferent solids; prevention of dehydration by hydrophobic components. The correct choice of the base is very important for wet and dry skin disorders. If the skin is neither dry nor wet the choice of the base is much less important than the active substance. The classification of a number of bases appropriate for several skin conditions has been summarised in Table 12.3 for a gradual transition from wet to dry skin and for specific skin conditions.

Usually the base of a cutaneous preparation is prescribed by the physician. But sometimes the pharmacist is free to choose it on his own authority. Both, physician and pharmacist, have to take the following factors into consideration:

- The base should not irritate or sensitise.
- The base should not adversely influence the active substances.
- The base has to be cosmetically acceptable, preferably not shiny and not sticky after spreading on the skin.
- The choice of the base depends on the skin conditions (whether the disease is in an acute or chronic state) and the skin type.

12.3.4 Base and Different Skin Disorders

12.3.4.1 Acute Skin Disorders

Acute exsudative skin disorders are usually treated with wet packs first, for example with black tea because of the astringent effect of the tannin content. Dressings wetted with

physiological saline solutions or water are used as well. As a result of evaporation of water the dressings will absorb fluid and purulence from the skin. The dressings have to be changed a few times a day. They should not be wrapped in plastic because that prevents water from evaporating and the dressings will not be effective. The treatment with wet dressings results in cooling and drying of the skin.

Not recommended for the treatment of acute exudative skin disorders are:

- Hydrophilic suspensions, because the powder that remains on the skin after drying can irritate and damage it
- Powders for cutaneous application for the same reason, except powders consisting of absorbable sterile lactose

For the acute state of the disorder, if without strong exudation, hydrophilic suspensions are appropriate. They typically contain a relatively high amount of water and solid substances. Solid substances act as a drying agent on the skin because of their water absorbing property. The combination of a solid substance and water increases the evaporation surface area of water. This increases the cooling effect. Examples for such preparations are zinc oxide cutaneous suspensions.

When the skin has become dryer and is changing to a subacute state it can further be treated with a hydrophilic cream.

12.3.4.2 Normal Skin

For patients with normal skin conditions and also for patients with a subacute dermatosis hydrophilic creams are frequently used. If a preparation with more fat is needed for a slightly drier skin, hydrophilic creams with a higher amount of lipophilic components are applied. For an example a cream with added soft paraffin (Table 12.4).

A slightly dry skin may be treated with an extra fat containing hydrophilic cream. Patients with a very dry skin use cutaneous preparations with a high amount of lipophilic components. Lipophilic creams are suitable for the treatment of the chronic state of atopic eczema. Hydrophobic ointments or saturated hydrocarbons are not indicated because they have an occlusive effect, which causes heat accumulation and enhances itching.

Table 12.4 Soft Paraffin Cetomacrogol Cream [8]

Cetomacrogol emulsifying wax (BP)	15 g
Paraffin, liquid	12.5 g
Paraffin, white soft	22.5 g
Propylene glycol	10 g
Water, purified	40 g
Total	100 g

12.3.4.3 Strong Keratotic Disorders

A strong keratotic skin is treated with hydrophobic ointments. Hydrophobic anhydrous bases cover the skin and prevent evaporation of water, the skin becomes hydrated. Examples for such disorders are ichthyosis or psoriasis.

12.3.4.4 Greasy (Oily) Skin

For a seborrheic skin hydrophilic bases have to be chosen: hydrophilic gels, emulsions or creams. Especially for acne treatment bases without or with only a small percentage of lipophilic components are indicated.

12.3.4.5 Itching Skin Disorders

Hydrophilic suspensions (liniments, lotions) are suitable for application on large itching areas if the skin is not damaged. The evaporation of the liquid components will cool the skin and reduce the itch.

12.3.4.6 Scalp

For the treatment of the scalp hydrophilic solutions and hydrogels, liquid emulsions and washable liquid oils are used. Examples are olive, almond or refined castor oil, as well as fatty alcohols such as octyldodecanol, all in combination with a surfactant, for instance macrogol lauryl ether 4. The decision for one or the other base depends on the skin conditions. A seborrheic scaling scalp is often treated with hydrophilic preparations, a dry and scaling one is treated with liquid oils.

12.3.4.7 Piles

Hydrophilic creams with a high amount of lipophilic components are appropriate for the treatment of haemorrhoids. These creams cover the painful, damaged mucous membrane. Soft Paraffin Cetomacrogol cream FNA or Cream base DAC (Tables 12.4 and 12.6) are two examples for suitable bases. Thinner creams may flow off easily. A more lipophilic base is not desirable because of the chance on maceration: the weakening of the skin by long time exposure to moisture.

Preparations intended for application to other mucous membranes are described in Chaps. 6 Pulmonary, 7 Oropharynx, 8 Nose, 11 Rectal and vaginal, 14 Irrigation and dialysis.

12.3.4.8 Open Wounds

In modern wound management aqueous solutions (irrigations) and hydrogels are mentioned to be applied on deep and chronic wounds. Other preparations such as creams ointments and powders are described as well but have some disadvantages. Components of these preparations may not be removed from the wound easily and lipophilic compounds can hinder secretion. Cutaneous preparations with zinc oxide should not be used on open wounds because

they dry out the edges of the wound. The consequence is delayed wound healing. Talc can cause the formation of granulomas and should therefore be avoided as well. As a typical powder base for wound powders absorbable sterile lactose is often used. In general cutaneous preparations that are applied to large damaged areas of the skin (wounds) must be sterile, because the natural barrier of the skin against micro-organisms is lacking. The specific formulations are described in Sect. 12.7.17.

12.3.5 Method of Application and Dosing

12.3.5.1 Method of Application

In general hydrophilic creams (o/w-creams) and emulsions are used without a bandage. Whether to cover the application site after application of lipophilic creams (w/o-creams) and ointments depends on the skin conditions. To soften a skin area with a strong keratinisation covering the lipophilic preparation with a bandage is effective. Fatty pastes and pastes with a cooling effect can be put on lint first. Thereafter the application site is dressed with a bandage.

12.3.5.2 Quantity to Be Applied

If the cutaneous preparation is going to be applied because of its physical properties, such as the prevention of dehydration, ample application is desirable. If the preparation is mainly acting by its active substance, the amount to be applied is expressed in fingertip units to prevent underdosing when the patient is told "to apply thin", as well as overdosing [9].

The FTU reflects a stripe of cream or ointment with a length from the tip of the index finger of an adult to its first crease. One FTU is approximately 0.5 g of cream or ointment. This is sufficient to cover 300 cm^2 of skin. Depending on the body part to be treated more FTU's can be applied (see Table 12.5).

Another approach is that for hydrophilic creams the amount should be limited to as much as the skin can absorb. Lipophilic creams and hydrophobic ointments should be applied in a thin layer until the skin feels slightly fatty.

12.3.5.3 Application Frequency

Neutral bases should be applied at least twice a day, but may be applied as often as desired. Cutaneous application of corticosteroids results in the formation of a depot of the active substance in the stratum corneum. As a consequence the frequency of application may be reduced after some time. Application once a day is generally sufficient for effective therapy.

Table 12.5 FTU dosing

	Head and neck	Arm and hand	Leg and foot	Torso (front side)	Back and bottom	Whole body
Age	Number of FTU (fingertip units)					
3–12 months	1	1	1½	1	1½	40
1–2 years	1½	1½	2	2	3	24
3–5 years	1½	2	3	3	3½	18
6–10 years	2	2½	4½	3½	5	14
adults	2½	4[a]	8[b]	7	7	8

[a]For one hand of an adult one FTU is necessary
[b]For one foot of an adult two FTU are necessary

For the treatment with corticosteroids several options of therapy are established:

- Interval therapy implies treatment with the corticosteroid containing preparation for some days alternating with the base for some days.
- Gradual therapy starts with a stronger corticosteroid in the initial phase for up to 7 days. Then step by step weaker corticosteroids are used.
- Proactive therapy: After the symptoms have disappeared, the application of the corticosteroid will be continued with a frequency of two times a week.

12.3.5.4 Duration of Therapy

How long a cutaneous preparation has to be used depends on the disorder and the typical period in which an active substance reaches its therapeutic effect. Usually corticosteroids or antibiotics should be applied for only a few days if applied every day. The treatment with an antimycotic may take a longer time. In general the physician should see the patient regularly to assess the effectiveness of the therapy. The preparation should therefore be prescribed in a limited amount appropriate to the treatment scheme.

12.3.6 Occlusive and Transdermal Preparations

Cutaneous preparations are inefficient formulations since only small amounts of the applied active substance penetrate the skin and reach the site of action. The first attempts to understand the mechanism of skin permeation and formulation effects of cutaneous preparations were described in 1960 [10]. Since then more research has been performed on rational design of dermal formulations. Much research is focused on improved skin penetration [11, 12]. Skin

penetration is discussed in detail in Sect. 16.2.5 Dermal and transdermal administration.

Relatively new developments of enhanced skin penetration are cutaneous and transdermal patches. The European Pharmacopoeia distinguishes medical plasters and cutaneous patches which are classified as 'Semisolid Preparations for Cutaneous Application [4] and transdermal patches which are described in a separate monograph [4].

12.3.6.1 Cutaneous Patches

According to the European Pharmacopoeia 'cutaneous patches are flexible preparations containing 1 or more active substances. They are intended to be applied to the skin. They are designed to maintain the active substance(s) in close contact with the skin such that these may act locally'. Cutaneous patches consist of an adhesive basis spread as a uniform layer on an appropriate support made of natural or synthetic material. The adhesive basis is not irritant or sensitising to the skin. The adhesive layer is covered by a suitable protective liner, which is removed before applying the patch to the skin.

Skin permeation of the active substance after application of cutaneous patches is enhanced compared to conventional cutaneous preparations because of the occlusive effect of the patch. In this way relatively high concentrations in the skin are obtained. In contrast to transdermal patches plasma concentrations will be low and no systemic side effects are observed.

Examples of cutaneous patches are lidocaine containing patches that sometimes contain a second local anaesthetic. After applying the patch, lidocaine penetrates deep into the skin where it has a local anesthetising effect. Capsaicin containing patches are used in the treatment of peripheral neuropathic pain in non-diabetic adults. Following exposure to the patch, capsaicin penetrates the skin and interacts with the cutaneous transient receptor potential vanilloid 1 receptor (TRPV1) resulting in pain relief.

12.3.6.2 Medicated Patches

The European Pharmacopoeia also defines medicated plasters as semisolid preparations for cutaneous application. According to the European Pharmacopoeia "medicated plasters are flexible preparations containing 1 or more active substances. They are intended to be applied to the skin. They are designed to maintain the active substance(s) in close contact with the skin such that these may be absorbed slowly, or act as protective or keratolytic agents". 5-Aminolevulinic acid medicated plasters represent this dosage form. They are used in photodynamic/radiation therapy. The plasters are applied to mild to moderate actinic keratosis lesions. Four hours after application the plasters are removed and the lesions are exposed to red light.

12.3.6.3 Transdermal Patches

In contrast to cutaneous patches and medicated plasters, transdermal patches are designed for delivery of an active substance into the systemic circulation and consequently to achieve a systemic effect.

According to the European Pharmacopoeia "transdermal patches are flexible single-dose preparation intended to be applied to the unbroken skin to obtain a systemic delivery over an extended period of time". Manufacturers design patches in a variety of ways. However, in general patches can be categorised in two main types: the reservoir and the matrix systems. In reservoir systems the active substance may be dissolved or dispersed in a semisolid basis or in a solid polymer matrix, which is separated from the skin by a rate-controlling membrane. Matrix systems contain the active substance in a solid or semisolid matrix, the properties of which control the diffusion pattern to the skin. The matrix system may also be a solution or dispersion of the active substance in the pressure-sensitive adhesive. The releasing surface of the patch is covered by a protective liner to be removed before applying the patch to the skin. The principles of different types of transdermal patches are given in [13]. To improve drug delivery to the systemic circulation transdermal patches often contain excipients to enhance penetration into the skin.

Transdermal patches are an alternative for patients that are not able to take oral medication. Advantages of transdermal patches are that they are easily applied and may prevent more painful and arduous parenteral administration. Moreover, transdermal administration is advantageous for active substances that undergo extensive first-pass metabolism, active substances with narrow therapeutic window or active substances with a short half-life, which cause noncompliance due to frequent dosing.

For transdermal drug transport the active substance should have appropriate physico-chemical and pharmacological properties. Although different requirements are described in literature, in general the molecular weight of the active substance should not exceed about 500 Da, the partition coefficient (log P(octanol/water)) should be between 1.0 and 4.0 and the dose should be low (less than 20 mg/day). Recent research focusses on transdermal delivery of active substances that do not meet these requirements, such as relatively large molecules.

Transdermal patches registered at present are patches containing active substances such as buprenorphine, estradiol, fentanyl, glyceryl trinitrate, nicotine, oxybutynine, rivastigmine, rotigotine and scopolamine. These transdermal patches are used in the treatment of a variety of diseases. They release the active substance during a period of 24 up to 72 h, depending on the type of patch used and the active substance. After application of the patch plasma concentration slowly rises until a steady concentration is reached.

During application a depot of the active substance is formed in the skin. After removal of the patch plasma concentrations will gradually but slowly diminish. Because of the absorption of the active substance from the depot in the skin even after the patch has been removed, elimination from the plasma will be slower than anticipated based on i.v. or oral elimination data. Therefore, when switching from transdermal patches to oral medication it should be taken into account that the active substance is still present in the systemic circulation. The oral dosing time and dose should be adapted accordingly.

Well known as transdermal patches are those containing fentanyl. Fentanyl is used in the treatment of severe chronic pain. Fentanyl is rapidly metabolised in the liver resulting in low bioavailability after oral administration. After application of the patch, 90 % of the released amount reaches the systemic circulation. After first application the plasma concentration increases gradually, stabilises after 12–24 h and is stable up to 72 h [14]. Fentanyl transdermal patches often offer an adequate alternative to parenteral opioid administration in patients who are not able to take their medications orally.

12.4 Adverse Effects

Adverse effects of cutaneous preparations may be: undesirable systemic effects, (photo) toxicity, irritation or (photo) allergic responses after sensitisation. Substance monographs [15], package leaflets or SmPCs of licensed products and medicine databases give information about these adverse effects.

Toxic systemic effects have been reported for salicylic acid, resorcinol, lindane or mercury substances. These effects are related to the substance, the amount of preparation and the body surface area to which it is applied, the skin conditions and duration of treatment. Symptoms for systemic intoxications are for example headache, nausea and vomiting, convulsions, fall in blood pressure, kidney damage or metabolic acidosis. Apart from salicylic acid the mentioned substances are no longer used because of these systemic adverse effects and the limited therapeutic significance in cutaneous preparations. Especially infants and toddlers are susceptible for systemic adverse effects because their skin is thinner. Additionally, the relative body surface area in relation to body contents in children is larger than in adults. For salicylic acid in infants and toddlers the only indication is psoriasis. It should be used in low concentrations and on a limited body surface area.

Irritation is induced by active substances that chemically damage cells of the skin. The strength of the effect depends on the concentration of the irritating substance. Irritation is expressed by redness, itching and sometimes erosion of the skin. Decreasing the concentration can prevent irritation. However, the therapeutic effect will be reached later as well. As irritation also depends on the individual sensitivity of the patient´s skin the tolerance differs individually. An example of an irritating active substance is tretinoin. The decrease of the concentration can lead to better tolerance. Some patients have to get used to the irritating effect in order to be able to tolerate later during the treatment higher or more irritating concentrations. Some active substances that are known to be irritating in cutaneous preparations are benzoyl peroxide, dithranol, hydroquinone, iodine, capsaicinoids and salicylic acid.

An allergic reaction is an immunogenic reaction that may be limited to redness of the skin but may also be severe. An allergic reaction occurs if the patient is sensitised against the substance. The risk of getting sensitised via the skin is relatively high. Once a person is sensitive to a substance, he or she will never tolerate the substance anymore. If the allergic reaction is caused by an excipient, the active substance can still be used, but in a base with different excipients. Excipients that are known to be sensitising are methyl parahydroxybenzoate and propyl parahydroxybenzoate, wool alcohols and cetostearyl alcohol. Examples for sensitising active substances are neomycin, tetracain and clioquinol.

A photosensitisation or phototoxic reaction occurs if the skin is exposed to sun light or artificial sun light (e.g. solarium). Examples of substances that are known to cause such reactions are benzoyl peroxide, coal tar, methoxsalen and essential (volatile) oils. Intensive exposition to (artificial) sunlight has to be avoided while and after using these substances. Appropriate clothing and sunscreen are recommended. Methoxsalen and in special cases coal tar are applied for a treatment with ultraviolet light. It is monitored by the physician and the photosensitisation is desired.

Some medicines can cause abnormal reactions to sun light or artificial light equally whether they are intended for oral or dermal administration. The phototoxic reaction may be toxicological or immunological. It is very difficult to distinguish a phototoxic reaction from a photoallergic one. Moreover, a combination of these reactions also occurs. The substance is than phototoxic as well as photoallergic.

12.5 Product Formulation

Cutaneous preparations may consist of a simple or a more complex formulated base in which one or more active substances can be dissolved, dispersed or mixed. Bases often contain several phases: a solid phase, an aqueous, a lipophilic phase and an interphase. In this section the properties, function and excipients of each phase are discussed. Active substances or excipients may make up the solid phase. The aqueous phase may contain the active substance, excipients that improve the microbiological stability or sometimes excipients that improve physical stability of the preparation. The lipophilic phase influences and improves the consistency of the cutaneous preparation. If there is an aqueous and a lipophilic phase in the preparation,

there is also an interphase. In cutaneous preparations a number of specific emulsifying agents are applied, which are described. Because of the presence of several phases, the physical and chemical stability and potential incompatibilities have to be considered in the design of the formulation. Last but not least the preservation and packaging which can play a role in the chemical, physical and microbiological stability and shelf life of cutaneous preparations are important issues of this section.

12.5.1 Solid Phase

The solid phase contains solid substances which are dispersed in a liquid phase or a semisolid base. Powders for cutaneous application consist only of a solid phase. The solid substances can be active substances or excipients.

12.5.1.1 Particle Size

The particle size of solid substances of both excipients and active substances is important not just for biopharmaceutical properties (see Sect. 12.3.2) but also for the physical and chemical properties of cutaneous preparations. If the solid is dispersed in a liquid base, the particles must be sufficiently fine to obtain a physically stable suspension (see Sect. 18.4.2). However decrease of particle size may increase the rate of degradation. Additionally processing small particles may lead to agglomerates.

Solid particles should be small enough not to be felt when being applied onto the skin of the patient. The Ph. Eur. doesn't give detailed guidance for particle size in the chapters for cutaneous dosage forms (see Sect. 12.2) just that it has to be suitable for application. A maximum particle size of 90 μm in powders, hydrophobic and hydrophilic ointments and in creams is generally accepted and therefore recommended.

Many solid raw materials are meant to be used in cutaneous preparations are processed in their micronised state (see Sect. 23.1.8 for definitions) mainly for improving the release of the active substance (see Sect. 12.3.2).

In case of solutions small particles may increase the speed of dissolving.

Tetracycline hydrochloride is in the Netherlands available in two qualities, microcrystalline and 'ponderosum' ('heavy'). Tetracycline hydrochloride ponderosum consists of agglomerates of the microcrystalline substance and has a shelf life of 3 years, has a better flowability and is much less susceptible to degradation than the microcrystalline form. It is mainly used for capsule preparation. Because of the small particles microcrystalline tetracycline hydrochloride is easier to process in cutaneous preparations than the ponderosum quality. The disadvantage of the microcrystalline quality is that during storage epi- and anhydro degradation products may be formed. Only 1 % of these substances are allowed in tetracycline hydrochloride [16]. The degradation is visible as a discolouration to a darker yellow. Generally a cream prepared with the ponderosum quality has a lighter colour than a cream containing the microcrystalline quality.

In practice the more stable 'ponderosum' quality can be dispersed in cutaneous preparations anyway by firstly triturating with water in a mortar with a pestle. It is likely that due to the water the outer layer of the tetracycline hydrochloride particles dissolves causing the particles to disperse.

12.5.1.2 The Function of Solid Excipients

Sometimes it is not clear whether an excipient is solely an excipient or has active substance properties.

In dermal bases indifferent solid substances may:

- Act as filler material: powders for cutaneous application sometimes need a filler
- Increase the consistency
- Cause cooling and drying of the skin; finely divided solid excipients enlarge the surface of the skin resulting in increased evaporation of water and increased loss of warmth
- Act as an adhesive; some solid excipients, such as talc result in an improved adherence of the preparation on the skin
- Act as astringent; salts, aluminium oxide and zinc oxide cause the skin to astringe; the blood capillaries contract and slow down the exudation
- Prevent agglomeration (anhydrous colloidal silica)

Apart from the general descriptions in Chap. 23, some details, also on function, are given on the most important solid excipients for cutaneous preparations:

Talc is a silicate often used in powders and suspensions for cutaneous application. It is a fine substance that consists mainly of magnesium silicate, but also contains some aluminium silicate. It has good flow properties and adheres well to the skin. It has a very low water absorbing capacity. A disadvantage of talc is the chance on formation of granulomas if it ends up in wounds. The combination of talc and zinc oxide in combination with water or other volatile solvents results in cooling of the skin. The cooling is the result of an increased surface area which allows water to evaporate more easily.

Zinc oxide is an astringent. It dries, cools and protects the skin and is weakly antibacterial. It may be used in nearly all types of cutaneous preparations. However, it is unsuitable for the hairy skin because it cannot be washed out.

Calamine is a mixture of zinc oxide, basic zinc carbonate and zinc silicate with a small amount of ferric oxide. Calamine gives a salmon colour to preparations.

Magnesium stearate and *zinc stearate* cool and cover the skin and in combination with fatty oil, such as arachis oil, they form magnesium oleate and zinc oleate. These oleates act as thickening agents and render the oil into oleogels (see Sect. 23.7.3 and Table 23.20).

Potato starch or *rice starch* is generally used as a component of cutaneous powders and pastes with a high amount of solids. Starch absorbs a high percentage of water. As a result it swells. This may lead to the formation of a crust on wounds. It is therefore not suitable for acute exsudative skin disorders.

12.5.2 Lipophilic Phase

The lipophilic phase consists of hydrophobic, oily semisolid and liquid substances. With regard to chemistry only triglycerides are defined as fats. Hydrophobic substances such as hydrocarbons, waxes and fatty alcohols are not fats. However, the hydrophobic phase is often named as 'fat phase'. It covers the skin and prevents the evaporation of water. As a result the skin becomes hydrated. The degree of hydration depends on the properties of the hydrophobic components. Hydrophobic substances that do not penetrate the skin generally have a stronger hydrating effect as those that penetrate.

Hydrophobic substances are classified based on their structure:

12.5.2.1 Hydrocarbons (Paraffin Waxes)

Hydrocarbons such as liquid paraffin and white soft paraffin are also called mineral oils. They hardly penetrate the skin and in cutaneous preparations they are mainly used for protection of the surface of the skin or occlusion. They absorb little or no water. Because they cover the skin they prevent evaporation of water and hydrate the skin. Hydrocarbons are used in lipophilic creams, hydrophobic ointments and pastes.

12.5.2.2 Fatty Oils and Fats

In chemical terms fatty oils and fats are esters of glycerol and fatty acids. Arachidis oil and Miglyol 812 (medium chain triglycerides) are examples of often used fatty oils. In contrast to hydrocarbons they are biodegradable. They hardly absorb water but cover the skin less extensive than the hydrocarbons. Fatty oils and fats reduce the viscosity of semisolid cutaneous preparations and improve their spreadability. They are used in soft pastes for example.

12.5.2.3 Fatty Alcohols

Fatty alcohols such as cetostearyl alcohol and wool alcohols are lipophilic chains with a hydroxyl group at the end. Because of the combination of the lipophilic chain and the hydrophilic hydroxyl group these structures reduce the surface tension (see Sect. 18.4.3). Cetostearyl alcohol is a mixture of cetyl alcohol and stearyl alcohol. It is a weak water-in-oil emulsifying agent and it is a component of self-emulsifying waxes.

12.5.2.4 Waxes

Waxes such as bees wax, wool fat and decyl oleate are esters of fatty alcohols and fatty acids (see Sect. 23.3.5). The solid waxes are mainly used to improve the consistency of semisolid preparations. Due to the presence of impurities such as fatty alcohols some waxes are weak w/o emulsifying agents. Although wool fat is classified as a wax it has different characteristics due to its 'impurities'. Wool fat is extracted from the wool of sheep by water. It consists of a complex and variable mixture of several esters and polyesters of alcohols (wool fat alcohols) of high molecular weight and fatty acids. Wool fat is a stronger emulsifier than other waxes because of the presence of these esters. It can absorb water in a range up to 25 % of its weight. Hydrous wool fat (lanoline) is a w/o emulsion consisting of 75 % wool fat and 25 % water. Decyl oleate is a liquid and is used as a component of the lipophilic phase in o/w creams.

The liquid isopropyl myristate is closely related to the waxes. However it is not a wax as it is not an ester of a fatty alcohol and fatty acid. It has similar characteristics to fatty oils. It is mainly used to enhance the spreadability of oil-in-water emulsifying ointments.

12.5.3 Aqueous Phase

The aqueous phase may contain, apart from water, water-miscible liquids as humectants, co-solvents or penetration enhancers. The aqueous phase has to be preserved. If substances are dispersed in the aqueous phase they are considered part of the solid phase (see Sect. 12.5.1). For the substances reference is made to appropriate sections of Chap. 23 Raw materials. Just some functional details are mentioned here.

12.5.3.1 Water

The use of purified water is recommended to keep the initial contamination low and thereby to hold the Ph. Eur. requirements for microbiological quality of non-sterile pharmaceutical preparations. The requirements of the chemical and microbiological purity of purified water are well defined, see Sect. 23.3.1. The concentration of ions in purified water is low, which is an advantage as they may catalyse degradation of active substances and excipients and form complexes with active substances and excipients.

12.5.3.2 Co-solvents

Ethanol (see Sect. 23.3.2), propylene glycol (see Sect. 23.3.3) and glycerol (see Sect. 23.3.3) are often used as co-solvents (see Sect. 18.1.3).

The formula should allow hydrophilic active substances and excipients to dissolve completely in the aqueous phase. Information on solubility of substances can be found in several reference works [15, 17, 18]. However, the solubility in mixtures of solvents is only rarely to be found. It is not identical to the solubility in separate solvents because it is influenced by the interaction between the solvents.

12.5.3.3 Prevention of Water Loss (Humectants)

Water easily evaporates from warm skin. Due to evaporation a cutaneous preparation looses its characteristics. To prevent water loss humectants are added. Humectants are non-volatile solvents that prevent water loss during storage as well as after application to the skin. Examples are propylene glycol, glycerol 85 % and sorbitol 70 %. Humectants are often used in cutaneous suspensions, hydrophilic creams and hydrogels.

12.5.3.4 Viscosity Enhancement

Increasing the viscosity of the aqueous phase will result in the formation of a gel, which may be applied easier to the skin than water. In creams the increase of the viscosity may improve the physical stability of the emulsion, see Sect. 12.5.5. Carbomers 0.2–0.3 % (see Sect. 23.7.3.5) and cellulose derivates (see Sect. 23.7.3.2) are used for this purpose. A gel with carbomers is clear and leaves no residue on the skin. The disadvantage of carbomers is that the viscosity of the aqueous phase increases only at pH 6 or higher. Active substances that require a low pH, for example because of solubility or stability, are not compatible with carbomer gels. Additionally, the negative charge on the carbomer molecule causes many incompatibilities with cationic substances. Cellulose derivates show less incompatibility than carbomer but a disadvantage is the formation of a thin layer on the skin, a so called xerogel, after evaporation. This gives the patient a tightening sensation.

Enhancing the viscosity of an aqueous suspension is often necessary to obtain a reasonable physical stability (see Sect. 18.4.2.2). Apart from the already mentioned viscosity enhancers, also mineral viscosity enhancing substances, such as anhydrous colloidal silica (2–4 %, usually 2 %), and colloidal aluminium magnesium silicate (2–4 %, usually 2 %) or bentonite (1–2 %) are used. All percentages refer to the final amount of the preparation.

12.5.3.5 Preservation

Pharmaceutical preparations that contain water are susceptible of microbiological contamination. This applies specifically to preparations in which water is the outer phase (o/w emulsions). In hydrophilic emulsions microbiological contamination can easily spread throughout the whole preparation. Moreover, the outer phase has contact with the environment where microbiological contamination originates.

To ensure the microbiological quality of cutaneous preparations the following measures should be taken:

- Ingredients should have a low initial microbiological contamination (see Sect. 23.1.7). Specifically ingredients of natural origin and water may contain relatively high amounts of micro-organisms.
- The aqueous phase has to be preserved by the addition of preservatives or other substances with a preserving function. Many preservatives are sensitising; sorbic acid and methyl parahydroxybenzoate are commonly used. Consideration should be given to not using preservatives if the preparation is intended for large skin surfaces, in order to reduce the risk of sensitisation.

If the aqueous phase is emulsified in the lipophilic phase (w/o system) it is not always necessary to add a preservative. Theoretically, in w/o systems micro-organisms die inside the small water droplets due to a lack of oxygen and nutrients. If the initial contamination is low, if contamination during preparation is prevented and the microbiological quality is monitored at release, this theory may be applicable. If preservation is required in a w/o system propylene glycol could be added to the aqueous phase. Microbiological challenge tests for a w/o 'cooling ointment' (Table 12.31) showed that the addition of 10 % propylene glycol gave the formulation some preservative properties. The addition of 20 % would be even better, however in that formulation a compromise had to include improvement of microbiological stability without decreasing physical stability or increasing penetration too much.

Preservatives need to be hydrophilic as they act in the aqueous phase where micro-organisms live. To penetrate the cell wall of the micro-organism and interfere with the cell life cycle preservatives need to be hydrophobic as well. Because of the partly hydrophobic characteristics preservatives may diffuse into the lipophilic phase or will be solubilised in the aqueous phase. In this way the concentration of the preservative in the aqueous phase may become lower than required. Formulations of hydrophilic emulsions therefore will contain higher concentrations of preservatives than those of hydrophilic solutions.

Table 23.21 gives an overview of preservatives. For cutaneous preparations as said sorbic acid and methyl

Table 12.6 Cream Base DAC [19]

Glycerol monostearate 60	4 g
Cetyl alcohol	6 g
Triglycerides, medium-chain	7.5 g
Paraffin, white soft	25.5 g
Macrogol 20 glycerol monostearate	7 g
Propylene glycol	10 g
Water, purified	40 g
Total	100 g

parahydroxybenzoate are mostly used. Antimicrobial properties of ethanol and propylene glycol are often made use of.

The activity of the preservative depends on the concentration in the aqueous phase and therefore on the partition coefficient (n-octanol/water). Because of its relatively favourable partition coefficient sorbic acid is a suitable preservative for o/w emulsions. Therefore it is often used in hydrophilic cream bases. Sorbic acid holds a carboxyl group that is deprotonated above pH 4–5. Sorbic acid only takes effect in the non-ionised form that means only in acidic solutions. However, at relatively low pH sorbic acid is degraded by oxidation. To prevent oxidation sorbic acid is often used in combination with potassium sorbate in order to obtain a pH value of 4–5.

Methyl hydroxybenzoate has an unfavourable partition coefficient. Therefore it is not a suitable preservative for o/w emulsions. It is mainly used in hydrogels. In some countries a combination with propyl hydroxybenzoate is used as 'Preserved water'. A typical mixture contains 0.075 % of methyl parahydroxybenzoate and 0.025 % of propyl parahydroxybenzoate in purified water.

Propylene glycol acts as a preservative in concentrations above 20 % of the aqueous phase. However, it is less active than sorbic acid and methyl hydroxybenzoate. It is most effective in combination with surfactants (especially hydrophilic) and other components of creams and emulsions. Cream Base DAC (Table 12.6) is an example. It contains 20 % of propylene glycol in the aqueous phase and macrogol 20 glycerol monostearate as hydrophilic surfactant. It is well preserved in this way.

Propylene glycol can also be used in o/w emulsions with a pH higher than 5, because it is effective independent from pH. It has to be considered, that propylene glycol may be irritating and may act as a penetration enhancer.

Glycerol 85 % is a less potent preservative than propylene glycol. It acts as a preservative above 30 %. In lower concentrations it is less effective. Microbiological challenge tests of a zinc oxide cutaneous suspension for example showed an insufficient effect in a concentration of 110 mg/g Glycerol 85 %. Therefore it was replaced with propylene glycol (150 mg/g) (Table 12.21). Another option is the increase of the glycerol 85 % concentration up to 30 %.

Ethanol acts as a preservative when present in a concentration above 15 %. If sufficient ethanol is present other preservatives are not needed.

12.5.4 Interphase

The interphase is the phase between the aqueous and the lipophilic phase. For the integration of the aqueous phase and the lipophilic phase a surfactant is needed (see Sect. 18.4.3). Surfactants reduce the surface tension between both phases resulting in the formation of an emulsion, see Sect. 12.5.5. Surfactants are used in emulsions for cutaneous application such as creams and water emulsifying ointments. The emulsifying capacity of the surfactant is determined by the HLB value (see Sect. 18.4.3). These characteristic and to a certain degree the ratio water-fat determines whether an emulsion will be an oil in water (o/w) or a water in oil (w/o) emulsion. Surfactants are described in Sect. 23.6. In this section their function in cutaneous emulsions is summarised.

12.5.4.1 Oil- in-Water Emulsions

In o/w emulsions often combinations of o/w and w/o substances are used because the combination gives a more stable emulsion than only one o/w emulsifier (see Sect. 18.4.3).

The following emulsifiers are used for cutaneous o/w emulsions:

- Cetomacrogol emulsifying wax BP [20] – non-ionic, containing 20 % of macrogol cetostearyl ether, a strong o/w emulsifier and 80 % cetostearyl alcohol, a weak w/o emulsifier
- Emulsifying wax BP [20] (Lanette emulsifying wax) – anionic, containing 10 % of sodium laurylsulfate, a strong o/w emulsifier and 90 % cetostearyl alcohol
- Sodium cetostearyl sulfate
- Polysorbate 80
- Cetrimide

The selection of the surfactant is mainly based on the compatibility with the active substance. Sodium lauryl sulfate is an anionic surfactant and therefore incompatible with cationic active substances. Cetomacrogol emulsifying wax BP is incompatible with high concentrations of phenolic substances due to an interaction of the phenolic group with the polyethylene glycol chains in the macrogol cetostearyl ether. It is compatible with acids, high concentrations of electrolytes and cations.

12.5.4.2 Water-in-Oil Emulsions

In water-in-oil (w/o) emulsions and hydrophobic creams, glycerol mono-oleate and wool fat are mainly used as emulsifiers. These substances are part of the lipophilic

Table 12.7 Lauromacrogol Hydrophilic Emulsion 5 % [21]

Lauromacrogol 400	5 g
Propylene glycol	20 g
Carbomer 980 or 974 p	0.25 g
Trometamol	0.2 g
Cream base DAC[a]	10 g
Water, purified	64.55 g
Total	100 g

[a]See Table 12.6

Table 12.8 Dimethyl Sulfoxide Paraffin Cream 50 % [22]

Dimethyl sulfoxide	50 g
Carbomer 974P	1 g
Soft paraffin Cetomacrogol cream FNA[a]	46 g
Paraffin, white soft	3 g
Total	100 g

[a]See Table 12.4

Table 12.9 Calamine Cutaneous Suspension [23]

Calamine BP	15 g
Aluminium magnesium silicate	3 g
Glycerol (85 %)	6.1 g
Phenol, Liquefied BP	0.5 g
Sodium citrate	0.5 g
Zinc oxide	5 g
Water, purified	90.9 g
Total	121 g (= 100 mL)

phase and are weak emulsifiers. If a stronger w/o surfactant is needed sorbitan esters of fatty acids, such as sorbitan oleate (span 80), can be used. Triglycerol diisostearate is a w/o surfactant used in a lipophilic cream with a high content of water (Table 12.32).

12.5.5 Physical Stability

12.5.5.1 Emulsions

Emulsions consist of hydrophilic and hydrophobic ingredients. Therefore emulsions are not physically stable and the phases may separate into a water layer and a fatty layer. The physical stability of emulsions can be increased by decreasing the size of the droplets of the inner phase, by increasing the viscosity of the outer phase and first of all by decreasing the surface tension between the aqueous and the lipophilic phase. The presence of an active substance can influence the stability of an emulsion negatively. Enhancing the viscosity of the aqueous phase may increase the physical stability of an emulsion. Thereby sometimes the percentage of fatty phase can be decreased. An example is the emulsion base in Table 12.7, where carbomer has been used for the viscosity enhancement.

Another example of the use of carbomer for enhancing the viscosity is a 50 % dimethyl sulfoxide paraffin cream (Table 12.8). Dimethylsulfoxide is commonly needed in high concentrations in creams, which cause destabilisation of the cream base. With the formulation of Table 12.8 a stable cream with a fine emulsion structure is created. The physical stability of emulsions can be tested by temperature cycles, see Sect. 22.5.3.

12.5.5.2 Suspensions

Liquid suspensions are physically unstable as well due to settling of the solid particles. The settling rate can be decreased (see Sect. 18.4.2.1) by:

- Decreasing particle size
- Diminishing the difference in density between the internal and the external phase (fluid)
- Increasing the viscosity of the external phase

Zinc oxide cutaneous suspensions are usually stable without a viscosity enhancer because of the fineness and the high percentage of the solid particles. The addition of a viscosity enhancer may cause a decrease of the cooling effect of the preparation.

Resuspendability can be increased by increasing the degree of flocculation of the particles (see Sect. 18.4.2.1) by the addition of a flocculating agent. An example of such is sodium citrate which is used in a cutaneous suspension with calamine (Table 12.9).

12.5.5.3 Solutions

Dissolved substances (whether active substances or excipients) may crystallise during preparation or storage. Crystallisation may occur if the solvent (mixture) has not the potential to dissolve all solid or if the solubility changes by mixing several bases or by the addition of a solution to a base. The storage temperature plays an important role as well. Crystallisation may lead to crystal growth (see Sect. 18.1.6) leading to faster settling and having biopharmaceutical consequences.

The solubility of salicylic acid for example depends on its concentration, on the type of oil used as vehicle, or on the ratio in the solvent mixture. Fatty oils except castor oil have limited solubilising properties for salicylic acid (Table 12.10). Higher concentrations in oily solutions usually need the addition of castor oil to avoid crystallisation and crystal growth.

12.5.6 Chemical Stability

Chemical degradation in cutaneous preparations usually concerns oxidation (see Sect. 22.2.2) and hydrolysis (see

Table 12.10 Salicylic Acid Cutaneous Solution 10 % [24]

Salicylic acid	10 g
Castor oil, raffinated	60 g
Octyldodecanol	30 g
Total	100 g

Table 12.11 Tretinoin Cutaneous Solution 0.05 % [25]

Tretinoin	0.05 g
Butylhydroxytoluene	0.055 g
Propylene glycol	50 g
Ethanol (96 %)	49.9 g
Total	100 g

Sect. 22.2.1). Oxidation occurs in the presence of oxidising agents and hydrolysis in the presence of water. Therefore the components of the base and the pH influence the chemical stability of active substances. The chemical form of the active substance can affect the biopharmaceutical characteristics of the preparation which should be taken into account before adjusting the pH.

Table 12.12 Dithranol Cream 0.1 % [26]

Dithranol	0.1 g
Ascorbic acid	0.1 g
Salicylic acid (90)	1 g
Lanette cream I FNA[a]	98.8 g
Total	100 g

[a]See Table 12.34

Table 12.13 Betamethasone Valerate Cream 0.1 % [27]

Betamethasone valerate	0.1 g
Triglycerides, medium chain	0.4 g
Citric acid	0.025 g
Sodium citrate	0.025 g
Purified water	4.95 g
Cream base DAC[a]	94.5 g
Total	100 g

[a]See Table 12.6

12.5.6.1 Oxidation

Oxidising agents in cutaneous preparations may be active substances (benzoyl peroxide), peroxides from the base, oxygen from the air, light and ions of heavy metals. Oxidation is promoted by an increase in pH and temperature.

> Benzoyl peroxide is explosive and incompatible with active substances that can easily be oxidised. The raw material is moisturised with water and supplied as hydrous benzoyl peroxide. It contains at least 20 % of water. Benzoyl peroxide containing products should not be heated above 60 °C. It is recommended to use the content of one package with benzoyl peroxide completely to prevent evaporation of water upon repeated opening of the container.

Peroxides occur and may be generated in fat and oil but also in hydrocarbons, waxes and macrogols. Macrogol ointments (Table 12.29) are therefore not appropriate for active substances which are susceptible to oxidation.

To prevent oxidation the addition of an antioxidant (see Sect. 22.2.2) may be helpful but is not always necessary. The following measures may avoid or decrease risk of oxidation:

- Use of excipients of high quality, for instance fats and oils with a low peroxide value
- Choosing the right storage conditions, for instance in the refrigerator
- Storage in the right container, such as airtight containers that protect from light and heat
- Removal of air from the container in which the preparation is stored

If the addition of antioxidants is expected to be necessary the effectiveness always has to be tested, see Sect. 22.2.2. All-*rac*- alfa-tocoferol or butylhydroxytoluene (BHT) may be suitable antioxidants for the lipophilic phase. In the aqueous phase sodium metabisulfite or ascorbic acid are often used as antioxidants.

An example of a cutaneous preparation in which an antioxidant - butylhydroxytoluene - is added to prevent oxidation of the active substance is a tretinoin cutaneous solution (Table 12.11). During preparation tretinoin has to be protected from light and no metal utensils should be used.

Dithranol is oxidised rapidly in aqueous bases. Usually, ascorbic acid is added to the aqueous phase of hydrophilic creams containing dithranol (Table 12.12). Salicylic acid is added to the lipophilic phase. In hydrophobic dermal bases the addition of just salicylic acid is sufficient.

12.5.6.2 Hydrolysis

Hydrolysis is catalysed by water and is typical for water containing bases. pH influences hydrolysis as such and also by changing the fraction of dissolved substance that is available for degradation.

If an acidic environment is required for the stability of the active substance the pH may conveniently be adjusted to 3.5–5.5 with a citric acid-citrate buffer (Table 12.13).

For instance in creams with the easily hydrolysing tetracycline hydrochloride the pH is adjusted with a citric acid-citrate buffer to keep it undissolved.

12.5.7 Incompatibilities

The complexity of many cutaneous preparations may cause incompatibilities. This may lead to an excipient not functioning and an active substance being not effective anymore. In literature [28, 29] many excipients and their incompatibilities are described.

12.5.7.1 Cation/Anion

A known incompatibility by charge differences is the reaction of anionic surfactants with cations. Sodium cetostearyl sulfate (as compound of emulsifying cetostearyl alcohol type A, also known as Lanette N) and sodium lauryl sulfate (as compound of emulsifying cetostearyl alcohol type B, also known as Lanette SX) may cause this incompatibility. As a result the lipophilic and hydrophilic phases separate and the cream becomes almost fluid. An example of this effect is the incorporation of chlorhexidine gluconate in lanette creams. The anionic part of the emulsifier precipitates with the chlorhexidine gluconate, which not only decreases the physical stability of the cream but also the effectiveness of chlorhexidine.

12.5.7.2 Polyethylene Glycol Chains/Phenolic Groups

An often used o/w emulsifier in hydrophilic creams is cetomacrogol wax. This emulsifier is incompatible with high concentrations of phenols. It may cause immediate separation of the lipophilic and aqueous phase. The phenol group and the polyethylene glycol (PEG) chain of cetomacrogol interact rendering the PEG-chain less hydrophilic and decreasing the emulsifying power of cetomacrogol. But not every cream base containing an emulsifier with PEG-chains will become unstable with phenolic excipients. An example is Nonionic Hydrophilic Cream SR DAC (Table 12.33). It shows physical stability with salicylic acid up to 50 % and hydroquinone up to 2 %. That makes it difficult to assess the relevance of this incompatibility in advance.

12.5.7.3 pH Shift

Incompatibilities may also be created by a change in pH caused by addition of an excipient or active substance, for example salicylic acid. Degradation, dissolution or precipitation of other substances may be the unintentional result. For example erythromycin is only stable under weak alkaline conditions. It is inactivated quickly if processed with acids or acidic bases or stronger alkali. The pH value has to be adjusted within a close range. The choice of the stabilising agent depends on the pH value in the preparation. A too low pH has to be adjusted with an alkaline agent, for example trometamol; a too high one with an acid, for example citric acid.

> To increase the penetration of ketoconazole into the skin the prescriber sometimes requires the addition of 3 % salicylic acid to ketoconazole 2 % cream. Ketoconazole however is unstable in an acid environment [30]. Addition of salicylic acid to ketoconazole cream leads to an immediate degradation of ketoconazole, causing a blue discolouration.

Zinc oxide gives an alkaline reaction in water which leads to chemical incompatibilities in cutaneous preparations. One of the best known is the interaction with salicylic acid which is turned into salicylate. The keratolytic or penetration enhancing effect of salicylic acid is based on the acid function. Salicylate does not have these effects. The incompatibility may be prevented by replacing zinc oxide by titanium dioxide. Titanium dioxide is in comparison to zinc oxide only soluble in very strong acids. Therefore no interaction is expected.

12.5.8 Improvement of Colour and Smell

Colour correction of cutaneous preparations that have a covering colour (zinc oxide or titanium dioxide), may be desired for cosmetic reasons. The colour of the skin can be approximated by a mixture of ferric oxides. Zinc oxide mixtures can be made skin coloured with a mixture of yellow, red and brown or yellow, red and black ferric oxide. Because of the large variation in skin colours it is only possible to give some suggestions for such mixtures. For instance for 100 mL zinc oxide cutaneous suspension, 1 g of an iron oxide concentrated orange-like blend (Table 12.14) will probably do.

A calamine cutaneous suspension (Table 12.9), that is coloured pink by the ferric oxide in the calamine, may be adapted to the skin colour with water-soluble chlorophyll.

Table 12.14 Iron Oxide Concentrated Blend [31]

	Yellowish	Orange-like	Reddish
Iron oxide red	15 g	20 g	25 g
Iron oxide yellow	75 g	70 g	65 g
Iron oxide black	10 g	10 g	10 g
Total	100 g	100 g	100 g

Table 12.15 Containers of cutaneous preparations

Type of dosage form	Container with dosage delivery devices
Collodion	Bottle with brush or spatula
Creams and gels	Aluminium tube with internal coating, dose dispenser
Drops (external)	Bottle with dropper or another dosage device
Solutions, suspensions, emulsions	Bottle, possibly with roll-on or dabbing applicator or another dispensing cap (for example flip top cap with spray orifice)
Pastes	Jar with spatula
Shampoos	Plastic squeezing bottle (shampoo bottle)
Sticks	The lower part in aluminium foil, the whole stick in a jar
Powders for cutaneous application	Sifter-top container
Ointments	Aluminium tube with internal coating; for thick ointments jar with spatula

Surprisingly the green colour of chlorophyll compensates the excessive red of calamine.

Skin disinfection preparations sometimes get a signal colour to mark the disinfectant on the skin. Patent blue V (10 mg/L, for aqueous solutions) or azorubine (for alcoholic solutions) are suitable for this.

Smell correctors are only exceptionally added to dermatological preparations because of possible allergic reactions. Usually volatile oils are being used. The risk of an allergic reaction is supposed to be small for rose oil and lavender oil. An example of a smell corrector in a skin preparation is rose oil in a cooling ointment (Table 12.31).

12.5.9 Containers

The selection of a container is determined by the consistency, the purpose, the compatibility with the packaging materials and the degradation type (oxidation!) of the active substance. Many substances, active substances as well as excipients such as sorbic acid, may degrade under the influence of light. Cutaneous preparations are preferably packaged in a primary container that does not transmit light. General guidelines for packaging pharmaceutical dosage forms can be found in Chap. 24. Table 12.15 gives an overview of the containers and dosage delivery devices for cutaneous preparations.

Semisolid preparations that are prepared in stock and stored 'in bulk' may be packaged in well closable containers of polypropylene or brown glass. The size of the stock container is chosen in connection with the storage time, the speed of turnover of the preparation and in connection with the number of times the container will be opened (see Sect. 22.3.1).

As tubes may get dented, they can be packaged in a secondary container such as a tube folding box.

Table 12.16 Triamcinolone Salicylic Acid Cutaneous Solution 10 % [32]

Salicylic acid	2 g
Triamcinolone acetonide	0.1 g
Benzalkonium chloride solution	0.09 g
Alcohol denaturated 70 % V/V	86 g
Total	88.2 g (= 100 mL)

Fluid cutaneous preparations and cutaneous preparations with volatile substances such as ether or ethanol require a tightly closable container to prevent evaporation.

The alternative is to adjust (shorten) storage time to the increase of evaporation by opening. A triamcinolone salicylic acid cutaneous solution (Table 12.16) may be kept 2 years in a closed container, and just 6 months after opening.

Evaporation from collodion may be diminished by dispensing, if only 20 mL bottles are available, 20 mL instead of 10 mL and by turning the bottle upside down after closing so that the cap is sealed with the collodion.

12.5.10 Dosage Delivery Devices

See also Table 12.15. Those dosage delivery devices are described in Sect. 24.4.19.1. Physically unstable cutaneous preparations that have to be stirred before use by the patient should be dispensed with a plastic spatula (for example a tongue spatula). On the label the text 'stir before use' should be written. Wooden spatulas are not suitable, because microorganisms may grow on the spatula especially when the spatula is wet.

For the administration of cutaneous solutions a dabbing or roll-on applicator may be very useful.

12.5.11 Labelling

The container of cutaneous preparations is labelled with "not to be taken" or "for external use". If next to a primary container also a secondary container is used, such a label should be fixed to both containers. The label should meet the requirements that are mentioned in Sect. 37.3. On all sterile cutaneous preparations the word "sterile" should be mentioned. A label with the words "shake well before use" should be fixed onto the container of emulsions and suspensions for dermal use.

If a preparation contains flammable substances, such as ethanol, acetone or ether, there should be a warning for the patient. Which H(azard) statement warning sentence (Sect. 26.3.4) and which symbol should be put on the label,

depends mainly on the flash point of the flammable substance. If labelling of flammable preparations with a specific symbol is not legally required, an advice should be given anyhow.

Some active substances such as clioquinol, dithranol and methylrosaline hydrochloride (gentian violet) stain clothes and bedding. A label for example with the text "Stains clothing and bedding" can warn of this property. In the case of benzoyl peroxide the text "Bleaches hair, textile and bedding" is more appropriate to warn of its bleaching effect. Also for active substances that irritate strongly if they are spilled accidentally on mucous membranes or in the eyes, such as capsicum, there should be a warning.

12.5.12 Storage

Cutaneous preparations can usually be stored at room temperature. In case of chemical instability or microbiological vulnerability storage in the fridge (2–8 °C) may be necessary. For example a hydrophilic cream with diltiazem hydrochloride for rectal application (Table 12.1) and preparations that contain tretinoin are kept at low temperature to reduce the degradation rate. A zinc oxide cutaneous suspension (Table 12.21) is microbiologically vulnerable and therefore has to be stored in the fridge.

Dissolved substances may recrystallise in large crystals when kept too cool. Preparations should thus not be stored in the fridge unnecessarily.

12.6 Method of Preparation

General methods of mixing, solving and dispersing are described in Chap. 29. This section shows typical procedures in the preparation of dermatological medicines. It includes the preparation of the bases and the different phases. It is followed by methods for incorporating active substances into the base.

12.6.1 Preparation Method of the Base

The preparation method of the base depends on the phases of which it is composed. A base with only one phase can be prepared by mixing the components. If more than one phase, each phase has to be prepared separately. Finally they have to be mixed.

12.6.1.1 Solid Phase

Solids with particles larger than 90 µm are ground and sieved. Sieving with sieve 90 may be very laborious. Therefore raw materials already having a particle size of less than 90 µm should be preferred.

The solid phase of suspensions and paste bases is dispersed in the aqueous or lipophilic phase. The method of dispersing depends on the amount of the solid and the consistency of the aqueous or lipophilic phase.

12.6.1.2 Lipophilic Phase

A lipophilic phase is prepared by mixing the components. Basically it is possible to mix compatible liquids or semi-solid substances at room temperature, but mixing is easier if they are heated on a water bath (see Sect. 29.6). Stirring the mixture while it is cooling down is important for getting a homogeneous product and for prevention of recrystallisation of substances with a relatively high melting point, such as cetostearyl alcohol. White wax, solid paraffins and high molecular macrogols always have to be heated for further processing because of their consistency.

12.6.1.3 Aqueous Phase

Bases consisting of only an aqueous phase are prepared by mixing the hydrophilic fluids and dissolving the solid substances in this mixture. See also Sects. 29.5 and 29.6.

Preservatives are in general slightly soluble in water because the molecules are partly hydrophobic which property is needed for the function as a preservative. Therefore, the concentration at which they are used is relatively high compared to their solubility in water (see Sect. 12.5.3). They dissolve slowly in the desired concentration. To increase the dissolution rate preservatives are generally dissolved while heating. Sorbic acid needs boiling water to dissolve, in a closed vessel because of its volatility with water vapour. It is easier to work with the combination of potassium sorbate and an acid, such as citric acid, to form sorbic acid while preparing. Both substances are freely soluble in water without heating.

The dissolution rate of methyl hydroxybenzoate can be increased by heating which may be advantageous through simultaneously killing micro-organisms already present in water. If large volumes have to be dealt with, heating brings about the risk of boiling retardation and bursting of glass vessels. A safer way for processing is the preparation of a concentrate in advance, such as a solution in propylene glycol (Table 12.17). This solution should commonly be added to the main part of the aqueous phase; if using too little water precipitation of methyl parahydroxybenzoate will occur. Up to batch sizes of 500 mL prepared by hand, it is manageable to add the concentrate in one portion and shake immediately after. With larger batches the concentrate has to be added in smaller portions under continuous stirring.

For Preserved water (see Sect. 12.5.3) methyl and propyl hydroxybenzoate (0.075 % / 0.025 %) are dissolved by

Table 12.17 Methyl Parahydroxybenzoate Solution 150 mg/mL [33]

Methyl parahydroxybenzoate	15 g
Propylene glycol	91 g
Total	106 g (= 100 mL)

heating. A special order of addition to the preparation is not needed.

The method of processing viscosity enhancing substances in the aqueous phase depends on the type of substance. The general rule is: The viscosity enhancer has to be wetted completely at first. Otherwise lumps may occur that cannot swell anymore because they are insulated by the outer, swollen part. Section 23.7.2 gives elaborate information on different preparation methods.

12.6.1.4 Aqueous and Lipophilic Phase

Preparations consisting of an aqueous and a lipophilic phase (creams and emulsions) usually contain an emulsifier. The preparation method depends on the type of the emulsion: w/o or o/w. For preparing water-in-oil-emulsions the substances that build the lipophilic phase are melted on the water bath and stirred until the mixture reaches room temperature. The aqueous phase with the dissolved substances is added in portions. For preparing oil-in-water-emulsions both phases are separately heated to 70–80 °C. They are mixed by continuous stirring. The temperature at which the emulsion becomes stable is about 45 °C. Afterwards it is adequate to stir occasionally until it is cooled down to room temperature.

12.6.2 Incorporation of Active Substances

Active substances can be incorporated during the preparation of the base or they can be mixed with the completed base. Only active substances that are soluble in the lipophilic or aqueous phase can be directly dissolved in it. Insoluble substances have to be dispersed in the base. In pharmacies often the cream and ointment bases or gels are kept on stock as such. In this case the active substances can only be incorporated into the base, not into the appropriate phase.

> Examples for substances that are soluble in the lipophilic phase in a limited concentration are benzyl benzoate, lidocaine, levomenthol and triclosan. Dithranol is soluble in vegetable oils by warming. But because degradation rate is increased by temperature and dithranol may recrystallise after cooling, it is not recommended to process dithranol in this way.

12.6.2.1 Processing the Active Substance with the Base

There are several methods to process the active substance with the base. The method of choice depends on the substance's properties (particularly solubility) and the formulation of the base.

Solids can be triturated with the base or with an appropriate liquid excipient. If agglomerates are present, they may be dispersed in this way, but the effectiveness always should be validated. That liquid excipient should be part of the base or added in a negligible percentage. It must not dissolve the active substance, because of the risk of subsequent recrystallisation. For trituration the solid active substance should have the required primary particle size, often being micronised. Substances with larger primary particles than required have to be ground and sieved for further processing. As an alternative method, the active substance, whether existing of agglomerates or too large primary particles, may be mixed with a small amount of the base, and passed through an ointment mill. Afterwards the remainder of the base is added and mixed.

Dispersion of agglomerating substances, as most micronised substances are, requires much attention, see Sect. 29.3. In small batches of cutaneous preparations it is common practice to use a minimal amount of base for the first phase of dispersion.

Subsequently the triturate has to be mixed with the remainder of the base by geometrical dilution, see Sect. 29.7.2.

If an active substance is soluble in the base, it can be dissolved in a small amount of an appropriate solvent which is compatible with the base. If the incorporation of an additional (amount of) solvent is not desired, freely soluble substances can be directly mixed with the base. The substance dissolves during the dispersion so mixing has to be continued to cover complete dissolution; this has to be validated. Liquids which are miscible with the base can be directly mixed with it as well.

As an illustration of several preparation methods the processing of triamcinolone acetonide in different bases is given.

Triamcinolone acetonide is a low dose active substance, usually micronised and thus agglomerised as well. For homogeneous dispersion in a base the use of a concentrate is recommended: a trituration of triamcinolone acetonide with rice starch 1:10 or a semisolid trituration with a cream or ointment base. In this way a better mixing ratio as well as deagglomeration can be achieved (see Sect. 29.3).

If the substance or the powder trituration should be processed in ointments or creams it has to be triturated with an appropriate liquid that is preferably a part of the base. Subsequently the trituration is mixed with the ointment or cream base.

In liquid emulsions it can be triturated with a small amount of the base and subsequently be mixed with the remainder of the base. In solutions (typically alcoholic) the substance has to be used not the powder trituration. It is soluble in alcoholic bases and needs no special measures for processing.

Active Substances with Special Processing Methods

Isosorbide dinitrate is used in the treatment of anal fissures. The substance is explosive. For safety reasons it is used as a 40 % dry mixture with a powder base. According to Ph. Eur. it may contain mannitol or lactose monohydrate. Commercially available mixtures usually contain lactose monohydrate and isosorbide dinitrate in a crystalline or amorphous form. They are mixed with the cutaneous base via geometrical dilution (see Sect. 29.4.1).

Viscous tar products such as ichthammol (ichthyol, Sulfobituminosum ammonicum) and coal tar (Pix lithantracis) should be weighed onto a small portion of fat or ointment base because there is no other way to remove it quantitatively from a weighing dish.

12.6.3 Large Batches

The focus in this chapter is on small scale preparation: with a mortar and a pestle, a rotor stator mixer or an ointment mill. For preparation on a larger scale pharmacies in several countries use the mixing-dispersing apparatus Stephan mixer. This mixer exists in various models and is suitable for the preparation of almost all cutaneous preparations (see Sect. 28.6.1).

The formulation of cutaneous preparations and the excipients to be used are usually independent of the scale of preparation. Upscaling brings about natural differences in the practical performance. A main difference is that on a small scale often a base is used into which active substances are dispersed. For large scale preparation the product is usually prepared from the individual substances. The active substance is processed as one of the substances. Some practical guidelines are:

- The equipment and utensils should be based on the batch size. Lifting and weighing of large amounts of starting materials may lead to physical problems. Sometimes extra tools may be necessary.
- For validation of the mixing process the mixing equipment, the sequence of adding starting materials, the mixing time and speed, physical parameters such as temperature and pressure in the mixing device have to be specified.
- Air may easily be included during mixing. This is to be prevented by mixing in vacuum. If this is not possible limits have to be set to the maximal amount of air inclusion.
- Sometimes pre-processing is necessary, for example melting the solid substances or dissolving active substances or excipients in one of the components, or dispersing agglomerates.

The following examples give an explanation to these guidelines.

12.6.3.1 Processing of Sorbic Acid

Sorbic acid has to be dissolved in boiling water due to slow dissolution in cold water. But because sorbic acid is volatile with water vapour, loss of sorbic acid has to be prevented by immediately closing the vessel after the addition of the boiling water. When the preparation is processed in a Stephan mixer in vacuum the sorbic acid may evaporate fast as well. An alternative is to use potassium sorbate instead of sorbic acid and to adjust the pH of the preparation subsequently.

12.6.3.2 Processing of Low-Dosed Substances

Trituration of low-dosed, solid substances directly with the base may lead to insufficient homogeneity. These substances may therefore be pre-dispersed in a small amount of fluid. Or they may be dissolved at first and then mixed in very controlled circumstances with the rest of the base preparation to get a fine precipitate.

Lipid soluble substances can be dissolved separately in an extra amount of a fluid component of the base and subsequently added to the lipid phase. The extra amount is subtracted from the amount of cream base to be used. A well water soluble substance can be dissolved separately in extra water and subsequently added to the aqueous phase. The amount of water that is used is again subtracted from the amount of cream base to be used.

12.6.3.3 Air Inclusion and Lumps

Air inclusion occurring with the preparation of creams may be reduced by mixing just until the cream forms. At cooling down the mixture should only be stirred occasionally. Combining the oil and the aqueous phase should occur at a minimum temperature difference between those phases (not more than several degrees). A too large difference may cause lumps of fat and emulsifier and leads to an inhomogeneous appearance. To avoid long mixing and thus air inclusion the phases should be mixed at a minimum temperature but well above the temperature at which the emulsion is formed.

12.6.4 In-process Controls

For the control of the process steps (unit operations, see Sect. 17.6) of pharmacy preparation the following in-process controls are recommended:

- Recording the tare of the devices (mortars, bowls, pestles, vessels et cetera)
- Re-weighing the weighing dishes or weighing papers (used for small amounts of solids) (see Sect. 29.1.6)
- Macroscopic control on agglomerates and homogeneity in manually as well as mechanically prepared products
- Parameters in the use of mechanical mixing systems (speed and duration)
- Clarity and homogeneity of solutions; inhomogeneity of solutions may look like trails or strings
- Temperature (important for the preparation of hydrophilic emulsions, formulations with thermolabile ingredients and sterilisation processes)
- pH measuring (for an in-process control pH measuring paper or indicator sticks may be used)
- Control and recording of the total amount (important for hydrophilic creams, gels and alcohol containing formulations)

The in-process controls for stock preparations are generally the same as those for small scale. Usually the preparation method is validated and the parameters for processes are known.

12.6.5 Release Control and Quality Requirements

For quality requirements and tests reference is made to Chap. 32.

The release control includes at least the appearance, packaging and labelling.

Texture, colour, smell, clarity (solutions) and particle size (suspensions) may also have to be controlled.

Appropriate tests for liquid preparations (suspensions, emulsions or shampoos) are homogeneous appearance, stability of the emulsion (after shaking), resuspendability of suspensions and their particle size.

Ointments, creams and gels with dispersed solids are tested by putting a small amount of the preparation between two microscope slides or other glass slides with only small pressure. In transmitted light agglomerates must not be found in the preparation. To determine the particle size in a larger sample a grindometer can be used.

If the consistency of specific preparations is relevant for therapeutic use, it could be easily checked by using an extensometer.

The extent of quality control of stock and extemporaneous preparations depends on a risk assessment, see Sect. 21.6.3.

12.6.5.1 Quality Requirements

For cutaneous preparations the following quality requirements may apply (see also Table 32.2)

- Identity
- Appearance (homogeneity, clarity of solutions, resuspendability of suspensions)
- Microbiological stability
- Content of active substance(s)
- Sterility (for preparations applied on wounds)

12.7 Specific Formulations and Preparation Methods

This section describes more detailed how to design the formulation and preparation method of specific groups of cutaneous preparations. Examples show how general methods and rules (as given in Sect. 12.5 for formulation design and Sect. 12.6 for method of preparation) are implemented in practice.

12.7.1 Powders for Cutaneous Application

12.7.1.1 Formulation

Powders for cutaneous application are consisting of one or more solids forming the base (see for example Table 12.18).

As said in Sect. 12.5.1 different excipients are used as filler, for cooling and drying the skin, as astringent or to prevent agglomeration. Specific for cutaneous powders may be the addition of substances that improve the adhesiveness on the skin, for example wool fat or white soft paraffin or substances that enhance the binding capacity for liquids, for example kaolin.

12.7.1.2 Preparation Method

See Sect. 12.6.1 for general information. The substances in cutaneous powders usually have a very small particle size and will thus cause dust, static charge and agglomerates. Cutaneous powders have to be sieved by sieve 90, leaving not more than one percent remaining on the sieve. After sieving of mixtures, mixing is necessary because separation may have taken place.

Table 12.18 Base for Cutaneous Powder [34]

Zinc oxide	10 g
Talc	90 g
Total	100 g

Lipophilic substances can be added, after melting, in small portions by mixing and passing through sieve 180. Sieve 90 is not suitable, because the particles are too large. The powder that remains on the sieve is dissolved in a volatile solvent, added and mixed with the bulk.

12.7.2 Solutions

Solutions for dermal use are liquid hydrophilic or lipophilic bases with dissolved active substances and excipients.

12.7.2.1 Formulation

The formulation of hydrophilic solutions is discussed in Sect. 12.5.3 comprising co-solvents, humectants, viscosity enhancers and preservation. The formulation of lipophilic solutions is discussed in Sect. 12.5.2 which elaborates on the functions of the various 'fatty' excipients.

As an example of a lipophilic solution a salicylic acid and triamcinolone acetonide oily cutaneous solution is shown in Table 12.19. It is a lipophilic solution based on octyldodecanol, a fatty alcohol. Salicylic acid is soluble up to approximately 8 % in this base. For higher concentrated solutions castor oil is needed. Triamcinolone acetonide is practically insoluble in the oily base. To dissolve it about 10 % of isopropyl alcohol has to be added to the solution base. The preparation method is such that triamcinolonacetonide is dissolved in isopropyl alcohol at first. The formulation is applied to the scalp. It has to be washed out after a certain time. An additionally processed surfactant eases this and reduces the amount of shampoo which is usually necessary. Therefore the DAC/NRF [35] has a second formulation with macrogol lauryl ether as surfactant (Table 12.20). Because of the dissolving properties of macrogol lauryl ether neither isopropyl alcohol nor castor oil is needed. Both formulations play a role in the dermatologists practice. The decision for one or the other depends on the patient´s skin conditions. Surfactants may irritate a sensitive skin. In that case the formulation without surfactant may be preferred.

Table 12.19 Salicylic Acid and Triamcinolone Acetonide Oily Cutaneous Solution [36]

	2 %	5 %	10 %
Salicylic acid	2 g	5 g	10 g
Triamcinolone acetonide	0.1 g	0.1 g	0.1 g
2-Propanol	9.9 g	9.9 g	9.9 g
Castor oil, refined	–	–	50 g
Octyldodecanol	88 g	85 g	30 g
Total	100 g	100 g	100 g

Table 12.20 Salicylic Acid and Triamcinolone Acetonide Washable Oily Cutaneous Solution [37]

	2 %	5 %	10 %
Salicylic acid	2 g	5 g	10 g
Triamcinolone acetonide	0.1 g	0.1 g	0.1 g
Macrogol lauryl ether	10 g	10 g	15 g
Octyldodecanol	87.9 g	84.9 g	74.9 g
Total	100 g	100 g	100 g

12.7.2.2 Preparation Method

See Sects. 12.6.1 and 29.5 for the preparation method of lipophilic and hydrophilic solutions. Volatile solvents should be processed in a closed vessel or added at the end. Warming is only appropriate for substances which remain completely dissolved at room temperature.

12.7.3 Suspensions

Suspensions for dermal use generally are hydrophilic. Well-known as pharmacy preparations are zinc oxide cutaneous suspensions. These (Table 12.21) are often used without any (other) active substance.

12.7.3.1 Formulation

See Sect. 12.5.3. The liquid phase of hydrophilic suspensions generally consists of water, a humectant, a preservative and a viscosity enhancer to decrease the settling rate.

If the concentration of solids, for instance zinc oxide, is high enough, the suspension is relatively stable and the addition of viscosity enhancers is not necessary. Furthermore viscosity enhancers may be unsuitable if they ruin specific effects such as the cooling effect from evaporation of water or alcohol. If the addition of preservatives is not desirable, e.g. in case of a large skin area that is affected, the preparation should be dispensed in single-use (or at least few times use) containers and the use period should be restricted to a few days.

Typical active substances in zinc oxide cutaneous suspension are levomenthol (Table 12.22) and ichthammol (Table 12.23). Levomenthol dissolves completely only in an alcohol containing base. Therefore a zinc oxide suspension with ethanol is the right base for it. Ichthammol may be formulated in an aqueous as well as in an ethanol-containing one.

12.7.3.2 Preparation Method

If the suspension does not contain a viscosity enhancer the insoluble solid (after grinding and sieving if necessary) is dispersed in the mixture of the hydrophilic liquids in which

Table 12.21 Zinc Oxide Cutaneous Suspension [38]

Zinc oxide	16.7 g
Propylene glycol	16.7 g
Talc	16.7 g
Water, purified	61 g
Total	111.1 g (= 100 mL)

Table 12.22 Levomenthol Zinc Oxide Cutaneous Suspension [39]

Levomenthol	1 g
Ethanol (95 %)	23 g
Zinc oxide	13.83 g
Propylene glycol	13.83 g
Talc	13.83 g
Water, purified	61 g
Total	111.1 g (= 100 mL)

Table 12.23 Ichthammol Zinc Oxide Cutaneous Suspension [40]

	2.5 %	5 %	10 %
Ichthammol	2.5 g	5 g	10 g
Bentonite	1 g	1.5 g	2 g
Zinc oxide	20 g	20 g	20 g
Talc	20 g	20 g	20 g
Glycerol 85 %	30 g	30 g	30 g
Water, purified	26.5 g	23.5 g	18 g
Total	100 g	100 g	100 g

soluble ingredients already have been dissolved. See Sects. 12.6.2 and 29.7 for dispersion methods.

If a viscosity enhancing agent is used, a gel has to be prepared first (see Sect. 23.7). Soluble substances are dissolved in the gel or added as solution to the gel.

If a rotor-stator mixer is used, its mixing time and speed have to be limited in order to minimise the inclusion of air. As the inclusion of air cannot be completely avoided, the preparation has to be prepared by weight not by volume.

12.7.4 Emulsions

Emulsions for cutaneous application are usually oil-in-water emulsions. The formulation resembles hydrophilic creams (see Sect. 12.7.10). The only difference is the higher content of water (Table 12.24). Water-in-oil emulsions are not common and therefore not described.

Table 12.24 Cetomacrogol Cutaneous Emulsion [41]

Cetomacrogol emulsifying wax (BP)	3 g
Decyl oleate	4 g
Potassium sorbate	0.09 g
Sorbic acid	0.13 g
Sorbitol, liquid (crystallising)	0.8 g
Water, purified	91.96 g
Total	100 g

12.7.4.1 Formulation and Preparation Method

For formulation see Sect. 12.5.4. Emulsions usually have an aqueous phase/lipophilic phase ratio of about 4. The aqueous phase usually contains a preservative and a humectant (see Sect. 12.5.3).

For the preparation method see Sect. 12.6.1.4. The preparation method resembles that of hydrophilic creams (see Sect. 12.7.10).

A specific preparation method for cutaneous o/w emulsions is a dilution of hydrophilic creams. These are typically diluted in a ratio of 1:2 up to 1:6 with water (with added preservative), the ratio depending on the properties of the cream, the consistency that is desired and the location of application. Warming is not necessary for diluting the cream base with water. In some cases the use of a rotor-stator-mixer is recommended to get finer emulsions and thereby a higher viscosity.

For the incorporation of active substances see Sect. 12.6.2. Solids that do not dissolve in the base, such as corticosteroids, are preferably dispersed by triturating with an equal amount of the emulsion. Water soluble solids, such as urea, will dissolve when mixed with the aqueous phase long enough (to be validated). Fluids that are miscible with the base, such as coal tar solution, are added by simply mixing with the base.

12.7.5 Hydrophobic Ointments

Hydrophobic ointments, frequently called fatty ointments, are plastic lipogels, in which active substances and excipients may be dissolved or dispersed. A hydrophobic ointment can absorb only a small quantity of water or water-miscible fluids. They are not washable.

12.7.5.1 Formulation

See Sect. 12.5.2. Suitable substances for hydrophobic ointments are white soft paraffin, liquid and solid paraffin, vegetable and animal fats and fatty oils, synthetic esters of glycerol or alcohols or mixtures of these substances.

Table 12.25 Coal Tar Soft Paraffin Ointment [42]

	5 %	10 %	20 %
Coal tar topical solution DAC	5 g	10 g	20 g
Carbomer 50,000	1 g	1 g	1 g
Paraffin, white soft	94 g	89 g	79 g
Total	100 g	100 g	100 g

12.7.5.2 Preparation Method

See Sect. 12.6.1.2. Hydrophobic ointments are usually prepared by melting all lipophilic ingredients and stirring the mixture while it is cooling down. The consistency of the product depends on the speed of the cooling down and the stirring speed.

For the incorporation of active substances see Sect. 12.6.2. Coal tar is miscible with white soft paraffin and can be added directly without melting. Insoluble active substances are best triturated with an equal amount of an ingredient of the base (wool fat or paraffin) or an appropriate lipophilic liquid. For the dispersion of high amounts of insoluble solid substances (such as zinc oxide) passing the preparation through an ointment mill is recommended. Hydrophilic liquids are not appropriate as dispersing agents because they are not miscible with the base or only miscible in a very small amount, depending on the emulsifying properties of the ingredients of the ointment base. Just glycerol 85 % is miscible in a reasonable amount. Alcoholic liquids usually are insufficiently miscible with hydrophobic ointment bases, but small amounts can be added drop wise. The hydrophilic coal tar solution can be mixed (up to 10 %) with hydrophobic bases (Table 12.25.) with the help of carbomer (1 %) that increases its viscosity.

12.7.6 W/o Emulsifying Ointments

W/o emulsifying ointments consist of a lipophilic phase containing w/o emulsifiers. Because of these properties the water binding capacity is much higher than in hydrophobic ointments.

12.7.6.1 Formulation

The ingredients used in w/o emulsifying ointments are the same as in hydrophobic ointments, but a w/o surfactant is added such as:

- Wool fat
- Wool alcohols
- Sorbitan esters
- Monoglycerides
- Fatty alcohols

Table 12.26 Emulsifying Hydrophobic Base Gel DAC [44]

Isopropyl palmitate	8 g
Triglycerol diisostearate	10 g
Hydrophobic base gel DAC	82 g
Total	100 g

Table 12.27 Cetomacrogol Ointment Base [45]

Cetomacrogol emulsifying wax (BP)	30 g
Paraffin, liquid	25 g
Paraffin, white soft	45 g
Total	100 g

See Sect. 23.6 for descriptions of these surfactants.

White soft paraffin and wool fat are commonly used excipients for w/o emulsifying ointments. Emulsifying Hydrophobic Base Gel DAC (Table 12.26) is an ointment base free of wool fat and wool alcohols. It consists of plastibase (also named as Hydrophobic Base Gel DAC [43]: polyethylene processed with liquid paraffines), isopropyl palmitate and triglycerol diisostearate.

12.7.6.2 Preparation Method

Basically the preparation of w/o emulsifying ointments and the processing of active substances are similar to hydrophobic ointments. Whether heating is meaningful depends on the properties of the ingredients. Emulsifying Hydrophobic Base Gel (Table 12.26) for example is prepared by mixing all substances at room temperature. The Hydrophobic Base Gel does not tolerate temperatures above 70 °C.

Insoluble active substances are usually incorporated by trituration into a paste with wool fat or a lipophilic liquid if it is a component of the base. Afterwards this paste is mixed with the other lipophilic ingredients.

12.7.7 O/w Emulsifying Ointments

O/w emulsifying ointments consist of a hydrophobic base with an o/w surfactant (Tables 12.27 and 12.28). Addition of water to these ointments leads to an oil-in-water-emulsion, which makes them somewhat washable.

12.7.7.1 Formulation

The lipophilic base is formulated in the same way as hydrophobic ointments, see Sect. 12.5.2. The o/w emulsifiers are usually the same as in o/w creams: for example cetomacrogol emulsifying wax and lanette emulsifying wax (lanette wax SX or N). As these bases are anhydrous

Table 12.28 Lanette Ointment Base [46]

Cetostearyl alcohol (type B), emulsifying	30 g
Paraffin, liquid	25 g
Paraffin, white soft	45 g
Total	100 g

Table 12.29 Macrogol Ointment DAC [47]

Macrogol 300	50 g
Macrogol 1500	50 g
Total	100 g

no preservatives or humectants are needed. By addition of appropriate substances these ointments can be modified for different applications. Examples for additives are:

- 15 % of isopropyl myristate to Cetomacrogol Ointment Base and Lanette Ointment Base (Tables 12.27. and 12.28). These preparations are known as Cetomacrogol Ointment and Lanette Ointment in the FNA (see Sect. 39.4.5). These water emulsifying ointments have better spreading properties than the parent ointment base.
- 25 % of decyl oleate to Cetomacrogol Ointment Base and Lanette Ointment Base which makes them applicable to the scalp and easy to be washed off.

By the addition of water the o/w emulsifying ointments are turned into hydrophilic creams with a relatively high content of lipophilic ingredients and good application properties (Table 12.4). Propylene glycol is added for preservation.

12.7.7.2 Preparation Method

O/w emulsifying ointments are prepared by melting all ingredients on a waterbath and stirring while the preparation is cooling down. Stirring has to occur continuously to prevent crystallisation of cetostearyl alcohol whereby the ointment would become granulous. Active substances are incorporated in the same way as in hydrophobic and w/o emulsifying ointments (see Sects. 12.7.5 and 12.7.6). Water soluble substances can be easily processed in o/w emulsifying ointment bases, for example urea as an aqueous solution.

12.7.8 Hydrophilic Ointments

Hydrophilic ointments consist of a water miscible base, usually containing a mixture of liquid and solid macrogols (polyethylenglycols or PEGs, see Sect. 23.3.4).

12.7.8.1 Formulation

An example of a hydrophilic ointment base is Macrogol Ointment (Table 12.29). The consistency can be modified by variation of the ratio between liquid and solid macrogols. Sometimes water is added to make the ointment less hygroscopic and irritating. Being anhydrous, no preservation is necessary.

Macrogol ointments can absorb up to 5 % of water and up to 5 % of ethanol. If 5 % of macrogol 4000 is replaced by stearyl alcohol or cetyl alcohol the ointment base can absorb up to 25 % of water.

12.7.8.2 Preparation Method

Hydrophilic ointments are prepared by melting the ingredients on the water bath and stirring while the mixture is cooling down. Soluble active substances are dissolved in macrogol or another solvent which is contained in the formulation. Insoluble active substances have to be dispersed in the melted cooling base. If formulated, water and alcohol are added after the base has cooled down completely.

12.7.9 Lipophilic Creams

Lipophilic creams or w/o-creams are emulsions with a lipophilic outer phase. Active substances are dissolved in the aqueous or lipophilic phase or are dispersed.

12.7.9.1 Formulation

The lipophilic phase comprises usually about 70–75 % of the total amount of the cream base. The lipophilic phase may consist of fatty oils (usually arachis oil), waxes such as decyl oleate, wool fat and white wax or hydrocarbons such as liquid paraffins or white soft paraffin (see Sect. 23.3.5 for descriptions). They determine consistency and spreadability. A w/o surfactant is added (see Sect. 12.5.4). The emulsifying properties of w/o surfactants are weaker than those of o/w surfactants. Therefore they are often used in a higher quantity. The physical stability of w/o creams is limited. For instance the addition of phenols, acids and alcoholic fluids may lead to phase separation. Most hydrophobic creams only include less than 5 % alcohols.

A specific hydrophobic cream base is Cooling Ointment. A cooling ointment should be unstable, separate on the skin and cool the skin through evaporation of water.

The Cooling Ointment given in Table 12.30 does not contain any physical stabilisers. The aqueous phase is only physically bound. It is not very suitable for the addition of active substances that affect the physical stability such as lauromacrogol 400, coal tar solution or urea. After a relatively short time water can separate. Only a limited number of substances can be added often in a low concentration. Solid substances such as glucocorticosteroids, salicylic acid

Table 12.30 Cooling Ointment DAB [48]

Arachis oil, refined	60 g
Beeswax, yellow	7 g
Cetyl palmitate	8 g
Water, purified	25 g
Total	100 g

Table 12.31 Cooling Ointment FNA [49]

Arachis oil, refined	57.5 g
Beeswax, white	12.5 g
Glycerol mono-oleate	5 g
Rose oil (USP/NF)	1 drop
Water, purified	25 g
Total	100 g

and sulfur usually can be processed directly without any influence on physical stability.

Another cooling ointment is depicted in Table 12.31. The name Cooling Ointment is actually not correct anymore for that formulation. In the course of time different formulations have been used. In practice the physical instability was not appreciated anymore because it made the addition of active substances impossible. The formulation is too stable to be a good cooling ointment, because it contains glycerol mono-oleate, a w/o surfactant. But addition of active substances is possible and this Cooling Ointment functions firstly as preservative free cream base.

Although cooling ointments are w/o systems, they are microbiologically vulnerable to bacteria, fungi and yeasts (see Sect. 12.5.3.5). But the preservation is often not desired. Cooling ointments are regarded as bases that are well tolerated on the skin and preservatives may cause sensitisation and irritation. Typically they are not preserved and thus the shelf life has to be shortened.

An example for a physically stable w/o cream base is given in Table 12.32. It consists of Emulsifying Hydrophobic Base Gel (Table 12.26) and an aqueous phase preserved with sorbic acid (using a combination of potassium sorbate and citric acid). The base contains 65 % of water and is free of wool fat. It is for example an appropriate base for corticosteroids, urea, tretinoin and triclosan. The active substance lauromacrogol 400 can only be added to a base with less water. Otherwise the preparation becomes physically unstable.

12.7.9.2 Preparation Method

Lipophilic creams are usually prepared by melting the lipid components and the surfactant (and possibly lipid soluble substances that tolerate 70 °C) and subsequently stirring to cool. The hydrophilic phase is added in portions to the cooled lipophilic mixture and mixed. Hydrophobic Base Gel, which is a component of Hydrophobic Cream Base (Table 12.32) should be processed without heat because it does not tolerate temperatures of more than 70 °C.

Table 12.32 Hydrophobic Cream Base DAC [50]

Citric acid, anhydrous	0.07 g
Glycerol (85 %)	5 g
Hydrophobic base gel DAC	24.6 g
Isopropyl palmitate	2.4 g
Magnesium sulfate heptahydrate	0.5 g
Potassium sorbate	0.14 g
Triglycerol diisostearate	3 g
Water, purified	64.29 g
Total	100 g

12.7.10 Hydrophilic Creams

Hydrophilic creams or o/w creams are emulsions whereby the outer phase is the aqueous phase.

12.7.10.1 Formulation

Hydrophilic creams are preferably formulated with combinations of emulsifying agents (mixed layer emulsifying agents or emulsifying agent complexes, see Sect. 18.4.3). For examples of o/w surfactants see Sect. 12.5.4. Generally hydrophilic creams may be anionic-active or non-ionic-active. Because of incompatibilities of active substances with anionic or non-ionic-active surfactants mixtures of these types of emulsifiers have to be avoided. The lipophilic excipients improve the consistency of the cream. These may be hydrocarbons such as white soft paraffin or waxes such as decyl oleate.

The outer phase of hydrophilic creams consist of water, dissolved active substances, preservatives and humectants see Sect. 12.5.3.

The formulation in Table 12.33 represents a non-ionic-active hydrophilic cream base. It contains a liquid wax (ethylhexyl laurate), which is well absorbed by the skin. The robust cream base tolerates processing of organic solvents and of phenols such as salicylic acid, in spite of its nonionic character. Lanette creams 12.34 are anionic-active bases. The two formulations differ in their consistency. The higher amount of emulsifying cetostearyl alcohol in Lanette cream II leads to a more stiff cream. It is especially suitable for preparations with a larger quantity of liquids.

Table 12.33 Nonionic Hydrophilic Cream SR DAC [51]

Nonionic emulsifying alcohols DAC	21 g
Ethylhexyl laurate DAC	10 g
Citric acid, anhydrous	0.07 g
Glycerol (85 %)	5 g
Potassium sorbate	0.14 g
Water, purified	63.79 g
Total	100 g

Table 12.34 Lanette Cream I and II [52]

	I	II
Cetostearyl alcohol (type B), emulsifying	15 g	24 g
Decyl oleate	20 g	16 g
Sorbic acid	0.2 g	0.15 g
Sorbitol, liquid (crystallising)	4 g	4 g
Water, purified	60.8 g	55.85 g
Total	100 g	100 g

Table 12.35 Hydroxyethylcellulose Gel DAB [53]

Hydroxyethylcellulose 10,000	2.5 g
Glycerol 85 %	10 g
Water, purified	87.5 g
Total	100 g

12.7.10.2 Preparation Method

For the preparation of the hydrophilic cream base the excipients have to be divided into hydrophilic and lipophilic ones, forming the aqueous and lipophilic phase respectively. The aqueous phase consists of: water, often sorbitol solution 70 %, glycerol 85 %, propylene glycol or sorbic acid and other dissolved substances as far as they are not volatile or degrade while being warmed. The lipophilic phase consists of: fats, fatty oils, surfactant(s) and oil-soluble substances. The two phases are warmed separately to about 70–80 °C. The aqueous phase is added to the lipophilic phase, usually in one time or sometimes in portions. The mixture is stirred immediately after the addition and continued until the structure of the cream is built. Then stirring can be slowed down to prevent too much air being included in the cream. The evaporated water has to be compensated for.

The way of processing active substances follows general recommendations for the incorporation of active substances (see Sect. 12.6.2).

Specific Processing Method

Sometimes the active substance may best be dispersed by precipitating during preparation. Tetracycline hydrochloride dissolves readily causing a pH of 2.5 at which it is degraded by more than 10 % after 1 month. In a tetracycline hydrochloride cream (Table 18.4) tetracycline hydrochloride is added to a cream base after being dispersed in a small amount of water. Mixing with the cream base causes tetracycline hydrochloride to dissolve completely. Immediately sodium citrate solution is added which causes fine precipitation of tetracycline, as well as an increase of the shelf life to 6 months.

12.7.11 Hydrogels

Hydrogels consist of a hydrophilic fluid (such as water, glycerol, propylene glycol and alcohol) or a mixture of hydrophilic fluids in which a viscosity enhancing substance has been incorporated.

12.7.11.1 Formulation

The most often used viscosity enhancers in hydrogels are carbomer salts and the cellulose derivates hypromellose and hydroxyethyl cellulose (see Sects. 12.5.3 and 23.7.3).

Carbomer gels (see Table 23.17) tolerate the addition of ethanol or isopropyl alcohol without losing the gel structure, although the extent depends on the type of neutralising substance (see further Sect. 23.7.3). They have a limited compatibility with salts and cations depending on their concentration; the viscosity may be decreased. Zinc oxide disturbs the gel structure by cross-linking the polymer. If any addition causes the pH to decrease under 6, the gel structure will be lost as well.

If processing of a substance in Carbomer gels is not possible because of incompatibilities, a gel with cellulose derivates may be prepared (Table 12.35). Hypromellose and hydroxyethylcellulose are nonionic and compatible with salts, acids and bases.

Depending on their viscosity type cellulose derivates create firm gels in concentrations of 2.5–8 %.

Salicylic acid, erythromycin and calcium gluconate are incompatible with carbomer gels and may be formulated with a hypromellose gel. An alcoholic gel of erythromycin (Table 12.36) for example is based on a mixture of ethanol, glycerol 85 % and water thickened with hypromellose. For stability of erythromycin, citric acid is used to adjust pH to 8–8.5. Glycerol 85 % functions as humectant.

Because of the presence of water a preservative should be added to hydrogels, see Sect. 12.5.3. Suitable preservatives are sorbic acid, glycerol and propylene glycol. Methyl hydroxybenzoate or a combination of methyl and propyl

Table 12.36 Erythromycin Alcohol Gel [54]

	0.5 %	1 %	2 %	4 %
Erythromycin, anhydrous	0.50 g	1 g	2 g	4 g
Citric acid, anhydrous	0.038 g	0.075 g	0.15 g	0.30 g
Ethanol (96 %)	45 g	45 g	45 g	45 g
Glycerol (85 %)	2 g	2 g	2 g	2 g
Hypromellose 4,000	3 g	3 g	3 g	3 g
Water, purified	49.462 g	48.925 g	47.85 g	45.7 g
Total	100 g	100 g	100 g	100 g

hydroxybenzoate (Preserved water, see Sect. 12.5.3) can be used as well because there is no lipophilic phase that removes part of these substances.

Gel for Iontophoresis

Iontophoresis is a technique whereby ionic active substances are transported into the skin with the help of an electric field. Gels for iontophoresis should not contain charged excipients because these excipients may penetrate into the skin as well and reduce the penetration of the charged active substance. Gel bases for iontophoresis may contain hypromellose as gelling agent (Table 12.37).

Table 12.37 Base Gel for Iontophoresis [55]

Hypromellose 4,000 mPa.s	2 g
Propylene glycol	30 g
Water, purified	68 g
Total	100 g

12.7.11.2 Preparation Method of Carbomer Gels

Carbomer dust irritates the eyes, mucous membranes and respiratory tract. Therefore this substance should be processed carefully avoiding any handling that causes dust. Small batches of carbomer gels (up to 300 g) can be prepared with a mortar and pestle. First the carbomer is partially ionised by dry mixing with the neutralising substance (for instance trometamol), which makes it hydrophilic. Then disodium edetate is added to remove by cross-linking bivalent ions (for example calcium ions) that can hinder the creation of the gel. Subsequently this mixture is triturated with fluid. Dispersion and creation of the gel in this case takes place at the same moment.

For the preparation of batches up to 500 g a rotor stator mixer is recommended. With the rotor stator mixer carbomer is moistened and dispersed in the aqueous phase in which water soluble substances such as disodium edetate have already been dissolved. Herewith a somewhat viscous solution is created. Adding an alkali reacting substance causes deprotonating of carbomer and thereby an increase of viscosity. The addition of alkali and the stirring is done by hand and not with the rotor stator mixer because otherwise too much air would be entrapped.

12.7.11.3 Preparation Method of Gels with Cellulose Derivatives

For the preparation of gels containing cellulose derivatives, the following methods are known, see also Sect. 23.7.2.

- Cellulose derivatives are triturated in a mortar with a viscous hydrophilic fluid in which it will not swell, such as propylene glycol, glycerol 85 % or sorbitol solution 70 %.
- The gelling agent is mixed with hot water. For some types of cellulose derivates this technique leads to a fast dispersion and gelling while cooling down.
- The gelling agent can be sprinkled on the liquid base while stirring continuously and vigorously.

Generally gels may also be prepared with the use of a Stephan mixer (see Sect. 28.6.1). Lumps will be dispersed immediately in this way. Processing with a Stephan mixer under vacuum has another advantage. It results in an air bubble free (and thereby transparent) gel.

Active substances that are sufficiently soluble in the gel base may be added to the finished base by dissolving them in water or in another fluid that can be mixed with the base. However, addition of a large amount of fluid to the finished base leads to a less viscous preparation. If this is undesirable, direct mixing is to be preferred if the active substance is well soluble, or the gel should be prepared from the single components and not with the finished product.

For example in the alcoholic erythromycin gel (Table 12.36) erythromycin is dissolved in ethanol first. Hypromellose has to be dispersed in this water free solution. Finally water and glycerol 85 % are added and the gelling agent starts to swell. The gel can be prepared in a flask because it is relatively thin. Substances that are insoluble in water such as corticosteroids and metronidazole are dispersed in an equal volume of gel and subsequently geometrically mixed with the rest of the base.

12.7.12 Oleogels

Oleogels or hydrophobic gels consist of an oil like or fatty fluid in which a viscosity enhancer is processed.

12.7.12.1 Formulation and Preparation Method

Oleogels may be mixtures of liquid paraffin with polyethylene (Hydrophobic Base Gel DAC [43]) or fatty oils combined with anhydrous colloidal silica, aluminium or zinc soaps as viscosity enhancer. Hydrophobic gels are prepared by mixing the oil phase with the viscosity enhancer. If the

Table 12.38 Zinc Oxide Cutaneous Paste DAB [56]

Zinc oxide (90)	25 g
Paraffin, white soft	50 g
Wheat starch	25 g
Total	100 g

Table 12.39 Zinc Oxide Calcium Hydroxide Weak Paste [57]

Zinc oxide (90)	33 g
Arachis oil, refined	33 g
Beeswax, white	1 g
Calcium hydroxide solution[a]	33 g
Oleic acid	q.s.
Total	100 g

[a]Contains at least 1.4 mg dissolved calcium hydroxide per mL. Preparation is according the monograph Solutio calcii hydroxidi. In: Nederlandse Farmacopee, Zesde uitgave, 2e druk. 's-Gravenhage: Staatsuitgeverij, 1966:600

oleogel contains a solid substance it is being dispersed in the fatty base.

12.7.13 Pastes

Pastes are semisolid preparations that consist of a lipophilic phase in which a high percentage of solid substance is dispersed. The range of solid substances is typically 30–50 % or more. The consistency varies dependent on the formulation of the base. In connection with the amount of solids this classifies the preparations into stiff and weak pastes. Another kind of paste is an aqueous paste containing the solid in a hydrophilic base. Zinc oxide is the most frequently processed solid in pastes. Zinc oxide containing formulations are used as examples of these different kinds of paste.

12.7.13.1 Stiff Pastes

Stiff pastes typically have a semisolid base with a high percentage of solid (50 % or more) dispersed in it (see Table 12.38). Their main function is to protect the skin, for instance around a stoma, from body exsudates and humidity. The absorptive capacity is determined to be not relevant [59a].

Stiff pastes usually are based on white soft paraffin. Sometimes a part of white soft paraffin is replaced by liquid paraffin to improve the applicability, as for example in zinc oxide pastes. Zinc oxide pastes contain wheat starch and zinc oxide as the solid phase.

Stiff pastes are prepared by dispersing insoluble substances (after grinding and sieving if necessary) in the base. Sometimes it may be helpful to melt the base before adding the solid. Because of the large percentage of solid substance it is difficult to remove all agglomerates by hand. Therefore stiff pastes are commonly passed through an ointment mill. Additional mixing has to take place afterwards.

Table 12.40 Zinc Oxide Cutaneous Paste [58]

Zinc oxide (90)	60 g
Arachis oil, refined	39.3 g
Oleic acid	0.7 g
Total	100 g

12.7.13.2 Weak Pastes

Weak pastes may have a liquid or a weak semisolid base. They are used for wetting skin disorders. Formulations differ in their potential to adhere to a very wet skin. The weak zinc oxide paste containing a calcium hydroxide solution (Table 12.39) for example adheres much more on wet skin than a paste based only on an oil (Table 12.40). The phases of the former, water containing, preparation separate after application and as a result the cooling effect is intensified.

The weak paste with zinc oxide and calcium hydroxide solution in Table 12.39 is actually a lipophilic cream, but because of the large amount of solid substance it is classified as a paste. The w/o emulsifiers calcium oleate and zinc oleate are created during the preparation process in the presence of oleic acid. The amount of oleic acid necessary for emulsifying depends not only on the acid value of the used arachis oil (corresponding to the amount of fatty acid already present), but also on the method of preparation. When mixed and dispersed well usually no oleic acid is needed. When too much oleic acid is added, the emulsion will break.

The viscosity of the zinc oxide cutaneous paste depicted in Table 12.40 is increased by zinc oleate that is formed from zinc ions with free fatty acids from the fatty oil. The preparation may be considered as a cutaneous oleogel of zinc oleate in arachis oil in which the excess zinc oxide is suspended. During preparation the product is still fluid. During storage more zinc oleate is created and the product thickens into a semisolid preparation that may be called a weak paste. This paste is used in subacute and chronic eczemas and in intertrigines.

Weak pastes are prepared by dispersing the insoluble components (e.g. zinc oxide) (after grinding and sieving if necessary) in the base. Stable weak pastes such as Zinc oxide cutaneous paste (Table 12.40) may be passed through an ointment mill. Sieving of the zinc oxide is not necessary in that case. Active substances, for example corticosteroids, lidocaine, miconazole nitrate and sulfur, can be added to

Table 12.41 Zinc Oxide Aqueous Paste

Zinc oxide (90)	22.5 g
Aluminium magnesium silicate	2.5 g
Propylene glycol	10 g
Talc	22.5 g
Water, purified	42.5 g
Total	100 g

this paste by dispersing them in an equal weight of propylene glycol and subsequently mixing them with the paste.

In Zinc Oxide Calcium Hydroxide Weak Paste (Table 12.39) active substances may be processed by dispersing them in a similar volume of the paste and subsequently mixing with the remainder of the paste. However, the paste is unstable as such and every added (active) substance may disturb the physical stability. Therefore no extra liquid should be added to dissolve active substances nor should they be triturated.

12.7.13.3 Aqueous Pastes

Aqueous pastes, also called hydrophilic pastes, consist of a hydrophilic base with 40–60 % solid substance. This type of paste may consist of water only, made viscous by a viscosity enhancer (see Table 12.41) or by the addition of a hydrophilic cream or emulsion. They are supposed to have a good absorptive capacity and are therefore used in the treatment of wetting skin disorders [59b].

The formulation of aqueous pastes strongly resembles the formulation of cutaneous suspensions (see Sect. 12.5.5.2). Aqueous pastes contain, however, a higher percentage of solid substances which makes them semisolid. For typical excipients see Sect. 12.5.1. The formulation of an aqueous paste with colloidal aluminium magnesium silicate as viscosity enhancer is described here. Propylene glycol preserves the aqueous phase.

Aqueous pastes are prepared by dispersing insoluble substances (after grinding and sieving if necessary) in the mixture of liquids that may be thickened to a gel first.

12.7.14 Collodia

A collodion is used when a prolonged contact of the active substance with the skin is required, for example salicylic acid in the treatment of warts (see Table 12.42).

12.7.14.1 Formulation

A collodion is a solution of cellulose nitrate (4 %) in a mixture of alcohol and ether. The cellulose nitrates increase the viscosity of the alcohol-ether mixture. After evaporation of the solvents a stiff cellulose nitrate membrane remains on the skin. It enables an intensive contact between active substance and skin. The flexibility of the membrane is improved by adding castor oil. Collodia contain a high concentration of alcohol and ether. In this environment no micro-organisms will grow. Therefore preservation of a collodion is not necessary.

Table 12.42 Lactic Acid Salicylic Acid Collodion 10 % [60]

Salicylic acid	10 g
Lactic acid	11.1 g
Collodion, elastic DAC (containing castor oil, refined)	78.9 g
Total	100 g

Table 12.43 Shampoo Base

Hypromellose 4,000 mPa.s	1 g
Methyl parahydroxybenzoate	0.1 g
Sodium chloride	1.6 g
Sodium lauryl ether sulfate 28 % m/m (local standard)[a]	60 g
Water, purified	37.3 g
Total	100 g

[a]Texapon NSO®

12.7.14.2 Preparation Method

Active substances are dissolved. Speeding up the dissolution process by warming is not possible because of the high inflammability of collodion (due to the presence of ether and ethanol). Ventilation should be sufficiently effective as to prevent the concentration of their vapours exceeding critical limits (see Sect. 26.11).

12.7.15 Shampoos

Shampoos are semisolid or fluid preparations for the scalp. They contain foaming surfactants and often additives for ‘hair care’.

12.7.15.1 Formulation

Shampoos are hydrophilic solutions, hydrophilic suspensions or hydrogels with a high percentage of surfactants (Table 12.43). Active substances may usually be processed without problems in a neutral base shampoo, available as a mild or everyday shampoo. The addition of coal tar solution or coal tar alcoholic solution may decrease the viscosity slightly.

Shampoos are packaged in a plastic squeezing bottle (shampoo bottle) and not in a glass bottle because of the risk of breakage in the bathroom.

12.7.15.2 Preparation Method

The processing of active substances in shampoos is in principle similar to the one in aqueous suspensions (Sect. 12.6.2). Because of foam formation the mixture should not be stirred firmly. Salicylic acid (up to 3 % m/m, dissolved in a threefold amount of alcohol 95 % v/v) and coal tar alcoholic solution (up to 10 % m/m) may be directly mixed with the base shampoo of Table 12.43. Coal tar (Pix lithanthracis) may be mixed with the shampoo base after trituration with some sodium lauryl ether sulfate solution.

12.7.16 Sticks

Sticks, also called ointment sticks, are meant to be used on lips.

12.7.16.1 Formulation

The consistency of ointment sticks has to be high enough to prevent deformation while being used, but it should enable for active substances to be abraded. A suitable base is made from equal amounts of cocoa butter, white wax, wool fat and cetyl palmitate (synthetic spermaceti) or cocoa butter only. Ointment sticks with cacao butter only are used for cracked lips or to prevent lips cracking. Ointment sticks are packaged in aluminium foil and dispensed in a glass or synthetic jar. They can also be placed in lipstick holders.

12.7.16.2 Preparation Method

The preparation of the base and the processing of the active substances is similar to the preparation of suppositories with a fat base (see Sect. 11.5). The melted mass is preferably poured into molds for ointment sticks.

12.7.17 Sterile Cutaneous Preparations

Sterile cutaneous preparations undergo sterilisation in the final container if possible. Many active substances, base preparations and package materials for cutaneous preparations however are not resistant to the common sterilisation methods, see also Sect. 30.8. If sterilisation in the final container is not possible, cutaneous dermal preparations should be prepared aseptically and packaged in sterile packaging materials, see Chaps. 30 and 31. On the label of sterile cutaneous preparations the word sterile has to be mentioned. After opening, these preparations can only be stored for 24 h.

12.7.17.1 Sterile Cutaneous Powders

Sterile cutaneous powders usually contain lactose as the base, because lactose is absorbable and does not cause granuloma, as talc does.

The raw materials should preferably purchased sterile. The substances to be processed are ground and sieved if necessary. They are dried and when they are resistant they may be sterilised with dry heat (see Sect. 30.5.2). Lactose can be dried and sterilised (drying 1 h 130 °C, sterilisation 3 h 140 °C).

The substances should be spread out in a thin layer so that the heat can penetrate well. If they can be sterilised at the same regimen and no interactions will take place during sterilisation, then they should be mixed before sterilisation. Otherwise they should be mixed after sterilisation, aseptically. The mixture is not sieved anymore. The powders are packaged in a sterile sifter-top container.

12.7.17.2 Irrigations for Wounds

To rinse large wounds, non-intact skin or non-intact mucous membranes sterile aqueous solutions have to be used. Also dressings that are applied to non-intact skin should be sterile. Additionally, irrigations for wounds have to be pyrogen free. Sterile dressings may also contain macrogols. Aqueous macrogol solutions may be steam sterilised. In Chap. 14 other aspects of the formulation and preparation are discussed.

12.7.17.3 Sterile Hydrophobic Ointments

The preparation of sterile hydrophobic ointments is similar to that of eye ointments, see Sect. 10.7.3. The base however does not have to be filtrated until particle free.

Insoluble active substances are processed as in eye ointments (Sect. 10.7.3).

12.7.17.4 Sterile Creams

Sterile creams are prepared aseptically from sterile components, similar to eye creams, see Sect. 10.7.3.

Some components that are usually warmed with the oil phase of cutaneous preparations are not resistant to 140 °C. These substances are sterilised with the aqueous phase. An example is sodium lauryl sulfate (and also lanettewax SX). Cetomacrogol wax is resistant to 140 °C.

With sterile lipophilic creams the cooled aqueous phase is added drop wise to the oil phase and mixed in aseptic circumstances. With sterile hydrophilic creams the preparation method should be planned as such that both phases are cooled to around 70 °C at the same time. The aqueous phase is aseptically processed with the oil phase to a hydrophilic

emulsion by firstly stirring continuously and later every now and then.

Insoluble active substances are processed as in eye creams (Sect. 10.7.3).

12.7.17.5 Sterile (Wound) Gels

For the formulation of sterile wound gels reference is made to Sect. 12.7.11. If the gel has to be iso-osmotic, for example when used in wounds, then mannitol may be used for that purpose.

With the preparation of sterile (wound) gels firstly the gel is prepared and subsequently steam sterilised. Some cellulose derivates (methylcellulose and hypromellose) will separate when heated, but dissolve again when cooled. While cooling down the mixture has to be stirred gently otherwise a glass-like lump will be created that cannot or only laboriously be dispersed. If insoluble substances have to be triturated then the gel has to be poured in time (still warm) in a sterile mortar or dish for further processing. Carbomer Gel (Table 23.17) can be steam sterilised. Catheter gels are always dispensed in a package for single use. This could be a bottle, but a 5 ml Redipac (see Sect. 24.4.2) is also suitable.

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Parenteral

13

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Contents

Based upon the chapter Parenteraal by Yvonne Bouwman-Boer and András Vermes in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_13,

Abstract

This chapter gives an overview of parenteral dosage forms and the rational for their use. Parenterals are sterile preparations that are injected intravascularly, administered into body tissues or into visceral cavities. The parenteral route of administration is often chosen for active substances that are poorly absorbed via the oral route or when rapid systemic availability and effects are required, or both. An introduction to the formulation and preparation of parenteral dosage forms is provided. Parenteral medicines can be formulated as solutions, emulsions or suspensions. Products, such as implants and microspheres are only briefly discussed. Knowledge about these types of products is a prerogative for the sound education of patients and caregivers in using the products.

Formulation strategies for reconstitution of ready to administer medicines are described in detail.

This chapter includes formulation considerations, preparation and quality control of parenteral nutrition. An overview of the administration methods of the parenteral dosage forms is also discussed

Keywords

Injections • Infusions • Parenterals • Parenteral nutrition • Administration • Reconstitution • Infusion systems • RTA • Formulation • Preparation • Phlebitis

13.1 Orientation

13.1.1 Advantages and Disadvantages of the Parenteral Route

Common reasons for parenteral administration of medicines are:

- A need to rapidly achieve therapeutic concentrations and effects of the active substances.
- A poor bioavailability when given orally.
- The plasma concentration of the active substance needs to be carefully controlled to avoid under or overdosing.
- The patient is unconscious or resists cooperation, or when enteral route is not possible (following major abdominal surgery or a critical illness).

Some medicines are administered parenterally for a combination of these reasons.

The parenteral route also has some disadvantages:

- The production is expensive.
- There is always a risk of infection.
- An injection is an inconvenient way of administration for most patients.
- There is a chance of tissue damage in the injection area.
- Possible mistakes in the route of administration.
- Side effects or allergic reactions can appear fast, require immediate action and cause major damages compared to other routes of administration.
- Accidentally injected air may produce an embolism.
- Administration requires specific knowledge and skills of an authorised and qualified person.
- An infusion brings along specific problems:
  - Occlusion of the infusion set
  - Formation of a biofilm in the infusion line which increases infection risk
- Infusion is not patient friendly, because the mobility of the patient is reduced and inserting and maintaining the infusion line is aggravating.
- Inserting and maintaining the infusion line is labour-intensive.

Poorly prepared or administered parenterals can cause patient harm such as thrombus formation, severe hypersensitivity reactions and infection. Because of the disadvantages of the parenteral route other administration routes are preferred. The parenteral route is only considered when other routes cannot be used or when the active substance can only be administered parenterally. This is often the case for patients in the hospital and especially for intensive care patients and other critically ill patients.

13.1.2 Type of Parenteral Administration

The appropriate type of parenteral dosage form and administration site has to meet the medical needs of the patient. Criteria that have to be considered are: onset and duration of pharmacological activity, site of therapeutic action, the volume to be administered, inpatient or outpatient.

The site of the pharmacological action of an active substance is not always known. In most cases the active substance can reach the site of action when it is injected subcutaneously or intramuscularly, or into the venous or arterial bloodstream. Sometimes it is necessary to inject the medicine directly into a deep compartment such as the central nervous system. Some active substances can only reach a specific compartment with a transport carrier. Some charged or large molecules can reach specific tissues incorporated in liposomes (see also Sect. 13.2.2).

The pharmacokinetic and pharmacodynamic characteristics of the active substance mainly determine whether a bolus (= a high quantity at once) injection or a continuous administration via infusion or injection pump is appropriate. An active substance with long duration of action or long half-life can be administered via bolus injection. Active

substances with a short duration of action or short half-life are to be administered continuously if a continuous action is required. The administration route of parenterals depends also on the type, i.e. solution, emulsion, suspension and vice versa. Aqueous solutions and emulsions from the O/W type (particle size of the disperse phase <1 µm) can be administered intravenously. Injection volumes usually amount to 5–10 mL. Larger volumes of aqueous solutions or emulsions are usually administered by infusion over time intervals from 15 min up to continuously. Some toxic (antineoplastic, vasoconstrictive agents) or tissue-injury causing medicines can only be administered intravascularly.

Parenteral suspensions and oil-based parenterals must be administered either subcutaneously or intramuscularly (see Sect. 13.5.3). The volume of subcutaneous injection typically amounts to 1 mL. To increase the applicable volume at the subcutaneous application site, hyaluronidase can be added to the formulation [1]. The volume of intramuscular injection is also small, usually 1–3 mL or up to 10 mL in divided doses. In practice the pharmacist also may dispense special injections (see Sect. 13.5.15).

The availability and competence of a caregiver also influences the choice of the parenteral form. Only specialised nurses or physicians are allowed to administer medicines by intravenous injection. In addition nurses are qualified to administer medicines subcutaneously and intramuscularly or to connect the administration set of an infusion solution to the already inserted peripheral or central venous access.

13.1.3 Availability of Parenteral Administration Forms

Many medicines coming to the market during the last decade are formulated for parenteral administration. The main reason is the (glyco)protein structure of the active substances and the lack of bioavailability after oral administration. Parenteral formulations with ‘common active substances’ (also called ‘small molecules’) are available as licensed pharmaceutical preparations across Europe. In the countries where those preparations are not on the market or not available, mostly for economic reasons, preparation of parenteral formulations can be done in the (hospital) pharmacies.

To decrease the delay required to draw up the medicine in emergency, and to reduce the risk due to dilution errors or infection or both, hospital pharmacy also supplies ready-to-administer (RTA) preparations (see Sect. 13.8) [2, 3]. Hospital pharmacy preparation of RTAs should be limited to clinically approved products not commercially available in a practical form.

For example noradrenalin is commercially available in ampoules of 1 mL containing a solution of 1 mg/mL. For intensive care patients 50 mL of noradrenaline solution in a diluted concentration is used for continuous infusion with a syringe pump. Prefilled 50 mL vials with noradrenaline injection solution (prepared from raw material, packaged, sterilised and labelled in the hospital pharmacy) reduce risks due to dilution errors or infection.

13.2 Definitions

13.2.1 Definitions of the European Pharmacopoeia (Ph. Eur.)

The Ph. Eur. defines parenteral preparations as “sterile preparations intended for administration by injection, infusion or implantation into the human or animal body”. They are categorised as:

1. Injections (solutions, emulsions or suspensions)
2. Infusions (aqueous solutions or emulsions with water as the continuous phase, mostly isotonic with blood, meant for administration in a large volume)
3. Concentrates for injections or infusions (meant to be administered per injection or per infusion after dilution)
4. Powders for injections or infusions (sterile solids that result in a solution when mixed with the right amount of the recommended reconstitution solution; to this category belong freeze-dried preparations)
5. Gels for injections (extended release of the active substance after injection) (see Sects. 13.3.2 and 13.5.15.2)
6. Implants (solid administration forms that release the active substance over a prolonged period of time) (see Sects. 13.3.2 and 13.5.15.3)

In the European countries volumes larger than 10 mL are rarely administered as an injection. But it is difficult to define a strict limit for volumes to be injected or to be infused.

According to the United States Pharmacopeia (USP) parenteral formulation can be divided into two categories, namely Small Volume Parenterals (SVP) up to a volume of 100 mL and Large Volume Parenterals (LVP) with a volume >100 mL.

13.2.2 Colloidal Forms

Poorly soluble active substances can be administered as colloidal solutions such as micelles, liposomes or microspheres (see also Sect. 18.4.1).

Micelles are spherical or laminar colloidal aggregates consisting of ≥ 50 monomers. Micelles are not rigid particles, but there is a constant exchange between the monomers in the solution and bound in the micelles. Micelles do not have an aqueous phase within the particle as it is the case in liposomes. Taxanes are formulated as micellar solutions for intravenous administration [4].

Liposomes are microstructures composed of one or more concentric spheres of (phospho)lipid bilayer, separated by water or aqueous buffer compartments. Those particles can encapsulate and deliver both hydrophilic and lipophilic substances. Water soluble substances can be entrapped in the central aqueous core, lipid soluble substances in the membrane and peptide and small proteins at the liquid aqueous interface. The size of such a particle can differ from 20 nm to 10 μm. Liposomes are in general made synthetically e.g. by the lipid hydration method. Liposomal medicines are on the market for the treatment of systemic fungal infections, tumours and for vaccination.

Microspheres consist of natural and synthetic polymers such as Eudragit®, chitosan, ethyl cellulose and egg albumin, which can be loaded with active substances.

13.2.3 Routes of Administration

Commonly used parenteral administration routes are (see Fig. 13.1):

- Intravenous
- Subcutaneous
- Intracutaneous
- Intramuscular

Intravenous injections are injected into the vein, so in the direction of the heart to diminish chance of bleeding on the puncture place (as would occur easily if intra-arterially would be injected). By this route the active substance is spread very fast through the circulatory system.

Subcutaneous injections are injected into the subcutaneous connective tissue of the upper arm, the upper leg, below or above the waist or the upper area of the buttock. Absorption of the active substances takes place through the vascular wall of the small vessels in the connective tissue. Heparins and insulins are usually injected subcutaneously.

Intracutaneous injection is done into the dermis layer of the skin, which is the tissue located under the epidermis. It is frequently done as a diagnostic measure, such as for tuberculin testing (screening test for tuberculosis referred to as a Tine test) and allergy testing (placing very small amounts of the suspected antigen or allergen in a solution under the skin).

Intramuscular injections are administered into the deltoid muscle of the upper arm or vastus lateralis muscles in the anterolateral aspect of the middle or upper thigh.

13.2.4 Specific Routes of Administration

Other more specific routes are employed for the administration of the active substance directly to the therapeutic site. For administration into the central nervous system the intrathecal, epidural or intracisternal injection route is used. Intrathecal injection is an injection into the spinal canal, more specifically into the sub-arachnoid space so that it reaches the cerebrospinal fluid and is useful in spinal anaesthesia, chemotherapy, or pain management applications. This route is also used for antibiotic treatment of infections, particularly post-neurosurgical. Medicines given intrathecally must not contain any preservative.

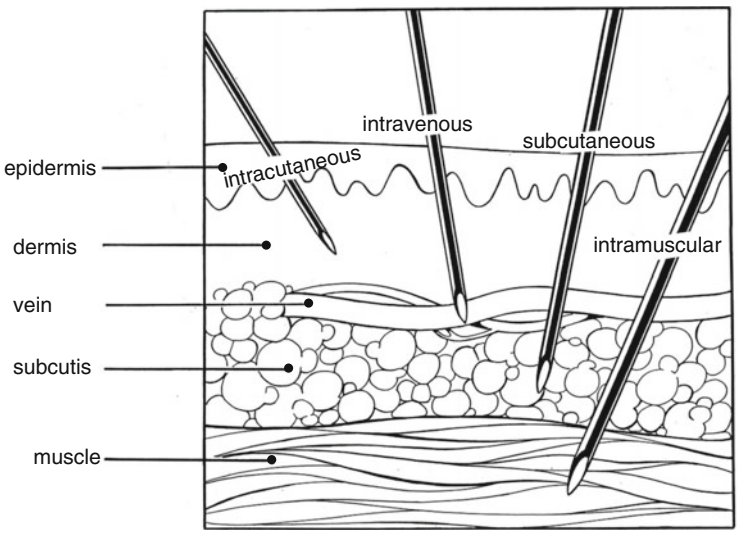

Fig. 13.1 The most frequently used parenteral administration routes. Source: Recepteerkunde 2009, ©KNMP

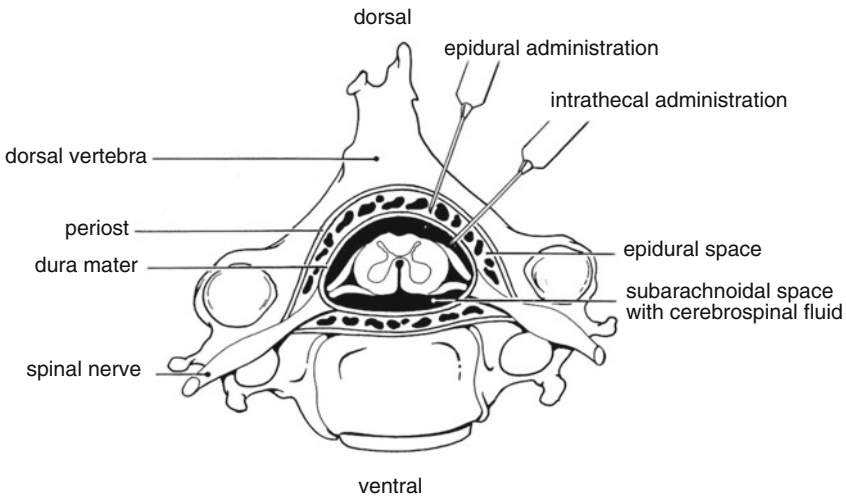

Fig. 13.2 Epidural and intrathecal administration route. Source: Recepteerkunde 2009, ©KNMP

Since intravenous solutions have been accidentally applied into intrathecal space, international guidelines have been issued to prevent this occurring. A major recommendation is to use a non-luer connector (see Sect. 13.10.2) in neuraxial procedures. The first non-luer connectors for intrathecal administration were launched in UK. However, standardisation of these connectors is required [5].

Spinal anaesthesia (spinal block or sub-arachnoid block) is used to administer the injection into the subarachnoid space. Several local anaesthetics are used for spinal anaesthesia such as procaine, lidocaine, tetracaine, and bupivacaine. Vasoconstrictors such as adrenaline (0.1–0.2 mg) and phenylephrine (0.5–2 mg) can be added to subarachnoid blocks to decrease vascular uptake and prolong duration of action.

Local anaesthetics are synergistic with intrathecal opioids and intensify sensory block without increasing sympathetic block. The combination makes it possible to achieve spinal anaesthesia with otherwise inadequate doses of local anaesthetic.

The difference in density between the cerebrospinal fluid (CSF) and local anaesthetic solutions should be considered to restrict their distribution to the subarachnoid space. The relationship between the density of the local anaesthetic solution and the density of the CSF is called baricity. Solutions of anaesthetic substances, which have a greater density than CSF, are hyperbaric. Hyperbaric solutions are especially practical in small doses for unilateral anaesthesia. Several commercially available hyperbaric solutions contain 50–80 mg/mL glucose [6].

Epidural anaesthesia is a technique whereby a local anaesthetic is injected through a catheter placed into the epidural space, see Fig. 13.2.

Spinal and epidural techniques are shown to provide effective anaesthesia for caesarean section. Spinal block differs from an epidural block in a number of ways:

- A smaller needle is used to perform a spinal block compared to an epidural block.
- With the spinal technique the medicines are injected into the cerebrospinal fluid that bathes the spinal cord; with an epidural block, the medicines are delivered outside the dura, in the epidural space.
- With the spinal technique small doses of local anaesthetic are required because they spread more easily in the spinal fluid.
- A spinal block is a single injection of local anaesthetic medications and so there is only one opportunity to deliver the medications; in an epidural, an indwelling catheter may be placed that avails for additional injections.

Intraventricular administration is used for antineoplastic treatment of gliomas or delivering the therapeutic agents to different areas of central nervous system.

Intracisternal injection is used to deliver therapeutic agents to the cisterna magna.

Intraocular (or intravitreal) injections, containing active substances such as triamcinolone, antivascular endothelial growth factor (VEGF) inhibitors, antibiotics, antivirals, or antifungals, are administered into the eye.

By intraarticular injection medicines, e.g. containing corticosteroids, local anaesthetics as active substances, are administered into the joint.

In case of cardiac emergency medicines (e.g. adrenaline) are administered directly into the muscles of the heart.

More routes can be distinguished
Intracostal punction and insertion of a cannula into the pleural cavity is mostly used to induce pleurodesis and thereby reduce pleural effusions. Intrapleural administration of sclerosing agents such as sterile talcum powder, doxycycline or bleomycin destroy the mesothelial cell layer and incite pleuritis, adhesions, and destruction of the pleural space.

The arterial route is used to deliver some antineoplastics (e.g. cisplatin) to treat head and neck cancer.

Parenteral administration can also be done endotracheally. Through the tracheal tube medicine (containing e.g. atropine or epinephrine) is delivered directly into the patient's bronchi.

13.2.5 Administration Methods

Parenterals can be administered by:
- Direct (bolus) injection
- Infusion by gravity
- Injection/infusion by pump
- During extracorporeal circulation.

Different types of veins can be punctured to be used for intravenous administration:
- Small venous vessels (e.g. veins in the forearm)
- Middle size venous vessel (e.g. vena brachialis)
- Large central veins (e.g. vena jugularis or vena subclavia)

An infusion can also be administered subcutaneously. However the volume to be administered is limited to 20–30 mL per 24 h (see Sect. 13.10.3). During extracorporeal circulation procedures such as haemodialysis a parenteral liquid can be administered via ports in the dialysis devices.

13.3 Biopharmaceutics

The rate of absorption of the active substance and subsequent duration of action will be determined by:
- Nature of the vehicle
- Physico-chemical characteristics of the active substance
- Interaction of active substance with vehicles, tissue and body fluid

13.3.1 Rapid Action

In emergency cases, e.g. cardiac arrest, anaphylactic shock or severe asthma, immediate action is required. Aqueous parenteral solutions administered intravenously are suitable for rapid onset of action.

13.3.2 Prolonged Action

Prolonged action of parenteral medicines is achieved by a different route of administration and different formulations. In general for example parenteral suspensions have a later onset and prolonged activity compared to parenteral solutions.

13.3.2.1 Intramuscular Administration

Administration into the muscle results in a delayed onset of action because the active substance has to be absorbed in the muscle, passed through capillary walls to be transported via the bloodstream to reach the site of action. Because most capillaries are fenestrated, all substances, whether lipid-soluble or not, cross the capillary wall at rates that are extremely rapid compared with their rates across other body membranes.

In addition the nature of the formulation affects the absorption rate of medicines administrated by intramuscular route.

Differences Between Muscles
The absorption rate after intramuscular administration differs depending on type of muscle chosen. Studies have shown that intramuscular injections result in different plasma concentrations of narcotics and perceived pain relief depending on the type of muscle used for administration. This was also found for the response to vaccination and use of antibiotics and insulin [7]. Absorption of active substances from the intramuscular site depends on the quantity and composition of the connective tissue and the rate of vascular perfusion of the area. Blood flow in the muscles varies (it is increased in deltoid muscle) and is influenced by the exercise of the muscle and morbidity. The muscles are covered with the subcutaneous connective tissue, a lipid layer (adipose layer) and the skin. The thickness and the lipid content of these tissues are different in different body areas. The subcutaneous fat layer at the gluteal intramuscular injection site is thicker in females (mostly > 3 cm) than in males. The medication should be administered with a needle long enough to reach the muscle without penetrating underlying structures.

13.4 Side Effects and Toxicity

Parenteral administration can be associated with pain and additional side effects and toxic reactions. These reactions can be more rapid and intense than with oral or cutaneous administration and may need fast intervention. Relevant types of adverse reactions are Protein hypersensitivity, (Thrombo)phlebitis, Pain, Extravasation and Damage by foreign particles.

Specific active substances exert their common adverse reactions when administered parenterally. Their rapid onset may lead to severe problems and therefore some substances require special attention beforehand:

- Benzylpenicillin (potential allergic reaction).
- Rituximab and other chimeric antibodies (infusion-related reactions such as hypotension, cardiopulmonary reactions, angioedema; mild to moderate infusion-related reactions such as fever, chills and rigors occur frequently).
- Phenytoin (cardiovascular reactions, slow injection is associated with a high probability of precipitation).

13.4.1 Protein Hypersensitivity

With an increasing use of parenterally administered proteins there is an increased risk for hypersensitivity reactions. Proteins of any origin might elicit an immune response. Antibody formation against the protein may induce different results, e.g. no impact on efficacy, decrease of efficacy and neutralisation of the physiological protein. Reduced activity is derived from reduced half-life of the protein molecules in the circulation and rapid clearance by immune cells. Many factors influence the immunogenicity of proteins, including changes in the primary structure (sequence variation and glycosylation), storage conditions and changes in the tertiary structure (denaturation or aggregation) (see Sect. 18.4.1.4), contaminants or impurities arising from the production process, dose and length of treatment, the route of administration, and patient characteristics. Aggregation, which includes formation of dimers and high-order aggregates, may be mediated by pH, ionic strength, concentration, counter-ion composition of the formulation, temperature, sheer stress. Purification and concentration processes such as ultrafiltration, ion-exchange chromatography, lyophilisation, precipitation or 'salting out' can induce aggregation (see Sect. 22.2.5). Appropriate formulation of a protein product and stabilisation of the active substance is therefore extremely important. In any case the proteinaceous medicine should be stored and handled under optimal conditions. Freeze-dried particles should be completely dissolved, the recommended storage conditions should be adhered to, the preparation should not be shaken and should be not be administered with a peristaltic pump. The route of administration can influence the immunogenicity of the protein. Subcutaneous injection is associated with higher potential of immunogenicity than i.v. administration [8].

13.4.2 (Thrombo)phlebitis

Phlebitis is an infection of a blood vessel. Infusion-related phlebitis is characterised by pain, tenderness, erythema, induration, oedema and a local temperature increase. These circumstances may lead to thrombus formation or venous tissue destruction or both.

The incidence and duration of phlebitis seems to be dependent on a variety of factors. Physical-chemical factors such as low pH, hypertonicity, particles and precipitation play a role in the cause. Active substances that are poorly soluble in water may precipitate and can cause acute phlebitis. Active substances with adequate aqueous solubility may tend to cause phlebitis only because of prolonged or chronic administration. Clinical factors involving injection technique (infiltration, extravasation, type of needle, duration of infusion) but also irritating characteristics of the active substance can contribute to the occurrence of phlebitis [9, 10]. Sometimes (septic) phlebitis is caused by bacterial infection (e.g. cause of inappropriate aseptic technique during catheter insertion) and is characterised by inflammation with suppuration of the vein wall. Local responses to the parenteral challenges can be diminished by dilution of the medicine or by central venous instead of peripheral venous administration (see Sect. 13.10.3).

13.4.3 Pain

Parenteral administration can be associated with pain at the injection site. The so-called injection fear may be diminished by applying topically anaesthetics prior to injection. Eutectic mixtures of local anaesthetics (e.g. lidocaine/prilocaine cream or a tetracaine gel) have proven to be effective and well-tolerated in the relief of pain associated with intramuscular injections, venepuncture or intravenous injection in adults and children.

Non-physiological osmolality and pH or increased buffer concentrations in formulations can be responsible for pain at the injection site. Therefore some formulations for intramuscular use contain a local anaesthetic. Needle-free injection

technologies are alternatives to reduce the intensity of injection pain [11].

13.4.4 Extravasation

Extravasation is the process by which any injection or infusion solution accidentally leaks into the surrounding tissue. The degree of damage due to extravasation depends on the active substance, the concentration, the localisation of the extravasation and the length of time an active substance may develop the damage. According to the type and severity of damage, active substances are categorised as irritants or vesicants [12].

13.4.5 Damage by Foreign Particles

The presence of visible foreign particles, which cannot be metabolised, must be avoided in injection solutions (see Sect. 32.12). However, the release of particulate matter (such as rubber chips, chemical fibres, glass fragments) is an intrinsic element of the production process. They originate from the formulation, processing equipment, primary package or the preparation process prior to use. Particles larger than 8 μm are generally trapped in the capillaries of the lungs, causing (thrombo) phlebitis and embolism. Smaller particles can be trapped in the liver, spleen and spinal cord [13]. Foreign body granulomas may result from intramuscular or subcutaneous injection of products containing foreign particles.

13.5 Product Formulation of Injections

13.5.1 Active Substance

The parenteral route is used for the administration of 'small' molecules as well as for 'large' molecules (proteins, monoclonal antibodies, vaccines, immunoglobulins).

13.5.2 Solubility of the Active Substance

Solubility can be improved by chemical modifications (change of pH, use of buffer, derivatisation, complexation, salt formation) and other techniques (use of excipients such as surfactants, solubilisers, cyclodextrines and phospholipids).

13.5.2.1 Buffers and pH Adjustment

For active substances that are ionisable, aqueous solubility can be raised by pH adjustment (see Sect. 19.1.1). An example for this principle is a quinine injection (Table 13.1). Quinine has low water solubility and a pK_a around 4. By adjusting the pH of the quinine solution to pH 3, about 90 % of the quinine is ionised, resulting in a clear solution in the desired concentration.

Table 13.1 Quinine Hydrochloride 600 mg = 5 mL (120 mg/mL) Solution for Injection [14]

Quinine hydrochloride	12 g
Hydrochloric acid	q.s.
Water for injections	ad 100 mL

13.5.2.2 Salt Formation

Salts of acidic and basic active substances have, in general, higher solubility than their corresponding acid or base forms. Haloperidol is almost insoluble in water (< 0.1 mg/mL) but haloperidol hydrochloride dissolves up to 3 mg/mL. Salt formation of haloperidol with lactic or tartaric acid results in increased water solubility and allows producing haloperidol injection solution (Haldol®) with a concentration up to 5 mg/mL.

On the other hand decreased solubility of an active substance and the formulation as a suspension may be advantageous. The duration of action of insulin is enhanced by forming salts with protamin and zinc with a lower solubility and lower rate of dissolution of insulin.

13.5.2.3 Complexation

Aqueous solubility of an active substance with low water solubility may be increased by molecular complexation with cyclodextrins, polyvidone and macrogols.

13.5.3 Vehicle

Water for injection is the preferred vehicle for the preparation of parenteral solutions (injections and infusions). When the active substance is poorly or not soluble in water, co-solvents or non-aqueous vehicles can be employed, or dosage forms such as liposomes or microspheres can be used.

13.5.3.1 Co-solvents

Co-solvents lower the surface tension of water resulting in increased solubility of poorly water soluble active substances. The most often used co-solvents in licensed injections are ethanol, glycerol, propylene glycol and macrogols (see Sects. 23.3.2, 23.3.3 and 23.3.4). The combination of propylene glycol and ethanol is commonly used to dissolve lipophilic active substances [15].

Diazepam is only slightly water-soluble and has a pK_a of 3.4, which is not suitable to increase solubility by pH adjustment. The brand Diazepam-injection CF® 5 mg/mL contains diazepam solubilised in a co-solvent mixture of propylene glycol and ethanol.

Nimodipine is poorly soluble in water: < 0.1 mg/mL. The licensed pharmaceutical product Nimotop® infusion solution contains 0.2 mg/mL nimodipine and 170 mg/mL macrogol 400. This high concentration of macrogol is needed to dissolve the active substance but causes phlebitis when Nimotop® is administered via a peripheral vein. Therefore in the product information it is recommended to administer Nimotop® via a central venous catheter.

After diluting the infusion or injection concentrate with an aqueous solution or with blood the active substance may precipitate. This is due to the concomitant dilution of the co-solvent(s) and oversaturated solutions. Whether or not precipitation occurs in mixtures of water and co-solvents can be calculated in analogy to the calculation of the chance of precipitation in water, see Sect. 18.1.1.

Supersaturated solid solutions of poorly water-soluble compounds are inherently prone to recrystallisation over time (see Sect. 18.1.6). If the appropriate formulation principles and production processes are utilised, such systems can represent a formulation option for injection of poorly water-soluble active substances. However, crystallisation is not predictable. Serious clinical problems have been reported when precipitates have caused venous blockages [16].

Co-trimoxazole is the combination of trimethoprim (solubility 0.1–1 mg/mL; $pK_a = 7.4$) and sulfamethoxazole (solubility < 0.1 mg/mL; $pK_a = 6$). The licensed pharmaceutical preparation Bactrimel® is a concentrated co-trimoxazole solution of 16/80 mg/mL in propylene glycol, ethanol and water, with ethanolamine and sodium hydroxide. The pH of the solution is 9–10.

Before administration, the injection fluid 16/80 mg/mL has to be diluted to the concentration range of 0.125/0.625–8/40 mg/mL. The dilution causes reduced concentrations of organic solvents and a decreased pH value. Since the active substance precipitates slowly, the diluted preparation can be administered safely.

For an overview of the toxicity of co-solvents, when used parenterally, reference is made to the literature [17]. Glycerol is a safe co-solvent, but it is used infrequently in injectable formulations. It is often not able to achieve the desired concentration of the active substance. Ethanol improves the solubility, but is, in concentrations higher than 10 %, painful when injected. Propylene glycol elicits a haemolytic response *in vitro* and *in vivo*, which could be reduced by the addition of either saline or macrogol 400. Macrogol 300 and macrogol 400 are generally considered to be among the safest organic co-solvents. Although macrogols are biocompatible, peroxide impurities in macrogols can cause the degradation of oxidisable active substances [15].

13.5.3.2 Lipophilic Solvents

Vegetable oils such as cottonseed oil, peanut oil, and soybean oil can dissolve very lipophilic substances. Oils must be free from rancidity. Also semi synthetic lipophilic products such as isopropyl myristate and medium chain triglycerides are used in licensed parenteral liquids. They are stable and colourless.

Oily injectable formulations are only administered by intramuscular injection providing a depot for sustained drug delivery. A good example is the oil-based extended release injection product that contains haloperidol esterified to a decanoate dissolved in sesame oil. The volume to be injected is deposited deep into the gluteal muscle and forms a depot from where it is leached over a 1 month period into the blood stream according to its oil/water partition coefficient. This phenomenon together with the time needed for circulating enzymes to hydrolyse the ester into the active base is responsible for the prolonged length of action of this formulation.

Another example for a long-acting formulation is the intramuscular injection of fulvestrant, dissolved in castor oil and organic solvents. It is administered once monthly to treat hormone receptor positive breast cancer.

For intravenous or intramuscular administration, oil-soluble actives can be formulated as an oil–water-emulsion. When administered intravenously it is essential that the droplet size is about the same size as the lipid particles that circulate in the blood, the chylomicrons (0.2–3 μm). A typical emulsion contains 10–20 % soybean oil, 2 % glycerol and 1 % egg lecithin. These emulsions cannot be autoclaved. Coalescence of the droplets of the internal phase is a typical sign of instability. All-in-one total parenteral nutrition admixtures are a typical example for parenterally administered emulsion (compare Sect. 13.9).

Diprivan® or Disoprivan® is an example of a licensed medicinal product formulated as an emulsion. The active substance propofol (di-isopropyl phenol) is solubilised in an emulsion composed of 10 % soybean oil with egg phosphatide.

13.5.3.3 Microspheres and Liposomes

Microspheres and liposomes are described in Sect. 13.2.2 Some examples, described below, illustrate how these techniques are used to process substances with poor solubility into an injectable liquid.

DaunoXome®, used in treatment of Kaposi's sarcoma, is an example of a liposomal antineoplastic medicine. Daunorubicin hydrochloride (1 mg/mL) is encapsulated in small liposomes. Amphotericin B, which is used in the treatment of systemic fungal infection, is also formulated as a stable colloidal particle.

The Swiss Serum Institute developed liposomal-based vaccines against hepatitis A and B, influenza, diphtheria and tetanus [18].

A liposomal injection solution of verteporin (Visudyne®) is formulated with egg phosphatidylglycerol and dimyristoylphosphatidyl choline. The freeze-dried powder, contains apart from the liposomes, verteporin, lactose as lyoprotector, and osmolality adjusting excipients. By reconstitution with water an opaque dark green injectable solution is generated, which is injected intravenously within the scope of photodynamic therapy.

Microsphere sizes range from 10 to 200 µm. The smaller the microspheres are, the better is their syringeability and the smaller are the needle diameters required for injection, which results in reduced patient discomfort. The larger the microspheres, the lower is the risk that the particles will be cleared from the injection site by macrophages. 10 µm is generally considered to be a safe lower size limit to avoid particle uptake by macrophages. The common microsphere size is about 30 µm. Microspheres can be administered at the site of action and guarantee prolonged activity by slow release of the active substance. Furthermore, sensitive active substances such as peptides and proteins may be protected from chemical and enzymatic degradation when entrapped in microspheres.

Several injectable prolonged release biodegradable microspheres are available as licensed products, e.g. Lupron Depot® and Risperdal® Consta [18, 19]. The injectable ultrasound contrast agent (Optison®) consists of heat-denaturated albumin microspheres filled with the gas octafluoropropane. In a similar manner sulphur hexafluoride containing microspheres (SonoVue®) are used as injectable contrast agent in echocardiography.

13.5.3.4 Surfactants

Surfactants reduce surface tension and increase the solubility of lipophilic active substances in aqueous medium; solubilisates are formed (see Sect. 18.3.3). Lecithin, various phospholipids, polysorbate (Tween®) and polyoxyethylene castor oils such as Cremophor® EL can be used in injections [15].

Phytomenadione (Vitamin K_1) appears as a non-ionisable, water-insoluble viscous liquid. In Konakion® MM injection fluid 10 mg/mL it is solubilised with lecithin and glycocholic acid creating micelles.

Amiodarone hydrochloride, which has a poor water solubility of 0.7 mg/mL, is solubilised in licensed pharmaceutical preparations thereby achieving a concentration of 50 mg/mL. Infusion solutions prepared with 5 % glucose as a vehicle still have amiodarone concentrations (6–15 mg/mL) exceeding by far the maximum concentration of water solubility. The resulting infusion solution contains the active substance still solubilised.

Polysorbate (Tween® 20 and 80) and Cremophor RH40® (macrogol glycerol hydroxyl stearate) or Cremophor EL® (polyoxylated 35 castor oil) can cause serious hypersensitivity reactions when administered parenterally [15]. They may cause incompatibilities by leaching plasticisers (such as phthalates) from polyvinyl chloride infusion devices.

The combination of 200 mg/mL polyoxyethylene hydrogenated castor oil and ethanol is used to solubilise the active substance tacrolimus (water solubility < 0.1 mg/mL) up to 5 mg/mL in Prograf® injection concentrate. The product is administered intravenously after dilution to concentrations of 0.004–0.1 mg/mL.

13.5.4 pH and Buffer Capacity

Solubility and stability of the active substances are to be considered when evaluating the optimal pH of parenteral solutions. Moreover the pH of the solution has an impact on the infusion tolerance, which is also depending on the volume and rate of administration and the buffer capacity of the formulation. To prevent possible adverse effects the pH should preferably be in the physiological range. The pH of the blood varies between 7.35 and 7.45 and has a large buffer capacity and, theoretically, a deviant pH of an intravenous injection will be corrected fast. The mixing, and thus the neutralisation process, however takes rather long as blood flows are laminar. Fast infusion will disturb this laminar flow and with irritating solutions might be preferred above slow infusion. This effect is confirmed in animal tests [20]. Intravenous injections have a higher chance of causing phlebitis in smaller vessels than in larger vessels where the blood flows faster. If the injection remains for too long at the place of injection such as with subcutaneous and intramuscular administration there is more chance of irritation than with intravenous administration.

If a larger volume is given intravenously, the tolerated pH range is 3–11 [1]. The more the pH of the formulation approximates to the lower and upper limit of this pH range the higher is the probability of discomfort and irritation at the injection site. Non-toxic acids and bases are used to set the pH of parenterals. Lactic, maleic and hydrochloric acid and sodium hydroxide are used most often. They have some buffering capacity in the acid area. Whether the resulting solution has sufficient buffering capacity depends on the pK_a of the used base or acid and the pH of the solution (see Sect. 18.1.1).

Buffers, mostly phosphate buffer solution, are included in the formulations to ensure the pH of the solution being maintained throughout the shelf life of the product. The buffer prevents pH changes caused by degradation products or leaching of ions from glass containers (see Sect. 24.2.1). Buffers may increase the hydrolysis rate of the active substances (see Sect. 22.2.1) and may decrease solubility (Sect. 18.1.1). High buffer capacity should be avoided in order to minimise irritation and pain at the injection site and disturbance of the physiological pH.

However, due to active substance stability, it is still necessary to develop injections with extreme pH values. A currently licensed intravenous product in UK with a very low pH of 2.8 is Persantin® (dipyridamol 5 mg/mL). The solubility of dipyridamol is < 0.1 mg/mL, but higher at a pH ≤ 3.3 [21]. Experiments showed that even after dilution with 0.9 % NaCl or glucose 5 % solution (1:2 ratio), the pH still amounts to pH 3. Information about the pH of the diluted parenterals is not to be found in the literature for all licensed products [20].

13.5.5 Osmotic Value

As a measure of the tonicity of blood one can calculate with the osmotic value because active substances and additives cannot pass the membrane of the erythrocyte (see Sect. 18.5.2). The osmotic value of blood is around 290 mOsm/kg. Some parenteral fluids however contain substances that can pass the membrane fast: ethanol, glycerol, urea. Hyperosmotic solutions of these substances may cause haemolysis; so they are hypotonic. The iso-osmotic concentration of ethanol is for example 1.39 % m/m. Ethanol 5 % v/v infusion fluid is therefore hyperosmotic but appears to be practically isotonic.

Parenteral products with osmotic values differing from the physiological value may cause phlebitis and irritation. This is especially applicable when the injection remains relatively long at the site of injection such as after subcutaneous, intramuscular, epidural and intrathecal administration. There is a higher chance of phlebitis in small vessels after intravenous administration. However, it is not known which limits should be considered to prevent phlebitis and irritation. According to some sources [22] the osmolarity of an intravenous injection should not be higher than 500 mOsm/kg. For subcutaneous and intramuscular administration the range is smaller.

As is the case for the pH level and buffer capacity, adjustment of osmotic value to physiological conditions is advisable. Sodium chloride or glucose are mostly used to adjust tonicity of parenterals. Sometimes deviating medical requirements are to be met. For example, hyperbaric solutions of local anaesthetics are used in spinal anaesthesia (see Sect. 13.2.4). Hyperbaricity in comparison to the cerebrospinal fluid is achieved by a high glucose concentration (7.5 %) which is also a hyperosmolar.

Baricity and dose of the local anaesthetic along with the patient position determine the anaesthetic block height.

Nitroglycerin, Concentrate for Infusion 1 mg/ml
The alcoholic nitroglycerin solution 10 mg/g contains 90 % v/v ethanol (= 86.5 % m/m). The nitroglycerin infusion concentrate thus contains 86.5 mg ethanol per ml. It has an osmotic value of 1,800 mosmol/l and is thus hyper osmotic, but at the same time hypotonic because ethanol can pass the erythrocyte membrane freely. This solution can only be administered when it is mixed with NaCl 0,9 % or glucose 5 %.

13.5.6 Viscosity

Parenteral formulations should not be more viscous than water because as the viscosity of the formulation increases, the ease of administration decreases and the likelihood of pain caused by injection increases. Polymers that modify viscosity of the formulation are more frequently used in parenteral suspensions than in parenteral solutions. By addition of hydrophilic or lipophilic polymers parenteral suspensions are stabilised.

13.5.7 Excipients for Suspensions and Emulsions

Typical excipients used in parenteral suspensions include surfactants that are used to stabilise emulsions and suspensions as wetting agents (polysorbate 80, poloxamer), as micelle makers for the preparation of solubilisations and to influence the flocculation and deflocculation behaviour of a dispersed system (carmellose sodium, polyvidone). Parenterally used surfactants in high concentrations are toxic and may cause venous irritation and occasional thrombophlebitis. However, these high concentrations are not necessary to formulate stable parenteral suspensions.

Only a limited number of emulsifiers are commonly regarded as safe to use in emulsions for parenteral administration. Most important are lecithin, poloxamer and macrogolglycerol ricinoleate (Cremophor EL®). This latter excipient is linked to anaphylactic reactions and temporary haematological disorders.

13.5.8 Antioxidants

Antioxidants are used to reduce or inhibit the oxidation of active substances or excipients. Active substances in parenterals which may undergo oxidative degradation are e.g. phenothiazines, catecholamines, polyene antifungal agents, steroids, morphine. Antioxidants either prevent the formation of free radicals (i.e. butylated hydroxyanisole, butylated hydroxytoluene) or have a lower redox potential than the active substance to be protected (i.e. sodium metabisulfite, sodium formaldehydesulfoxylate). Edetate increases the activity of antioxidants by chelating polyvalent cations, which may generate free radicals or be involved in electron transfer reactions (see also Sects. 23.10 and 22.2.2.2). Another strategy to diminish oxidation is to remove oxygen by flushing the injection solution with nitrogen prior to closure (see Sect. 13.7.4).

Physostigmine salicylate can degrade successively by hydrolysis and oxidation by oxygen. To prevent oxidation during preparation, storage and administration to the patient physostigmine salicylate injection fluid (see Table 13.2) is stabilised with 0.1 mg/mL sodium metabisulfite. In general, to prevent oxidation sodium metabisulfite is used in higher concentrations i.e. 1 mg/mL. Because of the potential allergic reactions to sodium metabisulfite and the ability of metabisulfite to form adducts with physostigmine, the concentration is limited and arbitrarily set at 0.1 mg/mL. This concentration is adequate to protect the solution from discolouration.

Table 13.2 Physostigmine Salicylate 2 mg = 2 mL (1 mg/mL) Solution for Injection [23]

Physostigmine salicylate	0.1 g
Hydrochloric acid	q.s.
Sodium metabisulfite	0.01 g
Water for injections	ad 100 mL

13.5.9 Preservatives

Single dose vials should be used as much as possible to avoid microbial contamination entering the vial as in the case of multidose vials. However, for economic reasons parenteral solutions are still packaged in multidose vials and preservatives are incorporated in them. According to the Ph.Eur. multidose vials must contain a preservative. However, the single dose may not exceed 15 mL. Parenteral solutions which contain high concentrations of co-solvents such as propylene glycol or glycerol, or oil-based products, mostly do not require the addition of preservatives, although it has been established that micro-organisms may survive in non-aqueous solutions [24]. The activity of preservatives can be affected by the pH, the concentration, the presence of binding or complexing excipients, and incompatibility reactions with proteins and rubber as container closure material. Commonly used preservatives and typical concentrations used are: benzyl alcohol (1.0 %),

chlorobutanol (0.5 %), phenol (0.5 %), and metacresol (0.1 %). Some preservatives, such as the parabens, cause irritation or adverse reactions and are hardly used anymore in parenterals. If a formulation is intended for paediatric administration, restrictions for certain preservatives must be considered. European Medicines Agency (EMA) recommended that parenteral solutions containing benzyl alcohol should not be used in pre-term and full-term neonates, due to neurotoxicity, cardiovascular failure, intraventricular haemorrhage, gasping respirations and metabolic acidosis ('gasping syndrome'). Due to the risk of fatal toxic reactions arising from exposure to benzyl alcohol in excess of 90 mg/kg/day, this preservative should also not be used in children up to 3 years old [25].

Due to their toxicity preservatives are not allowed in injections for epidural, intrathecal, intracisternal or intraocular use [26].

13.5.10 Excipients Used in Freeze-Drying

Proteinaceous active substances are usually formulated in an elaborated excipient system prior to the freeze-drying procedure. Bulking agents, such as mannitol or glycine, are used to increase the bulk volume and provide a suitable matrix in which a small quantity of protein is dispersed [27]. Further details regarding use of cryoprotective excipients are described in Sect. 22.2.5.

13.5.11 Packaging and Labelling

Injection fluids are packaged in ampoules, vials or bottles (container size $\leq$ 100 mL), syringes, and cartridges manufactured from glass or plastic. The containers must be transparent to allow visual inspection of the content. Light sensitive active substances should be preferably protected by light-tight secondary packaging; amber glass is an option as well but it hinders checking for clarity.

Containers for injections are discussed in Sects. 24.2.1 (glass quality), 24.2.4 (rubber), 24.3 (closures), 24.4.14 (ampoules) and 24.4.17 (syringes). Although glass is a preferred material, care should be taken to avoid possible incompatibilities. In particular, for instance, adsorption and aggregation of proteins touching glass surfaces, release of glass particles in solutions with pH $>$ 7 and specific ions or both, release of aluminium from class I glass, etcetera. Class I glass is generally to be preferred but its suitability is not a matter of course and has to be tested. Rubber closures need attention as well because of release of rubber particles during autoclaving,

Because of the high price, type II glass is to be considered, and when tested might be found to be appropriate.

Labelling of parenterals is discussed in Sect. 37.3.2. For injections usually both the total amount of active substance and the concentration should be indicated.

13.5.12 Stability

Details of chemical and physical degradation reactions of medicines (including proteins), and stability investigation are given in Chap. 22.

Injection solutions containing 'small' molecules may degrade by hydrolysis, oxidation and epimerisation reactions. The reaction rate determines whether sterilisation by heat can take place or not. Injection fluids that tolerate autoclaving usually have a shelf life of several years at room temperature. Active substances that are not stable in solution are usually prepared as powder – commonly by freeze drying the solution – and have to be reconstituted immediately before administration by the caregiver or the patient. Physical instability regards mainly suspensions (resuspendability) and protein solutions (precipitation and aggregation). Incompatibilities (precipitation) have to be checked for when solutions of poor water-soluble substances in co-solvents are diluted or when parenteral solutions are combined.

Protein products are especially prone to changes of the tertiary and quaternary structure of the molecules and thereby loss of activity. Degradation is induced by heat and shear stress. Rigorous shaking and administration by peristaltic pumps should be avoided.

13.5.13 Storage Temperature and Shelf Life

See Sect. 22.6.1 for a general discussion of shelf life. As long as the container of injection fluids remains closed, the storage temperature and shelf life are determined by the rate of the degradation reaction. Most parenterals can be stored at room temperature, exceptions are vaccines and protein medicines. Parenterals that are not sterilised in the final container are to be stored in the fridge or freezer with regard to maintaining their sterility. Storage temperature and in-use stability after first opening of ampoules and bottles are also determined by the chance of microbiological contamination.

The EMA Note for Guidance on Unpreserved Sterile Products requires licensed parenteral medicines to be labelled as follows:

(continued)

Chemical and physical in use stability has been demonstrated for x hours/days at y °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 h at 2–8 °C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

The shelf life of reconstituted parenterals prepared in the hospital pharmacy is to be determined by the responsible pharmacist (see Sect. 22.6). When licensed injection fluids are reconstituted and prepared for individual patients the shelf life is determined by evaluation of the physico-chemical stability and risk of microbiological contamination. Shelf life depends from a microbiological viewpoint on the risks associated with aseptic preparation and the results of validation studies performed under the pharmacy's specified aseptic preparation conditions (see Sect. 31.3.6).

In-use stability of preserved injection fluids in multiple dose vials is limited to a maximum of 28 days. Typical examples are multidose vials of insulin preserved with methyl hydroxyl benzoate and multidose vials of low molecular heparin preserved with benzyl alcohol.

13.5.14 Quality Requirements

Parenteral solutions are to be tested for absence of visible and non-visible particles and sterility as specified in the Ph. Eur. Furthermore, freedom from pyrogens or endotoxins and the uniformity of dosage units and content are stipulated (see Sect. 32.8). Suspensions should be easily resuspendable to ensure precise dosing and uniformity of the dose during administration. Parenteral emulsions should be homogeneous.

13.5.15 Special Parenteral Preparations

In practice the pharmacist may dispense special injections. This section briefly describes their formulation and biopharmaceutic characteristics, but not their way of preparation and quality requirements.

13.5.15.1 Suspensions

Parenteral suspensions are injected subcutaneously or intramuscularly and are usually meant for an extended action [28]. Examples of parenteral suspensions licensed in Europe are penicillin G procaine suspension and medroxyprogesterone acetate suspension.

13.5.15.2 Gels

Biodegradable in situ gel forming implant systems secure prolonged activity. They are formulated by dissolving biodegradable polymers (such as poly (dl-lactide), lactide/glycolide copolymers, lactide/caprolactone copolymers) in a biocompatible organic solvent (e.g. N-methyl-2-pyrrolidone (NMP)). Active substances are either dissolved or dispersed in the polylactic-co-glycolic acid (PLGA) solution. When the liquid formulation is injected intramuscularly or subcutaneously, the organic solvent diffuses into body fluid and water penetrates into the solution. This leads to precipitation of the polymer forming a solid polymeric implant at the injection site. The active substance is released over a prolonged period when the polymer is biodegraded [29].

An advanced injectable gel product is Eligard® containing leuprolide acetate and PLGA 75/25 dissolved in NMP in a 45:55 (w/w) ratio. The 1, 3 and 4 months Eligard® formulations are supplied in two separate syringes. One syringe contains the PLGA/NMP solution and the second syringe leuprolide acetate. Prior to administration the content of two syringes is mixed until it is homogeneous.

13.5.15.3 Implants

Implants are solid polymers loaded with an active substance. The active substance is delivered at a constant rate as long as the implant stays at the administration site. Local or systemic activity can be achieved. The duration of activity varies from days to years. Insertion and removal (if not biodegradable) requires medical assistance [30].

In order to achieve high local concentrations of antibiotics in infected bone or joint, methyl methacrylate/methyl acrylate copolymer (PMMA) bead chains or mini-chains loaded with an antibiotic (mostly gentamicin sulfate) are inserted.

Gentamicin sulfate is heat resistant and highly soluble in water. A bead chain consists of 10, 30 or 60 beads (diameter 7 mm) threaded on a flexible steel thread. A mini-chain contains 10 or 20 oval mini beads threaded over a length of 10 or 20 cm. The beads are sterilised with ethylene oxide. The chain should be removed after a period of 7–10 days.

Another typical implantable product is the horse collagen sponge loaded with gentamicin. The implant is absorbable. High antibiotic concentrations are achieved at the site of implantation over several days.

13.5.15.4 Derivatives

Protein and peptide pegylation (conjugation to polymers of long-chain macrogol – or polyethylene glycol) improves the biopharmaceutical properties of active substances. The improvement encompasses increased stability, resistance to proteolytic inactivation and extension of the half-lives. By this the delivery and efficacy of proteins is improved [31].

The application of filgrastim pegylation technology resulted in a second generation molecule named pegfilgrastim, with significantly altered pharmacokinetic properties in comparison to filgrastim. Pegfilgrastim has the same mechanism of action as filgrastrim but the pegylation markedly reduces renal clearance, leaving neutrophil-mediated clearance as the major route of elimination. As a result, clearance of pegfilgrastim is decreased and serum concentrations are sustained throughout the duration of neutropenia. In clinical studies with standard, multicycle chemotherapy, a single subcutaneous dose of pegfilgrastim has been shown to have similar efficacy and safety as daily subcutaneous injections doses of filgrastim in patients with solid tumours [32].

Further examples of pegylated protein active substances are peginterferon and pegvisomant.

Polysialylation (the process whereby PSA-polysialic acid is conjugated with proteins) is an alternative to pegylation limiting potential toxic accumulation and immunogenic potential of macrogol [33].

13.6 Product Formulation of Infusions

Many formulation characteristics and quality requirements for infusions are the same as for injections.

13.6.1 Types of Infusions

Infusions are sterile solutions or emulsions that are administered intravenously, subcutaneously or intrathecally/epidurally. Infusions are used as:

- Solutions regulating the acid–base balance
- Vehicle solutions for continuous infusion
- Blood volume expanders
- Osmotic diuretics
- Partial and total parenteral nutrition

Shifts of the physiological pH may require administration of acid or base containing infusions. Metabolic acidosis is treated by infusion of sodium bicarbonate containing infusion solutions. Metabolic alkalosis is treated with hydrochloric acid containing infusion solutions.

Sodium chloride 0.9 % solution and 5 % glucose solutions are most suitable to be used as vehicle solutions for parenterally administered injections or infusions.

Blood volume expanders can be crystalloid or colloidal. The most often used crystalloid solutions are 0.9 % sodium chloride solution, 5 % glucose solutions and their combinations, e.g. 0.45 % sodium chloride/2.5 % glucose solution. In addition infusion solutions containing multiple electrolytes such as Ringer's solution or Lactated Ringer's are administered. These solutions contain also potassium, magnesium, calcium, and phosphate [34].

Blood volume expanders used to compensate loss of plasma are formulated as electrolyte solutions with macromolecular substances such as gelatine, polygeline, hydroxyethyl starch (HES), and albumin. Hydroxyethyl starch is similar to albumin but cheaper. However there are restrictions in its use. European Medicine Agency (EMA) has decided that HES solutions should not be used in critically ill adult patients, including patients with sepsis or burn injuries and excess bleeding particularly in patients undergoing open heart surgery in association with cardiopulmonary bypass, because an increased risk of mortality and renal injury requiring renal replacement therapy [35].

Osmotic diuretics are rapidly filtered in the glomerulus and not reabsorbed in the tubules. As a result of the osmotic gradients thereby achieved in the renal tubules, the reabsorption of water is inhibited, and urine excretion increased (see also Sect. 13.6.3).

Parenteral nutrition solutions are discussed separately in Sect. 13.9.

13.6.2 Buffer Capacity

Large volume infusions should have a physiological pH, e.g. pH 7.4 and little or no buffer capacity. In general infusions with pH 5–9 are tolerated by peripheral veins.

The pH values of commonly used infusion solutions vary between 4 and 8 depending on the type of formulation. A lower pH is acceptable if solutions are not buffered. The pH of 5 % glucose solutions amounts from 4.0 to 5.0. This is necessary to prevent degradation of glucose (see Sect. 13.6.4). Infusion fluids that are used to correct the pH of the blood have a deviant pH value (e.g. pH 8.0 for sodium hydrogen carbonate infusion).

13.6.3 Osmolarity

See Sect. 18.5 about osmosis and tonicity.

Infusion solutions have to be isotonic with blood because of the large volume administered. Typically used isotonic infusion solutions are 0.9 % NaCl solution and 5 % glucose solution.

Hyperosmotic mannitol 20 % infusion is used as osmotic diuretic. Hypotonic solutions such as 0.65 % sodium chloride are used in elderly patients to keep the salt load low, or in children to prevent dehydration.

Infusion fluids for neonates are often hyperosmotic, having no choice since only small volumes can be administered.

According to some recommendations [36] if osmolarity of the infusion is higher than 500 mOsmol/l, administration should occur via a central venous catheter that is inserted in a vessel with high blood flow such as the vena subclavia, proximal axillary vein or superior vena cava.

13.6.4 Stability

In addition to what has been said about the stability of injections (Sect. 13.5.12) some specific comments can be given regarding infusions. In practice most concern is about the chemical and physical (precipitation!) stability of active substances when mixing injections with the infusion vehicle. As a consequence of incompatibilities some active substances are only compatible with 0.9 % NaCl vehicle (e.g. furosemide-Na injection concentrate) and others are only compatible with 5 % glucose solution. As the mixtures often have to be kept after mixing also the chemical stability is an issue as well as minimising the chance of microbiological contamination by proper aseptic handling and administration.

Regarding the stability of infusion vehicles only glucose 5 % has to be mentioned. Glucose 5 % infusion solutions should have a pH lower than 5.5 before sterilisation. Higher pH values cause yellow or brown discolouration and formation of cytotoxic degradation products such as 3-desoxyglucosone, 3,4-dideoxyglucosone-3-ene, formic acid, 5-hydroxymethyl-2-furfural, acetaldehyde [37].

13.6.5 Container and Labelling

Infusion fluids are usually packaged in glass bottles or plastic containers (see Sects. 24.4.5 and 24.4.13). The adsorption of lipophilic substances to plastic infusion bags requires attention.

For the labelling of injections and infusion see Sect. 37.3.2. For infusions the concentration and the total volume would be enough. Electrolytes might be labelled as milliequivalents or millimoles or as milligrams or grams per mL or L. This differs from country to country and even within countries hospitals might have different policies depending the preference of the prescribers. This may lead to confusion about the type of unit. The material and adhesive of the labels are discussed in Sect. 24.2.6.

13.6.6 Quality Requirements

According to the Ph. Eur. parenteral preparations should be sterile, free from visible and non-visible particles and free from endotoxins/pyrogens (see Sect. 12.8).

13.7 Method of Preparation

The preparation of parenteral solutions encompasses the following steps:

- Starting material and equipment (provision and quality control of active substances, excipients and packaging material according to specifications, cleaning and disinfection or sterilisation of equipment and primary packaging material e.g. vials, elastomeric closures)
- Preparation of the bulk solution
- Control of bioburden
- Purging with inert gas
- Filling and closing
- Sterilisation (in final containers)
- Visual inspection
- Labelling

13.7.1 Starting Material and Equipment

Pyrogen-free starting materials, packaging materials and equipment is to be used. Water (see Sect. 23.3.1) and packaging material bear the highest chance for endotoxin contamination. A typical procedure for depyrogenation of glassware and equipment is by dry heating at 250 °C during 30 min. Adsorption on adsorptive agents is also an option, however difficult to perform and not too reliable that it can be used for the removal pyrogens from the solution. Selective adsorption of the chemical substances from solution to the filter may occur.

Water must meet the standards for Water for injections (Ph.Eur.) (see Sect. 20.3.1). The water should be prepared freshly or kept at a high temperature (≥80 °C) to remain sterile and pyrogen free.

Microbiological contamination of the starting material should be minimal to make sterilisation as effective as possible. Premises for preparation of parenteral products are classified as described in Sect. 27.4.1.

13.7.2 Preparation of the Bulk Solution

The active substance and the excipients are dissolved in an adequate volume of water for injections in glass or stainless steel vessels and stirred to obtain a homogeneous solution. To prevent particle contamination, starting materials with a low particulate burden should be used and materials liable to generate fibres should be kept to a minimum in clean areas. Particles that come from the starting materials or the preparation environment can be removed by filtration (see Sect. 30.6). Good preparation practice (clean rooms, clothing, cleaning, etc.) is to be followed to minimise particle and microbiological contamination during all processing stages (see Sect. 27.4.4 and Chap. 31).

13.7.3 Control of Bioburden

Components of parenteral solutions (active substances, excipients, intermediates and packaging material) should be routinely tested for bioburden and bacterial endotoxin level to ensure they are not adding an excessive microbial load. Bioburden is usually determined on the unfiltered bulk solution. Testing of filtered bulk parenteral solution either before or after filling into the final container may be done by comparison to the previously tested unfiltered bulk solution. Initial bioburden and endotoxin monitoring should be conducted to establish appropriately designed and sized terminal sterilisation methods such as filtration/aseptic filling or terminal heat treatment (see Sects. 30.5 and 30.6). Bioburden is also used as a parameter to evaluate process control.

In industrial production quantitative analysis of the microbiological burden of the product is carried out before and after every micro-organism reducing step. Rapid microbiological methods (RMM), such as ATP-bioluminescence are capable of producing results in real time, since traditional culture-based microbiological analysis techniques take at least several days to get a result [38, 39], see also Sect. 19.6.5

13.7.4 Purging with Inert Gas

Solutions containing active substances which are degraded by oxidation are preferably protected by introducing inert gas during and after filling. Helium, argon, carbon dioxide and nitrogen are the most commonly used gases for purging.

Efficacy of purging depends on the purging method, gas pressure, the shape and volume of the container. This process should be validated to ensure adequate displacement of air by the gas in each container. Research data [40], using nitrogen, showed that the best results are obtained by the following inert-gas purging method:

- Before and during the preparation purge nitrogen through water for injection.
- Purge nitrogen through an air dispersion device from the bottom of the vessel.
- Keep the contact surface between the solution and the air above the surface as small as possible, preferably by not using cylindrical but conical vessels.
- Keep the preparation vessel closed as much as possible.
- Seal the container immediately after filling.

However, validation possibilities of specific preparations are limited because it is still impossible to measure the oxygen concentration in the solution in ampoules for instance.

Once the need for inert-gas purging has been established, various strategies to reduce the loss of inert gas during shelf life should be evaluated. These approaches include selecting the proper closure (type and size) and optimizing vial headspace. Oxygen concentration in the headspace of the vials is monitored during the filling process and storage of the product by electrochemical methods, gas chromatography or Frequency Modulation Spectroscopy (FMS). With FMS it is possible to measure headspace oxygen concentrations in sealed containers in a rapid and non-destructive manner [41].

13.7.5 Filling and Closing

The Ph.Eur. states that each container should be filled with a sufficient overfill to ensure withdrawal of the declared volume. The required overfill is not described in Ph. Eur. Table 13.3 presents the recommended fill volumes permitted by USP to allow withdrawal and administration of the declared volumes [42].

Filled containers should be sealed as soon as possible, to prevent the contents from being contaminated. Container closure integrity may be evaluated by different methods: dye penetration pressure/vacuum decay, electrical conductivity and laser-based headspace detection [43], see also Sect. 24.3.1 for small scale methods. Validation studies of the “old fashioned” dye penetration method showed lack of sensitivity and reliability [44].

It is also possible to identify ampoules which are not closed tightly by applying a vacuum during the sterilisation program. Ampoules, which are not completely closed, will be empty afterwards.

Table 13.3 Recommended excess with filling injection fluids [after 42]

	Recommended excess volume	
Labelled volume (mL)	For mobile fluids (mL)	For viscous fluids (mL)
0.5	0.10	0.12
1.0	0.10	0.15
2.0	0.15	0.25
5.0	0.30	0.50
10.0	0.50	0.70
20.0	0.60	0.90
30.0	0.80	1.20
50.0 or more	2 %	3 %

13.7.6 Sterilisation

Products should always be sterilised as soon as possible after filling and closing. Important factors in determining the suitable sterilisation method are the type and the stability of the product. When stability of the formulation and containers allows autoclaving (15 min at 121 °C), this is the preferred method. It is rapid and inexpensive. However, stability of many pharmaceutical products will be affected by elevated temperatures. Heat-labile products can only be sterilised by a non-thermal method usually by filtration through bacteria-remaining filters or, with defined circumstances, with a method using less heat in combination with other measures. The starting materials and the equipment should be sterilised before preparation and the product should be prepared under aseptic conditions. For further details see Chaps. 30 and 31.

Adapting the formulation may allow the application of a more reliable sterilisation method. An example is talc powder used in pleurodesis. The easiest and cheapest sterilisation method for talc powder is prolonged dry heat exposure. But this sterilisation method is more difficult to validate than autoclaving. Instead of pure talc powder, a talc suspension in 0.9 % NaCl solution was prepared and autoclaved [45].

13.7.7 Visual Inspection

Parenteral solutions should be free from visible particles and may only contain a limited amount of particles that are not detectable by visual inspection (see Sects. 13.5.12 and 13.6.6).

Each final container should be checked for visible defects (cracks, presence of visible particles, etc.). Products in which particles are detected should be discarded.

The container must be transparent to permit inspection of the content. If this is not the case (opaque container) an alternative particle counting method has to be applied (see Sect. 32.12).

Inspection of the parenteral preparations may be done by operators or semi-automated and automated.

A number of factors affect the accuracy and reliability of the visual inspection by operators, so individual performance is the determinant. Inspection is best performed under recommended light conditions (250–375 foot-candles (Fc)) and against a black and white background. Recent studies showed that a single 18 % grey backdrop may be as effective as the black/white backdrop and has the advantage of reducing inspection dwell [46].

The operator gently swirls or inverts each individual container, making sure that no air bubbles are introduced and observes for about 5 s in front of the white and dark panel. Particles present in the product are seen as illuminated dots.

Semi-automated systems provide container handling for the operator, but the inspection process is still a manual inspection. The advantage of the semi-automated systems is that the lighting and container rotation reduce inspection time and a group of several containers is constantly being passed in front of the inspector. The time interval must be long enough to guarantee reliable inspection but short enough not to tire the eye of the operator.

Automated inspection is performed by light transmission and camera-based systems. This process decreases human contact with the packaging component. Compared with manual inspection, an automated vial inspection process is more consistent and can be more cost-effective over a longer time period of use.

Visual inspection is a process that requires high concentration of the inspector. In hospital pharmacies the inspection period is limited, e.g. to 30 min followed by a minimum 15 min break between two periods. Inspection personnel should be appropriately trained and have their competency assessed. Candidates are given a set of characterised containers bearing container closure defects and particulate matter and must be able to identify the contaminated products.

13.7.8 Labelling

Labelling is the last step of the production process (see Sect. 37.3). The labelling process should be preferably performed in the preparation area, where no additional unlabelled products are present. Identity of the labels should be checked and reconciliation performed: number of applied labels should to be equal to the number of produced containers. Labelling and final packaging operations in the hospital pharmacies is becoming increasingly automated.

13.7.9 In-process Controls

The following in-process controls are recommended as a minimum:

- Visual inspection of the solution after each process step
- Filling volume
- Integrity of the filter device by a bubble point test or forward-flow-test (see Sect. 30.6.5)
- pH of aqueous solutions
- Time, temperature and pressure during the sterilisation process
- Container-closure integrity test
- Yield

In-process controls may be performed in regular intervals during a process step or at the end of a process step. The objectives of in-process controls are both quality control and process control.

13.7.10 Release Control

Finished products are the subject of release controls. As a minimum:

- The correctness of container type and labelling used.
- Each vial is checked for visible particles. The finished product is also controlled on particulate matter (see Sect. 32.12).
- Sterility: samples withdrawn are tested for sterility and freedom from endotoxins (see Sect. 19.6.1).
- Assay of identity, purity, content and withdrawable volume (see Chap. 32).

13.8 Reconstitution

13.8.1 Definition

Most parenteral medicines need at least a minimal manipulation e.g. withdrawing the product from a vial or an ampoule in a syringe) in order to be administered. This process is called reconstitution and it leads to Ready To Administer medicines (RTAs). Reconstitution of parenterals is not always described in the Summary of Product Characteristics (SmPC) and Package Information Leaflet (PIL). If so this process may be called 'reconstitution in excess of the SmPC' (see Fig. 1.2). If this is considered to be a variance from the SPmC, it results legally in off-label use and should be supported by evidence, e.g. an appropriate risk assessment including the benefits and evidence about compatibility and a possible longer shelf life (see Sect. 22.6).

Preparing RTAs is usually aimed at reduction of the risk on faulty composition and microbiological contamination during handling of parenteral medicines on the wards, see also Sect. 21.5.3. This is usually achieved by pre-filling of syringes, pre-diluting injections or mixing injections with infusion solutions. The concept of standard concentrations in pre-filled syringes supplied by the central pharmacy to the wards (for instance the intensive care department) is now the practice in several European countries. Patient specific dosing can subsequently be achieved by adapting the rate of infusion.

13.8.2 Product Formulation

The formulation of a RTA product should be based on currently available information on active substance stability and compatibility (see Sect. 22.6). Definition of specific characteristics is relevant for the design and description of a RTA product. In several European countries this information is included a locally, regionally or nationally standardised document: Parenteral Manual

13.8.2.1 The Definition of a RTA Product

The definition of a RTA product may contain the listed items and follow the examples given:

- Amount of the active substance
- Primary packaging
- Administration route
- Administration method

The combination of the active substance, the amount and the packaging determines the composition. The combination of the administration route and administration method describes the administration of the product. Sometimes comparable licensed medicines differ to such an extent that apart from the generic name also the brand name has to be part of the definition (see examples).

Several examples of RTA products are presented, derived and modified from a Dutch Parenteral Manual:

Example 1: Adalimumab Adalimumab is only available as Humira® 40 mg/0.8 mL solution for injection in a single-use pre-filled syringe. So for the description of the corresponding ready to administer product only the route of injection has to

be added, which results in: Adalimumab 40 mg in pre-filled syringe administered by subcutaneous injection.

Example 2: Parecoxib Parecoxib, can be administered in three ways:
- Intramuscularly
- Intravenously as a bolus
- Intravenously as an infusion

The commercially available product Dynastat® powder for solution for injection 20 mg and 40 mg must be reconstituted before use. The following ready to administer parecoxib preparations are possible:
- Parecoxib sodium in a syringe administered intramuscularly or intravenously as a bolus
- Parecoxib sodium, reconstituted with the solvent indicated in the SmPC, diluted in an infusion bag/bottle 100 mL, administered intravenously

Example 3: Amphotericin B Various amphotericin B formulations have been developed and commercialised: Fungizone®, Ambisome®, Abelcet® and Amphocil®. These differ by the physico-chemical principle that has been used to create a colloidal systems (see Sect. 18.4.1). As a result they differ in their serum pharmacokinetics as well as their tissue localisation, tissue retention and toxicity. These products should not be substituted by each other and therefore the brand name has to be part of the definition.

The following RTA product descriptions of amphotericin B may be necessary:
- Fungizone®: Amphotericin B colloidal dispersion 10–50 mg in an infusion bag/bottle 500 mL
- Ambisome®:Amphotericin B liposomal 40–120 mg in an infusion bag/bottle 100 mL
- Abelcet® Amphotericin B lipid complex 120–500 mg in an infusion bag/bottle 500 mL
- Amphocil®:Amphotericin B colloidal dispersion 40–400 mg in an infusion bag/bottle X mL

13.8.2.2 Solvent and Diluting

Many parenteral medicines, particularly protein derivatives, are available as dry powder in order to achieve long term stability. This powder has to be dissolved and diluted prior to use. Solvents for reconstitution or for diluting sterile concentrated solution include sterile water for injection and various sterile aqueous solutions of electrolytes or glucose or both.

To prevent aggregation of therapeutic proteins, the nature of the solutions used for reconstitution and for diluting them must be carefully chosen; 5 % glucose solutions are not indicated. Sodium chloride solution has a limited use due to incompatibility with several active substances. For example, amphotericin B injection fluids cannot be diluted with sodium chloride and other electrolyte solutions because of the destabilisation of the colloidal systems.

When diluting a parenteral product the presence of co-solvents, antioxidants, the pH, the solubility, etc. has to be taken into account:
- Dilution of a partly or complete non-aqueous injection vehicle with water or sodium chloride solution may decrease solubility causing the active substance to precipitate (see Sect. 18.1.3).
- Precipitation of active substances can occur due to pH change upon diluting (see Sect. 18.1.2): dilution of furosemide injection solution (pH of 8.0–9.3) with 5 % glucose (pH of 4.3–4.5) lowers its pH and therefore decreases its solubility resulting in precipitation.
- Diluting a solution containing an antioxidant may lead to an amount of antioxidant being insufficient for taking away all the oxygen dissolved in the diluting solution, and may lead thus to oxidation of the active substance in the reconstituted product.
- Suspension or emulsion can only be diluted according to the package leaflet otherwise the physico-chemical stability may be endangered (e.g. breaking of the lipid emulsion).

13.8.2.3 pH and Osmotic Value

Registration authorities invite the manufacturer to include pH and osmotic value of the product in the packaging leaflet. The pH and the osmotic value of the undiluted as well as the ready to administer product are important in order to estimate the chance of phlebitis. The information about pH is also useful for investigating the possibility of mixing reconstituted products.

13.8.2.4 Packaging

Ready to administer products may be packaged in the following primary containers:
- Injection syringe (see Sect. 24.4.17) closed with a cap when the product is not administered immediately
- Infusion bag or bottle (see Sects. 24.4.5 and 24.4.13)
- Vial
- Portable infusion system

Batch wise reconstitution of ready to administer parenteral products and keeping them in stock is only possible if compatibility of active substance with packaging system and the stability are known.

13.8.2.5 Storage and Shelf Life

Shelf life is particularly important when the reconstituted product is not used immediately. For obtaining and interpreting chemical and physico-chemical data on shelf life, stability and incompatibilities of reconstituted medicines see Sect. 22.6.3.

Reconstituted parenteral medicines often have a short shelf life and have to be administered immediately. The shelf life of some sensitive infusion solutions can be prolonged when they are stored under cool conditions and

protected from light. If appropriate light protection during administration should be obtained by wrapping it up in aluminium foil or using opaque syringes.

Shelf life may be shortened due to reaching body temperature if the infusion bags are carried on the body of the patient.

Preferable storage is at room temperature. But storage in the fridge or freezer may be possible and may lengthen the shelf life. If the reconstituted products are stored in the fridge or in the freezer, they should be brought to room temperature prior to administration. Otherwise infusion can disturb the blood- and body temperature of the patients [47].

Further disadvantages of storing in the freezer are:

- Unknown stability of the product (pH shift, precipitation) or primary package.
- While freezing, the contents expand in the administration system; therefore the administration system should not be filled to the maximal capacity.
- Defrosting takes a long time at room temperature; inducing it by heating in the microwave is not useful due to the fact of local overheating.

As to the shelf life from a microbiological viewpoint reference is made to chapter Aseptic handling (Sect. 31.3.6). A system is given for determination of microbiological shelf life in relation to the risk of microbiological contamination at aseptic handling.

13.8.2.6 Compatibilities and Incompatibilities

Mixing parenteral solutions of active substances or diluting a concentrate with certain solvents can lead to incompatibility and consequent precipitation and loss of activity of one or both active substances. There may be reasons for mixing two or more parenteral solutions in the same infusion bag or in the same syringe:

- Difficulties with venous access limiting the number of intravenous lines available for continuous administration of multiple medicines.
- Patient has restrictions to the volume that can be parenterally administered.
- Therapeutic necessity of combining active substances.
- Multiple active substances are required by parenteral administration within a short time frame.

During palliative care, patients at home require many active substances that are delivered from the same syringe in a syringe driver over 24 h. This method is only possible when the patient is stabilised; otherwise the ability to control the dose is lost. Regional guidelines and protocols are also developed for continuous subcutaneous home infusion [48].

Section 13.8.2.2 describes the (im)possibility of diluting the active substance with solvent as an (in)compatibility. It is important to be vigilant for incompatibilities associated with multiple infusions co-administered to a patient. Mixing parenteral solutions of active substances occurs in the infusion bag or syringe, but also at an Y-site junction (see Sect. 13.10.4) where two or more intravenous lines meet. The mixture should be inspected visually for precipitation, turbidity or colour change, but the absence of any visible change to a solution upon mixing does not automatically exclude degradation or precipitation of either or both components.

Numerous references are available for data on parenteral incompatibilities. Only current edition of these references should be used, therefore databases are to be preferred, such as Stabilis® (see Sect. 39.2.6). Pharmacists could also create their own compatibility charts resulting from literature data, experience and own testing.

13.8.3 Method of Preparation

Reconstitution of parenterals is commonly performed on hospital wards by physicians or nurses. The risk of erroneous preparation and microbiological contamination during handling, can be reduced if the hospital pharmacy performs reconstitution under specific precautions (see also Sect. 31.3 Aseptic handling). These reconstituted medicines are supplied to the wards either labelled for individual patients or as a batch as ward stock. Common products that are reconstituted in the pharmacy instead of on the wards (see also Sect. 31.3.2):

- Antineoplastics (high-risk medication as well as protection of the personnel from the product)
- Parenteral nutrition (a microbiologically vulnerable product to be protected from personnel, needing several complex process steps)
- Blinded clinical trial medication
- Some emergency medication (to be placed as a depot on the ward)

Some European countries have developed national guidelines for the preparation of ready to administer products in hospital pharmacy (German Society of Hospital Pharmacists: Guideline for the aseptic preparation of ready to use-/administer parenterals) or at the hospital ward (Dutch Society of Hospital Pharmacist: Guideline for the preparation prior to use on the ward) [49, 50]. For further information on aseptic handling see Chap. 31.

The reconstitution of ready to administer products on the ward includes the following steps:

- Selection of the starting material and utensils according to standard procedures
- Preparation of the label for administration of the product
- Reconstitution of the product
- Quality control (see Sect. 13.8.4)

Basic steps of reconstitution may be: dissolving, volume measuring and mixing. They are conducted under a certain level of aseptic conditions. In order to obtain an accurate content the following instructions are given:

- Infusion bags are quite flexible and allow fairly large volumes to be added without difficulty (maximal 30 % of the volume); when a larger volume than the maximum has to be added, a larger infusion bag should be chosen.
- The smallest possible syringe should be used in which the dosage will fit, because the smaller the syringe, the more accurately the volume can be measured; syringes should be filled to a maximum of 75 % of the nominal volume.
- For accuracy of small volume solutions (less than 5 ml), small-sized syringes should be used and then the solution should be transferred into a larger syringe with help of the diluent.
- After reconstitution of a lyophilised powder, a new syringe and needle should be used to withdraw the correct volume of the reconstituted solution into the syringe, because of the dead volume of solvent used for reconstitution.

As an example this reconstitution in excess of the SmPC may be given:

To be prepared:	Dobutamine HCl 250 mg in injection syringe 50 mL
Licenced pharmaceutical product:	Dobutamin HCl 250 mg powder in infusion bottle.
Instruction for preparation:	Add 10 mL sterile water for injection to the bottle; gently rotate the bottle until the solution is clear (concentration of 25 mg/mL). Fill a 50 mL perfusor syringe with 40 mL 0.9 % NaCl solution and withdraw the air to the volume of 55 mL. Use a small-size syringe to withdraw 10 mL solution from the bottle and add the solution via a connector to the diluting solution. Mix and expel excess air from the syringe.

When the reconstitution takes place on the hospital wards recommendations for safe handling include:

- Area in which the product is to be prepared should be clean, tidy and quiet (use of laminar airflow workbench when possible)
- Cleaning the hands according to local policy.
- Wearing clean working clothes that must be replaced once daily and disposable protective gloves.
- Use a 70 % V/V alcohol (see Sect. 26.7.2 about the occupational safety and health aspects) or other disinfectant for the disinfection of the surface, the rubber of the injection bottles, neck of the glass ampoules, and injection point of infusion bag.
- Reconstitution of the product following the SmPC or preparation according to local guidance.
- Labelling the product with the administration label immediately after preparation.
- Use of a waste container for the needles.

13.8.4 Control and Quality Requirements

13.8.4.1 Control

The following passage describes how the control on a ward of a healthcare establishment can be done. A second person checks whether the preparation has been done following the agreed method on the workplace:

Materials:

- Right medication order
- Right medicine (by means of empty ampoules or bottles)
- Right strength (by means of empty ampoules or bottles)
- Shelf life/expiry date
- Right calculation
- Right solvents if applicable
- Right amount of diluting fluid if applicable
- Right method of preparation

Reconstituted medicine:

- Right administration label
- Appearance: check on discolouration/turbidity/crystallisation
- Storage: room temperature or 2–8 °C, under light-protecting conditions (if necessary)

When injection solutions are prepared by the pharmacy further checks are implemented. The used preparation record as well as the batch number and the labelling are also controlled by a second person.

13.9 Parenteral Nutrition

13.9.1 Orientation

Parenteral nutrition formulations provide nutritive support for patients who are not able, not allowed or not willing to eat for a critical period of time. Indications for parenteral nutrition include pre- and postoperative periods of major surgery or trauma, severe obstruction of the gut (e.g. by tumours), severe motility disorders (e.g. ileus), severely impaired absorption capacity (e.g. short bowel syndrome, mucositis in stem cell transplantation patients). Parenteral

nutrition can be used supplemental to enteral nutrition (given by oral route or feeding tubes) or exclusively. The latter type of nutritional support is called total parenteral nutrition (TPN). The intravenous route should only be used when oral, (naso)gastric or intestinal routes are not readily available and for a period as short as possible. Enteral nutrition is advantageous because it provides the uptake of the nutritive substances in a physiological manner and promotes the integrity of the gastrointestinal mucosa. Standard enteral preparations have been modified by the addition of immunonutrients, such as arginine, glutamine, omega-3 fatty acids, nucleotides and others. These components should stimulate the immune system, control inflammatory responses and improve the nitrogen balance and protein synthesis after injury [51].

13.9.2 Product Formulation

13.9.2.1 Components

Components used in parenteral nutrition formulations include amino acids, carbohydrates, and lipids, as well as electrolytes, vitamins and trace elements. The amounts of the components are to be calculated according to the needs of the individual patient with regard to the caloric requirements, metabolic status, fluid and electrolyte balance, acid–base status, and other specific goals of parenteral nutrition. The components are dissolved in either water or a lipid phase. Both phases have to be combined in the right ratios into an emulsion. The compatibility and stability of all components and the physical stability of the resulting emulsion is to be taken into account. The design of parenteral nutrition mixtures therefore requires a high level of formulation knowledge. Individualisation of the nutrient products may be limited by these formulation constraints.

Parenteral nutrition is administered by different approaches:

- 'All-in-one' admixture – all components are admixed in a single container and administered simultaneously through an intravenous line
- 'All-in-two' system – combination of two containers, where the lipid emulsion is provided in a separate container
- 'All-in-three' system (or multi-bottle system, modular system) – combination of three containers, where the carbohydrate solution, amino acid solution, and lipid emulsion is provided in a separate container each

'All-in-one' (AIO) admixtures can be industrially manufactured standard AIOs or individually compounded AIO admixtures. The commercially available standard AIO is provided in three-chamber infusion bags which contain the amino acids, carbohydrates, lipids, and electrolytes in three separate compartments. The contents of the three chambers are mixed just prior to infusion, by breaking the separation seals between the bag chambers. Vitamins and trace elements are added to the infusion bag prior to the administration or administered as a separate infusion solution. AIO admixtures reduce manipulations, save materials and personnel workload. They require only one intravenous line and the risk of infection is lowered by reduced manipulation. AIO mixtures offer a convenient system for patients, clinicians and nursing staff. Table 13.4 shows an example of a standard adult parenteral nutrition admixture. The pH of such an admixture is 5.0–5.6 and the osmolarity comes to 1,000–1,200 mOsmol/L.

The calculation of the energy, substrate and volume needs in parenteral nutrition is given in textbooks and guidelines [52]. The needs depend on the patient's disease and nutritional status. The first step is the specification and calculation of the necessary amounts of fluid, glucose, and amino acids (macro-nutrients). The second step includes the calculation of the electrolytes. Vitamins and trace elements are commonly added in standard amounts according to professional guidelines.

Standard AIO admixtures are used in most adults patients. However, the patients' requirements regarding calories and electrolytes may vary. Dialysis patients require restricted administration of electrolytes, however patients with severe diarrhoea need a higher amount of electrolytes. Standard parenteral nutrition admixtures cannot be used in severely ill paediatric patients, neonates and premature newborns. These patients need individualised admixtures. In premature infants and newborns the all-in-two system is preferred [53]. The lipid emulsion is mixed with the vitamin combination in a separate container and either administered with the amino acid/glucose/electrolyte admixture in parallel (Y-site) or via a separate venous access.

Table 13.4 Example of Standard Adult Parenteral Nutrition Admixture

Fat (soja oil or olive oil)	100 g
Glucose	250 g
L-amino acids (mixture of essential and non-essential)	90 g
Sodium	80 mmol
Potassium	60 mmol
Calcium	5 mmol
Magnesium	10 mmol
Phosphorus	25 mmol
Trace elements (Cr, Cu, F, Fe, I, Mo, Mn, Se, Zn)	
Water-soluble vitamins (vit. B_1, B_2, B_3, B_5, B_6, B_{11}, B_{12}, C)	
Fat-Soluble vitamins (vit.A, D_2, E, $K_{1)}$	
Excipients	
Water for injection	ad 2,000–2,500 mL

The fluid, energy, and substrate requirements and the composition of the admixtures is stated in different guidelines [52]. Fusch et al. presented a standardised questionnaire, which takes into account partial parenteral nutrition and enteral nutrition and should be used for prescribing parenteral nutrition to neonates [53, 54]. Examples for the composition of a neonatal AIO admixture can be found in the literature [53].

13.9.2.2 pH

The pH of different amino acid infusion solutions manufactured by different companies varies from pH 5.0–7.4. Glucose infusion solutions have a pH 4–5. When mixed, amino-acids will function as buffers and prevent the decline of pH below 5. In an all-in-one-mixture the amino acids also prevent the enlargement and merging of the lipid globules. Paediatric amino acid solutions are more acidic than those used in adults and cause a lower pH of the combined admixtures.

13.9.2.3 Osmotic Value and Fluid Supplement

Parenteral nutrition admixtures are hypertonic. Glucose, amino acids and electrolytes induce a hyperosmolar (1,300–1,800 mOsm/L) infusion solution.

Fluid supplementation has to be considered carefully because the relative body water-content is age-related and highest in premature infants. The amount of water provided by the nutrition solution and the water used for the dissolution of medicines should not exceed the total need for water. Thereby, often highly concentrated nutrition admixtures with low final volume are to be administered.

13.9.2.4 Compatibility

Monovalent cations do not cause physical incompatibility of parenteral nutrition admixtures, unless they are present in high concentrations. The positive charged divalent ions (Ca^{2+}, Mg^{2+}) and even more crucial trivalent ions (Fe^{3+}) neutralise the zeta potential (see Sect. 18.4.1) of the lipid droplets and can cause aggregation, coalescence and phase separation.

The Critical Aggregation Number (CAN) corresponds to the cationic concentrations at which lipid particles aggregate. The result amounts to the cations expressed as monovalent cations and should not exceed 600 mmol/L.

CAN is calculated by the following equation:

$$\text{CAN (mmol/L)} = a + 64b + 729c \qquad (13.1)$$

a = concentration of monovalent cations
b = concentration of divalent cations
c = concentration of trivalent cations

Admixture of calcium and phosphate ions in the same nutrition solution may lead to precipitation of calcium phosphate. These precipitates are hardly detectable in the nutrition admixtures by visible inspection and are not detectable in lipid containing AIO admixtures.

The solubility of calcium phosphate depends on the type of amino acid product used, the type of calcium and phosphate salts used, temperature, magnesium concentration, and the final volume of the admixture. The pH of the parenteral nutrition admixture influences the equilibrium between the trivalent phosphate ion and its monobasic ($H_2PO_4^-$) and dibasic (HPO_4^{2-}) forms. The aqueous solubility of the monobasic and dibasic calcium phosphate amounts to 18 g/L and 0.3 g/L, respectively. At the physiological pH of 7.4 about 60 % of the phosphate exists in the poorly soluble dibasic form. If the pH of the nutrition admixture is lower than pH 6.4, the monobasic form is the predominant one and the chance of precipitation is diminished (see Sect. 18.1.1).

FDA Safety Alert: "Hazards of Precipitation Associated With Parenteral Nutrition" The Food and Drug Administration warned against the risk of precipitations in parenteral nutrition mixtures in 1994 [55]. This warning occurred after two deaths and at least two patients with dyspnoea after infusion of all-in-one nutrition admixtures. The FDA suspected that these admixtures contained calcium phosphate precipitates.

Temperature has a large influence on the calcium phosphate solubility. Increased temperature shifts the phosphate equilibrium from the monobasic to the dibasic form thereby raising the chance of precipitation. Elevated temperatures also increase the dissociation of calcium gluconate thereby generating free calcium ions that precipitate with the phosphate ions.

In order to avoid high phosphate concentrations, organic phosphates, such as sodium glycerophosphate solutions, should be utilised in the formulation of nutrition solutions. The phosphate moiety is covalently bound and rarely hydrolysed.

If trace elements are added to the lipid-containing nutrition admixtures they can cause disintegration of the emulsion even in low concentrations, they catalyse chemical decomposition (e.g. of vitamins) and increase (lipid) peroxidation. Trace element solutions show a strong acidic pH, which also may reduce the stability of the emulsions. It is unknown why the concentrations of trace elements decrease during storage of the admixtures. It might be caused by adsorption to the packaging materials or precipitation of insoluble complexes [56]. In order to minimise lipid

peroxidation, lipid emulsions should be stored light-protected and refrigerated. Trace elements should be added immediately before administration or preferably administered as separate infusion [57]. Simultaneous administration of trace elements and multivitamins in AIO admixtures is problematic due to the physico-chemical reactions. If trace elements and vitamins are included in the same nutrient admixtures, compatibility of these elements and compatibility with the other components have to be studied.

13.9.2.5 Excipients

The most important excipients in parenteral nutrition solutions are emulsifying agents. Lecithin and phosphatides are mostly used. The emulsifying capacity of phosphatides correlates with their ionisation rate and thereby the pH of the emulsion. The pH also influences the stability of the lipid droplets [58]. If the pH decreases below 3, the droplet surfaces are no longer negatively charged and the droplets coalesce (see Sect. 18.4.1). If necessary, the pH is adjusted with an aqueous solution of sodium hydroxide or hydrochloric acid.

Although lipids, oils and fat-soluble vitamins, such as tocopherol, undergo oxidation reactions, antioxidants are usually not added to the nutrition admixtures because of toxicity. Maximum recommended amounts of antioxidants, e.g. metabisulfite, are readily exceeded in the target patient population.

13.9.2.6 Stability

The large number of components (sometimes > 50 different components) and the underlying meta-stabile emulsion system are obvious reasons for incompatibility (as described above) and instability. The occurrence of incompatibility and instability is often invisible. Physico-chemical reactions with negative effects on the stability are [58]:

- Aggregation of lipid droplets, lipid coalescence, and even phase separation of the emulsion
- Precipitation of calcium phosphate
- Complexation of trace elements
- Oxidation of oxygen-sensitive vitamins
- Chemical degradation of amino acids such as glutamin, cysteine; reaction of amino-acids with glucose (Maillard reaction)
- Oxidation of lipids catalysed by trace elements

Administration of aggregated lipid droplets with a size of 5 µm or larger may cause fat embolism, by obstructing small capillaries in the lungs (internal diameter 4–9 µm) [59]. The reticuloendothelial system located in the liver eliminates the enlarged lipid globules from plasma, but this can result in increased oxidative stress and organ injury.

Vitamins such as retinol, riboflavin and tocopherol are known to be degraded by light (especially UV-light) and oxygen. The products should be stored light-protected in the refrigerator. Degradation of ascorbic acid produces oxalic acid which may form the insoluble calcium oxalate. The oxidation rate of ascorbic acid depends on the amount of oxygen present. Stability is maintained by optimising both the formulation and packaging of the products (e.g. use of multilayer bags). Removal of oxygen during preparation and storage reduces the degradation rate significantly [60].

13.9.2.7 Packaging

Parenteral nutrition fluids can be packaged in plastic bags, preferably ethylene-vinyl-acetate (EVA) bags or syringes depending on the total volume of the admixtures. Neonatal nutrition admixtures can be administered by syringe pumps. If the volume to be administered per day exceeds 50 mL, repeated filling of the syringe can be performed with a specific closed syringe-filling system (see Fig. 13.3). Prefilled infusion lines further enhance patient-safety.

Interactions of lipophilic nutrition components with the surfaces of the containers and administration devices may occur. Nutrition components can be adsorbed or absorbed by plastic materials and components of the plastic materials can be leached. Vitamin A is absorbed by polyvinyl chloride containing infusion bags and intravenous tubing [61].

It is still a matter of discussion whether parenteral nutrition admixtures should be protected from light [58]. The light-sensitive vitamins should be added to the lipid-containing admixtures because lipid emulsion provides light-protection and reduces the degradation rate. When exposed to light those lipids however alter and may deliver a high load of exogenous toxic hydroperoxides to the patient [62]. Admixtures from the all-in-two or all-in-three type should be packaged in an additional light-protective secondary bag in order to achieve a longer shelf life.

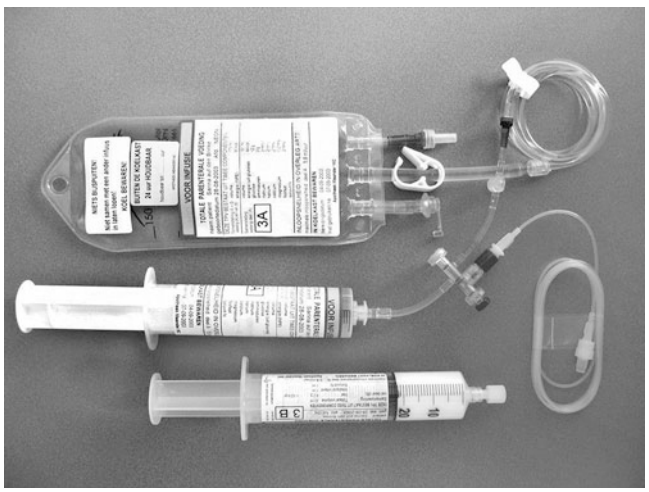

Fig. 13.3 Parenteral nutrition with closed syringe-filling system (Photo: R.Lange, Source: Recepteerkunde 2009, reprinted by permission of the copyrights holder)

13.9.2.8 Shelf Life

Industrially-manufactured standard multichamber bags usually have a shelf life of more than 12 months before mixing. Admixtures for the individual needs of a patient must be prepared in accordance with aseptic handling (see Sect. 31.3). The admixtures are prepared in general on a daily or weekly basis. The shelf life of standard admixtures is maximum 7 days when stored under refrigerated conditions at 2–8 °C, provided that physico-chemical stability is sufficient.

13.9.3 Method of Preparation

The industrially manufactured two and three chambers are mixed just prior to infusion, by breaking the separation seals between the bag chambers. The content is mixed in the closed system and vitamins and trace elements can be added via an injection port prior to administration or administered as separate infusion solutions. Nutrition admixtures (all-in-one, all-in-two system) for the specific need of patients are prepared using industrially manufactured lipid emulsions and aqueous solutions containing amino acids, carbohydrates, electrolytes, vitamins and eventually trace elements. All components are admixed in sterile empty infusion bags under conditions of aseptic handling (see Sect. 31.3).

AIO parenteral nutrition admixtures are commonly prepared by the following two methods:

- All components are admixed in the same infusion bag; the components are added in a predefined order one after the other and thoroughly mixed after each admixture step.
- Electrolytes and trace elements are if necessary diluted with water for injection and added to the premix of glucose and amino-acid solutions; water- and fat-soluble vitamins are admixed to the lipid emulsion; both premixes are combined and mixed.

The order in which the components are added is very important because specific components may cause incompatibilities if added too close after each other. Calcium gluconate and sodium/potassium phosphate should always be diluted before addition in order to avoid the precipitation of calcium phosphate due to high local concentrations. This is less relevant when organic phosphates are used.

Water soluble vitamins should be dissolved in water for injection and then added to the parenteral lipid emulsion containing the lipid soluble vitamins. In this way the emulsion will contain smaller lipid globules than if the vitamins are directly added to the emulsion. This may be relevant for the preparation of total parenteral nutrition for neonates and children.

As in process control (IPC) the components of a parenteral nutrition admixture are to be inspected visually with regard to irregularities in the appearance (homogeneity, clarity, particulates, and colour changes).

13.9.3.1 Automated Compounding Devices

Individualised TPN admixtures for paediatric patients are often prepared with automated compounding devices (ACD). A large number of different single source containers can be attached to an ACD using specific compounding tubing. The tubing device is a single use system and has to be changed on a daily basis. With a bar code reader the identity of the source components can be identified. ACD utilises fluid pump technology and software that controls the compounder pump. The fluids are pumped from the source container to the final container by a volumetric (rotary peristaltic pump) or a gravimetric pump system. The volumetric pump systems also checks the actual total bag weight (to the expected weight). The systems incorporate an audit record for quality assurance and accuracy.

The advantages of automated preparation compared to manual technique are reduction in expenditure of time and labour and thereby higher efficiency, higher accuracy, lower probability of microbial contamination, and a lower chance of work related musculoskeletal disorders. The implementation of an ACD however is labour- and cost-intensive. Processes have to be defined, described and validated [63] and the designated personnel must be well educated and trained. Accuracy checks must be done on a regular basis, e.g. by daily pumping sterile water and comparing the actually pumped volume and weight with the expected one. Another option is the preparation of a standard admixture and the quantitative analysis of one easy to analyse component such as potassium. Media fill simulation tests are to be designed and regularly performed by the operators.

13.9.4 Release Control and Quality Requirements

The operators should monitor the appearance of the PN admixtures during and after the preparation procedure. The infusion containers of the preparations are to be checked for leakages by visual inspection and imposing pressure on the infusion bag.

For release control the responsible pharmacist should review the preparation records and check the recordings of the weighing of the fluids. Furthermore the correctness of the labelling is to be checked and the data on the label have to be compared with the original data of the prescription and the preparation records.

According to the Ph. Eur. emulsions for infusion should not show any evidence of phase separation, which is

detectable by visual inspection. The most critical parameter is the diameter of lipid droplets and its distribution. There is no unique, reliable, method for measuring the size of the lipid droplets over the whole size distribution range (starting from a few nanometres to many micrometres). Details about different analysis methods of lipid emulsions can be found in the literature [64–67].

The United States Pharmacopeia [59] suggests two methods to measure the lipid globule size distribution and the percentage of fat globules (PFAT): light scattering method and light obscuration (LO) or light extinction (LE). To be considered stable and safe, a TPN must meet the USP requirements where mean lipid droplet size cannot exceed 500 nm and PFAT must be less than 0.05 % for PFAT of 5 µm ($PFAT_5$).

Peroxide levels, pH and zeta potential represent further physico-chemical parameters which are useful to characterise the quality and stability of PN admixtures.

During batch preparation sterility testing can be performed on randomly selected preparations either by direct inoculation or by the filtration method. During extemporaneous preparation dummy solutions should be prepared and sterility tests performed with rapid detection methods such as the bioluminescence test (see Sect. 19.6.5) or the colorimetric detection of CO_2 production in culture bottles; although commonly used for blood cultures this last method was shown to be adequate for sterility testing of multicomponent admixtures [68].

13.9.5 Administration of Parenteral Nutrition Admixtures

Osmolarity of the nutrient admixtures and thereby the infusion route is determined by the type and amount of the components mixed. In general the admixtures are hyperosmolar and to be administered via a central venous catheter in a big vein (vena cava superior or vena subclavia). Only admixtures with a maximum osmolarity of 900 mOsm/L can be administered via a peripheral vein and only for a limited period of time [69]. Long term parenteral nutrition can be also administered via a port (see Sect. 13.10.3) especially when patients are treated at home. Because of the high probability of incompatibilities nutrition admixtures should always be administered via a separate line and Y-site infusion should be avoided.

Patients with end-stage renal failure are maintained very fluid-restricted which limits the amount of calories that can be delivered intravenously. Intradialytic parenteral nutrition (via the dialysis solution, see Sect. 14.4.2) enables the provision of additional calories and nutritive substances [70].

13.10 Administration

13.10.1 Terminology

The term ‘injection’ stands, in practice, for the parenteral administration of a limited volume of injection fluid usually from a syringe with nominal volumes varying from 1 mL to 50 mL into different sites of the body. Injections are executed direct or up to a couple of minutes, e.g. slow injection means 10 min or more. Slow injection is appropriate when the injection is performed subcutaneously or intramuscularly or during intravenous injection when rapid dilution of the injection fluid by the bloodstream is necessary to avoid high local concentrations that may lead to phlebitis or to precipitation.

The term ‘infusion’ stands for the parenteral administration of a larger volume of infusion fluid over a period of time. Infusions are administered over short periods such as 15 to 30 min, over prolonged periods such as 2 to 3 h or continuously over 12 h, 24 h or even several days.

13.10.2 Injections

Disposable plastic (mostly polypropylene, PP) syringes are used as containers for the injection of fluids. Prior to administration they are connected to the needle, catheter or port system which is used to access the injection site.

Syringes are available as 2- or 3-piece syringes. Two piece syringes consist of a barrel and a plunger with the finger grip, both made of polypropylene. A gasket is not necessary in the 2-piece syringes to achieve a smooth and steady operation. Three piece syringes consist of a barrel, plunger made of polypropylene and a polyisoprene gasket. The inner site of the barrel is siliconised in order to ensure slippage of the plunger in the 3-piece syringes. The plunger may be coloured for easy recognition of the filling volume and may have a special plunger tip in order to reduce the dead volume of the syringe. This is especially helpful when 1 mL syringes are used to inject small volumes of highly effective and costly medicines. In general disposable syringes are free from di-2-ethylhexyl phthalate (DEHP) and latex. A backstop of the plunger prevents it from accidental plunger withdrawal. Injection syringes have a tip in a standard design called Luer® Slip tip (centric or eccentric) as opposed to a Luer-Lo(c)k, see Fig. 13.4.

This ‘male’ tip fits into the female part of the needle, stopcocks or other administration devices for making leak-free connections between a male taper fitting and its mating female part. Key features of Luer taper connectors are defined in the ISO 594 standards [71] and in the DIN and

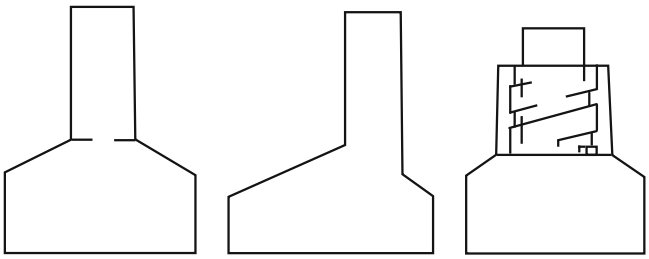

Fig. 13.4 Syringe tips, from *left* to *right*: Luer Slip centric, Luer Slip eccentric, Luer-Lo(c)k

EN standard 1707:1996 [72]. Luer-Slip fittings simply conform to Luer taper dimensions and are pressed together and held by friction (they have no threads). A Luer-Lok tip is a variety of the Luer tip were the fittings are securely joined by means of a hub on the female fitting which screws into threads in a sleeve on the male fitting. 'Luer-Lok' and 'Luer-Slip' are registered trademarks of Becton Dickinson. 'Luer-Lok' style connectors are often generically referred to as 'Luer lock'. Luer-lock tips are always placed centrally.

Syringes for oral administration have a differently shaped tip that does not match with female part of the injection devices. By this measure inadvertent parenteral injection of oral liquids can be avoided.

Commonly used volumes of syringes are 1 mL, 2 mL, 5 mL, 10 mL, 20 mL, 30 mL and 50 mL. Transparent barrels enable the visual inspection and bold graduations enable accurate measurement of the volume. In order to measure the injection volume precisely, always use syringes with the smallest volume suitable for the volume to be injected. Filling to more than 50 % of its capacity will result in an inaccuracy not exceeding 5 %. If the filling degree is around 20 % the inaccuracy will rise to 10 % and filling to not more than 10 % may lead to an inaccuracy of about 20 %. Imprecision depends very much on individual handling, but will be smallest when the capacity is nearest to the quantity to be measured (see further Sect. 29.1.7).

Hypodermic needles are made of stainless steel and are available in a wide range of lengths and diameters (18–30 gauge, G, (18 G = 1.3 mm, 24 G = 0.7 mm). Disposable needles are embedded in a plastic or aluminium hub that attaches to the syringe barrel by means of a slip or twist-on fitting. Coloured hubs reveal easy identification of diameter. A smooth surface and silicone coating of the needles enhances comfort for the patient during injection. The thinner the needle the less painful is the injection. Thicker needles are necessary for the injection of viscous fluids. A longer needle is necessary to inject deeply into tissues and to inject into the epidural space, requiring more thickness to be robust enough. Intrathecal injection is generally performed through a 9 cm long (3.5 in.) needle. For obese patients, some anaesthetists prefer spinal needles that are 12.7 cm long (5 in.).

For safety reasons needles should not be recapped after usage and needles should not be disconnected from syringes before depositing them. There are special waste containers to prevent re-use and puncture during storage, transport, and disposal of the waste (see Sect. 26.10).

There are different devices commercially available for needle-free injection. Commonly jet injectors produce a high-velocity jet of medicine that penetrate the skin. Medicines and vaccines can be administered either intramuscularly or subcutaneously by means of a narrow, high velocity fluid jet that penetrates the skin. The gas-forced needle-free injection systems are typically made up of three components including an injection device, a disposable needle free syringe and a gas cartridge.

13.10.3 Infusions

Several ways exist for the access of the circulation with infusion devices:

- Peripheral access devices
- Midline and Peripherally inserted central catheters
- Central venous catheters
- Port systems

The following factors are relevant for the selection of a venous access device:

- Subcutaneous infusion is less wearisome for the patient than intravenous infusion.
- The effort of insertion increases from the butterfly cannula to the port system, which is to be implanted surgically. The latter procedure is connected with a higher infection risk.
- Administration is not possible via a peripheral cannula because of hyperosmolality, irritating potential or large volumes of infusion solutions.
- Higher chance of thrombophlebitis when irritating infusion solutions are infused in a peripheral vein.
- Irritation when the infusion is administered subcutaneously.
- Duration of infusion (the longer, the higher the probability of damaging the blood vessel).
- Frequency of infusion (the more often, the higher the probability of damaging the blood vessel).
- The larger the vein, the lower is the probability of damaging, but more care is needed to prevent infection and occlusion.
- A central venous access gives more arm mobility than a peripheral venous access.

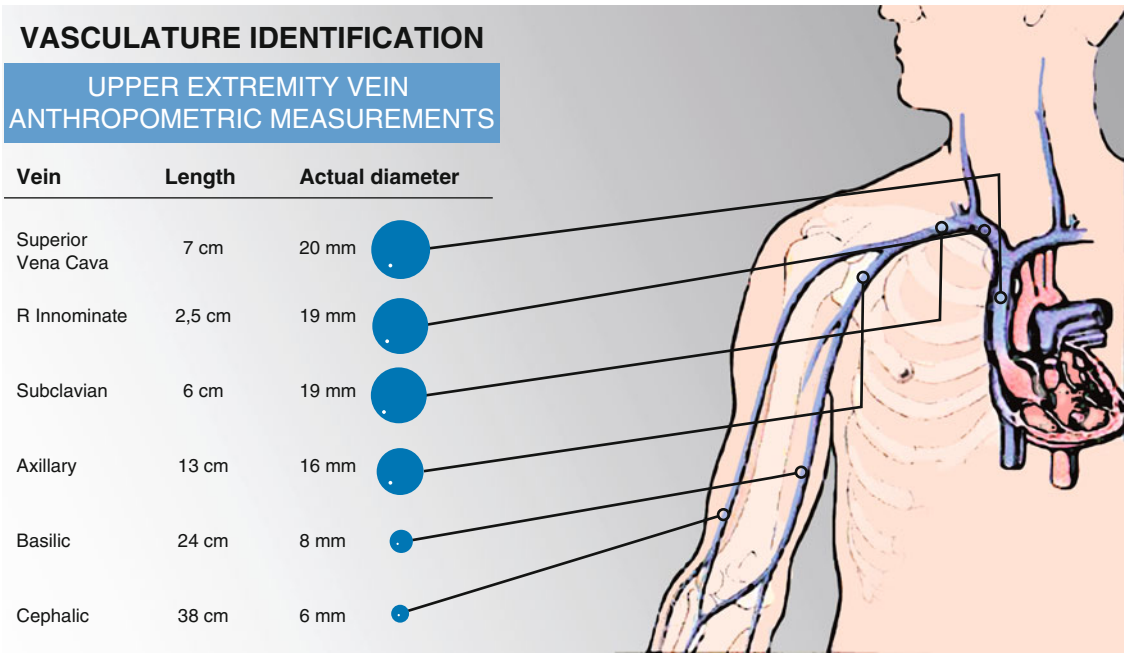

Fig. 13.5 Diameters of different large vessels, adapted from Recepteerkunde 2009, ©KNMP

Vascular access devices are classified in peripheral and central venous access devices. Central veins are located in the trunk and neck and are larger in the diameter than peripheral veins. Figure 13.5 shows the diameter of different large vessels.

Peripheral veins are located in the arms, hands, legs and feet. These veins are most commonly used for intravenous access. The diameter of peripheral small veins is 0.1–1 mm. These veins can be punctured with a needle, a butterfly needle or a venous cannula.

13.10.3.1 Peripheral Access Devices

Butterfly needles are short steel needles with flexible plastic wings that are fold before insertion and lay flat with tape on the skin for stabilisation (see Fig. 13.6).

Since the butterfly needle uses a flexible tube, there is less chance causing damage if the patient moves during the manipulation. The wings allow grasping the needle very close to the end to ensure accurate insertion. Butterfly needles are only suitable for short term use because the steel cannula can dislodge and puncture the vein. For subcutaneous administration butterfly needles can be inserted into the skin.

A peripheral venous catheter or indwelling venous cannula (see Fig. 13.7) is the most commonly used vascular access. Often these infusion devices are named by their brand name such as Venflon ® marketed by BD or Braunüle® marketed by B.Braun Melsungen. The cannula or peripheral venous catheter is inserted into a peripheral vein at the hand or the arm to administer infusion solutions

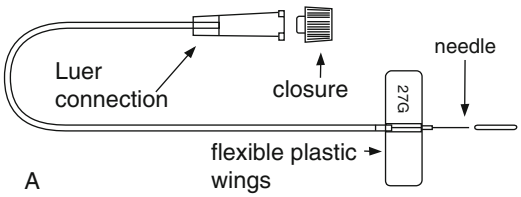

Fig. 13.6 Butterfly needle for peripheral access, schematic. Source: Recepteerkunde 2009, ©KNMP

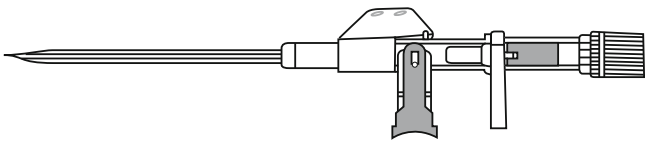

Fig. 13.7 Cannula or venous catheter for peripheral access, schematic. Source: Recepteerkunde 2009, ©KNMP

over a prolonged period and can also be used for drawing blood samples. It is composed of:

- A small tube for insertion into the vein
- Wings for manual handling and securing the catheter with adhesives
- A valve to allow injection of medicines with a syringe
- An end which allows connection to an intravenous infusion line and capping in between uses
- The needle which serves only as a guide wire for inserting the cannula

Lately the catheters have been equipped with additional safety features to avoid needle stick injuries (see Sect. 26.10).

The tube consists of synthetic polymers such as fluorinated ethylene propylene (FEP) or polyurethane (PU). For infusion of viscous fluids such as blood and for rapid infusion cannulas with diameters of 14–16 G have to be used. Smaller size diameters (18–24 G) of catheters are suitable for continuous and intermittent administration of parenteral solutions. Thorough management of the device (e.g. flushing, dressing, daily inspection) reduces complications (e.g. phlebitis) caused by a peripheral access. The need to replace the cannulas routinely is debated.

13.10.3.2 Midline and Peripherally Inserted Central Catheters

Midline catheters and peripherally inserted central catheters (PICC) are inserted in a peripheral vein but the tip rests in a larger vein. The infusion fluid flows directly in the larger vein which diminishes the chance of phlebitis. Both types of catheters are typically inserted in a vein in the upper arm. The midline catheter ends at armpit height; the tip of the PICC rests in the vena cava superior. The PICC may have single or multiple lumens. The PICC line can be used as a central venous catheter for infusion which needs fast dilution or distribution or both such as antibiotics, pain medicine, chemotherapy, nutrition, etc.

13.10.3.3 Central Access Devices: Central Venous Catheters

Central venous catheters (CVC) are directly inserted by different techniques (mostly Seldinger technique) into a large vein in the neck (internal jugular vein), chest (subclavian vein or axillary vein) or seldomly in the groin. Depending on the reason for use, the catheters have 1, 2 and 3 lumens. Some catheters even have 4 or 5 lumens for intensive infusion therapy. The catheter is usually held in place by an adhesive dressing, suture, or staple which is covered by an occlusive dressing at the site of insertion. Tunnelled catheters are passed under the skin from the insertion site to a separate exit site, where the catheter and its attachments emerge from underneath the skin.

13.10.3.4 Central Access Devices: Port Systems

A port is similar to a tunnelled catheter but is left entirely under the skin. The system consists of a reservoir compartment that has a septum for needle insertion, with an attached catheter (see Fig. 13.8).

The catheter is connected to the reservoir, made from e.g. titanium, and is inserted into a large vein (usually the jugular vein, subclavian vein, superior vena cava). The septum is made of a special self-sealing silicone rubber; it can be punctured hundreds of times with non-coring 90° 'Huber' needles. Ports are typically used in patients requiring only occasional venous access over a long duration course of therapy. Prior to use the port is flushed with a saline solution. After each use, a heparin lock is made by injecting a small amount of heparinised saline into the device. This prevents occlusion and clotting within the port or catheter. The port can be left accessed for as long as required. Due to its design, there is a low infection risk.

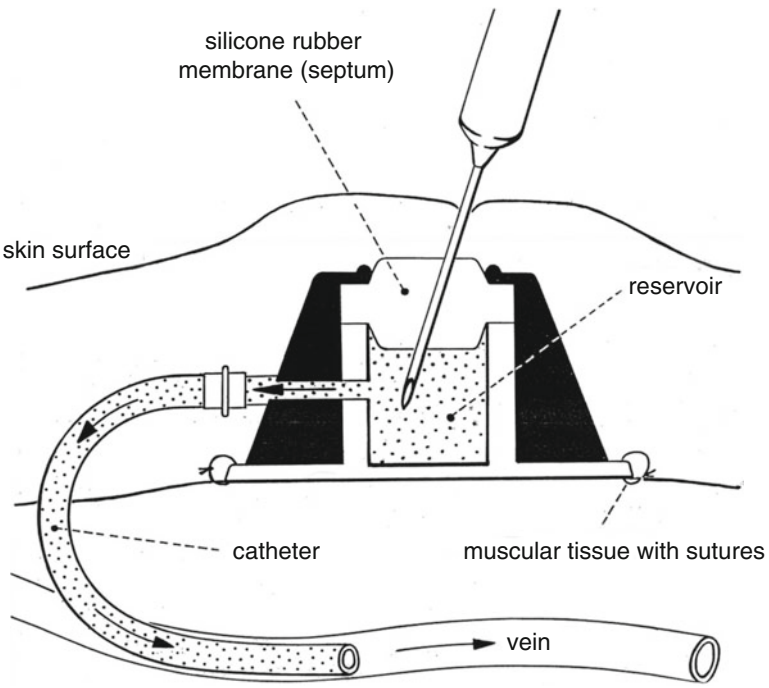

Fig. 13.8 Port system. Source: Recepteerkunde 2009, ©KNMP

13.10.4 Infusion- and Administration Systems

A tube or line is necessary for the transport of the infusion solution from the container to the venous access device. The administration can be done by gravity or pump-infusion or by syringes and syringe pumps.

Infusion pumps deliver the infusion fluid by pressure at a constant rate. They are electrically or mechanically driven. The different types of pumps used are:

- Syringe pump, which pushes the plunger of a syringe at a constant rate
- Infusion pump
- Portable elastomeric pumps

Various types of administration sets, e.g. gravity tubing, pump tubing, flow-regulating devices, and volume-controlled tubing are available. The administration sets are delivered sterile, particle-free and pyrogen-free. Lines are flexible, transparent and made of different plastic materials. The different components (e.g. catheter or cannula and line or administration set) are usually connected via screw tight Luer lock fittings. With stopcocks the caregiver or patient can adjust the desired flow directions or stop fluids in order to control the administration. Moreover stopcocks are used as an access to inject medicines or to withdraw blood. One or more infusions can be administered in parallel to the patient via the female accesses in IV-Sets (Y-site). For applications where several stopcocks are needed simultaneously 3-gang and 5-gang manifolds can be used.

13.10.4.1 Infusion by Gravity

Standard administration sets are used to administer infusion fluids by gravity. The basic product features, including a clear tubing, are (see Fig. 13.9):

The spike is used to connect the system to an infusion bag (or a bottle). The drip chamber is used in combination with the roller clamp to control the flow rate. The drip chambers of the administration systems are equipped with 15 µm filters which ensure particle removal. The system is connected to an access point (e.g. venous cannula) with a Luer fitting. Often access points are available to connect a second infusion.

The flow is maintained by gravity and therefore the container with the infusion solution has to be attached to a pole in an elevated position. With gravity flow, the flow stops when occlusion occurs and thereby extravasation is unlikely. The use of infusion pumps increases the chance of extravasation because the pump overcomes back pressure. However the pumps are designed to give alarm when the pressure increases.

When gravity infusion with precise infusion rates is intended, administration sets with precision flow regulators are to be used. Infusion rates can be set over a wide range

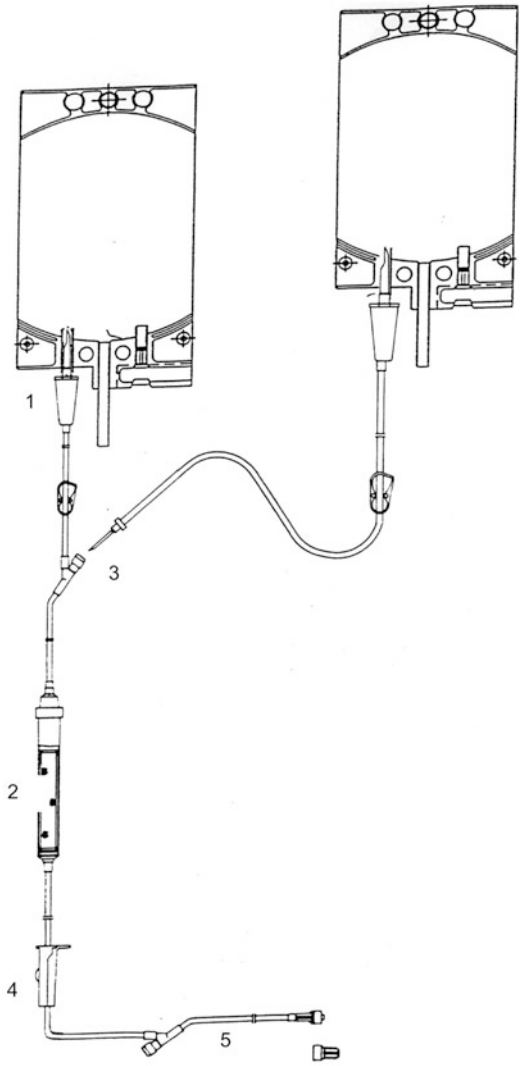

Fig. 13.9 Administration set for infusion by gravity (1. Spike; 2. Drip chamber; 3. Access point for the connection of another infusion bag; 4. Roller clamp; 5. Luer fitting). Source: Recepteerkunde 2009, ©KNMP

(e.g. 10 mL/h to 250 mL/h). A constant flow rate with low deviation is given if other flow determining factors remain unchanged, such as fluid viscosity and pressure determined by the level difference of the container and patient.

13.10.4.2 Syringe Pump

A syringe pump is used to inject small volumes of infusion fluids in a continuous and precise manner. The infusion fluid is drawn into a syringe (usually 50 mL or 10, 20, 30 mL) and placed in a syringe-holder of the pump. The tip of the syringe is connected to an in infusion line (PVC, PE) ending at the patient's venous access. After safe fixation of the syringe plunger the piston brake releases and the plunger of the

syringe is moved forward to infuse the fluid at a preselected rate. Injection rates can be precisely adjusted starting from 0.1 mL per hour. The accuracy is about ± 2 % of set delivery rate. To minimise the risk of administration errors the pumps are equipped with different safety features (e.g. air sensor, occlusion detection, low battery alarm, customisable medicine library in so called smart pumps with information about the medicines to be infused). Syringe pumps (see Fig. 13.10) are used to infuse active substances such as catecholamines, analgesics, heparin, insulin, electrolytes, anaesthetics and other medicines in particularly accurate manner to patients in intensive care units and operating theatres.

A number of ready-to-use products are commercially available to be filled into the 50 mL syringes. If not available products are to be prefilled, possibly after dilution, it has to be performed in the syringe as primary container. Often the doctor prescribes the dosage in milligram per minute or per hour. The right infusion rate depends on the concentration of the solution; the rate has to be calculated by the nurse or can be found in tables.

A 250 mg ampoule of furosemide-Na is diluted to 50 ml resulting in a concentration of 5 mg/ml. When 0.5 mg/min (30 mg/h) furosemide is prescribed by the physician, the injecting rate of 6.0 ml/h is to be set.

Over the last years many hospitals have adopted standard concentrations of injectable medicines to improve safety. It makes prescribing safer, especially when concentrations are predefined in the electronic prescribing software. The chance of preparation and administration errors is also reduced, especially when the type of medicine and the administration rate can be chosen from a medicines library in the pump or identified by barcode when placed in the syringe holder.

13.10.4.3 Infusion Pump

Infusion pumps are used to infuse large fluid volumes when precise control of the flow rate and total amount delivered is necessary. The large volume pumps usually use some form of peristaltic pump. Computer-controlled rollers compress a silicone-rubber tube of the administration line through which the medicine flows. The features of infusion pumps are similar to these of the syringe pumps. In intensive care units various pumps are used to manage the complex parenteral therapy individually. Bedside-docking systems are used to keep the high number of infusion pumps manageable.

Patient-controlled pumps are specific infusion pumps that can be activated by the patient via a pressure pad or button. It is the method of choice for patient-controlled analgesia (PCA), in which repeated small doses of opioid are delivered, with the device coded to stop when the maximum dose per interval is reached.

13.10.4.4 Portable Pumps

The term portable pumps is often used as synonym for elastomeric pumps although electricity driven syringe pumps are also designed as portable pumps. These pumps are infusion pumps that commonly are used by outpatients or patients that require a high level of mobility. The elastomeric pumps can easily be carried in a pouch. They are used to administer antineoplastics to oncology patients, antibiotics for e.g. cystic fibrosis patients, and pain therapy. Elastomeric pumps are designed for single use. They are available from different companies with different designs, filling volumes (e.g. 50 mL, 100 mL, 250 mL) and flow rates (e.g. 100 mL/h, 2 mL/h) (Fig. 13.11).

The pressure for administrating the medicine comes from the elastomeric layer that is molded inside the pump. The elastic constriction drives the liquid through the tubing equipped with a flow restrictor (glass capillary or steel cannula). Filling of the reservoir is done through a one-way valve using a syringe or peristaltic repeater pump. A clamp is used to start and stop infusion.

13.10.5 Filters

Particle contamination of a ready to administer injection or infusion solutions can result from cracking glass ampoules and from piercing rubber stoppers. Particles can also originate from not fully dissolved powders or aggregation of protein substances. In general drip chambers of the administration systems are equipped with 15 µm filters which ensure particle removal and allow a sufficient flow even when gravity infusion is performed. Filters with smaller pore

Fig. 13.10 Example of a syringe pump: Perfusor® Space (Copyright©"2014" B.Braun Melsungen AG)

Fig. 13.11 Example of a portable elastomeric pump (Copyright © Baxter Deutschland GmbH)

sizes require higher pressure to ensure a reasonable flow rate, but are more effective in reducing the particle load. In-line filters reduce the incidence of infusion-related phlebitis. They are positioned between the administration line and the venous access device of the patient and connected with Luer lock fittings. Filters with a pore size of 1.2 µm are suitable to filter lipid emulsions because the lipid drops have a 0.8 µm size and are not retained. Filters with a pore size of 0.2 µm significantly reduce the particle burden and remove bacteria and fungi. They are to be exchanged after 24 h. Additionally filters with a positively charged membrane are sometimes used to retain endotoxins. In-line filters are recommended for preventing particles entering the blood stream. They are not considered to control infection, because a positive impact on the rate of catheter-associated septicaemia is not evident [73–75]. One reason for the lack of that result may be that the filters are blocked by particles and higher viscous solutions, thereby increasing the number of line manipulations and thus increasing opportunities for infection.

13.10.6 Management of Parenteral Administration

Administration of fluids and medicines by the parenteral route is a demanding technology, especially when patients receive intensive care with multiple infusion therapies such as:

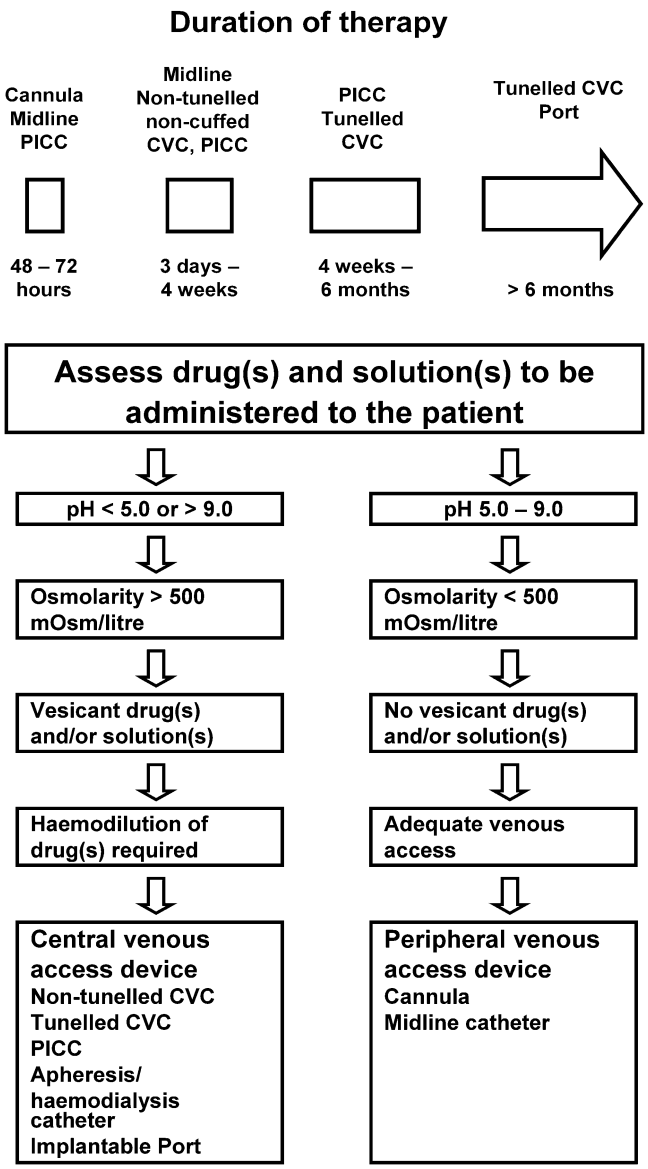

Fig. 13.12 Decision models for the selection of adequate venous access devices. Therapy related factors, such as duration and frequency of administration (*upper part* of the decision model) and characteristics of the infusion solutions (*lower part* of the decision model) determine the selection of proper venous access devices [76] (Copyright © C.R. Bard Inc)

- Hydration and plasma expander solutions
- Cardiovascular medication
- Pain therapy
- Parenteral nutrition
- Anti-infective therapy

Another sophisticated category of infusion therapy applies to the administration of parenteral medication in cancer patients.

Often local or national guidelines are implemented in order to enhance the safety of the infusion management. Health care staff should be educated and trained in the use

of catheters and infusion devices [75]. Moreover, decision models for the selection and use of the right infusion technology are developed [76, 77]. The decision models include therapy related factors (compare Fig. 13.12), device related factors and patient related factors. Patient related factors are: suitability of patients' veins, ability of the patient or care giver to maintain the vascular access device (VAD), lifestyle of the patient and co-morbid conditions.

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Irrigations and Dialysis Solutions

14

Daan Touw and Olga Mučicová

Contents

Abstract

Irrigations are sterile solutions that are used in many ways, such as flushing a catheter, the bladder, the urethra, wounds, body cavities, and the operation area or for drenching a bandage.

A special form of irrigations are solutions for dialysis that are necessary for the different types of dialysis such as haemodialysis, haemo(dia)filtration and peritoneal dialysis.

Because irrigations are used in or on body areas that are usually sterile or have a low degree of contamination, there are strict requirements for their production and quality control. In this chapter the use, the design of formulation and preparation method as well as the on site preparation of irrigations will be discussed. With regard to solutions for various types of dialysis, the use of concentrates, the water quality and the requirements for bacterial endotoxins are fully discussed.

Irrigations have various uses, and therefore various users. Not only the one who prepares and dispenses them should know their purpose, but also the patient or the professional caregiver. Solutions for the different types of dialysis form a separate category. Surveillance and monitoring of the whole process, but especially the quality management of the installation for the production of water for the dilution of concentrated solutions, are often more difficult than the preparation of the concentrates themselves.

Keywords

Formulation • Preparation • Irrigations • Dialysis solutions • Peritoneal dialysis • Haemofiltration

Based upon the chapter Spoel- en dialysevloeistoffen by Suzy Dreijer and Roel Bouwman in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_14,

14.1 Orientation

14.1.1 Irrigations

Irrigations come in contact with blood vessels, wounds or damaged mucosa or enter body cavities that normally have a low microbial count or are sterile. Therefore irrigations have to be sterile. The purpose of irrigations is usually a mechanical cleaning. A physiologic salt solution is suitable for this purpose. Often a disinfecting action is also required, especially when the irrigation remains in a body cavity. For this purpose chlorhexidine (0.02–0.1 %, see Table 14.1) or iodinated povidone are used.

Bladder irrigations with the purpose of eliminating bladder stones, or preventing the formation of bladder stones are another group. As well as a mechanical cleaning action a chemical reaction is necessary to dissolve the stone or slivers of stone, which consist of calcium and magnesium compounds. Therefore complexing agents such as citrate and edetate are added.

With transurethral prostate resection the bladder has to be irrigated with large quantities of solution to ensure that the view during the operation is not reduced by the presence of blood.

There are also solutions for intravesical use (use in the bladder) that have to act locally in disorders of the bladder and are not meant to irrigate. Examples are aluminium for bladder bleedings, antineoplastics for bladder cancer and oxybutinin for urge incontinence.

Eye lotions (irrigations for the eye) are discussed in Sect. 10.6.2. Vaginal solutions that don't need to be sterile are discussed in Sect. 11.12. Whole bowel irrigations are used before diagnostic examination. Those solutions for oral or rectal use are not described in this chapter.

14.1.2 Dialysis Solutions

Dialysis serves the purpose of removing waste products from the body when the kidneys cannot do this anymore. There are various forms of dialysis with their own characteristics.

With haemodialysis the blood passes an artificial kidney via extracorporeal circulation. The artificial kidney removes waste products and fluid. This happens mainly by osmosis (diffusion) via a semipermeable membrane, and partly by convection that is via the transport of water and waste products forced by pressure (ultrafiltration).

Table 14.1 Chlorhexidine Digluconate Irrigation 0.1 % [1]

Chlorhexidine digluconate solution	0.53 g
Acetic Acid (6 %) B.P.	q.s.
Water for injections	ad 100 mL

With haemofiltration the transport of fluid and waste products under pressure (ultrafiltration) is the main process. The pores in these membranes are a little larger than those at haemodialysis and the filtered fluid has to be substituted. The advantage is that waste products with a larger molecular weight are also removed, thus better resembling the filtration process in the normal kidney. This may have a favourable effect on cardiovascular health [2].

In practice a combination of dialysis and filtration is used, haemodiafiltration. Haemodiafiltration (HDF) is a combination of diffusion and convection. Diffusion is mainly effective for the removal of small waste molecules such as urea and creatinine. Larger molecules, for example beta-2-microglobuline, may only be removed from the blood by convection. For sufficient convective transport per HDF treatment an equivalent of 60 L of plasma is filtrated. At the same time the same volume is given back to the patient in the form of substitution solution. The substitution solution enters the circulation of the patient. This is the same process as the administration of an infusion, which is why some European Inspectorates regards solutions for HDF as parenterals.

With peritoneal dialysis the peritoneum, which is well supplied with blood vessels, functions as a semipermeable membrane. Peritoneal dialysis solutions are sterile hyperosmotic solutions. These solutions withdraw water from the blood through the peritoneum. The transport of small ions takes place at the same time.

Peritoneal dialysis is often self-administered, the solution has to be changed four to five times a day. This is known as continuous ambulant peritoneal dialysis (CAPD).

Another method is automatic peritoneal dialysis (APD), whereby a machine performs the irrigation during the night. There are advantages and disadvantages to haemodialysis and peritoneal dialysis.

Peritoneal dialysis gives the patient more freedom than haemodialysis, but requires a suitable space at home and appropriate skills. The patient may gain weight from these glucose containing solutions.

Haemodialysis almost always takes place in a dialysis centre, mostly three times a week during several hours or during night hours. It may in principle also be done at home, but hygiene and precision are very much required. Haemodialysis has the disadvantage that the patient usually is not allowed to drink much fluid and is restricted to a specific diet.

14.2 Definitions

The Ph. Eur. describes irrigations (Preparations for irrigation) as follows [3]: "Preparations for irrigation are sterile, aqueous, large-volume preparations intended to be used for irrigation of body cavities, wounds and surfaces, for

example during surgical procedures. Preparations for irrigation are either solutions prepared by dissolving one or more active substances, electrolytes or osmotically active substances in water complying with the requirements for Water for injections (0169) or they consist of such water alone. In the latter case, the preparation may be labelled as 'water for irrigation'. Irrigation solutions are usually adjusted to make the preparation isotonic with respect to blood."

This definition is valid for irrigations for the bladder, but also for other solutions for intravesical use.

Haemodialysis solutions (Solutions for haemodialysis) according to the Ph. Eur. are: "Solutions of electrolytes in a concentration close to the electrolyte composition of plasma (...). Because of the large volumes used, haemodialysis solutions are usually prepared by diluting a concentrated solution with water of suitable quality (see the monograph Haemodialysis solutions, concentrated, water for diluting (1167)), using for example an automatic dosing device." They are prepared in a way that ensures a contamination level as low as possible. Haemodialysis solutions do not have to be sterile, they are not in direct contact with the blood. However, new dialysis membranes with larger pores may entail a considerable amount of back-filtration which in the near future probably will result in stricter requirements for these haemodialysis solutions.

Haemofiltration and haemodiafiltration solutions (Solutions for haemofiltration and for haemodiafiltration) according to the Ph. Eur. are: "Preparations for parenteral administration containing electrolytes with a concentration close to the electrolytic composition of plasma." Because they are considered as parenterals they must be sterile (that is, they must comply with the test for sterility as described in the Ph. Eur.).

Peritoneal dialysis solutions (Solutions for peritoneal dialysis) according to the Ph. Eur. are: "Preparations for intraperitoneal use containing electrolytes with a concentration close to the electrolytic composition of plasma." Although it is not mentioned in the description that they have to be sterile, they must comply with the test for sterility.

14.3 Biopharmaceutics

Solutions for intravesical use are meant to remain in the bladder for a longer period and to exert a pharmacological effect, for example oxybutinin bladder irrigation for urine incontinence. The addition of bioadhesive polymers, for example hypromellose, may prolong the effect.

Solutions for CAPD are inserted into the abdomen via a catheter (Fig. 14.1).

The abdomen is surrounded by the peritoneum, an endothelial, single cellular layer that functions as dialysis membrane for water and small molecules. By using a hyperosmotic solution for peritoneal dialysis water and small molecules are withdrawn from the blood. After several hours the fluid is rinsed out and replaced with new CAPD solution. Solutions for peritoneal dialysis are made iso to hyper-osmotic with glucose to remove water from the body.

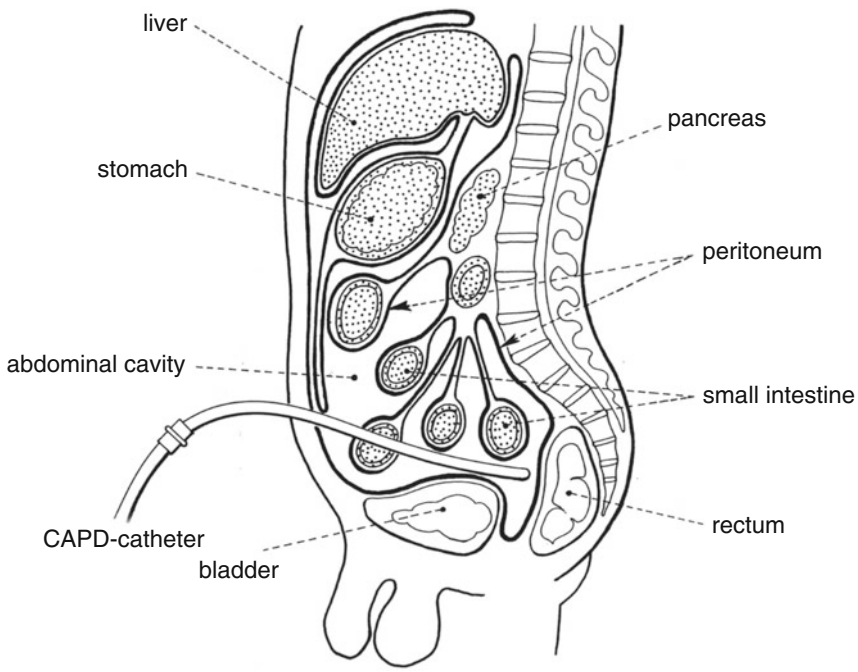

Fig. 14.1 Continuous ambulant peritoneal dialysis. Source: Recepteerkunde 2009, ©KNMP

The glucose concentration is 1.36–4.25 %. The absorption of glucose from the dialysis solution may therefore be considerable.

14.4 Product Formulation

14.4.1 Irrigations

Irrigations are aqueous solutions. Active substances to be added have to be sufficiently water soluble.

14.4.1.1 Bacterial Endotoxins

The Ph. Eur. requires irrigations to contain maximally 0.5 IU/mL bacterial endotoxins. This requirement, therefore, is indicative as to how irrigations should be prepared. For irrigations for superficial wounds the need for the absence of bacterial endotoxins may be questioned. Apart from the situation with deep surgical wounds, for example during major surgery, the absorption of bacterial endotoxins is unlikely.

Endotoxin-free solutions require the use of bacterial endotoxin free starting materials. For dialysis solutions separate requirements exist, see Sect. 14.4.2.

14.4.1.2 Osmotic Value

Irrigations to rinse a surgical area or a deep wound should be iso-osmotic. For disinfection or cleansing of superficial wounds this is not strictly necessary. Historically, a sterile hyperosmotic solution (NaCl 3 %, for example) is prepared for rinsing superficial moist wounds and bedsores. Hypertonicity is in fact the mechanism of action; the solution has a desiccating effect. For irrigations for the bladder iso-osmosis is less important. Hypo-osmosis is more problematic than hyper-osmosis, because the osmotic value of urine is twice to trice the osmotic value of blood [4].

Irrigations for transurethral prostate resection (TURP) should not contain salts. A transurethral prostate resection is performed with an electrosurgical instrument (resectoscope). The conventional TURP method in tissue removal utilises a wire loop with electrical current flowing in one direction through the resectoscope to cut the tissue. A grounding pad and irrigation by a nonconducting fluid is required to prevent this current from disturbing surrounding tissues. For making irrigations iso-osmotic for such surgeries mannitol, sorbitol or glycine may be used.

14.4.1.3 pH

Wound irrigations have to be iso-hydric (pH 7.4) or should have a very low buffer capacity. For irrigations for the bladder larger limits are allowed, but at pH < 3 irritation may occur [5]. Irrigations for dissolving bladder stones often contain citric acid as the active substance (pH 3.5–4).

14.4.1.4 Viscosity

Irrigations for rinsing should not normally be viscous. In solutions for intravesical use the use of a viscosity enhancer, like hypromellose, may exert a prolonged effect [4].

14.4.1.5 Stability

The chemical stability of the active substances is important with regard to the choice of sterilisation method and the pH. For example during sterilisation chlorhexidine degrades to *4*-chloro-aniline and other related substances. By adjusting the pH of the solution to 5 this degradation remains within acceptable limits (*4*-chloro-aniline < 0.5 %, total other related substances < 3.5 %).

Irrigations are meant for single use and do not contain a preservative.

14.4.1.6 Sterilisation Method

For irrigations steam sterilisation in its final container for 15 min at 121 °C (see Sect. 30.5.1) is preferred. These are the same requirements as for parenteral solutions. An aseptic preparation method with bacterial filtration through a 0.2 µm filter, followed by heating at 100 °C for 30 min (or another proper combination of temperature and time or validated aseptic conditions) is an alternative when one of the substances is sensitive to a higher temperature. If an active substance is not heat resistant at all, only an aseptic preparation with bacterial filtration over a 0.2 µm filter is possible. In such cases the starting materials should be sterile or have a low bioburden and the irrigation should be prepared aseptically. See also Sect. 30.6.

14.4.2 Dialysis Solutions

14.4.2.1 Formulation

Concentrates (concentrated solutions) for haemodialysis are diluted with water in the dialysis machine prior to use.

14.4.2.2 Bacterial Endotoxins

The Ph. Eur. requires solutions for haemodialysis, after dilution, to contain not more than 0.5 IU/mL. Solutions for haemo(dia)filtration and peritoneal dialysis have to be sterile and should not contain more than 0.05 IU/mL bacterial endotoxins according to the present Ph. Eur. requirements (Ph. Eur. 8.0). During a haemo(dia)filtration treatment a large volume of the solution is administered parenterally to the patient (about 60 L per dialysis session). The more stringent requirement for bacterial endotoxins in solutions for haemo(dia)filtration compared to that for solutions for haemodialysis is due to the large volume of solution administered with the first technique.

However, the limit should be even lower: a patient receives 60 L of water per dialysis treatment. A treatment lasts for 3 h. That means an intravenous administration of 20 L in 1 h. According to the Ph. Eur. the allowed maximum amount of bacterial endotoxins for parenteral use is 5 IU per kg bodyweight in 1 h. This means for a 60 kg patient that 300 IU bacterial endotoxins are allowed to be present in 20 L resulting in a requirement of <0.015 IU/mL. At this moment the assay technique allows an endotoxin limit of 0.025 IU/mL to be detected and present water treatment units are able to produce water of this quality. This topic and other requirements are under discussion within the Ph. Eur. committee on dialysis solutions.

14.4.2.3 Water Quality

It is obvious that for the preparation of solutions for haemodialysis or haemo(dia)filtration special requirements are needed to control the quality of water.

The Ph. Eur. gives formulations for all common dialysis solutions. Sodium, potassium, calcium, magnesium, acetate, hydrogen carbonate or lactate, chloride and glucose are specific components for this type of preparations. In the Ph. Eur. ranges are stated for the concentrations of these components. When the formulation contains hydrogen carbonate, sodium hydrogen carbonate should be dispensed in a separate package or a separate compartment. Sodium hydrogen carbonate can only be added to the solution just prior to administration because it may precipitate with divalent cations. Furthermore solutions for haemo(dia)filtration and peritoneal dialysis are not allowed to contain metabisulfite or other anti-oxidants. These special requirements are necessary because haemo(dia)filtration patients are exposed to about 180 L of fluid per week via the blood circulation. As a comparison: the Dutch law on potable water quality, that defines the requirements for drinking water, starts from an exposure of 2 L per day or 14 L per week via the gastro intestinal tract. Quality and purity of starting materials are defined by the Ph. Eur. A specific monograph (for information) exists for water for preparation of haemodialysis solutions: Water for diluting concentrated haemodialysis solutions. It sets an even stricter limit for specific impurities e.g. aluminium, when materials are used for preparation of haemodialysis solutions.

14.4.2.4 Stability of Added Active Substances

To solutions for peritoneal dialysis active substances may be added, for example antibiotics to treat peritonitis. In that case, their stability in a warm (37 °C) solution, in which in addition the pH will rise during dialysis, has to be taken into consideration. The biological availability of the antibiotic may decrease due to chemical instability.

14.5 Method of Preparation

The preparation of irrigations occurs in the same way as that of infusion solutions. See Sect. 13.7. Many irrigations are also available as medical devices.

Concentrates for haemodialysis are regarded as medical devices. However, they have to be diluted with water of which the quality is defined by the Ph. Eur. When a concentrate is diluted this should be done with water for injections but for practical purposes highly purified water is used.

With online haemo(dia)filtration the dialysis machine produces the diluent solution near the patient, so-called ‘online’. In some countries the pharmacist is responsible for the quality of the solutions, because health inspectorate regards this as the preparation of a medicine.

The requirements for the water which is used in an infusion during HDF are described in the Ph. Eur.: Water for injections. It is important to realise that in this monograph under the section heading ‘Water for injections in bulk’ next to chemical and biological requirements the method of preparation is also described (see also Sect. 23.3.1.3). This method of preparation is distillation, a technique that is not used in the preparation of water for dialysis in dialysis centres. In ISO 13959:2009 [6] this problem is overcome by advising the use of Highly Purified Water plus an extra filtration step for the preparation of the substitution solution for online haemodiafiltration. For the preparation of Highly Purified Water an in series connected double reverse osmosis installation is necessary followed by an electro-deioniser (see Sects. 28.4.3 and 28.4.4) or an ultrafilter. Also required is a system of periodical controls of the process to immediately detect deviations from the required quality. Where the pharmacist is responsible for the release of the preparation process, to be able to accept this responsibility, satisfactory agreements are necessary. In order to be able to take suitable action in time, if there are deviations in the required quality, a procedure, which lays down consultation between the user (usually the leader of the dialysis department or the treating nephrologist) and the responsible pharmacist is indispensable.

14.6 Containers and Labelling

14.6.1 Containers

According to Ph. Eur. “Preparations for irrigation are supplied in single-dose containers.”, for all sterile irrigations and dialysis solutions, with the exception of the concentrated solutions for haemodialysis, the container and the closure

should comply with the Ph. Eur. requirements for containers for parenteral use. According to the Ph. Eur. "the administration port of the container is incompatible with intravenous administration equipment and does not allow the preparation for irrigation to be administered with such equipment."

Irrigations are packaged in glass or plastic bottles or bags (see Sects. 24.4.6 and 24.4.13). For bladder irrigations special bags exist. When bottles are being used, it is important to have, after opening, a clear indication that the bottle has been opened, in order to prevent its re-use. This also applies to licensed medicines. Bottles with a crimp cap that is removed completely are suitable. Bottles with a screw closure are also suitable provided that they are sealed after filling. For small quantities, bags or ampoules that are not re-closable are a good alternative.

Plastic bags are usually made of PVC, through which water may diffuse and evaporate. Therefore a secondary package is necessary that is a better barrier to water vapour, but the shelf life is less than in a glass bottle anyway because of an increase of concentration. Next to this increase, the concentration of the active substance may decrease at the same time by sorption to glass or plastic. Chlorhexidine solutions are an example of this, but this is only relevant when low concentrations are present (<0.5 mg/mL).

14.6.2 Labelling

See Sect. 37.3 for general aspects of labelling. The intended use should be mentioned in the name of the irrigation as much as possible.

The label should indicate that the solution is meant for single use, and that the remainder should be discarded, and, for irrigations, that the solution is not meant for injection or infusion. The labelling of irrigations that are licensed as medical device is covered by the EU directive for medical devices [7]. Symbols or pictograms are usually part of the information.

14.7 Release Control and Quality Requirements

Irrigations should be checked for appearance, container and labelling. Control on appearance means a check on clarity and absence of particles. This usually happens before labelling.

For irrigations the following quality requirements apply (see also Table 32.2):

- Identity
- Appearance (clarity, no precipitation, sediment or foreign particles)
- Content of active substance(s)
- pH;
- Sterility
- Bacterial endotoxins

Irrigations unlike parenterals don't require a test on subvisible particles.

Quality requirements for concentrates for dialysis, the water for dilution and solutions for haemo(dia)filtration are to be found in the Ph. Eur. and in ISO 13959:2009 [6]. Quality requirements for concentrated solutions for haemo(dia) filtration and water to dilute them, are not yet defined in the Ph. Eur.

14.8 Storage and Stability

See General instructions for storage (Sect. 22.7) for background discussion. For chemically and physically stable sterilised irrigations, in a glass container, a maximum shelf life of 36 months at <25 °C, not in a refrigerator, is applied. For irrigations in plastic bags this term is shorter: maximally 12 months because of water diffusion through the plastic bag. This also applies for dialysis concentrates. For standard formulations the shelf life will be investigated and specifically indicated. With unknown chemically and/or physically stability the shelf life is maximally 1 month stored at <25 °C, not in a refrigerator.

The microbiological shelf-life of irrigations and dialysis solutions prepared by aseptic handling depends on the circumstances during the preparation. See Sect. 31.3.6.

Irrigations are meant for single use. Any opened container may only be stored for 24 h at maximum.

The diluted solutions for haemodialysis and haemodiafiltration that are prepared from the concentrate do not have a shelf life, because they are prepared in the dialysis machine immediately before use.

14.9 Administration and Dosage Delivery Devices

Irrigations for the bladder are administered via a catheter. Bags for irrigations therefore have mostly a conical connection.

For solutions for intravesical use, packaged in infusion bottles, a catheter with a Luer-lock connection is an alternative. After aspiring with a syringe from a bottle the needle may be replaced by the catheter. This variant is used mostly in the home situation, where no risk exists of mistaken intravenous administration.

Irrigations and haemodialysis solutions are mostly administered by a physician or a specialised nurse.

Peritoneal dialysis may be performed by a patient with proper instruction.

Dialysis occurs in specialised centres with staff that have the required knowledge. Also with irrigations it is important that professional caregivers know how to deal with them.

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Radiopharmaceuticals

15

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Abstract

Radiopharmacy is a discipline concerned with the preparation and quality control of radiopharmaceuticals. The term radiopharmacy is also used for the pharmacy where these activities are carried out. Radiopharmaceuticals are medicinal products that contain radionuclides (radioactive isotopes). Radionuclides are produced in nuclear reactors or in cyclotrons. The most important radionuclides used in nuclear medicine are ^{99m}technetium and ^{18}fluoride.

Many radiopharmaceuticals are used for diagnostic purposes; some are developed for therapeutic or palliative use. They are administered parenterally, orally or by inhalation. When radiopharmaceuticals are used for diagnostic purposes minute quantities are used. The radiopharmaceutical accumulates in target tissues and emits gamma-radiation that can be detected by imaging instruments. Therapeutic or palliative use requires higher dosages of alpha- or beta-emitting radiopharmaceuticals. Its ionising radiation is directed to damage the target tissue causing minimal damage to other parts of the body.

Radiopharmaceuticals are regulated both as medicinal products and as radioactive substances. Therefore, both medicine legislation and nuclear safety regulations (nuclear energy legislation) are applicable. These regulations dictate both design and layout principles of the radiopharmacy and the general handling and control procedures that should be applied when preparing and dispensing radiopharmaceuticals.

Radiopharmaceuticals used in hospitals are prepared, tested and released under the responsibility of a (radio) pharmacist. In this chapter the most important pharmaceutical aspects of radiopharmaceuticals are highlighted.

Keywords

Radiopharmacy • Radionuclides • Radiopharmaceuticals • Radiolabelling • Nuclear medicine • Alpha-emitters • Beta-emitters • Gamma-emitters • Positron emitters • SPECT • PET

Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_15,

15.1 Orientation

Radiopharmacy is a discipline concerned with the preparation and quality control of radiopharmaceuticals. Radiopharmaceuticals are defined by the European Pharmacopeia (Ph. Eur.) as "medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose".

Radiopharmaceuticals are regulated both as medicinal products and as radioactive substances. Therefore, both medicine quality regulations (GMP) and safety regulations (nuclear energy legislation) are applicable. Radiopharmaceuticals must be handled (often aseptically) as quickly as possible, with shielding, to avoid unnecessary exposure to radiation.

Most radiopharmaceuticals are used for diagnostic purposes, some for therapeutic or palliative use. They are administered parenterally, orally or by inhalation. When radiopharmaceuticals are used for diagnostic purposes minute quantities are used. The radiopharmaceutical accumulates in target tissues and emits gamma radiation that can be detected by imaging instruments. Therapeutic or palliative use requires higher dosages of alpha- or beta-emitting radiopharmaceuticals. Its ionising radiation is directed to damage the target tissue causing minimal damage to other parts of the body. Alpha or beta emitters are suitable for this purpose because of the limited pathway of their radiation in tissue [1, 2].

Radiopharmaceuticals are used in the hospital department of nuclear medicine or in research institutes. For diagnosis essentially two techniques are used: SPECT (single-photon emission computed tomography) and PET (positron emission tomography). SPECT is an imaging technique detecting gamma rays. In SPECT imaging a gamma camera acquires multiple two dimensional images (also called projections) from multiple angles. With the aid of tomographic reconstruction algorithms a three-dimensional image is calculated.

Positron emission tomography also produces three-dimensional pictures of organs and functional processes in the body. In PET pairs of gamma rays emitted indirectly by a positron-emitting radionuclide are detected. Computer programs reconstruct PET images.

Several techniques from radiology and nuclear medicine have been combined in hybrid imaging techniques, such as SPECT-CT, PET-CT and PET-MRI. In these hybrid systems the use of radiopharmaceuticals (sometimes next to conventional contrast agents) remains essential.

Radiopharmaceuticals used in hospitals are prepared, tested and released under the responsibility of a (radio)pharmacist. In this chapter the most important pharmaceutical aspects of radiopharmaceuticals are highlighted.

15.2 Definitions

ALARA	"As Low As Reasonably Achievable", an occupational safety and health principle pursuing minimal radiation exposure.
Alpha radiation	Ionising radiation by alpha particles (= $^{4}He^{2+}$-ions). In comparison with beta and gamma radiation, alpha radiation has the least penetrating power and the highest linear energy transfer.
Alpha emitter	Radionuclide that decays to a more stable nuclide by emission of an alpha particle.
Annihilation radiation	Two gamma rays with an energy of 511 keV that are emitted at an angle of 180° after collision of a positron with an electron.
Becquerel	Unit of radioactivity: 1 Becquerel (Bq) is equivalent with 1 disintegration per second (kBq = 1,000 Bq, MBq = 10^6 Bq).
Beta radiation	Ionising radiation by $beta^+$ (= positron) or $beta^-$ (= electron) particles.
Beta emitter	Radionuclide that decays to a more stable nuclide by emission of a $beta^+$ (= positron) or a $beta^-$ (= electron) particle.
Computed tomography (CT)	Technology that uses X-rays to produce images (virtual slices), allowing to see inside the body.
Cyclotron	Equipment in which charged particles, after acceleration in a circular pathway, are directed onto a target for evoking a nuclear reaction.
Decay	Spontaneous reaction of a radionuclide to form another (radio)nuclide accompanied by the release of ionising radiation.
Electronvolt (eV)	Kinetic energy gained by an electron when accelerated through a potential field of 1 volt (keV = 1,000 eV).
Gamma radiation	High energy photons that are emitted during radioactive decay.
Gamma emitter	Radionuclide that emits gamma rays during radioactive decay.
Generator	A device in which a daughter radionuclide with a shorter half-life is separated from a mother radionuclide with a longer half-life.
Half-life	The characteristic of a radionuclide that defines the time during which

	the radioactivity of a radionuclide is reduced to half of its original value.
Kit for labelling	Composed set of all non-radioactive reagents in appropriate quantities for the preparation of a specific radiopharmaceutical.
Magnetic resonance imaging (MRI)	A medical imaging technique to investigate the anatomy and physiology of the body using strong magnetic fields.
Nuclear reactor	Installation for the production of radionuclides by nuclear fission of e.g. ^{235}uranium.
PET	Positron emission tomography: an imaging technique that makes use of a radiopharmaceutical that is labelled with a positron emitter (e.g. ^{11}C, ^{13}N, ^{18}F).
Positron	A beta^{+} particle that, after collision with an electron, annihilates to two gamma rays of 511 keV.
Radioactivity	Spontaneous process in which an unstable radionuclide transforms to a more stable (radio)nuclide releasing energy in the form of particles (alpha or beta particles) or photons (gamma rays).
Radiochemical	Any compound containing one of more atoms of a radioactive isotope.
Radiochemical purity	Fraction of the total radioactivity present in the desired radiochemical form.
Radiolabelling	Process of attaching a radionuclide to a non-radioactive molecule.
Radionuclide	An unstable nuclide that decays spontaneously by the emission of particles (alpha or beta particles) or photons (gamma rays).
Radionuclidic purity	Fraction of the total radioactivity present as the desired radionuclide.
Radiopharmaceutical	A pharmaceutical substance that contains one or more radionuclides.
SPECT	Single-photon emission computed tomography: an imaging technique that makes use of a radiopharmaceutical that is labelled with a gamma emitter.

15.3 Radionuclides

Radionuclides (radioactive isotopes) are the most important components of radiopharmaceuticals. Desirable properties of radionuclides in radiopharmaceuticals are relatively short decay times (half-lives from hours to days) and ease of incorporation in the final molecule. The energy of the emitted radiation ranges from about 150 kiloelectronvolt (keV) (gamma-photons for diagnostics) to around 1,000 keV (beta-particles for therapy). The newer imaging technique of positron emission tomography (PET) uses radionuclides with half-lives going down to 2 min, emitting positrons that annihilate to gamma-photons of 511 keV.

Table 15.1 Common radionuclides and their use

Diagnostic use (SPECT)	Diagnostic use (PET)	Therapeutic/ palliative use
^{51}Cr	^{11}C	^{32}P
^{67}Ga	^{13}N	^{89}Sr
^{81m}Kr	^{15}O	^{90}Y
^{99m}Tc	^{18}F	^{131}I
^{111}In	^{68}Ga	^{153}Sm
^{123}I	^{82}Rb	^{177}Lu
^{133}Xe	^{89}Zr	^{188}Re
^{201}Tl	^{124}I	^{223}Ra

Radionuclides either originate from a nuclear reactor or are produced by a cyclotron. The description of the production methods of radionuclides in nuclear reactors and cyclotrons goes beyond the scope of this book and can be found elsewhere [1, 2].

The most important pharmaceutical radionuclide produced by a nuclear reactor is ^{99}molybdenum. This element is the mother radionuclide in a ^{99}Mo/^{99m}Tc-generator (see Sect. 15.6.4). During separation in this generator sodium ^{99m}technetium pertechnetate is formed. ^{99m}Tc-pertechnetate is the most frequently used radiochemical for coupling to a pharmaceutical ligand in the preparation of diagnostic radiopharmaceuticals.

Cyclotrons are found in nuclear industry, but their presence and use in hospitals is increasing. The principal radionuclide from cyclotrons is ^{18}F-fluoride. This radionuclide is often incorporated into ^{18}F-fludeoxyglucose through an automated synthesis procedure. ^{18}F-fludeoxyglucose is the major radiotracer used in PET.

The most frequently used radionuclides and their use are mentioned in Table 15.1.

15.4 Radiopharmaceuticals

15.4.1 Use of Radiopharmaceuticals

A radiopharmaceutical is a radioactive medicinal product for diagnostic, therapeutic or palliative use. Parenteral radiopharmaceuticals usually consist of a radionuclide coupled to another pharmaceutical compound, also called a ligand. Some radionuclides are administered as such. Alternative dosage forms are capsules for oral use or a radioactive gas for inhalation. All dosage forms are shielded, in lead or

tungsten for gamma and positron emitters and in plastics for beta and alpha emitters.

The physical and biopharmaceutical properties of a radiopharmaceutical determine its potential use [1, 2].

The design of radiopharmaceuticals is based upon the physiological function of the target organ. The mechanism of targeting a particular organ can be different, for example physical trapping of particles, binding to structures in tissues or organs or an antigen-antibody reaction. In general, a high target-to-background ratio is pursued.

A radiopharmaceutical emitting alpha or beta radiation can be used for therapeutic or palliative purposes. These types of radiopharmaceuticals deposit their energy on very short distances. For alpha emitters this distance is much shorter than for beta emitters. This high-dose locally accumulated radioactivity is used in radionuclide therapy (pain palliation of bone metastases, therapy for some specific types of cancer).

Some radionuclides are emitting a combined spectrum of radiation. One type of the radiation spectrum (alpha or beta) is used for its therapeutic properties; the other type of the radiation spectrum (gamma) might be used for localisation of the tracer and the targeted tissue or for dosimetry. These radiopharmaceuticals are called theranostics.

Sometimes other medicines are used in combination with the radiopharmaceutical, as co-medication in the diagnostic process, e.g. intravenous diuretics to promote renal clearance, adenosine to induce pharmacological stress and thyroid stimulating hormone in thyroid studies. These pharmacological interventions increase the sensitivity or specificity of a procedure used in nuclear medicine.

15.4.2 Biopharmaceutics

Most radiopharmaceuticals are administered intravenously. After injection, the radioactive substance is distributed fast to the target site thereby avoiding unnecessary radiation dose to the stomach and gut after oral dosing. Scanning may start immediately or after a certain period.

The selective biodistribution and pharmacokinetics of the radiopharmaceutical within the body are determined by the properties of the pharmaceutical agent, the stability of the labelling, the physical and radiochemical properties of the radiopharmaceutical, the purity of the radiopharmaceutical preparation, the pathophysiologic status of the patient and the possible influence of interfering medicines.

By choosing the radionuclide the diagnostic use of the radiopharmaceutical can be determined: gamma emitters or positron emitters can be used for diagnostic procedures by providing static or dynamic images following the distribution of the radiopharmaceutical within the body. For the detection of gamma radiation a classical gamma camera is used, for positron-emitters a PET-camera has to be used. See also next sections.

Adverse effects of radiopharmaceuticals for diagnosis are extremely rare [3]. Radiopharmaceuticals for therapy may have adverse effects, for example bone marrow depression if used for treatment of bone metastases. Radiopharmaceuticals can interact with other (non-radioactive) medicines given to the same patient [4]. Food and glucose in food can disturb the quality of certain types of imaging (interaction of glucose (dextrose) with ^{18}F-FDG in PET imaging).

15.4.3 Parenteral Radiopharmaceuticals

Parenteral radiopharmaceuticals are available as a simple radionuclide in solution, for instance ^{131}I-sodium iodide solution for injection, or are prepared by labelling a non-radioactive pharmaceutical moiety (ligand) with a radionuclide. Many kits or ligands for the preparation of radiopharmaceuticals are available in the form of sterile, freeze-dried powders in an injection vial. These kits are non-radioactive.

Radiopharmaceuticals for parenteral use must comply with the Ph. Eur. monograph for parenteral preparations, so they have to be sterile and with a very low or absent endotoxin concentration. For parenteral administration a sterile injection in a disposable injection syringe is often filled from a multiple dose solution in a glass vial.

15.4.3.1 Technetium-99m Radiopharmaceuticals

^{99m}Technetium labelled radiopharmaceuticals form a majority within all prescribed radiopharmaceuticals. ^{99m}Tc sodium pertechnetate is used for the labelling of the ligand of choice according to fixed preparation procedures. The ligand is a non-radioactive pharmaceutical substance that is part of a “kit for labelling”. Most kits contain additionally a stannous salt that brings the ^{99m}Tc in the right oxidation state for the radiochemical reaction with the ligand. Sometimes the reaction has to be accelerated by increasing the temperature. Many ^{99m}Tc-labelled compounds are prepared using this technique.

15.4.3.2 PET Tracers

PET imaging is performed with positron emitting radiopharmaceuticals. After collision of the emitted positrons with electrons, pairs of gamma-rays are formed that are detected by the PET camera. The most important PET tracer is ^{18}F-Fludeoxyglucose (^{18}F-FDG) with a physical half-life of 110 min. ^{18}F-FDG is nowadays synthesised by nucleophilic substitution of the precursor mannose triflate using fully automated synthesis procedures and cyclotron-produced ^{18}F-fluoride ions. After purification the resulting

^{18}F-FDG is diluted with saline, sterile filtered and dispensed in multiple dose vials or in syringes.

Because FDG accumulates in tissues with a high glucose uptake, ^{18}F-FDG can be used for the imaging of tumours, for the tracing of infections and for neuroimaging. ^{18}F-FDG is also useful for monitoring of therapy response.

15.4.3.3 Complex Parenteral Radiopharmaceuticals

Some radiopharmaceuticals are rather complex dosage forms. Radiolabelled nanospheres, nanoparticles, nanocolloids, peptides, monoclonal antibodies and glass particles for radioembolisation are a few examples. Also autologous blood cells can be radiolabelled, outside or inside the body. The radiolabelling of blood cells is used in routine practice.

15.4.4 Oral Radiopharmaceuticals

Oral radiopharmaceuticals are administered as gelatin capsules. Absorption after oral use is relatively slow so it will take time before the content is distributed in the body and delivered to target organs or tissues (the bone, the heart, the thyroid, brain etc.).

^{123}I and ^{131}I Sodium iodide are examples of radiopharmaceuticals that can be administered in capsules for oral administration.

15.4.5 Radiopharmaceuticals for Inhalation

Some radiopharmaceuticals are administered by inhalation in the form of a radioactive gas. ^{81m}Krypton is an example of a gaseous inhalation radiopharmaceutical that is used in inhalation or ventilation/perfusion studies.

15.5 Legislation

15.5.1 Sources of Legislation

Since radiopharmaceuticals are medicines, the purchasing, preparation, quality control and handling are subject to the same legislation and guidelines as other medicines (see Sect. 35.5). However, radiopharmaceuticals are regulated as radioactive substances as well. Therefore, two sources of legislation: medicine legislation and nuclear safety regulations (e.g. nuclear energy legislation) are applicable. Sometimes this can lead to conflicting situations, see Sect. 15.6.3 for the discussion about pressure hierarchy in pharmaceutical clean rooms, where GMP rules demand relative overpressure and radiation safety rules ask for relative underpressure. The most important regulations for the (small scale) preparation and dispensing of radiopharmaceuticals are summarised below.

15.5.2 Radiopharmaceuticals with a Marketing Authorisation

Like other medicinal products, licensed radiopharmaceuticals are covered by EU Directive 2001/83/EC [5]. The most important requirements are a marketing authorisation and a manufacturing license.

A marketing authorisation is mandatory for the production of radionuclide generators, radionuclide kits and radionuclide precursors.

15.5.3 Radiopharmaceuticals to be Used in Clinical Trials

For all investigational medicinal products (IMPs) used in a clinical trial EU Directive 2001/20/EC ("Clinical Trial Directive") and GMP Annex 13 are applicable [6, 7], see Sect. 35.5.10. The clinical trial directive has recently been replaced by the new and less stringent EU regulation 536/2014 [8, 9]. In this regulation, GMP and a manufacturing license will no longer be required for the preparation of diagnostic radiopharmaceuticals used in clinical trials when they are prepared in a hospital radiopharmacy from licensed sources and used within the Member State.

15.5.4 Good Manufacturing Practice (GMP)

Annex 3 (Manufacture of Radiopharmaceuticals) is the only part of the GMP framework entirely dedicated to radiopharmaceuticals [10]. Preparation of radiopharmaceuticals using authorised generators and kits is excluded from this Annex. The production of radionuclides in reactors and cyclotrons is a physical process and is regarded as a non-GMP activity. Annex 3 describes general GMP principles (quality assurance, personnel, premises and equipment, documentation, production, quality control, reference and retention samples, distribution) in relation to radiopharmaceuticals. As with other medicinal products, other GMP annexes may be applicable, for instance Annex 1 Manufacture of Sterile Medicinal Products [11].

15.5.5 Product Quality

The General Monograph 0125 Radiopharmaceutical preparations provides general information about the preparation and quality control of radiopharmaceuticals [12]. More

than 65 radiopharmaceutical monographs are available in the Ph. Eur., in which specific requirements are elaborated.

Recently a new General Chapter has been drafted on extemporaneous preparation of radiopharmaceutical preparations [13]. This new chapter will provide minimal requirements for kit-based preparations, PET radiopharmaceuticals and radiolabelled blood cells. As with all General Chapters it will not be obligatory, unless mentioned in a product monograph.

15.5.6 Extemporaneously Prepared Radiopharmaceuticals

Legislation for extemporaneous preparation of radiopharmaceuticals is in principle not different from extemporaneous preparation in general (Sect. 35.5). There is a great variation in interpretation and approach in Europe [14]. In some countries radiopharmaceuticals are prepared based on the pharmacy status of the radiopharmacy unit. In other countries radiopharmaceuticals are prepared in laboratories, in university institutions or research laboratories without pharmacy status, with authorisation based on radiation protection legislation only.

Anyway, several guidance documents are available, which can be used as standards. The European Association of Nuclear Medicine (EANM) issued guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals [15, 16]. In these guidelines GMP and radiation safety requirements are interpreted for radiopharmaceuticals not intended for commercial purposes.

Annex 3 of the PIC/S guide to good practices for preparation of medicinal products in healthcare establishments interprets GMP issues for the small-scale preparation of radiopharmaceuticals [17] (see also Sect. 35.5.5).

15.5.7 Legislation on Radiation Protection

Directive 96/29/EURATOM (Basic safety standards) provides safety standards for the protection of health workers and the general public against the dangers of ionising radiation [18]. Directive 97/43/EURATOM (Medical exposure directive) gives rules concerning radiation in relation to medical exposure and provides dose limits [19].

The International Commission on Radiological Protection (ICRP) has issued many recommendations and guidance documents on radiation protection. In addition to European legislation, national and local provisions can be applicable.

Radiation safety is based on general occupational safety and health risk mitigation principles (see also Sect. 26.7): justification (of the use of ionising radiation), ALARA (as low as reasonably achievable; this means aim for the lowest possible exposure) and exposure limits (dose limits for ionising radiation).

15.5.8 Interpretation of Legislation

It is not easy to interpret all above mentioned legislation and to give uniform guidance for each country and each situation. The determination of adequate quality assurance measures, for example the GMP-classification of the clean room, should be the result of a risk assessment [20]. Table 15.2 gives a practical overview of the applicable guidance and the appropriate quality assurance level when preparing radiopharmaceuticals.

15.6 Preparation and Dispensing

15.6.1 Location of Preparation

Preparation and dispensing of radiopharmaceuticals is limited to dedicated radiopharmacies. Radiopharmaceuticals for patient use are usually prepared, controlled and dispensed in a hospital radiopharmacy department, but can also be dispensed on a named patient base by a centralised radiopharmacy ('compounding centre') that operates on a commercial basis or by a centralised hospital pharmacy. The hospital (radio)pharmacist has the final responsibility for the quality of radiopharmaceuticals, also when purchased from an external (commercial) site. The responsible hospital pharmacist has to audit the external site and obtain a quality agreement, clarifying the mutual responsibilities.

Since radiopharmaceuticals are only used in a hospital setting and usually have very short shelf lives, radiopharmacies are often located in or nearby a hospital or imaging centre. Only for radiopharmaceuticals with a longer radioactive half-life the preparing radiopharmacy might be located at longer distance. Some PET radiopharmaceuticals with a very short half-life require the presence of both a cyclotron and a radiopharmacy in the neighbourhood of the imaging centre. ^{82}Rb is a PET radiopharmaceutical that must be prepared in a dedicated rubidium generator next to the patient because of its very short half-life.

Radiopharmaceuticals must be handled (often aseptically) as quickly as possible to avoid unnecessary exposure to radiation.

15.6.2 Prescription and Dose

Diagnostic radiopharmaceuticals are given in extreme low doses in order to minimise radiation exposure. This can be

Table 15.2 Overview of the guidance and main quality assurance issues of the different steps in the extemporaneous preparation of radiopharmaceuticals

Type of activity/ process	Guidance	GMP-classification	Quality control	Microbiological control	Local validation and product dossier
A. Obtaining a radionuclide					
Elution of a licensed generator (in particular, the Mo/Tc-generator)					
Aseptic handling	National guideline	Elution in class A; background: at least class D[a]	At the start of every working day; example: ^{99}Mo-breakthrough)	Microbiological monitoring of the eluate	No validation No product dossier
Elution of an unlicensed generator					
Aseptic handling	National guideline	Elution in class A; background: at least class D[a]	At each elution (extent depending on risk assessment)	Microbiological monitoring of the eluate; endotoxins	Product dossier with validation data on elution and QC; supplier assessment
Production of radionuclides using a cyclotron					
High-technologic process	Non-GMP [10]; radiation safety legislation				
Purchase of a radionuclide (licensed or unlicensed)					
Administratively	Not applicable	Not applicable	If unlicensed: assay as active substance (raw material)	Not applicable	If unlicensed: supplier assessment
B. Obtaining a pharmaceutical substance to be labelled					
Purchase of a kit (licensed or unlicensed)					
Administratively	Not applicable	Not applicable	If unlicensed: assay as an active substance (raw material)	Not applicable	If unlicensed: supplier assessment
Production of a kit or starting materials for preparation of a radiopharmaceutical					
Production from starting materials (regular pharmacy production)	National guideline	Production and filling: class D if terminally sterilised	Every batch	Environmental monitoring; bioburden; endotoxins	Product dossier with validation data on production and QC
C. Obtaining a radiopharmaceutical					
Preparation of a radiopharmaceutical using a licensed kit					
Aseptic preparation	National guideline	Preparation in class A; background: at least class D	Radiochemical purity according to SmPC; periodically, e.g. once a month or at each new batch	Environmental monitoring	No validation No product dossier
Preparation of a radiopharmaceutical using an unlicensed kit					
Aseptic preparation	National guideline	Preparation in class A; background: class D	At each batch; extent depending on risk assessment	Environmental monitoring	Depending on characteristics: radiochemical/ radiopharmaceutical validation of labelling; limited product dossier
Labelling of blood cells and other complex preparations					
Aseptic preparation	National guideline	Preparation in class A; background: at least class D; dedicated premises (preferred) or separation in time to prevent cross contamination	According to SmPC or own method, at each preparation	Environmental monitoring	If licensed: no validation, no product dossier If unlicensed: product dossier with validation data
Synthesis and purification of (PET) radiopharmaceuticals					
Complex radiochemical synthesis and aseptic preparation	GMP Part II and I including relevant annexes	Preparation in class A; background: depending on risk assessment	According to SmPC or own method, at each preparation	Environmental monitoring	If licensed: no validation, no product dossier If unlicensed: product dossier with validation data
Purchase of a ready to use or ready to administer radiopharmaceutical (licensed or unlicensed)					
Administratively	Not applicable	Not applicable	If not licensed: assay as an active substance (raw material)	Not applicable	If not licensed: supplier assessment

(continued)

Table 15.2 (continued)

Type of activity/ process	Guidance	GMP-classification	Quality control	Microbiological control	Local validation and product dossier
D. Aliquoting[b] of a radiopharmaceutical					
Aliquoting of an extemporaneously prepared or ready to use radiopharmaceutical					
Aseptic handling	National guideline	Aliquoting in clean environment, if administered within 8 h	Not applicable	Not applicable	No validation No product dossier
E. Preparation of a radiopharmaceutical for use in clinical trials[c]					
One or more of the abovementioned	GMP annex 3, 1 and 13	Preparation: class A; background: classification depending on risk assessment	According to IMPD, at each batch, release by QP	Environmental monitoring, extent depending on risk assessment	Manufacturing license required; IMPD with validation data required

[a]Generators for very short living radionuclides (for example a $^{82}Sr/^{82}Rb$-generator) are situated next to the patient, in an unclassified background. The eluate is transferred directly into the patient
[b]Aliquoting is individual dose dispensing from a multidose vial
[c]New clinical trial regulation is less stringent for diagnostic radiopharmaceuticals [9]

achieved by extending the imaging time of the camera. For therapy or palliation (e.g. thyroid gland, bone metastases) higher dosages of radionuclides with high energy transfer are applied.

Diagnostic as well as therapeutic radiopharmaceuticals are prescribed as medicines. The radioactive dosage is usually calculated on the basis of the body weight or (in therapy) the weight and shape of the target organ.

After verification and acceptance of the prescribed dose the prescription is transformed into a standardised preparation instruction (see Sect. 33.5). The requested dose is always corrected upwards for decay of the radionuclide during the time from preparation until administration to the patient.

15.6.3 Layout of the Radiopharmacy Department

For the design of premises reference is made to Sect. 27.2, including aseptic processes and the pressure conflicts that may occur when product safety as well as personnel safety have to be dealt with. A typical radiopharmacy department consists of one or more clean rooms, a quality control room and adjacent rooms such as locks for people and goods, a room for administration/storage, a room for cleaning materials and a waste disposal room [1, 2, 21]. Often the radiopharmacy department is called hot lab, while this term originally refers to the room(s) where radioactive materials are handled.

Ideally the radiopharmacy department in a hospital is situated next to or integrated in the nuclear medicine department. Restricted access to the radiopharmacy department must be assured for both radiation protection and GMP reasons.

The requirements for radiation safety (nuclear energy regulations) as well as aseptic processing (GMP guidelines) must be met. For radiation safety the pressure within the rooms of the radiopharmacy department where radioactive material is processed must be negative relative to the outside world. The level of underpressure needed in the preparation room depends on the maximal amount of radioactivity present in operation and must meet local regulations. A pressure difference of −10 Pa relative to the outside world is a typical value for a radiopharmacy clean room where kits are being labelled and PET radiopharmaceuticals are being handled. However, for the maintenance of aseptic circumstances GMP requires that the pressure in this room must be 10–15 Pa higher than in adjacent rooms of a different GMP class. The airflow must be directed from the cleanest environment towards less clean areas.

The classification of the clean room for preparation of radiopharmaceuticals should be the outcome of a risk assessment and could be class B, C or D [11, 16, 17]. The risk assessment should take into account the use of closed systems, the time between preparation and use and the nature of the product. The critical working zone should be class A and can be realised with a radiopharmacy safety cabinet, an isolator or a hot cell (see Sect. 15.6.4). A compromise to respond to these demands could be an extra airlock between the clean room clothing area (first lock) and the preparation clean room [21]. The first lock has an overpressure of 10–15 Pa to the outside world for keeping out particulate matter (product protection). The second lock has an extra underpressure of −10 to −15 Pa relative to the clean room to realise a deep underpressure (the so-called sink) for radioprotection and ‘GMP-overpressure’ of 10 to 15 Pa between the clean room and this extra lock. See also Fig. 27.1.

In some situations a simpler air pressure regimen, for example an underpressured isolator in an overpressured

clean room might be sufficient to meet all regulations [21]. However, this is subject to local requirements.

The pressure cascade inside the radiopharmacy premises has to be controlled, monitored and documented.

It should be stressed that pressure differences are not a guarantee for safe working conditions. Spreading of radioactivity can easily take place by contaminated shoes, gloves or materials, which only can be prevented by a safe working procedure.

Similarly to conventional clean rooms, qualification and periodic requalification of the clean room conditions, the aseptic workstations and personnel have to be carried out.

The scale-size, organisation and facilities of the radiopharmacy depend on the size and the demand of the nuclear medicine department and can range from simple dispensing of commercial available radiopharmaceuticals to complex synthesis of short-lived PET-radiopharmaceuticals.

In most radiopharmacy departments one or two ^{99m}-technetium generators are in place.

In larger departments facilities for the synthesis of PET radiopharmaceuticals are available for which a local cyclotron may be needed. The use of PET tracers may have advantages in terms of speed, image resolution and radiation burden. Reasons for installing a local cyclotron are the extent of PET diagnostics and research, the demand for very short-lived PET radiopharmaceuticals (e.g. based on ^{13}N and ^{15}O) and the lack of FDG availability from commercial suppliers.

In some departments facilities are in place for the labelling of peptides or proteins (e.g. antibodies) and blood cells. When handling blood cells cross contamination or mix-up must be prevented by working in a separate dedicated room.

15.6.4 Equipment in the Radiopharmacy

A radiopharmacy has dedicated equipment for synthesis, preparation and quality control of radiopharmaceuticals. The workbench for the safe and aseptic preparation of radiopharmaceuticals is often a sufficiently lead shielded radiopharmacy safety cabinet with downflow HEPA filtered laminar air providing a GMP class A working zone. The exhaust air is filtrated and expelled outside the radiopharmacy to the roof on top of the building. The cabinet has built-in radiation protection by installed lead plates in the walls and in the working field, a horizontally movable lead containing glass window, lead shielded instruments for radiation measurement and waste containment and special equipment for automatic preparation and dispensing such as a barcode scanner, printer, screen and mouse pad.

A hot cell is a lead shielded locked containment chamber with underpressure, often used for handling highly radioactive radionuclides and products. Hot cells are usually equipped with manipulators to perform all operations by an operator from outside or a robot inside. When the chamber is a GMP class A working zone, the material is introduced by the operator from a separate class B chamber, giving access to the class A working area. Materials enter the class B chamber from a GMP class C clean room environment.

An isotope dose calibrator is shaped as a cylinder and is often built in beneath the working area in the safety cabinet. It measures the radioactivity of a prepared dose in a vial or syringe. Each individual radionuclide can be measured accurately. Other equipment to measure radioactivity are scintillation counters (e.g. the NaI well counter) and semiconductor-based instruments (e.g. the Germanium detector).

A survey counter is a gas filled detector used to detect spilled radioactive materials that can be hazardous for the operators or may disturb accurate dose measurements. Survey counters can be mounted at critical places to measure the radiation level in rooms continuously. A hand-foot-clothing monitor is a suitable and obligatory instrument to detect possible contamination before leaving the area where radioactive materials are handled.

A thin layer chromatography (TLC) scanner is used for the quality control of a radioactive labelled product. It firstly separates the different radiochemical forms by chromatography and subsequently measures the radiation of the spot of the intended radiopharmaceutical and the unwanted by-products (see Sect. 15.6.7 quality control).

A fume cupboard provides safe working conditions when heating is needed, as some radiopharmaceuticals must be heated in a water bath for some time to finish the labelling. A fume cupboard is also used with the preparation of radioactive diagnostic pancakes and when working with organic volatile solvents as in thin layer chromatography for the quality control of radiopharmaceuticals.

15.6.4.1 Radionuclide Generators

Radionuclide generators are loaded by the manufacturer with a mother radionuclide. This radionuclide decays continuously to a daughter radionuclide with suitable properties for the preparation of radiopharmaceuticals. These generators can be used on site for a period of a week to several months, depending on the type of generator [1, 2].

The radiopharmacist is responsible for the proper use and pharmaceutical quality of radionuclide generators. Most radionuclide generators have to be eluted with a non-radioactive infusion fluid such as sterile sodium chloride 0.9 %. The most commonly used generator is the ^{99}Mo/^{99m}Tc- generator, which is described more in detail.

15.6.4.2 ^{99}Molybdenum/^{99m}Technetium Generator

The daily preparation of ^{99m}Tc-compounds requires the use of a ^{99}Mo/^{99m}Tc generator (see Fig. 15.1). A technetium

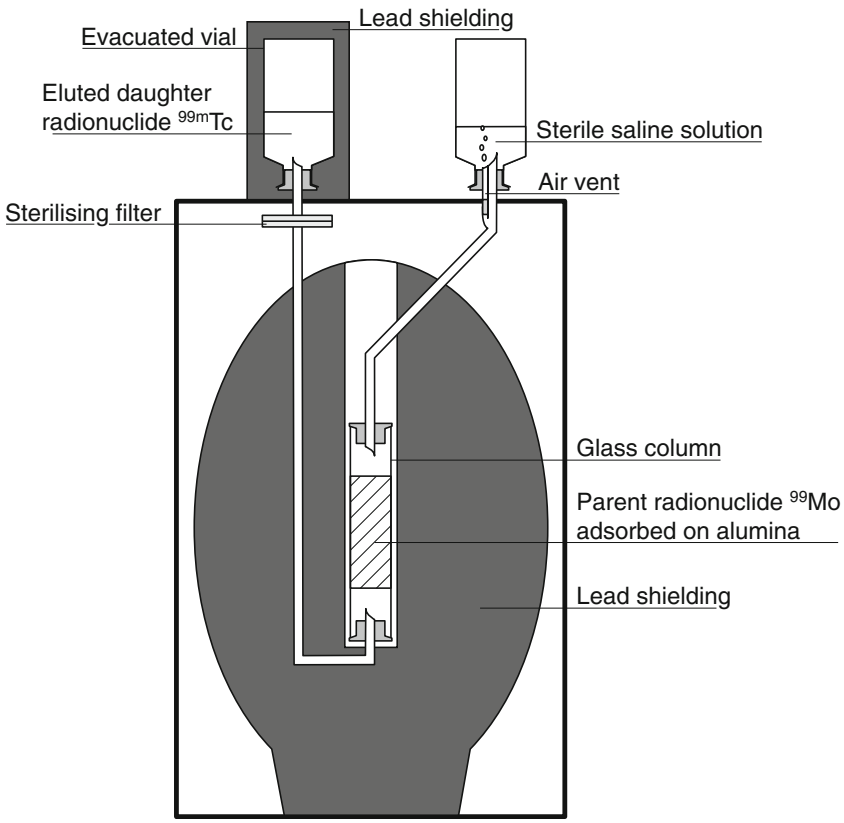

Fig. 15.1 Structure of a ^{99}Mo/^{99m}Tc generator. ©P.M.Berkemeyer

generator is made up of a glass column containing the reactor fission product molybdenum-99 adsorbed on alumina. ^{99}Mo has a half-life of 66 h and decays to ^{99m}Tc having a half-life of 6 h. The glass column is fitted within a lead container for radiation protection. The ^{99m}Tc is eluted from the column by a sterile saline solution into an evacuated sterile empty glass vial. The underpressure in the evacuated vial is the driving force. The resulting sterile solution of sodium pertechnetate is called the eluate. The sterile eluate can be used for radiolabelling of ligands or for preparation of a solution for injection. The ^{99m}technetium generator is typically eluted once or twice a day. After elution, the ^{99m}Tc-activity has to build up again by decay of the mother radionuclide to the daughter radionuclide. After delivery from the supplier the new generator has the highest activity, every day the activity decreases. After 1–2 weeks, the generator is returned to the reactor site for regeneration.

The quality of the generator system should be monitored every working day. Quality control consists of performing the ^{99}Mo breakthrough test (radionuclidic purity) and assaying the aluminium content, the pH, sterility and endotoxin level of the eluate. The radiochemical purity test is a routine test to quantify the different (wanted and unwanted) chemical forms of the radionuclide (e.g. $^{99m}TcO_4^-$ and $^{99m}TcO_2$). Not all above mentioned tests have to be performed on a daily basis. The extent and frequency of quality control of generator systems has to be determined by risk assessment.

15.6.5 Preparation and Handling

Radiopharmaceuticals for use in a hospital are prepared or aliquoted, labelled and dispensed for each individual patient. Usually no stock production or storage of radionuclides takes place in the radiopharmacy because of their short shelf lives due to radioactive decay. Most radiopharmaceuticals are administered within a working day.

The preparation and aliquoting of radiopharmaceuticals can be performed by pharmacy technicians, nuclear technicians or analysts, but is always the responsibility of a (radio)pharmacist. Gowning with clean room clothing is similar to gowning for other clean rooms (see Sect. 31.3.4). Disposable gloves are used in all rooms where radioactive materials are handled to prevent radioactive contamination of the hands. Personal dosimeters must be worn during all operations with radioactive materials. When handling radioactive materials, exposure must be minimised by limiting the handling time, maximising the distance to the source (e.g. by using a tong or forceps) and the use of shielding.

Most radiopharmaceuticals are administered intravenously and must therefore be sterile. Since terminal

sterilisation is usually not possible due to the radionuclide's short half-life, these products have to be prepared following aseptic procedures. The most appropriate procedure is the closed system technique. In this procedure the starting materials and medical devices are sterile and processed in a clean room without direct contact with the environment.

The most common preparation process is the so-called kit preparation, which comprises the following steps:

- Aseptical elution of the generator.
- Quality control of the eluate (see Sect. 15.6.7).
- Aseptic transfer of a measured eluate dose to the kit vial for incubation; the radiopharmaceutical is synthesised, sometimes under heating.
- Quality control of the radiopharmaceutical (see Sect. 15.6.7).
- Aliquoting (aseptic transfer of the radiopharmaceutical) into ready to administer dosage delivery devices. This includes the measurement of the calculated dose taking into account the half-life of the radionuclide and the time up to administration.
- Release and dispensing (see Sect. 15.5.7).

The reconstitution and quality control should follow the instructions of the manufacturer, the Ph. Eur. monograph or a locally validated preparation process and assay.

Just as with other aseptic preparation processes, a program of environmental monitoring and personal qualification for aseptic operation has to be carried out, see Sect. 31.6.

15.6.5.1 Radioactive Stock and Waste Management

At all times the identity and amount of radionuclides and radiopharmaceuticals in the radiopharmacy department must be known. This also applies to the radioactive waste. All places where radioactive materials (including waste) are stored must be protected from fire and unauthorised access.

Radioactive waste is produced in everyday practice within the radiopharmacy department as part of the preparation process. Examples are radioactive needles and syringes, residuals in vials and radioactive tissues.

In case of spilling radioactive materials, a safe procedure has to be followed to remove them. This leads to an extra amount of radioactive waste.

Radioactive waste must be sorted by the half-life of the radionuclide so that it can be stored separately. Radioactive waste from short-lived radionuclides is often disposed of by the so-called decay in storage method. The waste is set apart for a certain time period and the residual radioactivity is measured. If the level of radioactivity is as low as the background, the material can be seen as normal hospital waste and is disposed of in closed hospital waste containers. The waste of short-lived radionuclides can often be stored during the working day in a lead shielded container, built in the safety cabinet. Longer living radionuclides must be stored in dedicated lead shielded storage cabinets that may be placed in a separated waste disposal room with negative pressure. Also expired generators may be stored there, waiting for transportation. An authorised firm can take the longer living radioactive residuals to a special storage site.

15.6.6 Packaging and Labelling

Like other preparations, radiopharmaceuticals must be labelled with the required information. In most situations, the label has to be attached to the shielding needed for radiation protection.

Apart from the general requirements (see Sect. 37.3) the label has to bear the following items:

- Dose in combination with the calibration time (usually the time of administration)
- Radioactivity symbol

15.6.7 Quality Control and Release

The necessity and extent of quality control of radiopharmaceuticals depends on the situation.

The quality assurance and quality control of commercially available radionuclides, non-radioactive labelling kits and ready-to-use radiopharmaceuticals as well as their release are the responsibility of the manufacturer.

The quality assurance, quality control and release of radiopharmaceuticals prepared in the radiopharmacy and their radionuclide precursors are the responsibility of the radiopharmacist.

Sometimes real time or complete quality control is not reasonably possible, especially when the radioactive dose is extremely high (e.g. loading of generators with mother radionuclide) or when the half-life of the radionuclide is very short. In those cases all feasible quality control tests are finalised after release, but always before administration to the patient. This two-step release requires a strict recall procedure in order to prevent administration when the delayed quality control results do not meet the requirements.

The frequency of quality control of hospital prepared radiopharmaceuticals may be determined on the basis of a risk assessment. When using licensed generators and kits a quality control may be limited to the first vial of every new batch, for example.

Quality control tests can be divided in physico-chemical tests (mainly radionuclidic and radiochemical purity) and biological tests (sterility, endotoxins).

A visual assessment of the appearance of the product (e.g. the colour or clarity of the solution) may be difficult because of the radiation protection (e.g. lead glass). A visual

check of the radioactive solution without radiation protection may be too dangerous. Preparations containing colloids are not clear.

15.6.7.1 Radionuclidic Purity

A radiopharmaceutical has adequate radionuclide purity when the fraction in the form of the wanted radionuclide is high enough to meet the specifications. Impurities in the finished radiopharmaceutical may arise from impurities in the target material or from fission in the reactor. Radionuclide generators could also release unwanted impurities, for example the mother nuclides. When using a ^{99m}Tc-generator the ^{99}Mo breakthrough has to be measured in the eluate. In the eluate of a ^{82}Rb-generator ^{82}Sr and ^{85}Sr breakthrough have to be checked. Impurities must be limited because they may impart the quality of scintigraphic images. In case of different biodistribution of the impurities this also may lead to increased radiation dose to the patient, which is of course undesirable and unacceptable.

15.6.7.2 Radiochemical Purity

A radiopharmaceutical has adequate radiochemical purity when the fraction in the form of the wanted chemical form is high enough to meet specifications. Radiolysis (degradation due to own radiation) and the usual factors that affect stability (light, oxidation, reduction, pH shifts), may cause incomplete or slow labelling, degradation and create radiochemical impurities. Thin layer chromatography is the most widely used technique for the analysis of radiochemical purity. HPLC techniques may also be used, for instance for the assessment of the radiochemical purity of PET radiopharmaceuticals.

15.6.7.3 Non-radioactive Impurities

Sometimes non-radioactive impurities are present in radiopharmaceuticals or their precursors. To avoid undesired effects of these impurities (instability, sometimes toxicity) their content should be limited. Limits of well-known impurities can be found in Ph. Eur. monographs.

15.6.7.4 Sterility

Finished parenteral products prepared in the radiopharmacy department must be sterile. Based on a risk analysis one may conclude that the risk of non-sterility is very low for standard radiopharmaceutical kit preparations. The risk of contamination is somewhat higher for the eluate from radionuclide generators, especially when they are used for a long period. The injection bottle on top of a ^{99m}Tc generator (sterile sodium chloride solution for injection) is changed aseptically each day; however, the inside of the generator system is not sterilised nor disinfected. For that reason it is recommended to control the microbiological quality of the generator system on a regular basis. For a ^{99m}Tc generator system this can be done at the end of the life cycle. Small volumes of the eluate are used for assuring the microbiological quality of the generator system and its elution process.

15.6.7.5 Endotoxins

The Ph. Eur. gives limits for radiopharmaceuticals in general but for some individual radiopharmaceutical preparations as well. In most radiopharmacy departments the endotoxin content of radiopharmaceutical preparations is not tested before injection. In some situations, e.g. development of a new preparation process or when using generators for longer periods of time (weeks to some months) endotoxin testing may be useful (see further Sect. 19.3.4).

15.6.7.6 Quality Control of Purchased Ready to Use Preparations

If purchased radiopharmaceuticals are used without further processing (e.g. ^{99m}Tc-radiopharmaceuticals in syringes, ^{18}F-FDG in syringes or vial, ^{123}I in capsules), their receipt and supply to the nuclear medicine department is an administrative process. On receipt the certificate of analysis is checked under responsibility of the pharmacist and the radiopharmaceuticals are registered. In most situations no physical or chemical quality control is necessary. It is important to purchase only from a certified supplier. However, auditing and qualifying the supplier may be necessary.

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Biopharmaceutics

16

Erik Frijlink, Daan Touw, and Herman Woerdenbag

Contents

Abstract

Biopharmaceutics is the field that investigates and describes everything that happens with a medicinal product and the active substance between the moment of administration, the moment it exerts its action and the moment it is eliminated from the body. Biopharmaceutics connects the physico-chemical properties of an active substance and its dosage form with its action and fate in the living organism. It encompasses pharmacokinetics, pharmacodynamics and drug delivery technology. The route of administration, the way the active substance is released from the dosage form, and the way the body handles (absorbs, distributes, metabolises and excretes) the active substance, together determine its (duration of) action, its efficacy and the occurrence of adverse effects. This chapter explains general principles of biopharmaceutics and their implications on the design of medicines. It describes the general biopharmaceutical principles that are relevant to the major routes of administration: parenteral, oromucosal, oral, rectal, dermal, nasal, pulmonary and ocular. Topics discussed include solubility and dissolution, bioavailability, partition coefficient and pH partition theory, the biopharmaceutical classification system (BCS), excipient-, food-, drug- and herb-drug interactions, first-pass effects and drug metabolism, bioequivalence and new developments in the field of advanced drug delivery systems.

Keywords

ADME • Biopharmaceutics • Bioavailability • Dosage forms • Pharmacokinetics • Routes of administration • Advanced drug delivery • Slow release

Based upon the chapter 'Biofarmacie' by Erik Frijlink, Farida Kadir and Herman Vromans in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_16,

16.1 From Medicinal Product to Effect and Beyond

16.1.1 Design of the Medicinal Product

A medicinal product (also called medicine or drug product, formulation or dosage form) is characterised by the quantitative composition (encompassing both the active substance(s) and excipients), the physico-chemical state of the active, excipients and medicinal product as a whole, as well as the structure in which the different components are present in the medicinal product. These aspects together will determine the functionality of the medicinal product and will make it more or less suitable for its intended use. Because the final physico-chemical aspects and structure of a medicinal product are often determined by the process and process conditions used during production, a reliable, robust and reproducible production is of paramount relevance for pharmaceutical preparations.

The functionality of the medicinal product can be described both in technical and biopharmaceutical terms. The technical terms encompass aspects such as stability, uniformity of dosage and microbiological quality of the product. The biopharmaceutical functionality of a medicinal product relates to aspects such as the drug release profile, suitability of the medicinal product for administration via the intended route and ability of the active substance to reach the site of action. In this chapter the basics of biopharmaceutics are described and explained in relation to the different aspects of formulation, routes of administration and therapeutic objectives.

Medicinal products exist in a variety of forms, to be used for different routes of administration, aiming at either a systemic or a local effect. To obtain a systemic effect, the oral and parenteral routes are the most frequently used. Alternatively, medicinal products can be given through rectal, transdermal, nasal or pulmonary administration to achieve a systemic effect. Rectal and pulmonary administration may also be applied for a local effect. Medicinal products administered to the eye, nose and ear are mostly used for a local effect.

16.1.2 Pharmaceutical Availability and Bioavailability

In most cases, an active substance is not administered directly at its site of action. As a consequence transport is necessary from the site of administration to the site of action. The first step in this process is the release of the active substance from the dosage form. The delicate interaction between the physico-chemical properties of the active substance and its dosage form as well as the physiological conditions at the site of release, determine the extent and rate at which release will occur. However, a medicinal product can be designed in such a way that the extent and rate of drug release are determined by the physico-chemical characteristics of the dosage form. Controlled release being obtained in this way may affect the intensity, duration and moment of the effect. It may also affect (preferably reduce) the occurrence of adverse effects.

Often, the active substance is released from its administration form in a dissolved state. If this is not the case, the active substance must first dissolve in aqueous environment after it has been released. Only in the dissolved state, can an active substance pass biological membranes separating the site of administration from the systemic circulation (the blood circulation) via which transport to the site of action occurs. The fraction of the administered active substance that dissolves in the aqueous fluid adjacent to the biological membranes and thereby becomes available for passing them is called the pharmaceutical availability. The fraction of the total amount of the administered active substance that ultimately reaches the systemic circulation in an unchanged form is called bioavailability. By definition, an intravenously injected medicine will have a bioavailability of 1.0 (or 100 %). When a medicine is administered via a different route, its bioavailability will be reduced, due to, for example, incomplete dissolution or losses during the transport of dissolved active substance to the systemic circulation.

The transport of the dissolved active substance over the membranes to the blood circulation is called absorption. The extent and rate of absorption are determined by several factors, including the size and charge of the active substance molecule, its lipophilicity, the volume available for active substance dissolution, the surface and permeability of the absorbing membrane, the presence of metabolising enzymes and, in the case of active transport, the presence of transporters. As a consequence, poor bioavailability may be caused by incomplete dissolution of the active substance, by poor permeation over the absorbing membrane, or by metabolism during absorption.

In general, the bioavailability of an active substance is largely determined by the characteristics of the active substance and the medicinal product (which may, for example, determine the dissolution rate), the chosen route of administration (different membranes show different permeability) and the administration conditions (e.g. the concomitant intake of food with oral medicine administration). If, for example, a high dose of a poorly soluble active substance is administered, the concomitant intake of two glasses of water or a meal may increase its bioavailability. If, however, an active substance is metabolised in the liver to a large extent, the oral route may be less suitable, making it worthwhile to investigate whether a sublingual (under the tongue)

or nasal route of administration may be a better alternative. Since, in contrast to the intestines, blood vessels from the tongue and the nose do not end up in the portal blood vessel system that immediately transports the active substance to the liver where it is exposed to the action of metabolising enzymes.

After absorption into the systemic circulation, transport to the site of action occurs. Once arrived, the active substance can exert its action. During and after transport as well as during and after exerting its action, distribution, metabolism and excretion of the active substance occur. These processes, together defined as the pharmacokinetic behaviour of the active substance, largely determine to what extent a medicine will be effective. The rate of absorption and elimination plus the volume of distribution determine the time and height of the peak concentration of the active substance in the blood. Therefore, they often also determine the occurrence of adverse effects.

The following medicine-related physico-chemical aspects may influence the release and absorption (bioavailability) of an active substance and thereby its final efficacy:

- The chemical form of the active substance (e.g., free acid or base, a salt, ester or other type of prodrug)
- The physical state of the active substance (e.g., particle size, crystal modification)
- The nature and quantity of excipients and their interaction with the active substance
- The dosage form (e.g., a solid dosage form or a solution)
- The route of administration (e.g., oral, parenteral, rectal, etc.)
- The pharmaceutical formulation (e.g. the medicinal product, the quantitative composition or the structure in which the active substance and excipients are present in the dosage form)

Next to these factors other aspects, related to human physiology and external factors, may affect release and absorption of the active substance too. These include, amongst others:

- The interaction with food or concomitantly administered other medicines
- The presence of enzymes that metabolise the active substance before absorption
- The volume of the fluid, available at the site where the medicine dissolves
- The presence of endogenous substances (such as bile salts) that affect the solubility of active substances
- Variations in gastro-intestinal motility
- Blood flow variations at the site of absorption

In summary, biopharmaceutics relates the physicochemical characteristics of an active substance, the functionalities and a medicinal product and the route of administration to the performance in the living organism and to the efficacy and safety of the medicinal product. The biopharmaceutical characteristics are important aspects in the design of new medicinal products. They should be considered during the different stages of research and development as well as during the full subsequent lifetime of a medicine.

To achieve the desired therapeutic effect of an active substance, an adequate administration form in relation to the chosen route of administration must be used. The current pharmaceutical-technological knowledge offers possibilities to achieve optimal absorption of an active substance. Optimal in this context means: reliable, with a reproducible fraction absorbed and, if necessary, with a desired control of the release profile. Already small variations in excipients may significantly influence the pharmaceutical and biological availability and hence the therapeutic and adverse effects of a medicine. This applies to systemic as well as local administration. Furthermore, it is to be realised that the equivalence of these aspects may be of paramount importance for generic substitution.

16.1.3 Pharmacokinetics, Pharmacodynamics and Toxicology

Several aspects of the pharmacodynamic and toxicological behaviour of an active substance are highly relevant to the desired biopharmaceutical characteristics of a medicinal product. The efficacy of an active substance is determined by the intrinsic receptor affinity of the compound and the receptor occupancy. Since the last parameter is difficult to measure in man, drug blood concentrations (as measured in whole blood, serum or plasma) are usually taken as a surrogate parameter. This is based on the assumption that the drug concentration in the blood of a patient is related to the drug concentration at the site of action (and thereby the receptor occupancy). As well as the relationship between blood levels and therapeutic action, also blood levels and toxic action of a medicine are related. Based on this the concept of the therapeutic window has been defined.

The therapeutic window of an active substance is the blood concentration range within which the desired therapeutic effect will occur without serious side effects. The lower limit of the therapeutic window is the so-called minimal effective concentration (MEC). This is the lowest blood concentration of the active substance that exerts a therapeutic effect. The upper limit of the therapeutic window is the maximal tolerable concentration (MTC). When the MTC is reached or exceeded, unacceptable adverse effects of the active substance are likely to occur.

Figure 16.1 shows the blood concentration (can be either on linear as well as on log-scale) versus time curve of an orally administered medicine. It also shows the MEC and MTC. During the initial phase of the curve the active substance is being absorbed from the intestinal lumen into the

blood. At time T_{max} the maximum blood concentration (C_{max}) is reached. At that time the absorption rate has reduced (due to depletion of the active substance from the site of absorption) to such an extent that the elimination rate of the active from the body exceeds the absorption rate. From this moment on the blood drug concentration will therefore decrease. This process is characterised by the elimination half-life of the active substance ($t_{½}$). The duration of drug action is determined by the period during which the blood concentration exceeds the MEC. The total amount of absorbed active substance (bioavailability) is characterised by the area under the curve of the blood concentration versus time curve, relative to the total administered dose.

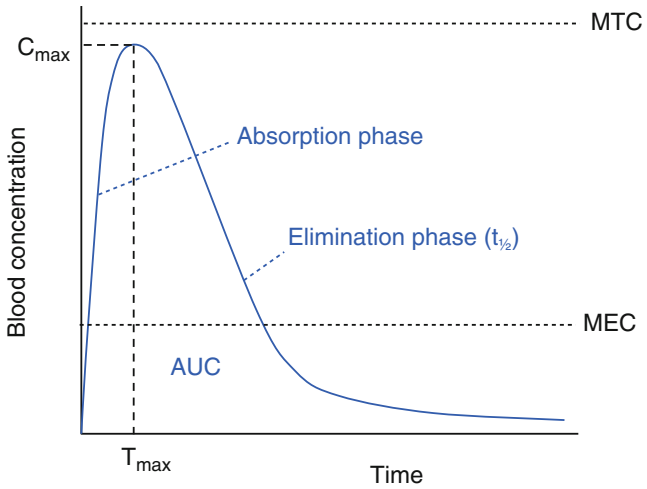

Fig. 16.1 Blood concentration (log-scale) versus time curve of an orally administered medicine

It is the major objective of any medicinal product to yield blood levels of the active substance within the therapeutic window for the period during which the therapeutic effect is desired. At the same time the C_{max} should not exceed the MTC and the medicine administration frequency should remain reasonable, preferably not more than two to three times a day. However, this objective is often not easily reached, since the degree of absorption, the absorption and elimination rates, the therapeutic window as well as the intrinsic pharmacological and toxicological activities of an active substance are varying and interactions may occur.

For example, an active substance with a longer elimination half-life may have the advantage of a lower dosing frequency. However, due to the lower elimination rate significant amounts of active substance may still be present in the body when the next dose is administered. Therefore the prescribed dose must be low and it may take several subsequent administrations before the pharmacokinetic equilibrium (the 'steady state') is reached and both peak and trough concentration levels will be within the therapeutic window. For medicines that are administered once daily this may even take several days and a booster dose may be needed to obtain a faster therapeutic effect. Active substances possessing a narrow therapeutic window often require therapeutic drug monitoring (TDM). Alternatively, their rate of absorption may need to be regulated through the use of technologically advanced controlled release products. If an active substance has to be administered frequently, because of fast elimination, the use of a slow release product may be considered. This technology may also be considered when toxic effects occur due to peak concentration levels above the MTC.

Concentration versus time relationships (Fig. 16.1) can be translated into concentration versus effect relationships, both for desired and for adverse drug effects (Fig. 16.2). Within

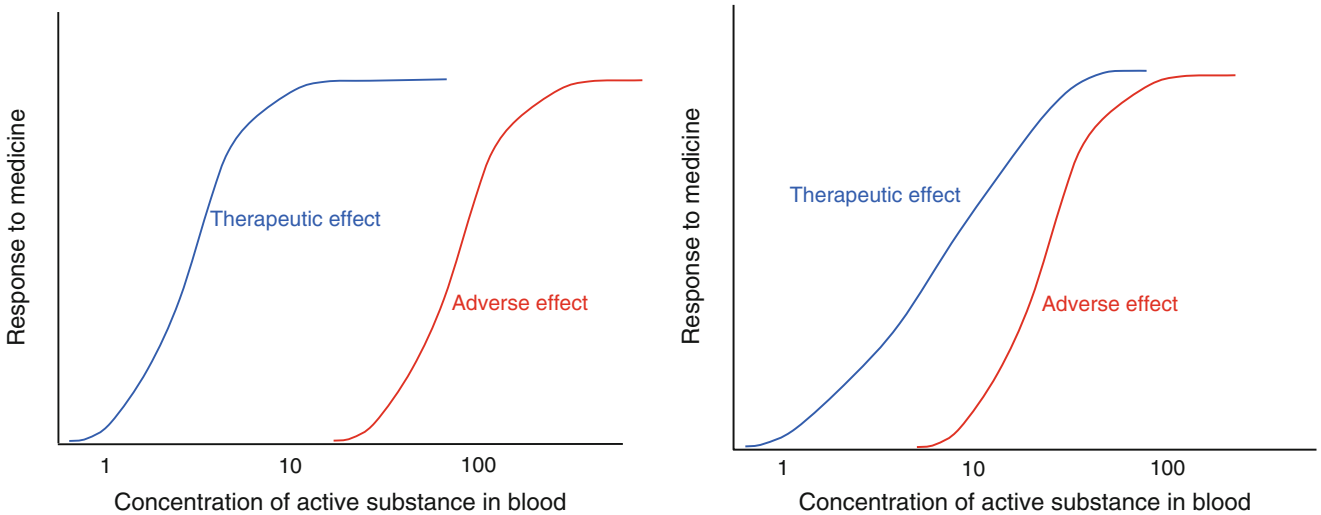

Fig. 16.2 Concentration versus effect relationship of different active substances. On the *left hand side* an active substance with a steep dose response and a large therapeutic window is shown and on the *right hand side* an active with a less steep response curve and a smaller safety margin

Effect of variations in bioavailability on drug efficacy and safety and the relevance of variations in drug sensitivity.

Figure 16.3 (left panel) shows the effects of an increased bioavailability of an active substance on safety and efficacy. This may happen when a given active substance ('drug A') interacts with another active substance ('drug B') on the level of transporting enzymes. If, for instance, drug B has a P-glycoprotein (P-gp) inhibiting effect and drug A is excreted back into the intestinal lumen by P-gp after absorption, this interaction will lead to an increase in the blood concentration and the bioavailability of drug A. However, the efficacy of drug A hardly increases as a result of this interaction, since the efficacy was already at its maximum before the interaction with drug B occurred (already at the lower concentration the occupancy of receptors causing the therapeutic effect was complete). Conversely, more adverse effects of drug A will occur, because of the increased blood levels leading to an increased occupancy of those receptors that are causing the adverse effects.

In Fig. 16.3 (right panel) the effect of a change in bioavailability is shown in relation to individual differences in drug sensitivity. The drug blood concentration versus effect relationships of the same active substance in two different patients are given in this figure. Patient A is more sensitive to the active substance than patient B. Due to an interaction between the medicine and food less active is absorbed (e.g. the effect of milk on tetracycline) in both patients. The bioavailability is reduced and the lower blood concentrations are reduced by about 30 %. For patient A this will not result in a significant change in efficacy. For the less sensitive patient B however, this interaction will lead to a more than 50 % reduction in efficacy. Such a reduction may, for example, lead to the emergence of drug resistant bacteria in the case of antibiotic therapy.

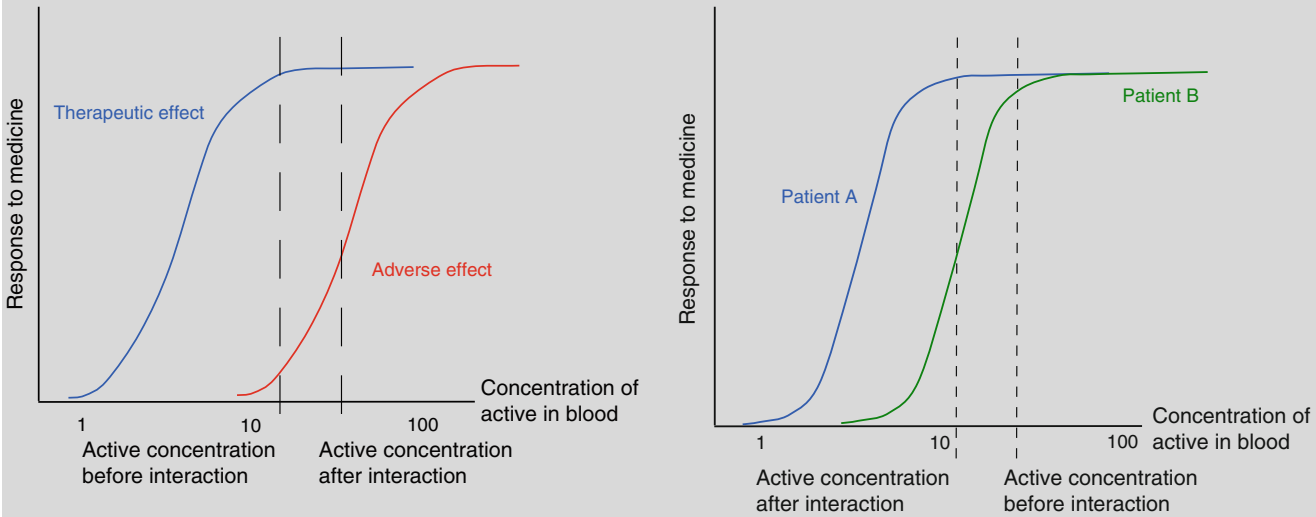

Fig. 16.3 Relationship between response to a medicine and blood concentration. The *left* figure shows the effect of an increased absorption on efficacy and safety. The *right* figure shows the effect that variation in bioavailability may have in patients with different sensitivity for an active substance

the therapeutic window, a low drug blood concentration will generally lead to a low efficacy and increasing the blood concentration will increase efficacy. Moreover, it is considered advantageous when the maximum therapeutic effect is reached already at a concentration that is significantly below the MTC since this would yield a broad safety margin for the patient. This is reflected in an increased margin between the therapeutic and the adverse effect in the curve.

Whether or not a concentration-effect curve is desired to be steep or flat depends on the drug action and on the intended therapy. For example, for an antihypertensive medicine it may be desirable to tune the effect and a somewhat flatter profile of the curve is preferred. For other situations, such as anti-migraine therapy or infections, tuning the effect is not or less relevant. A steeper curve may have the advantage that the desired effect will be obtained sooner, provided

that the maximum effect is reached at concentrations considerably below the MTC.

The impact of variations in the bioavailability on the efficacy and safety of an active substance can be easily understood from these figures. The effect of individual variations in drug sensitivity in relation to variations in drug absorption can also be demonstrated. Examples are given in the box.

16.1.4 Solubility, Dissolution and Partition Coefficient

For many medicinal products dissolution in an aqueous environment (e.g. the fluids of the gastro-intestinal tract or mucosal lining fluids in the airways) is the major release mechanism of the active substance. The dissolved concentration of the active substance is the driving force for all diffusion-based drug transport mechanisms, since only the dissolved active substance is able to pass the absorbing membranes. Therefore the aqueous solubility of an active substance and the dissolution rate of the active substance from a medicinal product are considered to be highly relevant characteristics. To a large extent they determine the performance of a medicinal product in terms of bioavailability, efficacy and safety. The fundamentals of solubility and dissolution (rate) are described in Sect. 18.1.

The solubility of an active substance and the dissolution rate of a medicinal product can be varied by changing either the characteristics that relate to the active substance (such as particle size, salt form, crystalline form, the use of a pro-drug like an ester) or characteristics of the medicinal product (such as the use of disintegrants, complex-forming agents like cyclodextrins or polymers that form highly viscous gels, and the application of diffusion limiting coatings). See the box for examples.

There are numerous examples of medicinal products in which dissolution rate enhancing technologies are applied to increase the bioavailability or absorption rate of an active substance. Cardiac glycosides should be given as micronised particles in a solid oral dosage form because otherwise their dissolution rate and hence their bioavailability is too low. Piroxicam was shown to be absorbed faster when given as a cyclodextrin complex, which increases the dissolution rate. Similarly, the bioavailability of albendazole as a cyclodextrin complex was increased compared to crystalline non-complexed albendazole, based on the same mechanism. And finally, the bioavailability of amorphous chloramphenicol is higher than that of crystalline chloramphenicol.

Biological factors may change the solubility or dissolution rate of the active substance from the medicinal product as well. The residence time in the stomach may increase the dissolution of poorly water-soluble active substances and change their bioavailability. The pH in the stomach or the intestine may influence dissolution rates of acidic or basic active substances whose solubility is pH-dependent. Bile salts may increase the dissolution rate and thereby the absorption of poorly water-soluble active substances such as ciclosporine, phenytoin, levothyroxine and tacrolimus. Though, it has been shown that the association with bile acids reduces the absorption of the hydrophilic beta-blocker atenolol.

It is not only the solubility in aqueous solutions that may affect the biopharmaceutical behaviour of an active substance. The solubility in non-polar solvents is of importance too. The solubility in a lipid phase is of relevance to the passive transport of the substance over lipid membranes, a process that plays an important role in the absorption of many drugs. In order to quantify the lipophilicity of an active substance in relation to its aqueous solubility the concept of the partition coefficient was developed. The partition coefficient is defined as the quantitative distribution ratio of a dissolved substance over two immiscible liquids at equilibrium. In the pharmaceutical sciences the ratio of the concentrations in an aqueous phase (water or aqueous buffer solutions) and a lipid phase (e.g. n-octanol) is often considered. For this purpose the so called log P value has been defined. The partition coefficient between an aqueous and a lipid phase (log $P_{o/w}$ value) of non-ionised substances is defined according to (16.1):

$$\log P_{o/w} = \log (C_{so}/C_{sw}) \qquad (16.1)$$

In this equation C_{sw} is the saturation concentration of the active substance in the aqueous phase and C_{so} is the saturation concentration in the lipid phase. In general, the partition coefficient between an aqueous buffer or water and n-octanol is determined.

For active substances that can be ionised the distribution coefficient (log D) has been defined. The oil-water distribution coefficient (log $D_{o/w}$ value) for a substance is presented in (16.2):

$$\log D_{o/w} = \log \left(C_o/\left(C_w{}^i + C_w{}^n\right)\right) \qquad (16.2)$$

In this equation C_o is the concentration of the substance in the lipid phase, $C_w{}^i$ is the concentration of the ionised substance in the aqueous buffer at a specific pH and $C_w{}^n$ is the concentration of the non-ionised substance at the same pH. From the definition it follows that the distribution coefficient varies with the pH of the aqueous buffer.

16.1.5 Absorption and Bioavailability

Poor aqueous solubility or a low dissolution rate or both may be the cause of poor bioavailability. For poorly water-soluble active substances, the amount and composition of endogenous aqueous fluid, present at the site of absorption will play an important role. In the stomach and in the small intestine there is ample aqueous fluid available, but in the mouth, the nose or the rectum a volume of only a few millilitres is available.

16.1.5.1 Absorption

After being dissolved the next step is the absorption, so passing the biological membrane. The surface area and type of membrane are major determinants for the extent and rate of absorption. Active substances may be transported over the membrane passively or actively. Absorption via passive transport may occur as paracellular transport through the interstitial spaces between the cells lining the absorptive membrane. For absorption by passive diffusion across a biological membrane, the concentration gradient is the driving force according to Fick's diffusion law. A high external (or luminal) concentration (dissolved active substance at the site of absorption), will increase the absorption rate over the biological membrane. The continuous blood flow in combination with protein binding of the active substance will keep the internal concentration low and maintain the concentration gradient.

This transport mechanism is typical for the absorption via mucosal membranes such as the intestinal tract, the intraoral (sublingual or buccal), nasal or pulmonary membranes. The size of the interstitial spaces in mucosal membranes may vary in size between around 0.4 nm for the duodenum up to about 4 nm for the alveolar membranes in the lung. In general the absorption through the interstitial space is limited to small hydrophilic molecules such as nitroglycerin after sublingual administration. The absorption of smaller proteins (up to a molecular weight of 20 kDa) via the alveolar membrane in the lung is an exception to this rule. The larger interstitial spaces between the alveolar type I cells (covering 93 % of the alveolar surface) enable what may be the only non-parenteral route for the administration of proteins.

Passive transport of lipophilic substances may occur via the fluid bilayer membrane of the cells lining the membranes. This transcellular route is the most important route for membrane passage of active substances. This transport mechanism is not only driven by the concentration gradient over the absorptive membrane, but also by the oil to water partition coefficient of the active substance (expressed as the octanol-water partition coefficient, which describes the ratio of the substance's solubility in aqueous and fatty phases, see Sect. 16.1.9). More lipophilic substances will be transported faster over the lipophilic absorption membrane than those with a more hydrophilic character. In general, lipophilic active substances will not accumulate into the lipid parts of the absorption membrane because the continuous blood flow in combination with protein binding of the active substance will keep the internal concentration low. They will also maintain the concentration gradient at a maximum causing rapid uptake of the substance into the systemic circulation.

The lipophilicity of an active substance, and thereby its tendency to pass lipophilic membranes, can be described in terms of the octanol-water partition coefficient and the polar surface area. The octanol-water partition coefficient, the log P value, should be within the 0.4–5.6 range and preferably below 3. The polar surface area of a compound is the total sum of the surface of the polar atoms in the molecule. In general this will refer to the oxygen and nitrogen atoms in the molecules and include the hydrogen atoms attached. Co-inclusion of sulfur and phosphor atoms in the calculations was shown to add little to the predictive value of the results. When the polar surface area of a molecule exceeds 140 $Å^2$ the molecule is too hydrophilic and considered to be unsuitable for absorption after oral administration. For special barriers such as the highly lipophilic blood brain barrier the threshold is 60 $Å^2$.

Apart from the partition coefficient and the polar surface area, several other molecular characteristics predict membrane permeation; major determinants are:

- Molecular weight, which is preferably below 300–500 Da
- Number of H-bond donors and H-bond acceptors, not more than 3 donors and not more than 3 acceptors
- Number of rotatable bond bonds, not more than 3
- Number of non-hydrogen atoms

Furthermore, a limited number of active substances are absorbed by active transcellular transport mechanisms, a process that may even occur opposing a concentration gradient. This mechanism is characterised by the involvement of transporter enzymes able to transport the molecules of the active substance over the intestinal membrane. An example is the absorption of angiotensin converting enzyme inhibitors such as lisinopril and enalapril, which is mediated by the di/tri-peptide transporter protein (PepT1). Competition for or induction of transport enzymes may have a significant effect on the absorption of these active substances. This makes them sensitive for drug-drug or drug-food interactions that may significantly affect the drug absorption, and thereby drug efficacy and safety.

16.1.5.2 Bioavailability

The bioavailability of an active substance is defined as the fraction of the administered active substance that enters the systemic circulation (for oral administration the circulation

beyond the liver) in unchanged form. The absolute bioavailability of an active substance is calculated from the area under the curve (AUC) of the blood concentration of unchanged drug versus time profile found following intravenous administration (by definition 100 % bioavailability) and the AUC found following the chosen administration route, corrected for the dose (D). The bioavailability after, for example, oral administration (F_{or}) is thus calculated from (16.3):

$$F_{or} = [(AUC_{or}. D_{iv})/(AUC_{iv}. D_{or})] . 100\% \qquad (16.3)$$

Differences in bioavailability of different medicinal products or after administration via different routes can also be deduced from the ratio of the AUCs of the blood concentration versus time curves.

As well as the total absorbed fraction, the absorption rate is also an important aspect of bioavailability. The absorption rate is characterised from the maximum blood concentration and the time at which the maximum concentration occurs in the concentration versus time curve.

The absorption rate of an active substance is relevant to the therapeutic effect for various reasons. If an active substance is used in an acute situation (e.g. epileptic insult, asthmatic attack, sleep induction, pain killing), a high absorption rate is preferred. A formulation design in which the active substance is already dissolved, may be useful in such case. A prolonged effect can be achieved however by a dosage form from which an active substance is released slowly (sustained release). Finally, if an active substance has a longer residence time in the absorbing organs, the bioavailability may be negatively influenced by, for example, enzymatic or chemical degradation.

16.1.5.3 Dose Number and Biopharmaceutical Classification System

The solubility of an active substance in the different body fluids and the efficacy of the absorption process, together with the dose determine the bioavailability of a medicine. The dose number (DN) is a dimensionless parameter that links solubility (C_s) to dose (D) and volume available for dissolution (V) during the absorption process. The dose number can be calculated from (16.4):

$$DN = D . (C_s. V)^{-1} \qquad (16.4)$$

When the dose number is less than 0.1 dissolution is not expected to affect the absorption process, whereas at a dose number above 10 dissolution is most likely to decrease the absorption (rate) of an active substance. In general, solubilisation technology has to be applied for such compounds. When the dose number is between 0.1 and 10 the effect of dissolution on drug absorption should be investigated, to find out whether the bioavailability is affected by the dissolution behaviour.

The corticosteroid dexamethasone has a poor aqueous solubility of 89 microgram/mL. It is given by the oral route for different diseases. When the medicine is given with a glass of water the oral route offers a dissolution volume of about 500 mL in the stomach. When the 4 mg dose used in rheumatic diseases is given by the oral route the dose number will be 0.09 and no major dissolution problems are to be expected. However, when dexamethasone is used in pyodermia gangrenosum the dose has to be 300 mg. At this dose, the dose number will be 6.7. This is close to 10 and the dissolution behaviour of the medicinal product has to be investigated in order to prevent incomplete absorption of the dexamethasone.

The biopharmaceutical classification system (BCS) not only considers solubility but also considers the permeability of the absorbing membrane. This system classifies active substances based on their water-solubility in relation to their dose and the route of administration and to their permeability over the absorptive membranes. The BCS divides active substances into four classes:

- Class I: high solubility, high permeability
- Class II: low solubility, high permeability
- Class III: high solubility, low permeability
- Class IV: low solubility, low permeability

This classification system is used to characterise potential problems related to bioavailability and bioequivalence of an active substance [1].

The variable solubility is determined by the intrinsic solubility of the active substance in the aqueous fluids available for dissolution, the dose at which the medicine is given and the volume of liquid that is available for a certain route of administration. A medicine that is administered orally will have a larger volume of liquid available (250–750 mL) for dissolution than a medicine that is administered via the sublingual or rectal route (5–15 mL) and the composition of the different fluids varies. As a result, dissolution problems are to be expected for the sublingual or rectal route at lower doses than for the oral route. In general an active substance is considered to be highly soluble when the highest dose applied dissolves in about one third of the total available volume for dissolution. For the oral route, for example, an active substance is considered highly soluble when the highest dose dissolves in 250 mL of an aqueous liquid with a pH between 1.0 and 7.5.

The variable permeability is determined by the absorption of the dissolved active substance over the membrane. This may be measured by the direct assessment of the mass transfer (rate) over the human intestinal membrane or predicted from relevant animal models or *in vitro* epithelial cell culture models. An active substance is considered highly permeable when the extent of absorption is 90 % or higher.

Knowledge of the bioavailability and absorption rate of an active substance is important because these are important determinants of efficacy and safety. Large variations in bioavailability or absorption rate may, in the case of decreased absorption (rate), result in insufficient efficacy. In the case of unexpectedly high absorption it may lead to toxicity or serious adverse effects. Quantitative data on the bioavailability and absorption rate are necessary to evaluate the equivalence or non-equivalence between different medicinal products with the same active substance. These data may be used as surrogate parameters to establish efficacy and safety of a (generic) product.

According to the EMA two products are considered to be bioequivalent when they contain the same active substance and when their respective bioavailabilities (rate and extent) after administration in the same molar dose and via the same route, lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy. The design and number of studies that is to be carried out to establish bioequivalence depends on the physico-chemical and pharmacokinetic properties of the active substance. In this respect reference is made to the BCS classification of the active substance. For BCS class I active substances it may even be possible to obtain a waiver for the *in vivo* studies (a so-called biowaiver), whereas for the active substances showing more complex pharmacokinetic behaviour extensive studies are to be carried out. In general bioequivalence will be determined from the parameters C_{max} and AUC. Two products are considered to be bioequivalent when the 90 % confidence interval of the ratio of test and reference product falls within the 85–125 % acceptance interval. However, for the required design of the bioequivalence study and statistical evaluation details for a specific active substance reference is made to the appropriate (most recent) guideline on this subject [2, 3].

When in daily practice substitution (e.g. by a generic product) is considered, bioequivalence is of course the first parameter to evaluate. However, other aspects of medicine's use related to both the product and the condition of the patient are to be taken into consideration as well. Among these are:

- For active substances that have a narrow therapeutic window or non-linear kinetics substitution is not advised since even the smallest variations in the product and its performance may result in significant fluctuations in effect or safety. Examples of such active substances include: ciclosporin, tacrolimus, digoxin, ergotamine, levothyroxine, capecitabine and phenytoin.
- Safety issues to be considered are the exact equivalence of the products (especially for 'biologicals' this may pose a problem) and the risk of allergy or intolerance for a specific excipient (e.g. colouring agents).
- When specific administration devices (affecting parameters of relevance to the performance characteristics such as efficacy and safety of a medicinal product) are used substitution should not occur. Different dry powder inhalers, for example, generate aerosols of significantly different particle size. As a result, relevant variations may occur in lung deposition of the active substance. Therefore substitution of these types of products (e.g. dry powder inhalers) should not occur.
- The appearance of the product. When large differences in appearance between both products exist, substitution may confuse the patient.
- The performance characteristics and handling of both medicinal products should be similar (e.g. for auto-injectors, or the occurrence of a score on the tablet that allows for dividing a dose).

Medicinal products administered at a specific site to obtain a local effect should preferably not be absorbed systemically. However, significant amounts of active substance can be absorbed, e.g. after application on the skin. Removal of locally acting active substances from the site of action by systemic absorption may result in systemic effects that can be considered as adverse effects. After nasal, ocular, pulmonary and rectal administration of active substances for a local effect, absorption into the systemic circulation is likely to occur. This may cause adverse effects and limit the duration of the desired drug effect. Conversely it should be realised that the systemic route is often also the main route for clearance of the active substance from the site of administration. The bioavailability of locally acting medicines is, of course, not determined by the amount of active substance that reaches the systemic circulation. As an alternative the fraction of the active substance that is dissolved in the aqueous fluids at the site of application is usually taken as a measure for the bioavailability.

16.1.6 Excipient and Food Interactions

An active substance, although initially released from its dosage form (and dissolved), may become unavailable for absorption due to reactions with other medicines or food components [4]. An example is the formation of insoluble complexes of tetracycline with calcium or aluminium ions from antacids or milk products. Interaction (chelation or binding) with iron ions leads to a reduced absorption for a variety of active substances such as doxycycline, penicillamine, methyldopa and ciprofloxacin. The absorption of active substances showing pH-dependent dissolution behaviour may be influenced by medicines that influence the gastric pH, such as H_2-antagonists, proton pump inhibitors and antacids. Antimycotic active substances such as ketoconazole or itraconazole dissolve better in acidic fluids. Therefore their bioavailability may be increased by the concomitant use of an acidic drink like cola, whereas the concomitant use of antacids or proton pump inhibitors is likely to reduce the bioavailability. Concomitant use of milk may increase the dissolution of acidic active substances, whereas fats from food may increase the bioavailability of lipophilic active substances like albendazole and griseofulvin.

In dermal preparations ion-pair formation between ionic surfactants and an active substance may reduce the local availability of the active substance. An example is the interaction between the anion laurylsulfate (from the surfactant sodium laurylsulfate) and the cationic neomycine or tetracycline in creams.

It is important that the (clinical) pharmacist always provides appropriate advice to the patient about how to take a medicine and warns against the concomitant use of other medicines or certain foods, in cases where interactions may occur. The potential risk of interactions may even be of greater clinical importance when they occur at the level of the metabolism of the active substance. This issue is discussed in Sect. 16.1.13.

16.1.7 Stability of the Active Substance in the Physiological Environment

Several active substances are unstable in an acidic environment and will degrade when in contact with gastric juice. Examples are omeprazole, pantoprazole, erythromycin and pancreatic enzymes. Such active substances are formulated in a tablet or pellets covered with an acid-resistant layer, a so-called enteric coating. The acidic nature of the polymers used in these coatings prevents dissolution in the gastric environment. The coating will dissolve in the small intestine (with higher pH values), after which the active substance is released. Alternatively, the active substance may be used in the form of a more stable salt, for example erythromycin ethylsuccinate.

Enteric coated products exist in various presentation forms. They include tablets surrounded with the coating, coated pellets in a capsule or coated pellets compressed into a tablet (see Sect. 4.10). This last form sets specific requirements to the quality of the coating around the pellets since the integrity of this coating must not be compromised during the tablet compaction process. Depending on the presentation form, tablet breaking may or may not be allowed. Tablets covered with an enteric coating may never be broken, whereas controlled release tablets produced from coated pellets may be divided or sometimes even dispersed for a short period of time in liquids or semisolid food (custard, yoghurt). The same can be done with capsules containing coated pellets. However, coated products should never be longer than 5 min in drinks or food before use. Crushing is not allowed for any controlled release formulation.

Metabolic instability of the active substance in the physiological environment may reduce bioavailability especially after oral administration. Enzymatic degradation of an active substance in the lumen of the stomach or intestine may reduce the amount of active substance available for absorption, whereas after absorption enzymes in the intestinal wall and the liver may reduce the bioavailability. This is called the first-pass effect.

After intramuscular or subcutaneous injection, bioavailability may become reduced because of enzymatic breakdown of the active substance at the site of injection.

16.1.8 First-Pass Effect

Following oral administration and absorption from the intestine, an active substance passes the intestinal wall and the liver. During uptake from the gastro-intestinal tract, enzymes present in the intestinal lumen or in cells of the intestinal wall can metabolise an active substance. Subsequently the absorbed active substance is transported to the liver by the portal vein system. During the first passage through the liver, liver enzymes may metabolise another part of the active substance. The metabolic degradation during the first passage of intestine and liver may significantly reduce the bioavailability since it occurs before the active substance is distributed over the entire body. This particular loss of active substance, after absorption but before distribution, is called the first-pass effect.

The extent of a first-pass effect of an active substance depends on the dose and absorption rate in relation to the enzymatic capacity. Moreover, the first-pass effect can be influenced by the concomitant use of food, which may affect the absorption rate or induce or inhibit the enzymatic

degradation of certain active substances. From this perspective it is clear that the bioavailability of an active substance can be optimised by taking a medicine at the appropriate time, e.g. before, during or after a meal. Examples of active substances that undergo a high first-pass effect after oral administration include: amiodarone, ciclosporin, 6-mercaptopurin, metoprolol, midazolam, morphine, nifedipine, propranolol, saquinavir, tacrolimus, terbutaline and verapamil.

The hepatic first-pass effect can be circumvented by giving a medicine through a route of administration that does not primarily absorb the active substance via the portal vein system, such as an intramuscular or subcutaneous injection, sublingual or nasal administration or via the pulmonary route. The rectal route is often mentioned as an option too. However, since two of the three rectal veins do end up in the portal vein, the maximum effect of this route will be a reduction of the first-pass affect by only about 30 %.

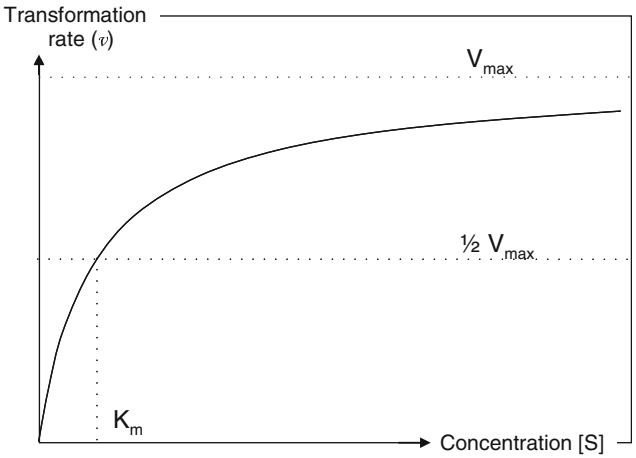

Fig. 16.4 Relationship between the substrate concentration [S] and rate of transformation [ν]

16.1.8.1 First-pass metabolism and controlled release products

In order to understand the relevance of first-pass metabolism for the formulation of controlled release products, one should have a basic understanding of enzyme kinetics. Enzyme kinetics are described using the Michaelis-Menten equation (16.5). This equation describes the rate of transformation of a substrate (the active substance) by an enzyme.

$$\nu = V_{max}.[S]/(K_m + [S]) \qquad (16.5)$$

In this equation ν is the enzymatic reaction rate, V_{max} represents the maximum transformation rate (the rate achieved at complete saturation of the enzymes), [S] is the substrate concentration and K_m the substrate concentration at $½V_{max}$. Figure 16.4 shows the relationship between the substrate (active substance) concentration and the transformation rate.

At low concentrations an enzymatic system is able to efficiently break down the presented active substance. When the concentration of active substance (substrate) rises, the transformation rate will increase proportionally to the increase in concentration of active substance. As a result the relative amount of active that is metabolised will remain the same. However, as the concentration increases further (significantly beyond the K_m) the enzymatic system will get saturated and the increase in rate of transformation will no longer be proportional to the increase in concentration. As a result relatively more active substance will escape from transformation by the metabolic enzymes.

This is exactly what happens when an active substance that suffers from high first-pass metabolism is given orally. After absorption from the intestinal tract the active substance is transported with the hepatic blood flow to the liver. The concentration in the hepatic blood determines the transformation rate and thereby the (relative) amount of active substance that will escape the metabolism and will become bioavailable. At lower concentrations the enzymatic system will be far from saturated and bioavailability will thus be low. If, in contrast, higher doses are given, concentrations levels far beyond the K_m may be present in the portal blood and a dose-dependent increase in bioavailability may occur (non-linear absorption kinetics).

When an active substance at a specific dose already generates portal blood concentrations around or even somewhat beyond the K_m even a minor increase in dose may already cause a significant increase in bioavailability. But even a new formulation with the same dose that dissolves somewhat faster may result in a faster absorption and thus in higher concentrations in the portal blood, which may lead to an increased bioavailability.

Conversely, if an immediate release product with a given dose yields a reasonable bioavailability (in spite of a significant hepatic first-pass metabolism) because the portal concentrations generated by the immediate release product are far beyond the K_m, one can easily image what the effect of a slow release formulation would be. Even although the dose may be higher, the release of the active substance and the subsequent absorption are slower. Consequently, significantly lower concentrations will occur in the portal blood, the enzymatic system will be less saturated and lower amounts of active substance will escape from the enzymatic degradation in the liver. At the end this may result in significant reductions in the bioavailability. It is for this reason that caution should be exercised during the development of slow release products of active substances that exhibit a significant first-pass effect.

In Fig. 16.5 the effect of a variable dose on the relative bioavailability of an active substance with a high first-pass metabolism is presented as well as the effect of absorption

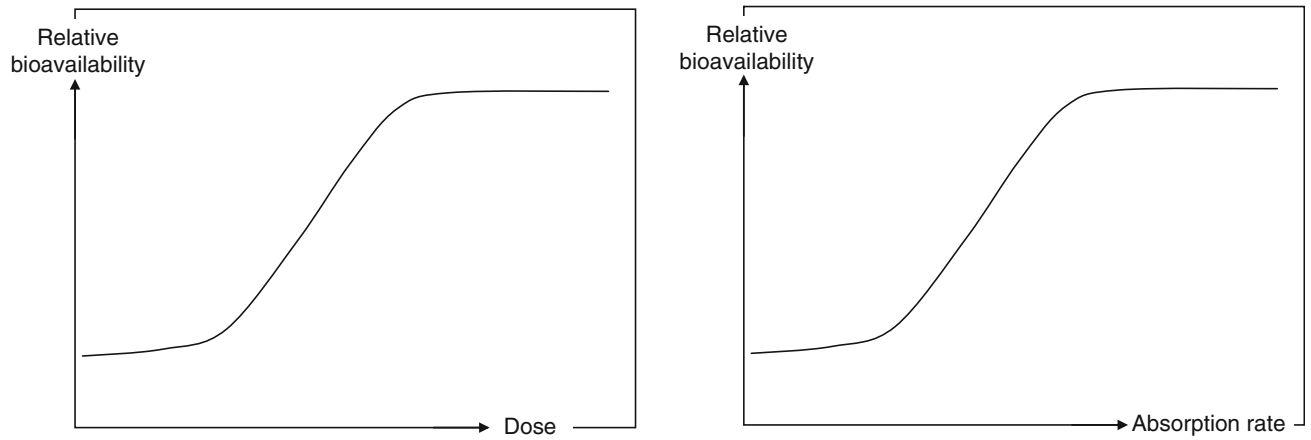

Fig. 16.5 Effect of the dose (*left*) and the absorption rate (*right*) on the relative bioavailability

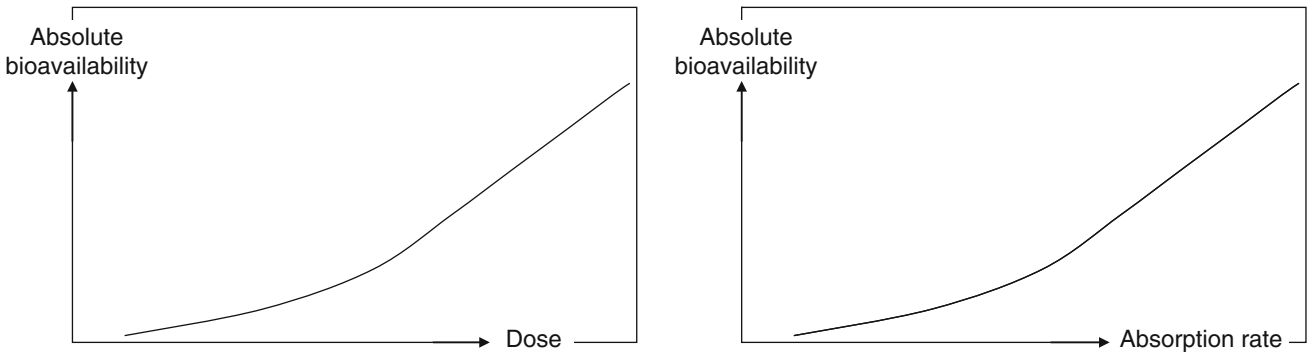

Fig. 16.6 Effect of the dose (*left*) and the absorption rate (*right*) on the absolute bioavailability

rate of a certain dose on the bioavailability of an active substance with a high first-pass metabolism. It is assumed that the dissolution rate of the active substance is not affected by the dose.

The effects of dose and absorption rate on the absolute bioavailability are presented in Fig. 16.6.

The phenomena described above clearly illustrate the significant effects on bioavailability that even small variations in absorption rate may cause. It should be realised that such small variations may easily occur upon formulation changes or due to food effects on dissolution and/or absorption rate.

16.1.9 Charge and the pH Partition Theory

Since the absorptive membrane is a lipophilic barrier, active substances are generally absorbed in a form that is able to pass lipophilic barriers. Therefore the difference in partition between the oil and water phase is a major driving force for the absorption process. Often the octanol-water partition coefficient is used to quantitate this (see Sect. 16.1.4). Active substances with a high partition coefficient will be absorbed rapidly once they are dissolved. Weak acids and weak bases are usually absorbed in their non-ionised form since this form has a much higher partition coefficient than the ionised form as follows from the distribution coefficient. The driving force of the passive absorption process is the concentration gradient of the non-ionised active substance. The pH partition theory states that the non-ionised fraction of a weak acid or a weak base is determined by the pK_a of the active substance and the pH of the surrounding environment. The non-ionised fraction of an active substance can be calculated using the Henderson-Hasselbalch equation, which after rearrangement looks for an acid as:

$$\text{Non-ionised fraction} = \left[1 + 10^{\text{pH-pKa}}\right]^{-1} \qquad (16.6)$$

For a base the equation is:

$$\text{Non-ionised fraction} = \left[1 + 10^{\text{pKa-pH}}\right]^{-1} \qquad (16.7)$$

The equations 16.6 and 16.7 show that for a weak acid the highest non-ionised fractions exist in an acid environment,

whereas a more alkaline environment will result in a higher non-ionised fraction of basic active substances. However, one should realise that the water-solubility of the ionised from is significantly higher than of the non-ionised form. This contradiction causes one of the major problems in medicine formulation and bioavailability. An environment in which the majority of the active substance is ionised is required in order to obtain a fast dissolution, whereas an environment in which the active substance is largely non-ionised is required for rapid membrane passage.

Fully ionised active substances, for which no specific carrier is available in the membrane, are generally too hydrophilic to be absorbed from the gastro-intestinal tract. Not many quaternary ammonium compounds are available in a non-ionised form in the gastro-intestinal tract after oral administration due to their high pK_a. These active substances are therefore only administered as an injection. Other active substances for which ionisation may hamper absorption after oral administration are those active substances that contain multiple H-bond acceptors and H-bond donors with varying pK_a values. Some of these active substances may not exist in a non-ionised form at any of the pH values that occur in the gastro-intestinal tract, which may significantly reduce their bioavailability after oral administration. An example is the angiotensin II inhibitor eprosartan (chemical structure shown in Fig. 16.7): an active substance with two carboxylic acid and two amine functions. The oral bioavailability of eprosartan is only 13–15 %. The limited oral bioavailability is explained by both the pH dependent dissolution behaviour of eprosartan in combination with the degree of ionisation of the dissolved active substance at the different pH values encountered in the gastro-intestinal tract.

It is also important to know that the acid-base equilibrium adjusts rapidly. If a non-ionised form of an active substance has a high partition coefficient, this may compensate for the presence of lower fractions of non-ionised active substance at the absorption site. Due to the fast absorption of the small fraction of non-ionised active substance in the vicinity of the absorbing membrane a continuous de-ionisation of ionised active substance will occur as a result of the continuous equilibrium adjustment. In this way even active substances with somewhat lower non-ionised fractions at the absorption site (active substances possessing only a single ionisable group) may still show a considerable absorption rate.

After being taken up over the membrane the second step in the active substance absorption process is the transport of the active substance into the blood. Again the concentration gradient and partition coefficient will be the rate determining factors for passive transport. However, even for lipophilic active substances the transport to the blood will be rather fast. This is caused by the continuous refreshment of the blood, keeping the concentration difference at a maximum, and by the binding of the active substances to proteins and cells in the blood. Therefore transport of active substances from the absorption membrane into the blood will in general not be the rate-limiting step in the absorption process.

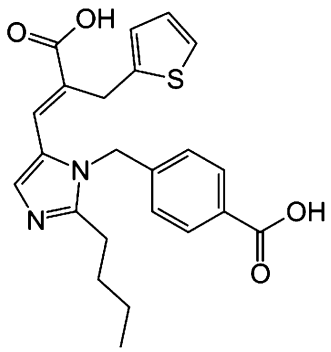

Fig. 16.7 Chemical structure of eprosartan

16.1.10 Distribution

Active substances are often distributed over the body and tissues via the blood. Interactions at the level of protein binding in blood are possible, for instance with another active substance competing for binding sites on the protein. This may result in different drug concentrations in various tissues since the free concentration in the blood determines the transport into the tissue (or to the site of action). If the free concentration increases the therapeutic efficacy may increase but it may also lead to toxic side effects. However, clearance may also be increased when the free drug concentration is increased. For active substances with a narrow therapeutic window such as valproic acid or carbamazepine, this type of interaction must be taken into account. However, after having gained a newly established equilibrium, the concentration of free active substance, responsible for the activity and subject to biotransformation, usually, hardly changes (as a result of the increased clearance). Most interactions on the metabolic level are caused by enzyme inhibition or induction (see Sect. 16.1.13).

16.1.11 Clearance

Many active substances are eliminated from the body after biotransformation. The metabolites are subsequently cleared via one of the excretion routes or further metabolised to products that can be excreted. The major routes of excretion encompass glomerular filtration followed by excretion into the urine, excretion of the active substance or its metabolites into the faeces (via the liver and bile, biliary excretion) or via

the exhaled breath. Biotransformation and glomular filtration are the major routes of elimination for most active substances. The bioavailability of an active substance can therefore be influenced by interaction with other active substances (or food components) that inhibit biotransformation enzymes, change the glomerular filtration rate or by genetic polymorphisms.

When an active substance is excreted via the biliary route a so-called enterohepatic circulation may occur. This means that the active substance that is removed from the circulation by the liver and (after glucuronidation) excreted via the bile into the lumen of the intestinal tract. In the intestinal tract (after deglucuronidation) the active substance can be absorbed again into the systemic circulation via the intestinal membrane. This effect will usually be seen as a second peak in the blood concentration versus time curve. The effect that this phenomenon could have on the AUC of a medicine should be taken into account when the bioavailability is determined since these effects may seriously compromise the outcome of the calculations.

16.1.12 P-glycoproteins

P-glycoproteins (P-gp) are membrane-bound transporters that are able to actively remove active substances and other xenobiotics from the cell. P-glycoproteins are energy-dependent and present in many tissues, including the blood-brain barrier, the intestinal wall, the liver and the kidney, and responsible for the active removal of among others, antineoplastics [5]. Typical substrates for P-glycoproteins are digoxin, metronidazole, saquinavir, talinol and calcium antagonists. P-glycoproteins may actively add to the absorption process of active substances, but they are mainly known for their capacity to remove active substances once they are absorbed. Many active substances are known to be excreted again by P-gp mediated transport into the intestinal lumen after being absorbed first. This may significantly reduce the bioavailability of these active substances. The bioavailability of such active substances may be significantly increased when they are administered together with other compounds (active substances) that are a substrate for P-gp transporters. For example the bioavailability of the antiretroviral medicine saquinavir is largely enhanced when it is administered together with a P-gp inhibitor such as ritonavir, also being a substrate for P-gp and competing for its binding places. Furthermore, ritonavir increases the saquinavir tissue concentrations in the central nervous system, since it also inhibits the effects of the P-gp in the blood-brain barrier.

16.1.13 Drug Metabolising Enzymes

Biotransformation of active substances largely occurs through the action of cytochrome P450 enzymes, a large group of mono-oxygenases located primarily in the liver and the intestine. They are responsible for oxidative metabolising steps, often preceding glucuronidation followed by urinary or biliary excretion. These enzymes can be inhibited by active substances (or by food substances). Conversely several active substances are able to induce them. Enzyme inhibition will increase the bioavailability of active substances that are metabolised by these enzymes, which may cause toxicity. However, enzyme induction will reduce bioavailability and increase systemic clearance, which in turn may reduce the therapeutic efficacy.

Especially the inhibition or induction of cytochrome P450 subtype 3A4 (CYP 3A4) is clinically relevant, because a variety of active substances and food substances (e.g. grapefruit juice) are able to affect this enzyme. Substances inhibiting CYP 3A4 include: ciclosporin, dihydropyridines, verapamil, midazolam, paclitaxel, simvastatin, lovastatin, atorvastatin, cimetidine, erythromycin, troleandomycin, ketoconazole (and other azoles). Substances inducing CYP 3A4 include: steroids, rifampicin, phenobarbital and St John's wort.

Drug metabolising enzymes can be over- or underactive in different individuals and between populations of different ethnic background. Genetic polymorphism may be the underlying feature. Polymorphisms with relevance for drug metabolism are found for N-acetyltransferases and for cytochrome P450 subtypes 2D6 and 2C19.

Herb-Drug Interactions

Herb-drug interactions may be clinically relevant [6, 7]. The dosage and the duration of treatment with herbal preparations should be taken into account to assess the possible interaction risks with regular pharmacotherapy. Special attention should be given to active substances with a narrow therapeutic window when combined with herbal medicines.

Pharmacokinetic herb-drug interactions occur when an herbal preparation changes absorption, distribution, metabolism or excretion of a medicine. Interactions at the level of metabolism, comprise the inhibition or induction of different cytochrome P450 enzymes, glucuronosyltransferases (UGTs) and P-glycoproteins. Herbal drugs rich in saponins and herbal products that alter the gastric pH or influence intestinal motility may influence dissolution and absorption.

(continued)

Furthermore, pharmacodynamic herb-drug interactions may occur. They can be the result of a similar or antagonistic action of an herbal preparation and a medicine. Knowledge of the pharmacological properties may help to predict such interaction.

Active substances that are considered to be most sensitive to interaction with herbal preparations include oral anticoagulants, cardiac glycosides, oral contraceptives, antidepressants and antihypertensives. Typical herbal products that may influence their activity are St John's wort, ginkgo, ginseng, garlic and laxatives (bulk formers and anthraquinones). Note that the composition of the particular herbal preparation should always be considered as the profiles of different extracts from the same plant may vary considerably.

16.1.14 Slow Release and Flip-Flop Pharmacokinetics

Slow release technology is generally applied to active substances that are connected with:

- Long-term or chronic therapies.
- Large and undesired differences in peak and trough blood levels, leading to adverse effects or periods with no or suboptimal therapy, respectively.
- Non-linear pharmacokinetic behaviour, meaning that the blood concentration increases are not proportional to increasing dose. This may lead to toxic blood levels. Examples of active substances with non-linear pharmacokinetics include: nitrates, nifedipine, fentanyl, theophylline, paclitaxel and lithium carbonate. Non-linear pharmacokinetic behaviour may be due to saturation of pre systemic enzymatic elimination mechanisms at increasing concentrations of the substrate.
- High dosing frequency (three or more times daily) due to their rapid elimination or excretion. Under normal circumstances the elimination will be slower than the absorption rate of the active substance. As a result of this difference, the elimination is reflected in the descending part of the blood concentration versus time curve. A fast elimination rate however would require it to be administered several (more than three to four) times a day. Slow release of the active substance from the dosage form (e.g. a slow release tablet) will cause the absorption rate to become slower than the elimination rate. As a consequence the elimination phase in the blood concentration versus time curve no longer reflects the elimination rate, but rather the absorption rate of the active substance, whereas the initial rising phase in the curve is a reflection of the elimination rate of the active substance. This phenomenon is known as 'flip-flop pharmacokinetics' [8].

When the occurrence of flip-flop kinetics is not recognised it may compromise the interpretation of results from studies on the pharmacokinetic behaviour of slow release dosage forms. Flip-flop pharmacokinetics may occur with any extravascularly administered parenteral slow release dosage form. Intramuscular depot injections of antipsychotics such as fluphenazine decanoate, haloperidol decanoate or flupenthixol decanoate show this behaviour. It also occurs after the administration of oral slow release products of active substances such as isoxuprine, carbamazepine, diclofenac, valproic acid, morphine and theophylline.

16.2 Dosage Forms and Routes of Administration

For the administration of medicines, various routes and dosage forms are available. The choice for the most suitable route and dosage form is complex and affected by a large number of interacting factors. Among these factors are aspects related to the physico-chemical characteristics of the active substance, the pharmacodynamics and pharmacokinetic characteristics of the active substance and various patient related aspects. This section gives, per route of administration, the basics for handling of the interacting factors. Chaps. 4–14 discuss the practical consequences for the formulations.

16.2.1 Parenteral Administration

Intravenous administration delivers an active substance immediately into the systemic circulation. It is often considered the fastest way to get a therapeutic effect. By definition, the bioavailability of an active substance given intravenously is 100 %. A typical characteristic of the blood concentration (as measured in whole blood, in serum or in plasma) versus time curve of intravenously administered active substances is the absence of the absorption phase (Fig. 16.8). Any other route of administration would show an absorption phase (see Fig. 16.1) but immediately after intravenous injection the blood concentration is at its maximum and is usually followed by a short distribution phase and the elimination phase of the active substance, both processes will reduce the blood concentration of the active substances.

The duration of the action depends on the dose, the duration of administration (in case of an intravenous drip or infusion), the distribution, metabolism and excretion of the active substance. Constant blood levels can be achieved

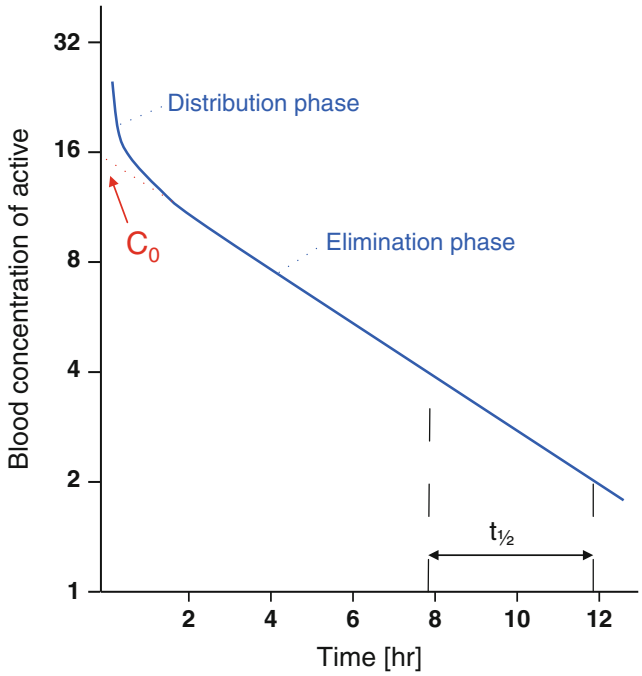

Fig. 16.8 Blood concentration versus time curve obtained after intravenous injection. Extrapolation of the elimination phase to the intersection with the y-axis gives the virtual C_0 value. This is the theoretical concentration of the active substance immediately after administration assuming that it is distributed over the full volume of distribution for the particular active substance. The C_0 can, together with the dose, be used to calculate the volume of distribution ($V_d = D/C_0$)

by a constant infusion. By regulating the speed of infusion, the height of a blood level can be adjusted and maintained at a constant level without fluctuations. This may be important for active substances with a narrow therapeutic window.

The blood concentration versus time profile shown in Fig. 16.8 is typically found after the injection of an aqueous solution of the active substance. When lipophilic compounds are administered as an oil-in-water emulsion the profile may be significantly altered, since the transport of the active substance over the oil-water interface may limit the distribution or elimination rate.

By intramuscular administration, the medicine is injected into muscle tissue, through the skin and subcutaneous fat layer. Suitable muscles for intramuscular injection are the upper arm and shoulder muscle (musculus deltoideus), thigh muscle (musculus vastus lateralis) and bottom muscle (musculus glutaeus maximus). The blood flow in these muscles differ from each other and hence also the extent and rate in which an active substance is absorbed from these sites. Activity of the muscle and physical movements (e.g. horse riding after an injection in the bottom muscle) will also strongly affect the absorption of the active substance from the injection site. Unlike the intravenous injection, oily liquids and aqueous or oily suspensions can be injected intramuscularly.

By subcutaneous administration, the medicine is injected into the subcutaneous connective tissue. These injections are experienced as more painful than intramuscular ones. Suitable places are the thigh and the belly pleat. The absorption after subcutaneous injection varies in rate and extent depending on the site of injection and on patient specific factors such as the amount of subcutaneous fat and physical activity. When a solution is injected the diffusion of the active substance through the tissue to the blood vessel will be the rate determining step for the absorption. When a suspension is injected the dissolution rate of the active substance may become rate determining for the absorption process, whereas for lipophilic active substances formulated as an oily solution or an oil-in-water emulsion the transport over the oil-water interphase may become rate determining. With suspensions and emulsions the absorption rate can be slowed down to such an extent that it will become rate limiting for the elimination rate of the medicine. In this way slow release injections can be formulated.

The bioavailability of an intramuscularly or subcutaneously administered active substance is determined by:

- Site and depth of the injection
- Physical form of the active substance in the injection (solution, suspension, emulsion)
- Physico-chemical properties of the active substance (solubility, charge, aggregation)
- Injected volume
- Thickness of the fat layer in relation to the depth of the injection
- Muscle activity
- Excipients used and composition of the injection (formulation: solvent or vehicle, osmotic value, viscosity, pH, surfactants, etc.)

Section 13.3 discusses the practical consequences for the formulations.

16.2.2 Oromucosal Administration

The mucosal membranes in the mouth can be used to administer active substances. The sublingual and buccal membranes are especially suitable for systemic absorption of an active substance. The rate of absorption of the active substance is determined by its size and lipophilicity. A high lipophilicity and a small size of the molecule are favourable for rapid penetration of the sublingual membrane. The thin and highly vascularised membrane under the tongue is especially suitable for a fast absorption. But before the active substances can be absorbed they should be dissolved. Specially designed oromucosal dosage forms have to provide dissolution of the active substance in the limited amount of saliva available. Since many persons experience difficulties keeping a product in the mouth for about 2 min, dissolution

must be rapid as well [9]. When given in a rapidly dissolving dosage form, lipophilic hormones like testosterone or estradiol can be absorbed efficiently via the sublingual route (circumventing the hepatic first-pass effect). Nitroglycerin is an example of a small slightly lipophilic compound that is effectively administered (showing a fast absorption within minutes) as a sublingual tablet or spray in acute cardiac insufficiency.

16.2.3 Oral Administration

For orally administered medicinal products the pharmaceutical availability, the rate of absorption and the bioavailability strongly depend on the design and formulation of the dosage form. During the transit through the gastro-intestinal tract, the active substance is exposed to varying conditions. Of importance are the variations in pH, residence time in different parts of the gastro-intestinal tract and digestive (metabolising) enzymes. The gastro-intestinal tract covers the mouth, oesophagus, stomach, small intestine (duodenum, jejunum, ileum) and large intestine (colon).

The oesophagus has only a transport function for active substances. It is important, however, that corroding and irritating active substances, like doxycycline and bisphosphonates, do not stick in the oesophagus as they can damage the tissue and cause ulcerations. Ample water should be taken when swallowing such medicinal products.

Within the stomach an acidic environment exists, with a pH between 1.5 and 3.0 (with extremes between 1.0 and 5.0). In addition, digestive enzymes are present. The residence time in the stomach depends on the nutritional status and on the physical form of the medicine and may be highly variable. An active substance in solution, taken on an empty stomach, will pass the stomach quickly, usually within 30 min. A non-disintegrating large tablet, taken after a high-fat meal, may remain in the stomach for several hours. Absorption from the stomach plays a minor role in the total absorption, because of the relatively small surface of the gastric wall in relation to the stomach volume and the thickness of mucus layer and membrane.

In the duodenum, the first part of the small intestine, the pH of the acid gastric content rises to values between 6.4 and 6.8, after pancreatic juice is added. This pH is maintained in the jejunum and the proximal part of the ileum. In the terminal part of the ileum, the pH rises to 7.1–7.5. The transit time through the small intestine is about 4.5–6 h. For many active substances the duodenum is the principal site of absorption. This is because of its large surface and the relatively large variation in luminal pH, as a result of which many active substances are present in the duodenum as a non-ionised molecule for some time. However, also in lower parts of the small intestine significant absorption can still occur.

In the colon the pH drops a little, to 6.4–7.4, due to the metabolic activity of the intestinal flora. The residence time in the colon varies between 6 and 12 h. Absorption from the colon is generally of minor importance for orally administered active substances.

The significant variations in pH and residence time in the gastro-intestinal tract strongly affect the solubility and the dissolution rate of many active substances as well as the transport over the intestinal membranes during the absorption process.

Interactions with food in the gastro-intestinal tract can influence the bioavailability of active substances at various levels (see also Sect. 16.1.6). Examples are:

- Food components (or active substances) that delay stomach emptying will delay the absorption of active substances that are only absorbed from the small intestine.
- Food (and active substances) that change the pH in the gastro-intestinal tract may influence the absorption of active substances of which the absorption process is pH dependent.
- Food components may form insoluble complexes with active substances, hampering their absorption.
- Swallowing a lot of fluid will increase the amount of liquid in the gastro-intestinal tract available for dissolution. As a consequence, larger fractions of poorly soluble active substances may dissolve and the bioavailability may increase.
- Fat in food stimulates the excretion of bile into the intestinal lumen. Bile contains effective emulsifiers that can increase the solubility of lipophilic active substances.
- Food components (fibres) that increase the motility of the intestine may decrease the absorption of active substances due to a shorter residence time.
- Food increases the blood flow to the intestinal tract. The absorption of active substances will increase, leading to higher portal drug concentrations. The first-pass effect decreases as a result of less effective extraction by the liver.
- Certain food substances and herbal preparations may inhibit enzymes that play a role in drug metabolism; e.g. cytochrome P450 3A4 enzymes by grapefruit juice.

Sections 4.3 and 5.3 discuss the practical consequences for the formulations.

16.2.4 Rectal Administration

Rectal administration of medicines aims at a local or a systemic effect. Suppositories and (micro-)enemas

(3–10 mL) are mainly used for a systemic effect, enemas with a larger volume (up to 100 mL) for a local effect (in the rectum and lower colon).

The rectum is the lowest part of the large intestine. It is 15–20 cm long with a diameter of about 5 cm. In the rectum 1–5 mL of viscous fluid with a pH between 6.4 and 7.4 and a small buffer capacity is present. The temperature (under physiological conditions) is 36.2–37.6 °C. The rectum is a flat tube, because of the pressure of the bowels. After administration of a fluid into the rectum the liquid will spread due to this pressure. Larger volumes (enemas) are spread into the colon as well. A defecation reflex will occur when volumes exceeding 100 mL are applied, which limits the volume of enemas.

In older literature the circumvention of the hepatic first-pass effect is mentioned as an advantage for rectal administration of medicines. This is now known to be an invalid argument, since two out of three rectal veins end up in the portal vein. Rectal administration can be useful when a patient is vomiting, has swallowing problems, is unconscious, experiences severe gastro-intestinal complaints when taking the medicine orally (e.g. indomethacin), or for active substances with an unpleasant taste (especially for children).

The most commonly used basis for suppositories is hard fat, which melts when brought into the rectum. Most active substances are suspended into the base, but some lipophilic active substances are dissolved. The first step after administration is melting of the base, followed by sedimentation of the suspended active substance particles to the fat-aqueous interface where the active substance is to dissolve in the aqueous rectal fluid. Subsequently, the active substance is absorbed by the rectum membrane after which it enters the systemic circulation. It should be known that due to the viscous nature of the mucus covering the rectal membrane direct transport from the molten fat to the membrane is not possible, the active substance always has to pass the aqueous mucus layer. Therefore, highly lipophilic active substances should not be formulated into a lipid suppository basis or an oily enema. Since the transport from the lipophilic base into the aqueous rectal fluids is an inevitable step in the drug absorption process, the high octanol-water partition coefficient of these lipophilic active substances will make this process inefficient and absorption slow and incomplete. As an alternative to fat, a water-soluble basis (macrogol (polyethylene glycol)) can be used for the preparation of suppositories. The aqueous suppository basis should especially be applied to those active substances that are highly lipid soluble and will not partition from the molten fat base into the aqueous rectal fluid.

The release of an active substance from a suppository depends on the pH and the buffer capacity in the rectum, the solubility in water and the lipophilicity of the active substance (the solubility in the fat basis), the volume of the suppository (usually 2–3 mL for adults), the nature of the suppository basis (lipid or aqueous, the viscosity of the molten lipid basis, the solubility for the aqueous basis) and the particle size of the active substance. To improve the absorption rate of less soluble substances, active substances can be formulated as a cyclodextrin complex in suppositories. For example, piroxicam is formulated as a beta-cyclodextrin (betadex) complex and cisapride is used as an hydroxypropyl beta-cyclodextrin (hydroxypropylbetadex) complex in fatty suppositories.

Rectal solutions have water or oil as a vehicle. If necessary to enhance the solubility of poorly soluble active substances, aqueous rectal solutions may contain cosolvents, such as ethanol and propylene glycol. However, cosolvents and surfactants should only be used in limited amounts because of the potential irritation and the defecation reflex they may cause. For the rectal absorption of active substances from enemas the same mechanisms as for suppositories apply. A major advantage of a rectal solution over a suppository may be the fact that the active substance is already in a dissolved state which may increase the absorption rate. Increasing the volume of a rectal solution to dissolve a poorly water-soluble active substance will enhance the dissolution rate and thereby increase the absorption rate. Because of the higher volume more active substance will be dissolved and the membrane surface over which absorption occurs, is increased as well.

Section 11.3 discusses the practical consequences for the formulations.

16.2.5 Dermal and Transdermal Administration

Medicinal products can be applied on the skin to treat local skin diseases (topical application) or to systemically administer an active substance (transdermal application). In the first case, the active substance should accumulate in or even on the skin and display its effect there. When transdermal administration is intended, the active substance should be transported through the skin followed by absorption into the systemic circulation. In the skin the stratum corneum (the most outer layer of 5–50 layers of dead cells, a horned layer of corneocytes, see Fig. 12.1 and Sect. 12.3.1) forms the major barrier for absorption of active substances. The layer is highly lipophilic in nature and is fully impermeable for hydrophilic active substances. Lipophilic active substances, when adequately formulated, may be absorbed via the skin. Typical characteristics which make an active substance suitable for transdermal transport are: an octanol-water partition coefficient (expressed as log $P_{o/w}$) between 1 and 3 and a molecular mass below 500 Da [10, 11]. Moreover the dose should not exceed 20 mg per day. Hydrophilic active

substances can be absorbed via the transdermal route when the stratum corneum is damaged, for example by the use of microneedles [11]. However, such action also compromises the natural protective function of the skin. The layers of the skin under the stratum corneum are permeable to both hydrophilic and lipophilic substances. Lipophilic substances may form a depot in the lipid parts of the skin before they are transported into the systemic circulation. The major route of penetration over the stratum corneum is the intercellular route. The transcellular route through the corneocytes is less relevant. Penetration may also occur via hair follicles, sebum glands and sweat glands, but because of the smaller surface these routes are of minor importance.

For a good therapeutic effect the choice of the active substance and the choice of the vehicle are important. Physical and chemical factors play an important role. The solubility of the active substance in the vehicle and the concentration, the size of the molecule of the active substance, the partition between vehicle and skin, the particle size (in case of suspensions) and the nature of the vehicle (aqueous or lipid) determine the penetration speed and depth. Hydrocortisone, for example, is more lipid soluble in the ester form (hydrocortisone acetate). The latter will penetrate into the skin faster and more complete. Hydrocarbons, such as soft and liquid paraffin, release lipophilic active substances only very slowly and substances formulated in these bases will penetrate only in limited amounts into the skin. Fatty oils (vegetable oils, triglycerides) are able to pass into the upper layers of the skin. Penetration enhancers (salicylic acid, dimethyl sulfoxide, propylene glycol, urea) increase the penetration of active substances into the skin.

The pH of the vehicle in relation to the skin pH (around 5.5) is very important. Many active substances, also in dermal preparations, are weak acids or bases. The pH partition theory (see 16.1.9) plays a role here as well and affects the effective partition of the active substance between the vehicle and the skin.

Physiological factors also determine the effectiveness of dermal preparations. The thickness of the skin varies across the body. The penetration rate is higher when applied on thin skin (e.g. behind the ear, on the eyelid or scrotum) than when applied on thick skin (e.g., palm of the hand, sole of the foot). Comparing the skin of babies and adults, the ratio between body surface (skin) and body volume is larger for babies. In addition, skin absorption in term and in preterm new-borns is increased because their stratum corneum is thinner and the epidermis of children is better perfused and hydrated compared to adults. As a result, the toxicity of active substances applied on a baby's skin can be much higher than on an adult's skin.

The rate of penetration through a damaged skin is higher than that through an intact skin. The state of hydration of the skin is also important. The rate of penetration is usually higher in a well-hydrated skin. Occlusion (e.g., by covering the part of the skin where the dermatological preparation has been applied) enhances hydration and hence enhances drug penetration of more hydrophilic active substances into the skin.

Technical factors, like rubbing and massage, also enhance the penetration of medicines. Several excipients may act as penetration enhancers, by reducing the thickness of the skin (salicylic acid or urea), or by changing the coherent structure of the stratum corneum, such as dimethyl sulfoxide, propylene glycol, or several surfactants. Whether the active substance is present in the inner or outer phase of an oil in water or a water in oil cream affects the extent and rate of transdermal absorption of an active substance. When present in the inner phase transport is generally slower, due to the fact that the active substance at first has to pass the outer phase before reaching the skin. When the partition between inner and outer phase is highly in favour of the inner phase only small amounts of active substance will enter the outer phase and transport will be slow. Conversely, when the inner phase consists of small droplets a large interface exists between the inner and outer phase and drug transport may still be relatively fast. As a consequence, active substances that are dissolved in the inner phase may still be faster and more completely absorbed into the skin compared to a suspension-type formulation. This is, for example, the reason why lipophilic corticosteroids are often formulated in oil-in-water creams.

Iontophoresis (see also Sect. 12.7.11), finally, is a means to enhance the penetration of charged active substances. When positively charged molecules are administered at the site of an anode and negatively charged active substances under the cathode, electric repulsion will increase the driving force for transport of the active substance into the skin. Variation of the electric charge that is applied will change the rate of transdermal drug transport. This can be used to rapidly adjust the dose for example in pain management: iontophoresis is used for example to control the delivery of lidocaine for local anaesthesia or of fentanyl.

Dermatological preparations for local use may exert a systemic effect as well. Especially for corticosteroids this can be a problem. The patient should be informed not to use such preparations for too long, and not more frequently than prescribed. Furthermore, the surface on which the preparation is applied and the thickness of the film should be limited.

Section 12.3 discusses the practical consequences for the formulations.

16.2.6 Nasal Administration

The application of medicines in the nose usually aims at a local effect (e.g., for decongestion of the mucous membrane of the nose, or to administer anti-allergic medicines). In recent years, it has become clear that the nose can be used as a route for systemic therapy as well. Nose drops and nose sprays are the most commonly used nasal preparations.

Many active substances, solvents and excipients possess ciliotoxic properties, meaning that they (irreversibly) damage the cilia. Cilia are hair-like projections of the nasal epithelium cells. They facilitate the movement of mucus from the nasal cavity to the nasopharynx. From there it is swallowed into the gastro-intestinal tract. The cilia play an important role in keeping the nose clean from particles and pathogens. In order not to damage this defence mechanism, special attention should be given to the constituents of nasal preparations, including the active substance, antimicrobial preservatives, antioxidants, salts for adjusting pH and tonicity, solvents and viscosity increasing agents. Also the pH and tonicity of nasal preparations lie within narrow limits.

As a consequence of the mucociliary clearance of the nasal cavity active substances that are unable to pass the nasal membrane will end up in the oropharynx and are swallowed into the gastro-intestinal tract, from where they may be absorbed. This gastro-intestinal absorption after nasal administration may erroneously be considered as nasal absorption. Such a phenomenon may, for example, occur when the nasal spray of the anti-migraine medicine sumatriptan is used.

The nasal administration was shown to be an effective administration route for lipophilic active substances like fentanyl. Moreover, the nasal route has also been used for the systemic administration of small peptides like buserelin acetate, nafarelin acetate and desmopressin, all of them containing ten or less amino acid residues. However, for these molecules the nasal route forms only a poor non-invasive alternative to injection, since the nasal bioavailability of these peptides is less than 3–5 %.

Section 8.3.2 discusses nasal absorption, mainly the enhancement, in more detail and the practical consequences for the formulations are dealt with in Sect. 8.5.

16.2.7 Pulmonary Administration

The human lungs consist of a branching system of airways with 23 bifurcations between the mouth and the alveoli. The transport of drug-containing aerosol particles by the airflow into the lung is one of the major obstacles in pulmonary drug administration. Due to their inertia (meaning that due to their mass and velocity the particles show the tendency to 'fly out of the bend') the particles that are transported by the airflow may be unable to pass the throat or subsequent bifurcations of the airways. Inertial impaction, especially in the throat, may significantly reduce the overall efficacy of the drug deposition in the lung. Throat depositions varying between 70 % and 90 % of the dose are not exceptional for widely used inhalation devices, such as nebulisers, metered dose inhalers or dry powder inhalers. Since the drug loss by throat deposition of aerosols is a mechanical phenomenon this problem should also be solved in a mechanical way. This can be done by reducing the particle size of the aerosol particles to a size between 1.5 and 3.0 μm, reducing the inhalation airflow rate and prolonging the breath-hold. In this way, throat and upper airway deposition can be decreased while optimising the lung deposition. It is for this reason that for pulmonary drug administration the device and the way it is used by the patient are considered to be as important as the choice of the active substance. Once particles have passed the upper airways particles in the size range between 1.5 and 3.0 μm will deposit by settling on the airways wall and a small fraction will deposit in the alveoli. Most of the particles smaller than 0.5–1.0 μm may penetrate deeply into the lung but sedimentation on the airway wall will be limited due to the limited effect of gravity on these particles. They will therefore to a large extend be exhaled again. This is discussed in more detail in Sect. 6.3.

The lungs can be considered to consist of two different organs: the airways and the alveoli. These two parts of the lung are physiologically different and the barrier function of their mucosal membranes differs completely. The airways are covered by a ciliated mucosal membrane covered with a mucus layer that is transported to the throat. The airway membrane is not permeable to hydrophilic molecules with a molecular weight over 1,400 Da. The alveoli on the other hand, have a completely different structure: their membrane consists for over 93 % of the alveolar type I cell. This is a non-ciliated cell type that is covered with the alveolar lining fluid, an aqueous fluid that contains huge amounts of the surfactant dipalmitoylphosphatidylcholine. Between the alveolar type I cells intercellular spaces occur with sizes up to 4 nm. Because of these large interstitial spaces proteins with a molecular weight up to 20 kDa can be absorbed into the systemic circulation after inhalation. This fact, and the low activity of proteolytic enzymes in the alveolar lining fluid, makes the pulmonary route probably the most suitable route of administration for small and medium size therapeutic proteins as an alternative to the parenteral route. However, it should be kept in mind that for proteins with a molecular weight over 1,400 Da absorption will only occur via the alveoli. Unfortunately the alveoli are found only at the end of the branching airway system and only a fraction of 10–15 % of the particles of 1.5–3.0 μm will reach the alveolar region. This limits the final bioavailability of inhaled proteins.

The Pulmonary Route for the Systemic Administration of Medicines

The systemic administration of medicines via the pulmonary route has attracted significant interest over the past decades. The development of an insulin formulation for inhalation is an example. A few years after the discovery of insulin in the 1920s, it was described that after inhalation in dogs systemic blood levels of insulin were obtained. Considering the fact that proteins with a molecular weight of up to 20 kDa can pass the alveolar membrane, it is not surprising that the less than 6 kDa insulin is systemically absorbed after inhalation as well. However, it took more than 60 years before inhalation systems and protein formulation technology had developed to a level that could guarantee a well-controlled and reproducible alveolar deposition of the insulin containing aerosol particles. In 2006 the first insulin dry powder inhaler was launched (Exubera™). This product had a low bioavailability of about 12 % and was available in two dose strengths only. After less than 2 years the product was withdrawn from the market because of safety concerns and poor sales performance. Following this withdrawal most other developments regarding inhaled insulin were also stopped.

In spite of this failure, the lungs seem to be a suitable port of entry for active substances that cannot be systemically administered by other routes such as the oral or transdermal route. Also for active substances that suffer from a high first-pass metabolism or a highly variable absorption behaviour after oral administration, the pulmonary route could potentially be a better route of administration. For a wide variety of active substances ranging from the therapeutic peptides such as somatropine or gonadoreline-agonists to small organic molecules such as fentanyl or ciclosporin, the systemic availability after inhalation has been proved. Furthermore, the lungs seem to offer a suitable organ for needle-free vaccine administration. For several vaccines such as the measles and influenza vaccine successful vaccination, eliciting an adequate (protective) immune response, has already been shown in humans [12, 13].

Pulmonary administration of active substances is common in the treatment of lung diseases such as asthma and COPD and infectious lung diseases. For these indications different levels of the airways are targeted with different medicines. For the beta-agonists such as formoterol the higher airways (generation 4 to 11, see Fig. 16.2) are the primary target, whereas for the anti-inflammatory corticosteroids the smaller airways should be the primary target. Long acting muscarinic antagonists should be targeted at the entire bronchial tree, whereas antibiotics should preferably be directed at the infectious loci in the lung.

Pulmonary drug administration can be considered as the most successful application of the drug targeting concept so far. Locally at the site of action, much higher active substance concentrations can be attained and the onset of action is faster than after systemic administration. Following inhalation, blood levels are usually lower and thus the occurrence of adverse effects is limited compared to systemic administration. When a patient is short of breath, he will experience the effect of pulmonary administered medicines fast, within a few minutes. This is of paramount importance when exacerbations are treated.

As described above, the pulmonary route can also be used for systemic administration of active substances. Smaller molecules (<1,400 Da) can already be absorbed via the airways and bioavailabilities of over 30 % can be reached. For the larger molecules penetration can only occur over the alveolar membrane and their bioavailability will be much smaller. However, no such products are on the market yet.

16.2.8 Ocular Administration

The ocular administration of medicines is only used for a local effect in, on or around the eye. The local application results in high local concentrations of the active substance. Pharmaceutical dosage forms for the eye encompass eye drops, eye washings, eye ointments, inserts and intra-ocular injections. In all cases, it is important that the preparations do not cause irritation of the eye. If they do, the medicine will be washed out quickly due to tear production, which may reduce the effect and limit its duration. In addition, small sharp particles can damage the eye. Strict limits exist for pH and tonicity of ocular preparations.

Active substances administered via the ocular route (with the exception of an intra-ocular injection) may be absorbed via the different membranes of the eye. When an active substance is active in the eye it should be able to pass the cornea. The epithelial and endothelial layers of the cornea are of a highly lipophilic nature as a result of which only lipophilic and non-charged active substances can pass the epithelium of the cornea. For active substances with a partition coefficient below 0.3 or active substances that are charged at the physiological pH of the eye the driving force for transport over the corneal epithelium (the first step of the absorption process) will be insufficient and absorption will generally be low. To obtain sufficient transport of the active substance over the corneal epithelium it is therefore necessary to administer the active substance in a formulation that has a pH at which a significant part of the

active substance is unionised. Examples are carbonic anhydrase inhibitors and beta adrenergic antagonists, used in the treatment of glaucoma.

Absorption into the systemic circulation of active substances administered to the eye may occur to a limited extent, via the conjunctival membrane and the nasal mucosa (after being washed from the eye the active substance may enter the basal cavity via the nasolacrimal duct). The residence time of medicines in the eye may be prolonged by increasing the viscosity of the eye drops (which reduces the efficacy of lacrimation to wash out the medicine from the eye) or via the application of polymeric ocular inserts which slowly release the active substance. It should be realised that many ocular inserts are placed in the conjunctival sac, as a results of which a significant fraction of the active substance will not be absorbed via the cornea but rather end up in the systemic circulation due to absorption via the membrane of the conjunctival sac.

The intraocular injection of active substances that are active in the eye leads to a bioavailability of 100 %. However, this route of administration is a serious burden to the patient and formulation related safety aspects are of paramount importance since elimination from the site of injection is generally slow. However, this route may be the only way to get an active substance to the site of action, or to get it in a sufficiently high concentration at the site of action (e.g., an antibiotic). Larger molecules such as monoclonal antibodies (e.g., bevacizumab or ranibizumab used against macular degeneration) are administered in this way to the eye. A further advantage of the intraocular route is that the large molecules are cleared slowly from the intraocular fluids and effects may last for days (or even weeks).

Section 10.4 discusses the practical consequences for the formulations.

16.3 New Developments and Advanced Drug Delivery Systems

Over the past years a range of new developments in the field of drug delivery has emerged. Advanced drug delivery systems have been designed and a few of them made it to the market. Examples of such advanced drug delivery systems are liposomal medicinal products, nanocapsules, antibody-drugs conjugates, polymer-drug conjugates (e.g. pegylated proteins) and higher drug excipient (polymer) associated medicines. Many of these delivery systems have been developed for active substances that suffer from intrinsic difficulties from a biopharmaceutical point of view such as therapeutic proteins, DNA or RNA and small organic molecules that require drug targeting because of their intrinsic toxicity when distributed over the entire body (e.g. antineoplastic medicines). Furthermore, advanced delivery systems have been developed to open new (mostly non-parenteral) routes of administration in order to improve the ease and comfort of drug administration for the patient. Certainly, the development of advanced drug delivery forms is not new. Oral slow release products and pro-drugs that target mesalazine to the lower part of the intestinal tract have been available for decades. However, the rapid developments in biotechnology as well as the development of new active substances that require site-specific delivery has propelled the development of more advanced drug delivery systems. Without these systems therapeutically successful administration of these new active substances will be impossible.

A common denominator of all advanced drug delivery systems is their aim to change the intrinsic pharmacokinetic behaviour of the active substance they contain. This may either be at the level of absorption or absorption rate, at the level of metabolism or distribution, or by changing the elimination. From a biopharmaceutical point of view these changes may have significant implications, since they may alter bioavailability, efficacy and safety as well as the duration of action. It is for this reason that in the development these advanced drug delivery systems should be considered as completely new medicines, requiring an almost full development program before they can reach the market. So far the number of advanced drug delivery systems that reached the market is limited. Obviously many of the concepts designed for improved bioavailability or drug targeting appeared to be not successful in real life, in the complex *in vivo* situation in man.

Among the advanced drug delivery systems that did reach the market are liposomal formulations of active substances like doxorubicin and amphotericin B. Recently trastuzumab emtansine which is a conjugate of the monoclonal antibody trastuzumab and the antineoplastic mertansine was introduced on the market [14]. Since the HER2-receptor is overexpressed in tumour cells a dual action will be obtained from this conjugate. Trastuzumab itself can already stop the growth of tumour cells whereas the antineoplastic mertansine is specifically targeted to the tumour cells by the antibody, which increases efficacy and reduces side-effects. The active substance is used in HER2-positive metastatic breast cancer. Using this product for the first time monoclonal antibody-based drug targeting has been applied successfully.

Another interesting innovation is the registration of alipogene tiparvovec, it represents the first gene therapy treatment that has reached the market [15]. The medicinal product consists of the human lipoprotein lipase gene that is encapsulated in a vector derived from adeno-associated virus (AAV), serotype 1. The viral vector will deliver the gene into the cell, in this case a muscle cell, where the gene can be expressed after which the lipoprotein lipase is produced. In

this way lipoprotein lipase deficiency can be treated. Taking into account the considerable efforts that are still being made in the development of the advanced drug delivery systems, several new advanced drug delivery systems may reach the market in the coming years.

16.4 Essentials

- Pharmacotherapy can only be optimal if the pharmaceutical formulation (the medicinal product) and its functionalities are appropriate for the chosen route of administration and intended therapeutic objective.
- The technical and biopharmaceutical functionalities of a medicinal product are determined by its qualitative and quantitative composition, as well as by the structure of the different components in the product.
- From a biopharmaceutical point of view, a pharmaceutical formulation should be tailored to the route of administration, the physico-chemical properties of the active substance, the desired mode of action, the onset and duration of the therapeutic effect, the site of action, and the pharmacokinetic and pharmacodynamic properties of the active substance.
- Active substances can only pass the absorptive membranes when they are dissolved in the aqueous fluids adjacent to these membranes.
- The bioavailability of an active substance is defined as the fraction of the active substance that reaches the systemic circulation intact. It equals the pharmaceutical availability *in vivo*, minus the loss of the active substance during the absorption into the systemic circulation, due to incomplete membrane passage or loss caused by metabolism of the active substance during the absorption process.
- Active substances undergoing substantial metabolism when passing the intestine and/or liver (first-pass effect) show a limited bioavailability, often with large intra- and inter-individual differences.
- Drug-drug interactions on the level of metabolising enzymes (cytochrome P450, p-glycoproteins) may causes significant changes in bioavailability and therefore cause undesired effects.
- Each route of administration for an active substance brings along specific requirements for the pharmaceutical formulation to ensure optimal bioavailability.
- The oral, parenteral and rectal routes are the most used routes to achieve a systemic effect of a medicine.
- Locally administered medicines may exert a systemic effect as well, due to drug absorption. The design of the dosage form (active substance and excipients processed into a specific structure) is important to reduce the systemic effect when only a local effect is aimed for.
- Quantitative data on bioavailability and safety data are required when two different pharmaceutical products with the same active substance are compared to determine bioequivalence (e.g., a branded product versus a generic product or two different generic products).
- Comprehensive information on the physico-chemical background and biopharmaceutics can be found in Chap. 19 of this book and in general textbooks covering (parts of) the subject, specifically:
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Product Design

17

Herman Vromans and Giovanni Pauletti

Contents

Abstract

Pharmaceutical companies, hospital and community pharmacies prepare medicines. Although batch sizes vary greatly, the underlying principles of product development are comparable and driven by physical chemistry, physiology and pharmacokinetics. When the medication is meant for only a small group of patients or even for individual use, these principles cannot be fully elaborated and formulation becomes more and more based on risk assessment.

The design phase encompasses all aspects of converting an idea into a safe and efficacious product. To ensure quality, all factors affecting product performance have to be identified and critical limits or specifications defined. Medicines can be designed according to the concept of Quality by Design (QbD), using its elements of defined target product quality profile, robust product and preparation processes, critical quality attributes, process parameters, sources of variability, and controlled preparation processes.

The QbD concept is essential for large scale production but also assists in effective design of pharmacy preparations. Starting with an active substance, the product profile and biopharmaceutical and pharmacokinetic qualities, the administration route and a specific dosage form are chosen. Physico-chemical properties of the active substance limit these options. Formulation and preparation method have to be designed. Based on critical product and process characteristics, the 'design space' can be defined. A robust process is associated with a large design space. Proper documentation of the design process assists in troubleshooting or when modifications occur. Successful life cycle management is underpinned by an active attitude towards improving the design quality of the product.

Based upon the chapter Ontwerpen by Herman Vromans en Reinout Schellekens in the 2009 edition of 'Recepteerkunde'.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_17,

Keywords
Quality by design • Product validation • Critical quality attributes • Process parameters • Product life cycle • Target product quality profile • Formulation

17.1 Orientation

The design phase is the first step in the product life cycle (see Sect. 35.4) of a medicine and comprises all aspects necessary to translate an idea into a product of sufficient technological and therapeutic quality. The philosophy of Quality by Design (QbD) is the guiding principle not only for the design of large-scale industrial medicinal products (as illustrated in the Bipolar Depression Case) but also for small-scale pharmacy preparations as illustrated in several boxes.

Prior to initiating the design phase, feasibility of a preparation or product has to be assessed. For pharmacy preparation this assessment is discussed in Sect. 2.2. At the end of the life cycle, a production is discontinued due to an unfavourable risk/benefit ratio or economic reasons. For pharmacy preparations, loss of feasibility may also be the reason for discontinuation.

This chapter represents the foundation for Chaps. 4–14 that outline details of administration routes and dosage forms.

17.2 Quality by Design

Design quality entails both the quality of the formulation as well as the preparation method. The QbD paradigm is covered by the CHMP/ICH guideline Q8 [1]. It stresses the importance of a proper and well-understood design,- meeting the requirements of the patient and physician, and the importance of incorporating product quality into the design (see also Sect. 35.4.3).

The Q8 guideline emphasises the importance of understanding the formulation and the method of preparation, as well as preparation process control that is based on scientific data and risk analysis of the preparation process (see also Chap. 21). Identification of all relevant sources of variability will result in a window (the design space) for all adjustable parameters (particle size, pH, mixing time, etc.). Practically, the QbD approach will lead to a robust formulation and preparation process that is still flexible enough to adapt to necessary modifications. Detailed documentation of the development research will help limiting time- and resource-intensive follow-up studies in order to explain process deviations or applying process modifications.

The design process guided by the QbD concept generally includes the following actions [2]:

- Define target product quality profile
- Establish robust product and manufacturing processes
- Identify critical quality attributes, process parameters, and sources of variability
- Control manufacturing processes to produce consistent quality over time

These four actions are subsequently discussed in this chapter with an emphasis on pharmacy preparations. In addition to pharmaceutical aspects, selection of a suitable administration route and specific bioavailability considerations were recognised as relevant input variables in formulation design.

17.3 Target Product Quality Profile

The design of a medicine requires clarity about its intended use in a target patient population. Commonly asked questions include: “What therapeutic benefit should a patient gain?”, “How large is the patient population?”, “Do patients have unique pathophysiological or practical situations?”, “Where in the body is the desired therapeutic target for the active substance?”, or “What is the duration of dose administration and where is it performed (e.g. patient self-administration at home or in-patient setting at a hospital)?”

Bipolar depression case study #1
The design specification for the long-term treatment of patients with bipolar depression is as follow: Self-administration of an oral solid dosage form containing x mg of the active substance Y, which has demonstrated efficacy in the central nervous system. Considering the known sedative side effect of Y and the absence of an established relationship between pharmacokinetics and pharmacodynamics (PK/PD), the medicine is preferably administered at night before bedtime. Since the active substance has an unpleasant taste, taste masking is desired. Furthermore, it is established that many patients diagnosed with bipolar depression experience (neurotic) difficulties with oral medicines. Therefore, the solid dosage form should be of neutral colour and easy to swallow. As rapid absorption of the active substance results in vertigo, a modified release dosage form is preferred.

For an assessment of the therapeutic rationale and feasibility of requests for pharmacy preparations, reference is made to Chap. 2.

17.4 Administration Route and Bioavailability

Chapter 16 Biopharmaceutics discusses bioavailability in detail. This chapter focuses on the line of thought and on guidance to enable global decisions about feasibility from a biopharmaceutical viewpoint.

For all extravascular administration routes, bioavailability is determined by the following two sequential processes (see Fig. 17.1):

- Release of the active substance from the dosage form facilitated by disintegration or dissolution or both (= pharmaceutical availability)
- Pre systemic elimination, membrane passage, first-pass metabolism, and appearance of the active substance in the systemic circulation (= biological availability)

An active substance generally exerts its effect through defined molecular interactions with a receptor. As a prerequisite, the substance needs to be dissolved and reach the receptor. For a local effect, the substance is usually administered in close proximity to the desired target and should penetrate into body tissues as little as possible. However, when a systemic effect is desired, the substance has to reach the blood circulation system for distribution. For extravascular administration routes, this requires membrane passage and may expose the substance to various pre systemic elimination mechanisms, including metabolism and efflux transporters such as P-glycoprotein.

In the request for a pharmacy preparation, the physician often prescribes the administration route. Pharmacists have to critically evaluate whether the proposed route is appropriate to reach the desired bioavailability. For example, conventional oral medications may not be suitable for patients with a nasogastric feeding tube, children, or nauseous patients and alternative routes such as parenteral, rectal, or nasal have to be considered (see also Sect. 37.6.3). When adapting a dosage form or administration route to special needs of a patient, the pharmacist is required to consider safety aspects. It is important to recognise that an active substance approved for oral administration may never have been tested for safety and efficacy when administered via a different route such as the cutaneous application. Formally, at least, local toxicity studies are then required. Furthermore, excipients that are approved for tablet formulations may not be used in parenteral formulations. These examples illustrate that when a different administration route is chosen there might be a need to reassess the appropriate selection of excipients. In some cases, additional safety studies will be required.

> "The European – United States Paediatric Formulation Initiative (Eu-US PFI) has established that there is a pressing need for a single authoritative comprehensive database of adverse effects of excipients for paediatrics. Safety and Toxicity of Excipients for Paediatrics (STEP) Database holds all the animal toxicity and human health data, regulatory information and toxicological reviews of excipients. STEP acts as repository for all the scientific communities to share the data for better understanding and paediatric medicines development" (European Paediatric Formulation Initiative. STEP Database. See [3]).

The selection of an adequate dosage form should also consider limitations associated with the preparation method. For instance, if an active substance is harmful to the operator, the pharmacist may decide to prepare a liquid dosage form rather than a solid dosage form to avoid exposure to the harmful agent via inhalation (see Sect. 26.7.1).

Physico-chemical properties of the active substance influence to a large extent the administration routes and dosage forms that are feasible. Relevant properties include solubility, partition coefficient (log P), pK_a, membrane passage, metabolic stability, and half-life. Conversely, the administration route and formulation influence safety and efficacy of the active substance. This cause-effect relationship implies that formulations designed for different or even the same route of administration may not be interchangeable. Chapters 4–14 discuss these (im)possibilities in more detail, for different administration routes.

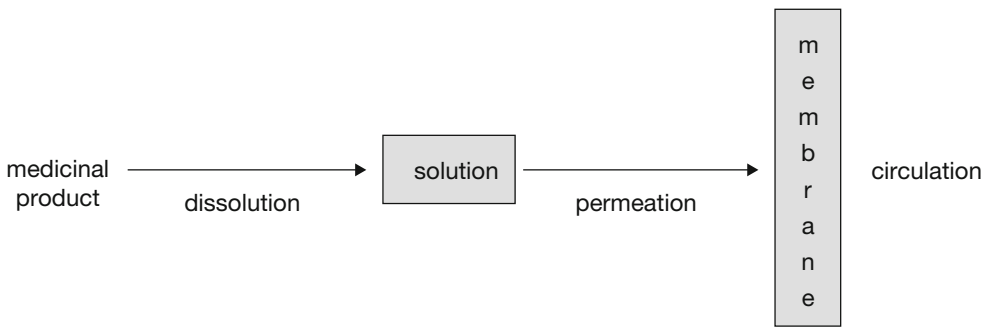

Fig. 17.1 Processes that determine bioavailability at extravascular administration routes

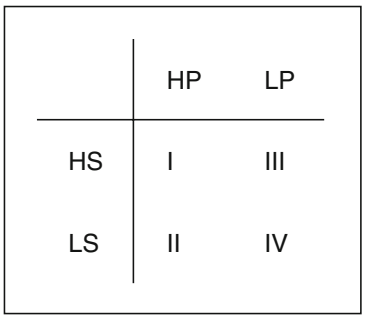

Fig. 17.2 Biopharmaceutics classification system

Although principally only valid for oral administration, it may be useful to assess the biopharmaceutical feasibility of any desired route of administration by the Biopharmaceutics Classification System (BCS, see e.g. [4]) (Fig. 17.2).

The BCS classifies active substances into four classes:
Class I: high solubility, high permeability
Class II: low solubility, high permeability
Class III: high solubility, low permeability
Class IV: low solubility, low permeability

17.4.1 Solubility

The relationship between the fluid volume available at the site of administration and the dose administered will determine whether or not solubility and dissolution rate of the active substance are adequate. Mathematically, this critical interaction is described by the dimensionless dose number (see also Sect. 16.1.5):

$$D / V \times C_s \qquad (17.1)$$

where:
- D = dose
- V = (aqueous) volume available for dissolution
- C_s = solubility in water

If the dose number < 0.1, solubility of the active substance is not considered limiting. If the dose number > 10, it is predicted that limited solubility of the active substance negatively affects oral bioavailability.

When the dose of the active substance does not dissolve in the approximately 250 mL of liquid that is present in the gastrointestinal lumen (a high dose number), the solid fraction of the substance will be unable to permeate across the intestinal mucosa and, consequently, will be eliminated in the faeces. Newly discovered active substances are often very poorly soluble in water, which requires unique formulations in order to achieve therapeutically relevant drug concentrations after oral administration. In [5] the selection of formulations for substances with poor water solubility is illustrated.

Table 17.1 Estimated physiologically available volumes

Administration route	Liquid	Volume (mL)
Oral	Intestinal volume/glass of water	250
Rectal	Volume rectum	3
Transdermal	Patch material	0.2
Buccal/sublingual	Saliva	0.9
Vaginal	Vaginal mucus	1.2
Nasal	Nose drops	0.2

For the dissolution properties of the active substance, the volume of liquid available at the site of administration is important. As outlined in Table 17.1, these volumes can vary significantly depending on the administration route.

A dose of a poorly soluble substance may be able to dissolve in the intestinal volume (250 mL). However, the limited volume of only 200 microlitres of fluid available in the nasal cavity will be insufficient to allow complete dissolution of the same dose when administered as a nasal formulation. It must be noted therefore that literature most often classifies substances into a certain BCS class based on the oral application of the highest available dose. When the oral application concerns class 1 characteristics this would not necessarily hold for the nasal use since this may be considered as class II, as indicated above.

For most pharmacological targets, a medicine has to permeate across a biological membrane (absorption) after dissolution is completed in order to exert its desired therapeutic effect. In general, absorption characteristics differ considerably between the various administration routes, mainly due to anatomical features of individual barriers. For example, the skin differs to a large extent from the barrier properties of the intestinal mucosa. Physiologically, the skin provides protection and, consequently, only lipophilic substances can passively permeate this barrier. In contrast, the gastrointestinal tract is specialised for absorption of nutrients and water to maintain a viable organism. To effectively accomplish this physiological task, a combination of active and passive transport mechanisms are available for absorption across the gastrointestinal barrier.

Bipolar depression case study #2: modification of administration route
For the acute phase, a fast acting, sedative preparation is required, such as an injection or fast acting mouth spray. However, such preparations may have not only a different absorption profile, but also a different metabolic profile (e.g. because of enzymatic saturation). Thus, additional clinical research is required.

Rectal Absorption of Oxcarbazepine [6]
A mentally disabled young woman with status epilepticus was admitted to the hospital. The parents had misunderstood that the oral oxcarbazepine (1,600 mg/day) should not be terminated, after which the seizure occurred. The clinical situation did not allow for administration of oxcarbazepine per feeding tube. Instead, oxcarbazepine was given rectally as lipid-based suppositories (three times a day 400 mg). After 40 h, still no therapeutic blood level had been obtained, and thus a feeding tube was inserted after all, making enteral therapy possible. Adequate levels were obtained within 1–2 days.

The pharmacist should have anticipated the biopharmaceutical consequences of the physico-chemical properties of oxcarbazepine. The drug is classified as a Class II substance for oral application. Logically, lack of adequate solubility is even more evident for the rectal administration as the volume of rectal fluid is limited (see Table 17.1). With an aqueous solubility of approximately 300 mg/L, the solubility of the substance in the lipophilic base of the suppositories would certainly not be higher than 9.5 mg/mL (being a direct consequence of the value of the log P = 1.5 of oxcarbamazepine). This means that oxcarbazepine is not dissolved in the lipid but dispersed as crystals, which settle from the molten suppository once introduced in the rectal cavity. The amount of rectal liquid is limited and therefore a saturated solution will exist which involves only less than 1 mg dissolved oxcarbamazepine. Low solubility yields a low concentration and hence a low driving force for diffusion to occur. As a consequence, the rate of absorption is relatively low. This slow release may lead to hardly any uptake, due to defecation within several hours after insertion.

17.4.2 Permeability; Membrane Passage

Transfer of an active substance across a biological membrane is influenced by different physico-chemical drug properties, which are combined in Lipinski's ([7] 'Rule-of-5'. This rule predicts poor absorption of an orally administered active substance when it:

- Has a molecular weight > 500 Da
- Is lipophilic (octanol-water partition coefficient, log P > 5)
- Has the ability to form multiple hydrogen bonds

Lipinski's Rule-of-5 is not a physical law but allows reasonable prediction of membrane permeation properties of molecules that are mainly absorbed by passive diffusion. Many exceptions to this rule are reported in the literature, mainly for substances that bind to membrane transporters, including vitamins and antibiotics.

17.4.3 Liver Passage

Before an active substance enters the systemic circulation, it may be subjected to metabolic processes in the intestinal wall and the liver (usually to a much larger extent). This first-pass effect may diminish the availability of the active substance even when all other biopharmaceutical characteristics are adequate. See also Sect. 16.1.8.

17.5 Formulation

Before initiating the design of a formulation and method of preparation, additional physico-chemical properties of the active substance should be defined such as particle size and particle size distribution, salt, polymorphism, aqueous solubility in dependence on pH, hygroscopicity, melting point, sublimation behaviour, water of crystallisation, dehydration temperature. The properties of the raw material are also relevant to the physical and chemical stability and the compatibility with the excipients and packaging. Furthermore, compatibility with other active substances has to be investigated when the new substance is to be administered through the same infusion line.

Requirements for an optimal effect may require a specific release profile.

Bipolar depression case study # 3. Target product quality profile for a tablet
The tablet contains x mg of active substance Y. Based on the biopharmaceutical properties, a good absorption after oral administration is expected. Substance Y shows a 50 % first-pass metabolism, one of the metabolites is moderately active. Substance Y has a half-life of 6 h and no relation between effect and plasma kinetics is apparent. However, there is a relation between side effects and plasma profile. To be effective, a receptor occupancy > 75 % is required, during at least 5 h a day. It can be concluded from PK/PD modelling that a good balance between efficacy and side effects can be reached when the tablet has the following controlled-release profile: after 30 min, the release is >10 % but <30 %, after 1 h the release is >30 % but <50 %, etc.

Y is chemically compatible with excipients a, b, and c, but not with d, e, f, and g. Once dissolved in water, Y

(continued)

does not crystallise upon drying, but forms an amorphous matrix that crystallises in time. The amorphous phase crystallises more rapidly at a relative humidity (RH) >75 %. That is why, after drying, the granulate must be stored for 24 h at 20 °C and 90 % RH.

After selecting a suitable dosage form, the chemical, physical and microbiological stability (see Chap. 22), the type of packaging (see Chap. 24), the compatibility with administration systems (see Sect. 13.10.4), and the labelling (see Sect. 37.3) have to be investigated. Formulation design ends with the draft of the quality requirements (see Chap. 32).

In Chaps. 4–14 for every administration route the relevant principles of formulation design are dealt with. An illustrative example can be found in Sect. 5.4.2 that discusses the choice between an oral solution or suspension (or neither of them).

17.6 Method of Preparation

A pharmaceutical preparation process usually comprises of a series of individual processing steps or unit operations to produce the finished product. Every process step represents a discrete activity that includes physical changes such as mixing, dispersing, grinding, granulating, drying, compressing, and coating. Chapter 29 Basic Operations discusses several of these operations.

An associated physical, chemical, or biological property of an input or output material is qualified as an attribute. Process parameters that influence these critical product attributes (e.g., batch size, operating conditions, or moisture) are defined as critical parameters.

As an illustration of working with process steps (unit operations), the preparation method of an oral suspension is described, see Table 17.2:

Table 17.2 Sulfadiazine oral suspension 100 mg/mL [8]

Sulfadiazine	10 g
Aluminium magnesium silicate	0.54 g
Carmellose sodium M	0.54 g
Citric acid monohydrate	0.63 g
Methyl parahydroxybenzoate	0.07 g
Raspberry essence (local standard)	0.3 g
Sodium citrate	4.7 g
Syrup BP (preserved with methyl parahydroxybenzoate 1 mg per g)	30 g
Water, purified	67.2 g
Total	114 g (= 100 mL)

The preparation process as described in [8] consists of the following process steps:

- Dissolve the methyl parahydroxybenzoate in 50 mL boiling purified water.
- Disperse the colloidal aluminium magnesium silicate in the hot solution.
- Disperse the carmellose sodium in this suspension;
- Mix with the sugar syrup.
- Dissolve the citric acid monohydrate and sodium citrate in approximately 15 mL purified water, if necessary under heating.
- Mix this solution with the suspension.
- Disperse the sulfadiazine.
- Mix the raspberry essence with the suspension.
- Add with purified water and mix.

The preparation process thus consists subsequently of the process steps: dissolving – dispersing – dispersing – mixing – dissolving – mixing – dispersing – mixing – complementing/mixing.

When drafting a batch preparation instruction for a pharmacy preparation, the process steps should be described more extensively. It should be exactly described how to mix, disperse etc. for a given batch size and given equipment (see Sect. 33.4). Each process step should be coupled to an in-process control (see Sect. 17.7).

17.7 Control Strategy: Critical Quality Attributes, Process Parameters and Sources of Variability

To control the quality of the product, any relationship among the critical raw material attributes, process parameters, and quality attributes for each process should be established during development. In addition, limits need to be specified for critical process parameters that define the design space where the quality of the product is guaranteed.

A design space can be defined for process conditions such as time, temperature, pressure, pH, rate, but also for ambient conditions such relative humidity. When the window of the critical parameters is relatively broad, the process is robust. As a consequence, usual deviations and variations in the conditions are predicted to affect product quality only insignificantly.

Since equipment maintenance, training of operators who are engaged in the process, and standard operating procedures may directly or indirectly affect product quality as well, risk assessment tools (see Sect. 21.4) are necessary to reduce the number of variables under investigation.

A preparation process such as tableting has many more process parameters than for example, dissolving. The

preparation of a sterile solution has more process parameters than the preparation of a non-sterile solution. In other words: tableting is much more complicated than the preparation of a solution. With regard to pharmacy preparations, the preparation of suspension suppositories has many more variables than dispersing an active substance in a cream base.

Limits are defined within a specific batch size. Deviations of the batch size should be handled as modifications of a critical parameter and must follow a predefined change control procedure (see Sect. 35.6.10).

Every process step has critical product and process parameters.

Bipolar depression case study #4
Once dissolved in water, Y does not crystallise upon drying, but it forms an amorphous matrix that can crystallise in time. The substance is chemically less stable in the amorphous phase than in its crystalline phase. Moreover, it dissolves too fast. This is a critical parameter, since the dissolution rate is critical for the occurrence of adverse effects. The amorphous phase crystallises at a faster rate at a relative humidity >75 %. Therefore, the granulate should be stored after drying at 20 °C and 90 % RH. This conversion should be regarded as a critical process step that should thus be validated, and preferably be controlled during the process.

Critical product and process parameters need to be monitored, preferably during production. Every process step can be provided with in-process controls that monitor whether or not the critical parameters are maintained within the limits.

Apart from simple in-process controls (visual observations, recording pH-values, weights, counting, etc.) it is also possible to perform analyses. For this, large scale production utilises the term Process Analytical Technology (PAT). PAT utilises a diverse array of analytical in-process controls such as near-infrared spectroscopy (NIR, see Fig. 17.3) to quantify water content, particle size, and homogeneity of mixtures.

In-process controls and PAT allow for a more robust product quality. Both are also used to adjust the process (see Sect. 34.6).

By collecting data on processes and products, the tolerances of product and process parameters (design space) can be determined. According to Q8, design space is: "the multidimensional combination and interaction of input-variables and process parameters, of which has been shown that they guarantee the quality".

For licensed medicines, regulatory authorities only approve a design space that has been defined by the manufacturer of the particular medicinal product. Consistent with the QbD concept, modifications to the product or process within the defined design space do not have to be presented for approval to the regulatory agencies.

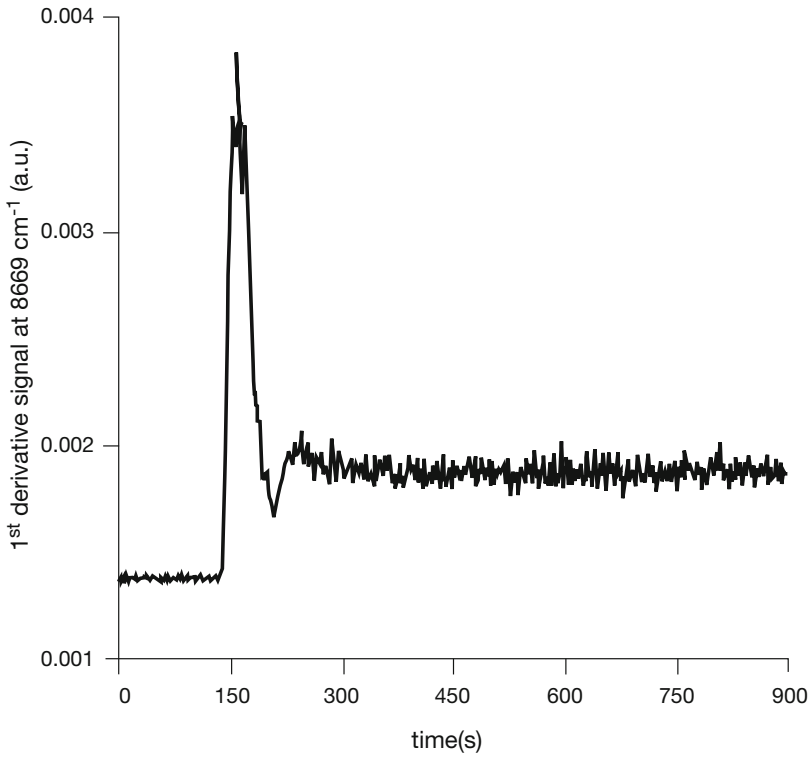

Fig. 17.3 In-process control: in-line control of the mixing with NIR (Taken from [9]). With NIR, the mixing of 15 g citric acid and 75 g Avicel PH-101 is measured. The peak resembles a quantity unmixed citric acid that passes the screen of the NIR system. After 300 s, homogeneity is obtained. Source: Recepteerkunde 2009, reprinted by permission of the copyrights holder

For pharmacy preparations, the process of standardisation of an individual formulation can be seen as defining its design space. This design space should be large enough to enable different pharmacies to prepare a product following the formulation and according to the requirements. Ways to perform that task are:

- Using raw materials of different suppliers at the design phase.
- Having a number of local and hospital pharmacies involved in preparation of test batches.
- After publishing the formulation: sampling batches from many pharmacies and analyse them, as is done in the Netherlands and Germany. These analyses provide data about the variation in practice and may lead to improvement of the formulation (and the way information about it is given) as well as to proper education of pharmacists. From a different point of view this can be seen as trying to create as many guarantees as possible to help pharmacies to remain with their preparation activities within the design space.

The individual pharmacist should control the design space with a system of professional development and product and process validation.

17.8 Product Validation

Product validation is performed to test whether the limits for the parameters have been set correctly. The main purpose of this strategy is to investigate which parts of the product and process design significantly influence the quality of the product. Such an investigation gives information about the robustness of the design. If, for example, the pH should be set within certain limits, it should be known outside of which pH-limits the properties of the product are essentially changed. Other examples are the amount of thickening agent required to prevent sedimentation of a suspension while taking a dose, or the type of mixing apparatus and the mixing time and its effect on the homogeneity of the product.

Furthermore, findings from the on-going stability investigation are a part of the product validation. This research may, for example, show that a solution would be better stored in a glass or plastic bottle. Information that is obtained during the validation research can later be used for the assessment of deviations during routine productions.

Product validation is independent of process validation, since it is independent of the location where the product is made. A validated product design subsequently requires a validated process (see Sect. 34.14) to allow for preparation of the product with a constant quality.

17.9 Product Documentation and Design in Pharmacy Preparation Practice

A product dossier allows for demonstration and transparency about the quality of medicines and if it provides all knowledge, data and experience used at the design of the product, it can be very helpful in troubleshooting or when modifications occur.

A product dossier that accompanies an application for authorisation should comply with the requirements of the European Medicines Agency (EMA). The sections and format of this product dossier – Common Technical Document (CTD) – can be found with the accompanying directives in [10]. The Q8 guideline gives guidance for the elaborating the product design in the CTD.

For agents for clinical trials, an Investigational Medicinal Product Dossier (IMPD) is required [8], see also Sects. 3.4 and 35.5.10. In the IMPD, the production and quality of both the raw materials and the products is described. Furthermore, all known data from preclinical and clinical research is summarised in this document.

Product files for pharmacy preparations are described in Sect. 33.8. National formularies such as FNA (see Sect. 39.4.5) and NRF (see Sect. 39.4.2) entail the product and process design of a large number of standard pharmacy preparations. These formularies contain the description of the formulations and method of preparation, as well as elaborate elucidations on them. Many of these elucidations reflect the QbD ideas about documentation of the design process. Information about product quality, efficacy, and safety is published in those formularies or in other clearly related sources: information leaflets for the patient or clinical information booklets for physicians.

For the scope and depth of the product file of a pharmacy preparation, no strict rules exist yet. However, the pharmacist should clearly connect the solidity of the investigation and documentation to the extent of the risk of a suboptimal design or suboptimal control strategy. A risk based approach leads for instance to the following practical solutions as they occur in the Netherlands.

17.9.1 Extemporaneous Preparation, Not Standard

When a pharmacist is to prepare an extemporaneous preparation for which no standard formulation exists, there is usually not much time for experiments and pilot batches. The risk assessment of the prescription should however be performed carefully (see Sect. 2.2). The preparation process should be validated on the level of dosage form and the preparation documentation (see Sect. 33.5), including the results of in-process controls, should be evaluated by the pharmacist before dispensing for use by the patient.

Preparation of Ivabradine Capsules (Low Dose)
A woman with persistent cardiac arrhythmia consults a cardiologist. Administration of flecainide, atenolol, and metoprolol for some weeks did not lead to improvement due to the sinus tachycardia. Having the patient's consent, the physician decides to start treatment with ivabradine (Procoralan®). Since the patient showed a hypotensive response to two doses of 5 mg, it is decided to start with a very low dose of 0.625 mg twice daily.

The raw material is not available. Therefore the pharmacist decides to prepare capsules from Procoralan® tablets. These tablets have a coating, but one without modified-release properties. Ivabradine has a high aqueous solubility and high membrane permeability (BCS class I), and thus the pharmacist disregards the coating. He mixes the ground tablets with lactose monohydrate and fills capsules with the powder blend. Product control shows that the preparation complies with requirements for uniformity of mass and deviation of the theoretical weight. Post-preparation analysis by HPLC with diode array detection shows a mean content within the acceptable limits (90–100 %) and a proper content uniformity.

17.9.2 Extemporaneous Preparation, Standard

When a pharmacist regularly produces a specific preparation for an individual patient, a better substantiation of the design quality is necessary. Both literature and experimental research may provide extra information about the pharmacotherapy and about pharmaceutical properties such as homogeneity, stability microbiological quality, compatibility, tolerability, and taste. For this, the pharmacist may use data from other pharmacies as well. Furthermore, more specific in-process controls may be added to the preparation process. An end control (usually non-destructive) by the operator is required for every batch, as well as a more specific validation of the preparation method.

17.9.3 Stock Preparation

Before a stock preparation is added to the range of products of a pharmacy, the design quality needs to be substantiated. The pharmacotherapy is evaluated and for the choice of dosage form and concentration, feedback from the users is highly valued. Production batch scaling may influence the preparation process. A strategy is set to control product quality by a combination of in-process controls (generally off-line), the testing of intermediate products, and end testing. The analytical test methods are developed and validated.

Information for patient and caregiver is drafted and, if necessary, substantiated with research, for example about the compatibility with other medicines in case of a multiple-use infusion line (so-called Y-site compatibility). The first batch that is prepared and analysed, is placed in quarantine until evaluation of the preparation and analysis has been performed. Preferably, the batch size is always the same, since batch size is a critical variable, and thus a modification requires a change control procedure. In case of a suspected short shelf life, the results of the first time points of the shelf-life analysis should be awaited before the product can be used.

17.10 Product Life Cycle Management

Life cycle management could support an active attitude towards improving the design quality of the product, as a contrast with just reacting to events, see also Sect. 35.4.1. In contrast to licensed medicinal products for instance, pharmacy preparations are usually not tested on efficacy and safety before use in patient care. Their safety is based upon literature. Therefore, it is important to evaluate the outcomes of a treatment (pharmacovigilance, see also Sect. 35.4.2) and to relate this knowledge to the continuation, modification, or discontinuation of the product. The treatment outcomes generally consist of observations by the physicians, case reports, or retrospective analysis of patient dossiers.

Midazolam Oral Solution Becomes Enema
For pre-operative sedation of children, the anaesthesiologist applies midazolam (0.5–0.8 mg/kg, maximally 15 mg orally or rectally). Midazolam has a beneficial profile for small surgical procedures because it has a fast onset of action, gives retrograde amnesia, and has a short half-life, which causes the patient to wake up quickly. However, the midazolam oral solution that is used in many hospitals has a very unpleasant taste. Especially during second and subsequent treatments, the oral administration of midazolam may stress the children. In some cases, children refuse to take the mixture or spit it out.

The physician requests the hospital pharmacy to develop and prepare an enema. At first, the pharmacist attempts to improve the taste of the oral solution. After testing and rejecting various possibilities, the pharmacist assesses the request for an enema as justified. The tolerability of the formulation of midazolam in the rectum is evaluated by adding a dye to the first batch.

(continued)

The nurses assess the amount of leakage by a pre-operative check of the underpants of the patient. Administration of the midazolam enema followed by a suppository results in no leakage. The entire dose can be administered, which is often not possible for the oral solution. The physicians are content with the sedation. Based on this experiment, the hospital pharmacist and physician decide to introduce the treatment to the entire hospital.

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Physical Chemistry

18

Wouter Hinrichs and Suzy Dreijer - van der Glas

Contents

Abstract

Many pharmaceutical dosage forms are liquids or semi-liquids such as solutions, colloidal systems, suspensions and emulsions. This chapter deals with the physico-chemical backgrounds that are important for the preparation of these types of dosage forms. Successively solubility, rheology, interfaces, surface active agents, disperse systems and osmosis are addressed. Physical chemistry plays an important role in the design of liquid or semi-liquid pharmaceutical dosage forms. By changing physico-chemical parameters intentionally or unintentionally, the biopharmaceutical properties and thus the therapeutic activity of an active substance can drastically change. Many physico-chemical properties are related to each other. For example, changing the composition of a solvent mixture does not only affect its solubility for an active substance but also its surface tension, osmotic value, etc. The chapter is primarily intended to explain physico-chemical aspects described in other chapters. Many examples of the design of pharmaceutical preparations are described to clarify and illustrate the concepts, considering excipients as well as active substances, and small molecules as well as proteins.

Keywords

Solubility • Viscosity • Suspensions • Osmotic value • Surface activity • pH • Rheology • Disperse systems • Colloidal systems

Based upon the chapter Fysische Chemie, by Wouter Hinrichs, Suzy Dreijer, Herman Vromans in the 2009 edition of Recepteerkunde.

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18.1 Solubility

Aqueous solubility is an important property of active substances. For example, incompatibility reactions leading to undesired precipitation in parental formulations can be avoided with a good knowledge of solubility properties [1–3]. Furthermore, there can be several reasons to influence

Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_18,

the aqueous solubility of an active substance. It may be required to increase the solubility to be able to prepare dosage forms in which the active substance is dissolved or it may be more useful to disperse an active substance as particles in a suspension, thus in the undissolved form.

Bringing active substances into solution can have important advantages:

- The preparation method is much simpler than that of disperse systems.
- The dosage accuracy is much better than of disperse systems.
- The rate of absorption and the bioavailability will be higher than those of disperse systems (see Sect. 16.1.5).
- Solutions in certain dosage forms are much better tolerated than suspensions. Suspensions (except for nanosuspensions) are not suitable for parenteral infusion for instance.

In a number of cases however, suspensions are preferable:

- If an active substance is unpalatable, the undissolved form can mask the taste.
- If the active substance is unstable in solution.
- If a reduction of the dissolution rate of an active substance is desired in order to slow down the absorption.

The pH of Tetracycline Mouthwash 5 % FNA (Table 18.1) is adjusted to 5.0–5.5 with sodium citrate to minimise the solubility of tetracycline hydrochloride. Tetracycline hydrochloride solutions are unstable.

Table 18.1 Tetracycline Mouthwash 5 % [4]

Tetracycline hydrochloride	5.0 g
Methyl parahydroxybenzoate	0.1 g
Sodium citrate	6.5 g
Sorbitol, liquid (crystallising)	65.5 g
Tragacanth	0.5 g
Water, purified	40.0 g
Total	118.2 g (= 100 mL)

Chloramphenicol has an extremely bitter taste. When this antibiotic is used orally, it should be formulated as a suspension, using the insoluble chloramphenicol palmitate.

In the European Pharmacopoeia (Ph. Eur.) various definitions for solubilities in water are described, i.e. from "very soluble" to "practically insoluble" (Table 18.2) [1]. The solubility is also indicated by the amount of water, in millilitres, necessary to dissolve 1 g of the substance at room temperature. The solubility of a substance can also be specified in grams per Litre.

Table 18.2 Explanation of the Definitions for the Solubility in Water as specified in the Ph. Eur.

	Solubility[a]
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble	More than 10,000

[a]Amount of water in millilitres required to dissolve 1 g of an active substance

Although the terms in Table 18.2 to describe the solubility of an active substance are still used in many handbooks, from a clinical view they are no longer used. The principle of solubility in perspective is now used. That is, the solubility of an active substance is connected to the dose that should be administered to the patient. Thus, solubility in perspective is not a pure physico-chemical characteristic of the active substance. For example, the solubility will not cause any problems when an active substance with a low solubility has to be given to a patient as a solution at a very low concentration. In Chap. 17 Product design and in Chap. 16 Biopharmaceutics this concept will be explained in more detail.

The rate at which an active substance dissolves does not only depend on the solubility of the active substance. The dissolution of an active substance is described by the Noyes-Whitney equation:

$$\frac{dm}{dt} = \frac{D \cdot A}{h}(C_s - C) \qquad (18.1)$$

where dm/dt is the dissolution rate, D the diffusion coefficient of the active substance in solution, A the contact surface area of the active substance with the solvent, h the thickness of the diffusion layer, C_s the solubility of the active substance and C the concentration of the active substance in the bulk of the solution.

Amongst other strategies, the solubility of a substance can be influenced by variation of the pH, salt formation, variation of the solvent, complex formation, or derivatisation. These concepts, with pharmaceutical preparations as examples, are explained below.

18.1.1 Solubility and pH

Most substances are more easily dissolved in water when they are ionised. The degree of ionisation for many substances depends on the pH. Many active substances are weak acids or weak bases. The degree of ionisation, and thus the solubility, can be influenced by adjusting the pH of the medium. The solubility of a non-ionised weak acid can be increased by raising the pH, while the solubility of a non-ionised weak base can be increased by lowering the pH.

The pK_a value of an acid indicates how weak the acid is: the higher the pK_a value, the weaker the acid. Thus when a weak acid is dissolved in pure water, the decrease of the pH and the extent of dissociation of the acid will be less when the pK_a value increases. The relationship of the pH, pK_a, and the concentrations of a non-ionised acid [HA] and its salt [A-] is given by the Henderson-Hasselbalch equation:

$$\mathrm{pH} = \mathrm{pK_a} + \log\frac{[A^-]}{[HA]} \qquad (18.2)$$

When the pK_a of a substance is known, the fraction ionised active substance as a function of the pH can be calculated using the following derivatives of this equation:

$$\text{fraction ionised } 1 - \left(10^{\mathrm{pH}-\mathrm{pK}_a} + 1\right)^{-1} \text{ (for a weak acid)} \qquad (18.3)$$

$$\text{fraction ionised } 1 - \left(10^{\mathrm{pK}_a-\mathrm{pH}} + 1\right)^{-1} \text{ (for a weak base)} \qquad (18.4)$$

The pK_a of phenobarbital is 7.4. When the pH is adjusted to 5.4, 7.4 or 9.4, the fraction ionised active substance will be: $1 - \left(10^{5.4-7.4} + 1\right)^{-1} = 0.01$; $1 - \left(10^{7.4-7.4} + 1\right)^{-1} = 0.5$ or $1 - \left(10^{9.4-7.4} + 1\right)^{-1} = 0.99$, respectively. This example emphasises that by varying the pH around the pK_a, the fraction of ionised active substance can be strongly affected: up to 2 pH units below the pK_a, only 1 % is ionised, whereas at 2 pH units above the pK_a 99 % is ionised.

For a further understanding of the dissolution of a substance by salt formation, some basic concepts of analytical chemistry are summarised (Fig. 18.1).

When an aqueous solution of a weak monovalent acid in water is titrated with NaOH, the pH strongly increases with the first amounts of added NaOH, but when the pH almost reaches the proteolytic constant or the pK_a value of the acid, the pH changes to a lesser extent. When the pH is one to two units above the pK_a, the pH again rises sharply upon adding more NaOH. For a titration, the amount of added reagent (in this case NaOH) divided by the quantity of the substance to be determined (both in moles) has been defined as λ. The

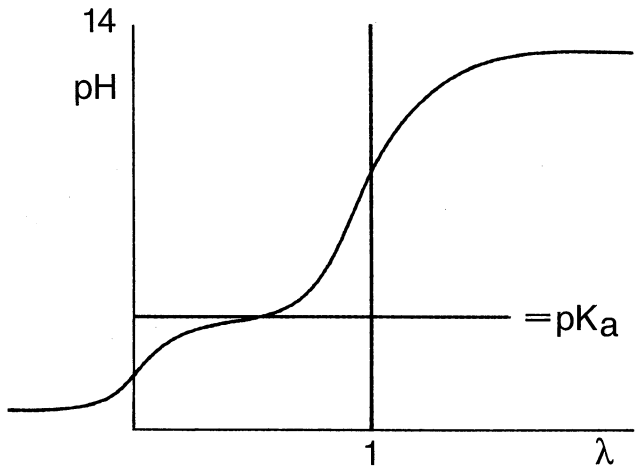

Fig. 18.1 Titration of a weak monovalent acid with a strong base

pH of the initially acidic solution (λ = 0) is dependent on the concentration and the degree of dissociation of the acid. When the pH is around the pK_a, the solutions acts as a buffer because the addition of a small amount of acid or base will hardly affect the pH. When λ = 0.5, the pH equal to the pK_a, there is an equal amount of acid and salt present. In this situation, the buffer capacity is maximal. The equivalence point of the titration is found when λ = 1.

A salt composed of a weak base and a strong acid lowers the pH in aqueous solution. Conversely, a salt composed of a weak acid and a strong base raises the pH in aqueous solution. Examples are lidocaine hydrochloride (acid reaction) and sodium phenobarbital (alkaline reaction), respectively. When the pH of aqueous solutions of these substances is adjusted to pH = 7, lidocaine and phenobarbital, respectively, are partially formed again and precipitate.

The so-called pHp equations (18.5 and 18.6) can be used to calculate the solubility of a weak acid or a weak base as a function of the pH [2, 5]. pHp is an abbreviation for pH precipitation, the pH at which just no precipitation occurs. At a given concentration, the weak acid will precipitate when the pH is lower than the pHp and the weak base will precipitate when the pH is higher than the pHp.

$$\mathrm{pHp} = \mathrm{pK}_a + \log\left(\frac{S - S_0}{S_0}\right) \text{ (for a weak acid)} \qquad (18.5)$$

$$\mathrm{pHp} = \mathrm{pK}_a + \log\left(\frac{S_0}{S - S_0}\right) \text{ (for a weak base)} \qquad (18.6)$$

where S_0 is the solubility of the undissociated acid or base and S the concentration of the acid or base which has been added initially (both in mole/L).

The pHp equation can be illustrated in more detail with an example of a calculation. Suppose a 1 % w/v solution of

Table 18.3 Furosemide Oral Solution 2 mg/mL [7]

Furosemide	0.2 g
Methyl parahydroxybenzoate	0.075 g
Propyl parahydroxybenzoate	0.025 g
Saccharin sodium	0.1 g
Trometamol	0.1 g
Water, purified	ad 100 mL

Table 18.4 Tetracycline Hydrochloride Cream 3 % [8]

Tetracycline hydrochloride	3 g
Sodium citrate	4 g
Water, purified	11 g
Cetomacrogol cream FNA[a]	82 g
Total	100 g

[a]Cetomacrogol emulsifying wax (BP) 15 g, Sorbic acid 200 mg, Decyl oleate 20 g, Sorbitol, liquid (crystallising) 4 g, Water, purified 60,8 g. Total 100 g

sodium phenobarbital should be prepared. The following information can be obtained from the Merck Index [6]:
MW phenobarbital = 232.32 g/mol;
MW sodium phenobarbital = 254.22 g/mol;
Solubility phenobarbital in water = 1 g/L;
pK_a (phenobarbital) = 7.4.

It follows:
$S_0 = 1/232.32 = 0.0043$ mol/L;
1 % w/v corresponds to 10 g/L; thus:
$S = 10/254.22 = 0.0393$ mol/L;
Thus the pHp becomes:
$pHp = 7.4 + \log\left(\frac{0.0393-0.0043}{0.0043}\right) = 8.3.$

It follows that in order to obtain a 1 % w/v sodium phenobarbital solution, the pH must be at least 8.3. At a pH lower than 8.3, phenobarbital will remain partially undissolved.

However, the choice of pH cannot be unlimited. In particular at a high or a low pH, the active substance can for example be chemically unstable. In addition, an extreme pH can be incompatible with other components in the solution, for example, preservatives. In addition, the selected pH should also be compatible with the route of administration.

Thus with the correct setting of the pH, either a solution or a suspension can be obtained. The preparation of solutions and suspensions by manipulation of the pH will be illustrated with a number of examples.

There are several ways to adjust the pH to a certain value, which are essentially not different. Either NaOH or HCl can be added to obtain a suitable pH at which the salt is soluble, or the pHp equation can be used to calculate the amount of an acid or a base with its corresponding salt that will be soluble.

Table 18.5 Tetracycline Hydrochloride Eye Drops Solution 0.5 % [9]

Tetracycline hydrochloride	0.5 g
Borax	0.5 g
Sodium chloride	0.7 g
Water, purified	ad 100 mL

Examples of pharmaceutical preparations in which the active substance is dissolved by influencing the pH are infusion or inhalation solutions with acetylcysteine and a furosemide oral solution (Table 18.3). In both cases, a weak acid is brought into solution by raising the pH. Usually sodium hydroxide is used for acetylcysteine and in the formulation of Table 18.3 the primary amine trometamol is used for furosemide.

Tetracycline hydrochloride easily dissolves in water, to give an acidic solution. In Tetracycline hydrochloride cream 3 % FNA, the pH is adjusted to about 5.5 by adding sodium citrate to a tetracycline hydrochloride solution (Table 18.4). At this pH, tetracycline is insoluble and therefore a suspension is formed. In undissolved state tetracycline is chemically more stable than in the dissolved state. Moreover, a pH of 5.5 is only slightly lower than the third proteolytic constant of citrate ($pK_a = 6.4$ at 25 °C), so a citrate buffer is formed. This saves tetracycline from dissolving again due to slight pH decrease.

Tetracycline is an amphoteric substance which forms salts in both an acidic and an alkaline environment. The substance dissolves at a pH higher than about 8. This was made use of in the preparation of a solution of tetracycline for eye drops (Table 18.5). By the addition of borax, a pH of about 8.2 is reached. As a consequence, tetracycline readily dissolves.

Is a bumetanide infusion solution 5 mg in 50 mL (syringe for a pump) possible as a solution? The pH of the licensed product (injection solution 0.5 mg/mL) is 7.0. According to information from the manufacturer, the concentration should be maximally 0.1 mg/mL when mixed with infusion fluids. The reason is that when the concentration is higher than 0.1 mg/mL bumetanide will precipitate unless the pH of the preparation is maintained. The solubility of (non-ionised) bumetanide is 0.1 mg/mL or even lower. The licensed product contains alkaline additives in order to reach a concentration of 0.5 mg/mL. If these additives are diluted, the pH becomes too low, which may cause precipitation of non-ionised bumetanide.

Theophylline can be dissolved by salt formation with ethylenediamine or other amines. Previously, ethylenediamine theofyllinate (aminophylline) was used in oral preparations. Soluble double salts of theophylline can be prepared using sodium acetate and sodium glycinate. However, excellent absorption is achieved after oral administration of theophylline as such, for example in capsules, so

Table 18.6 Solubility of some Mineral Salts in Water in grams per Litre

	22 °C	38 °C
$CaSO_4.2H_20$	2.41	2.22
$CaCO_3$	0.014	0.018
$Ca_3(PO_4)_2$	0.02	Not available
$CaHPO_4.2H_2O$	0.316	Not available
$Ca(H_2PO_4)2.H_2O$	18	Not available
$MgSO_4.7H_2O$	710	910
$MgCO_3$	0.106	Not available
$MgHPO_4.7H_2O$	3	2[a]

[a]Magnesium and phosphate ions can co-exist in mineral infusions. As can be seen in the table, the solubility of magnesium hydrogen phosphate decreases when the temperature is increased. As a result, during sterilisation a precipitate can be formed in a solution that was originally clear. After cooling, however, this precipitate will dissolve again

Table 18.7 Solubility Product of some Mineral Salts in Water

	Solubility product (S)[a]	pS (= – logS)
$CaSO_4$	7.1×10^{-5}	4.15
$CaCO_3$	5.0×10^{-9}	8.30
$Ca_3(PO_4)_2$	2.1×10^{-33}	32.7
$MgCO_3$	6.8×10^{-6}	5.17
$Mg_3(PO_4)_2$	6.5×10^{-5}	4.18
$Mg_3(PO_4)_2$	3.5×10^{-5} [b]	4.46

[a]Room temperature
[b]38 °C

administration as a solution does not seem to be necessary from a biopharmaceutical viewpoint. After absorption, at a physiological pH of approximately 7.4 there is obviously no difference in the degree of ionisation of the substance whether it was administered as such or as a salt. Therefore, no differences in physiological activity between an active substance and its salt are expected. However differences in solubility and dissolution rate and differences in absorption and absorption rate may generally influence the earlier stages of administration and lead to a difference in bioavailability. In addition, the counter ion may induce (undesirable) side-effects. The use of ethylenediamine was abandoned because of the sensitising properties, even after oral use [10]. In addition, it might be toxic, being a secondary amine.

18.1.2 Solubility and Salt Formation

Not all salts exhibit a good aqueous solubility. A number of inorganic salts having a relatively low molecular weight and a low water solubility are listed in Table 18.6. Also the solubility product often is given (Table 18.7). This allows us to determine the effect of other ions in the solution on the solubility of a given substance, for example, when sodium carbonate is added to a solution of magnesium chloride. Also the reduction of the solubility of the poorly soluble calcium carbonate can be calculated when a certain amount of the readily soluble sodium carbonate or calcium chloride is added. This reduction in the solubility of, in this case, calcium carbonate is also known as the common ion effect.

An example of this can be found in solutions for parenteral nutrition that contain calcium and phosphate ions (see Sect. 13.9.2). At the pH of parenteral nutrition mixtures dihydrogen phosphate and monohydrogen phosphate will both be present. The solubility of calcium dihydrogen phosphate is 18 g/L and that of calcium monohydrogen phosphate 0.3 g/L.

As long as the pH of the mixture remains below 6.4, precipitation is not likely to occur. But for instance at a pH of 7.4, 60 % of the phosphate will be present in the form of monohydrogen phosphate, with an increasing risk of precipitation. Therefore, it is always best to check the solubility of the product.

Solubilities of many active substances are listed in Merck Index [6] and in Martindale [11]. When a pharmaceutical preparation contains various salts there may be (multiple) combinations of ions that are incompatible and may result in the formation of a precipitate. For example, after addition of a chloride salt to a chlorhexidine digluconate solution, the insoluble salt chlorhexidine chloride is formed resulting in precipitation. Exact data on this are hard to find. In general, the risks of precipitation are high for combinations of large positive and negative ions. Examples are carmellose anion and lauryl sulfate, which is a component of Lanette wax.

Insoluble salts can be made to mask an unpleasant taste or to prevent local irritation of the gastrointestinal tract. Well-known examples are ferrous fumarate suspension and potassium hydrogen tartrate suspension. In Sect. 5.4.10 more examples of insoluble salts to mask unpleasant tastes are discussed.

18.1.3 Solubility in Non-aqueous Solvents

When the aqueous solubility of an active substance is too low, it can be dissolved in a different solvent or mixture of solvents, which is compatible with the route of administration. The solubility of a lipophilic substance (a substance which dissolves well in the oil or fat but poorly in water) can be increased by making the dissolution medium (water) less polar by the addition of less polar but water-miscible solvents. Often mixtures of water, ethanol and propylene glycol are used. Also glycerol and macrogol (polyethylene glycol) can be used. The polarity of a solvent can be expressed by its dielectric constant, ε (for examples see Table 18.8, the higher the dielectric constant, the higher the polarity).

Table 18.8 Dielectric Constants of Some Solvents

Solvent:	Dielectrical constant, ε (25 °C)
Water	79
Glycerol	43
Propylene glycol	32
Ethanol	24
Macrogol 400	12

The dielectric constant of a mixture of solvents can be calculated as the sum of the dielectric constants of its components, each multiplied by the volume fraction of that solvent. The dielectric constant of a mixture of solvents A, B, . . . is thus:

$$\varepsilon_{\text{mixture}} = f_A \times \varepsilon_A + f_B \times \varepsilon_B + \ldots \qquad (18.7)$$

where f_A, f_B . . . are the volume fractions of the solvents A, B, respectively, and ε_A, ε_B, . . . the dielectric constants of the solvents A, B, . . ., respectively.

This equation can be used when the composition of a liquid mixture is to be changed, while keeping the dielectric constant the same. For example, assume that an active substance dissolves in a mixture of 20 % v/v water and 80 % v/v ethanol. As such a large volume percentage of ethanol is not desirable for many pharmaceutical applications; it has to be reduced to 20 % v/v. In order to maintain the dielectric constant, macrogol 400 can be used to replace a large part of the ethanol. The volume percentages of water and macrogol 400 can be calculated as follows:

Original mixture:

$$\begin{aligned}\varepsilon_{\text{mixture}} &= f_{water} \times \varepsilon_{\text{water}} + f_{ethanol} \times \varepsilon_{\text{ethanol}} \\ &= 0.2 \times 79 + 0.8 \times 24 = 35\end{aligned}$$

Adjusted mixture:

$$\begin{aligned}\varepsilon_{\text{mixture}} &= f_{water} \times \varepsilon_{\text{water}} + f_{ethanol} \times \varepsilon_{\text{ethanol}} + f_{PEG} \times \varepsilon_{\text{PEG}} \\ &= \text{y} \times 79 + 0.2 \times 24 + (0.8 - y) \times 12 = 35\end{aligned}$$

It follows that the volume fraction of water, y, is 0.31 and the volume fraction of the macrogol 400, (0.8 – y), 0.49. The composition of the adjusted mixture by volume percentage is thus: water/ethanol/ macrogol 400 = 31/20/49.

Pharmaceutical examples of solutions where a relatively poorly water soluble substance is dissolved in a mixture of solvents are injections with diazepam or digoxin (Table 18.9). In both of these preparations a mixture of ethanol, propylene glycol and water is used as the solvent.

Paracetamol in an oral solution could at first be dissolved in 85 % glycerol (Table 18.10)

Table 18.9 Digoxin Solution for Injection 1 mL = 0.25 mg [12]

Digoxin	0.025 g
Citric acid monohydrate	0.075 g
Disodium phosphate dodecahydrate	0.450 g
Ethanol (96 %)	10 g
Propylene glycol	40 g
Water for injections	ad 100 mL

Table 18.10 Paracetamol Oral Solution 24 mg/mL [13]

Paracetamol (500-90)	2.4 g
Ethanol (96 per cent)	8.1 g
Glycerol (85 per cent)	74 g
Raspberry flavouring (local standard)	0.1 g
Sodium (S)-lactate solution 600 g/kg	6.65 g
Sorbitol, liquid (crystallising)	30.75 g
Total	122 g (= 100 mL)

Table 18.11 Phenobarbital Solution for Injection 50 mg/mL [14]

Phenobarbital	5.0 g
Ethanol (96 %)	31.5 mL
Propylene glycol	35.0 mL
Sodium hydroxide solution 2 M (local standard)	q.s.
Water for injections	ad 100 mL

The relationship between the solvent medium, the pH and the pK_a can be clearly illustrated using barbiturates as examples. Phenobarbital can be dissolved in water as its sodium salt. This requires a pH of 10 or higher. At this pH (it appears that) barbiturates decompose by ring-opening under the formation of malonylurea derivatives. The shelf life of such aqueous barbiturate solutions for oral administration is therefore limited to approximately 1 week. In addition, heat sterilisation of an aqueous solution for injection is not possible at this pH. In the formulation of injections, this problem has been solved by improving the solubility at slightly alkaline pH through the addition of a less polar solvent mixture e.g. a mixture of propylene glycol and ethanol.

In a mixture of 35 % v/v water, 35 % v/v propylene glycol and 30 % v/v ethanol at a pH of 8.9, the solubility of phenobarbital at room temperature is approximately 11 % w/v. An example of a formula for a phenobarbital injection of 50 mg/mL is given in Table 18.11. The pH is usually adjusted to a value between 7 and 8. Phenobarbital in these injections is thus partially in the ionised form. The non-ionised form is dissolved by the organic solvents.

An alternative way to prepare solutions of lipophilic substances is to use solvents that are not miscible with water such as oils or esters of wax alcohols.

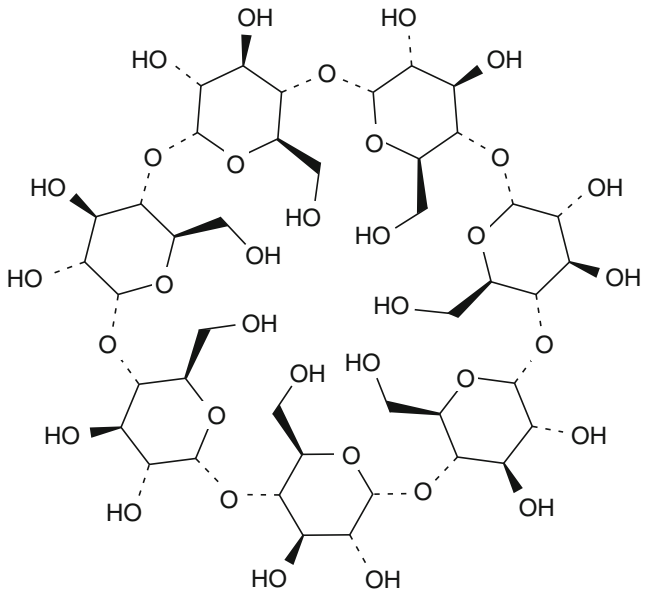

Fig. 18.2 Chemical structure formula of betadex (betacyclodextrin)

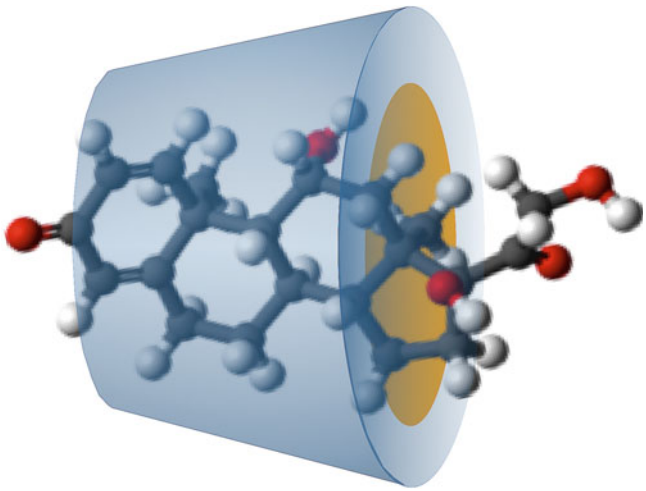

Fig. 18.3 Schematic representation of a betadex–prednisolone complex

18.1.4 Solubility and Complex Formation

Sometimes two substances strongly interact (non-covalent) with each other in solution. In these cases complexes are formed whose solubility is different from that of the individual components. For example, iodine is only soluble in water in the form of a complex with iodide ions or with povidone. Iodinated povidone has the additional advantage that its solutions do not irritate the skin, as is the case for solutions where iodine is dissolved by complexation with potassium iodide.

Cyclodextrins are another category of substances that are used for complex formation. Cyclodextrins are ring-shaped oligosaccharides consisting of six, seven or eight glucose units referred to as alpha-, beta-, and gammacyclodextrin, respectively (see Fig. 18.2 for the chemical structure of betacyclodextrin) [15].

The Ph. Eur. has a monograph for betacyclodextrin: Betadex. Cyclodextrin forms a hollow truncated cone structure which is hydrophilic at the outside and contains a non-polar cavity into which lipophilic molecules fit (Fig. 18.3).

The diameter of the non-polar cavity increases when cyclodextrin contains more glucose units. As a consequence, small lipophilic substances form better complexes with cyclodextrins having a small non-polar cavity and large lipophilic substances better with cyclodextrins having a large non-polar cavity. On the outside, cyclodextrins are polar by which they are fairly soluble in water. The aqueous solubility of cyclodextrins can be affected by derivatisation. Hydroxypropylbetacyclodextrin (Hydroxypropylbetadex Ph. Eur.) for example dissolves much better in water than the non-derivatised betadex (betacyclodextrin). Thus, the aqueous solubility of lipophilic molecules increases after complexation with cyclodextrins. By selecting the right combination of active substance and cyclodextrin, the solubility of poorly water-soluble substances can be increased.

Amongst other applications, cyclodextrins are used for the oral administration of lipophilic active substances. By complexing piroxicam with cyclodextrin a product is formed which shows an enhanced dissolution rate and therefore a more rapid absorption. An itraconazole oral mixture containing cyclodextrin has been developed to guarantee sufficient absorption of the active substance. Cyclodextrins are also used in parenteral preparations. Fluasteron is an antineoplastic agent which is preferably administered by injection to the patient at a concentration of 1,000 micrograms per millilitre. Its aqueous solubility, however, is only 0.045 microgram per millilitre. With a 20 % w/v hydroxypropylbetacyclodextrin solution, the desired concentration can be achieved [16].

18.1.5 Solubility of Derivatives

Derivatisation is a method of changing the properties of a molecule by means of a chemical reaction where an additional group is covalently coupled. By derivatisation, the solubility of substances can be either decreased or increased. In pharmacy, esters are important derivatives. This will be explained in greater detail on the basis of corticosteroids of which the C21-alcohol group can be esterified. These esters are not effective but should first be hydrolysed in the body. The rate of hydrolysis of esters in solution is strongly pH

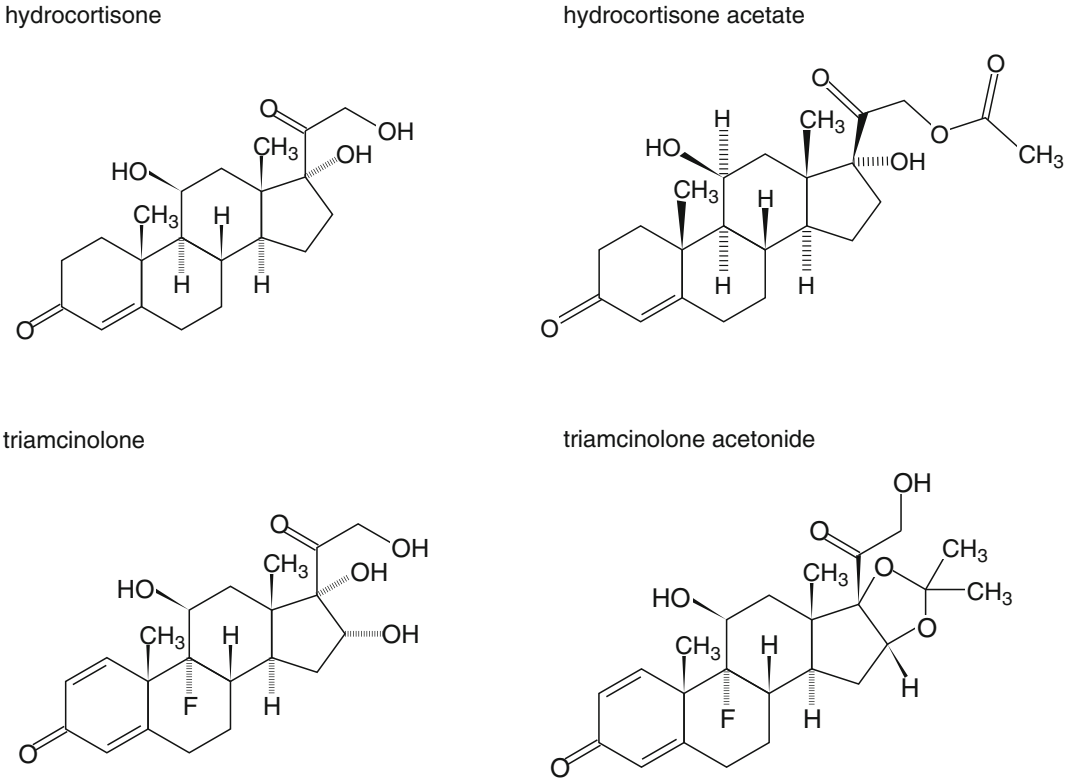

Fig. 18.4 Chemical structure formulas of hydrocortisone, hydrocortisone acetate, triamcinolone and triamcinolone acetonide

dependent. In a strongly acid or alkaline environment hydrolysis rapidly occurs. *In vivo*, the hydrolysis is catalysed by esterases.

Esters of corticosteroids with a polyvalent acid group, for example succinic acid or phosphoric acid, are soluble in their salt form. This is because most of the non-esterified acid groups are deprotonated when sufficiently high pH is chosen. Examples of corticosteroids which are esterified with polybasic acids are hydrocortisone sodium succinate, prednisolone sodium phosphate and dexamethasone sodium phosphate. In an aqueous medium with a pH of about 7 or higher, hydrocortisone sodium succinate is largely ionised and thus fairly soluble. At this pH, however, the hydrolysis of the ester is quite fast (this ester is most stable at a pH of about 4.5). As a result, dissolved in water, this substance is unstable and therefore its shelf life is limited.

In aqueous solution, prednisolone sodium phosphate and dexamethasone sodium phosphate are more stable than hydrocortisone sodium succinate. At a pH of about 8, the acid groups are sufficiently ionised to make the substance very soluble, while the phosphate ester is reasonably stable at this pH. Water soluble corticosteroids are mainly used in parenteral preparations, eye drops, oral mixtures and enemas. Examples are prednisolone oral mixtures and dexamethasone injections.

In order to increase their lipid solubility, corticosteroids have been esterified with monocarboxylic (fatty) acids. Examples include hydrocortisone acetate, beclomethasone dipropionate and betamethasone isovalerate. For triamcinolone, the following method has been developed to make the substance lipophilic: the hydroxyl groups at the C16 and C17-position of triamcinolone are used to form a cyclic acetal (Fig. 18.4). Although the formed substance, triamcinolone acetonide, is not a fatty acid ester, with regard to lipid solubility it behaves as such.

Fatty acid esters of corticosteroids may be used for the preparation of depot injections, either as oily solutions or aqueous suspensions. The nature of the fatty acid, in particular the length of the carbon chain, determines, to a large extent, its solubility and therefore its release and absorption rate into the bloodstream. In addition, in the case of corticosteroids, solutions or microcrystalline suspensions in either oil or water are used for intra- or periarticular injection.

Dermatology is another important field where fatty acid esters of corticosteroids are applied. Examples are creams with hydrocortisone acetate and triamcinolone acetonide, respectively. These fat-soluble derivatives are used because they show better penetration into the lipophilic stratum corneum of the skin.

Table 18.12 Hydrocortisone Eye Drops 1 % [17]

Hydrocortisone acetate (micronised)	1 g
Benzalkonium chloride	0.001 g
Disodium edetate	0.1 g
Disodium phosphate dodecahydrate	0.04 g
Povidone	2.5 g
Sodium chloride	0.85 g
Sodium dihydrogen phosphate dihydrate	0.03 g
Water, purified	ad 100 mL

Table 18.13 Acid Ear Drops with Hydrocortisone 1 % [18]

Hydrocortisone (micronised)	1 g
Acetic Acid (30 %) DAC	2.4 g
Propylene glycol	96.6 g
Total	100 g

Lipophilic esters of corticosteroids either suspended in water or dissolved in ethanol, propylene glycol, or macrogol 300 are applied in eye and ear drops, respectively. Table 18.12 gives an example of an aqueous suspension containing 1 % micronised hydrocortisone acetate.

Flumetasone pivalate and fludrocortisone acetate are commercially available as solutions in macrogol and a mixture of glycerol and propylene glycol, respectively.

The aqueous solubility of free, not esterified, corticosteroids and their lipophilic esters do not differ substantially. However, their solubility in ethanol is better. Examples are: hydrocortisone, prednisolone and dexamethasone. These free corticosteroids are mainly used in solid oral dosage forms. Hydrocortisone is applied in Acid Ear Drops with Hydrocortisone 1 % FNA (Table 18.13), because the underivatised steroid dissolves in propylene glycol, in contrast to its acetylated derivative. Although the lipophilic versions/variants are preferred in dermatological preparations, the free corticosteroids may also be applied.

18.1.6 Solubility and Supersaturation

If the solubility of a substance increases with temperature, its dissolution rate can be enhanced by heating. When a saturated solution is obtained at an elevated temperature, it will be supersaturated after cooling. Also solutions that are prepared at room temperature can become supersaturated when they have to be stored in the refrigerator because of their chemical instability. It may happen that supersaturation does not immediately result in crystallisation. Such a solution is called metastable and sooner or later crystallisation will occur. This process can proceed faster if solid particles are present in the solution. These solid particles may act as crystallisation nuclei and so initiate the crystallisation process.

Table 18.14 Magnesium Citrate Oral Solution 80 mg/mL [19]

Magnesium carbonate, light	3.00 g
Citric acid monohydrate	8.33 g
Lemon Spirit BP	0.40 g
Syrup B.P.	10 g
Water, purified	ad 100 mL

The rate of crystallisation increases when the difference between the temperature at which the solution is prepared and the storage temperature increases. This is because the driving force for crystallisation will increase when the temperature difference increases. Supersaturation can occur in starting materials or intermediates, but supersaturated compositions are also used in therapy. Some relevant examples will be briefly discussed below.

Liquid Sorbitol 70 % (crystallising) is a supersaturated starting material. Before using/processing this product in preparations the operator should check whether crystallisation has occurred. Crystals can be dissolved by heating and cooling again. Using a crystallised solution in several portions at different times will lead to a too low sorbitol concentration in the first portions, while in subsequent portions the concentration will be too high if the crystals have been dissolved again. Thus, when using a crystallised material in preparations, there is a risk that the content in the final product will not be correct.

Calcium gluconate 100 mg/mL is an example of a supersaturated injection solution.

Mannitol 20 % w/v is an example of a supersaturated solution for infusion. The solution should be inspected for the presence of crystals. As said, the crystals can be dissolved by heating and cooling again.

Magnesium Citrate Oral Solution 80 mg/mL FNA (Table 18.14) is a supersaturated solution of magnesium citrate. The patient should be warned that crystallisation can take place after about 2 weeks, or earlier when the preparation is stored in the refrigerator. Magnesium citrate mixture USP has a similar formula.

Given the risks of crystallised products, the use of supersaturated solutions in pharmaceutical preparations should be avoided as much as possible.

18.2 Rheology

The rheology describes the flow behaviour of fluids. When a force is exerted on a liquid, it will start to flow. The resistance to flow is called dynamic viscosity but in practice it is

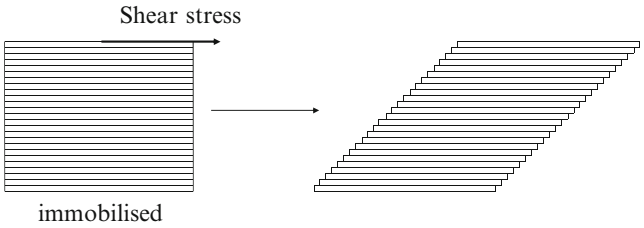

Fig. 18.5 Effect of shear stress on a cube of liquid

usually simply referred to as viscosity. Consider a cube of liquid composed of slices like a stack of cards (Fig. 18.5).

When the bottom of the cube is immobilised and a shear force is applied at the top, the upper slice will get the maximum speed, the slice underneath a little less speed, and so on, until the bottom slice which does not move. Consequently, there is a velocity gradient, D (shear rate). According to the Newton's law (18.8), viscosity (η) is defined as the force exerted per unit area (τ) (shear stress) divided by the shear rate (D). The dimension of viscosity is Pascal.second (Pa.s), but in practice the derived dimension millipascal.second (mPa.s) is generally used.

$$\eta = \frac{\tau}{D} \tag{18.8}$$

Rheology and viscosity are important for a proper understanding of the stability of disperse systems and for the accuracy of the dosage of liquid preparations.

18.2.1 Rheograms

Two types of flow behaviour can be distinguished, namely Newtonian and non-Newtonian flow. Non-Newtonian flow is further divided into plastic, pseudo-plastic and dilatant flow.

When the shear rate of a Newtonian fluid is plotted as a function of the shear stress, a straight line is obtained that passes through the origin (Fig. 18.6a). This means that at any shear stress, the viscosity of the fluid is the same, since shear stress divided by shear rate is constant. In this case, one may speak of the viscosity of a Newtonian fluid.

Conversely, the viscosity of non-Newtonian fluids is dependent on the applied shear stress and is referred to as apparent viscosity. When a fluid exhibits plastic flow, a certain minimum shear stress must be applied, called yield stress, before the fluid starts to flow (Fig. 18.6b). At a shear stress of less than the yield stress, the viscosity is thus infinitely large and the liquid behaves like a solid. Above the yield stress, the viscosity decreases with increasing shear stress. Also in the straight part of the curve in Fig. 18.6c, the viscosity decreases with increasing shear stress. This is

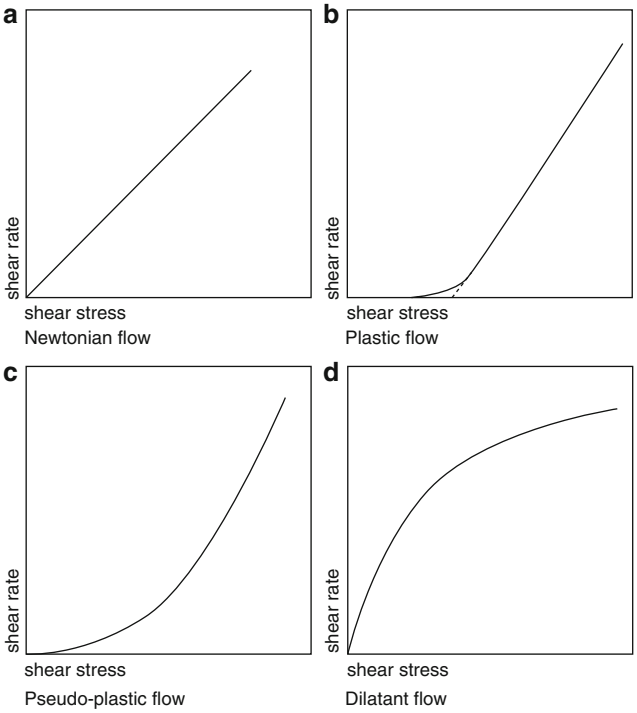

Fig. 18.6 Rheograms of liquids with Newtonian, plastic, pseudo-plastic and dilatant flow behaviour. Source: Recepteerkunde 2009, ©KNMP

because viscosity is shear stress divided by shear rate (τ/D), and not the change of the shear stress divided by the change of the shear rate ($d\tau/dD$). Pseudo-plastic flow strongly resembles plastic flow. The difference is that pseudo-plastic fluids do not exhibit a yield stress. The consequence of this is that the fluid never exhibits solid state behaviour because even at a very low shear stress flow takes place.

Gels and emulsions show plastic and pseudo-plastic behaviour. At rest, these systems are more viscous than when they flow. Creams and ointments should be easily spreadable, but they should not drip from the skin. Emulsions and suspensions should be as stable as possible and pouring should be easy.

This aim is even better achieved if, after a temporary high shear stress, the recovery of the higher viscosity is delayed. This phenomenon is called thixotropy. This phenomenon can often be seen in daily practice. For example, highly viscous emulsions like tomato ketchup and other cooking sauces temporarily have a lower viscosity after vigorous shaking. Also cutaneous emulsions often exhibit thixotropic behaviour.

Finally, if the viscosity increases with increasing shear stress, the flow behaviour is called dilatant (Fig. 18.6d). It is characteristic for pastes with a high content of solids. The pharmaceutical applicability of fluids with this flow behaviour is limited because they are often poorly

spreadable. Only in a few cases this may be an advantage, namely when the paste must possess abrasive properties, as in cases where chalk is the main component. During rubbing, the skin is vigorously massaged due to the increasing viscosity of the paste.

18.2.2 Measurement Methods

The techniques to measure viscosity can be subdivided into two groups.

In the first group of methods, the relationship between the shear stress, τ, and the velocity gradient, D, is measured. The main device within this group is the rotational viscometer. The method is described in the European Pharmacopoeia [1]. In a vessel, a measuring body (spindle) is rotated in the test sample. The resistance to the rotation speed is measured as torque in the shaft. Because several combinations of vessel and spindle can be chosen for this equipment, the torque of both fluids with a very high and very a low viscosity can be measured accurately. For each combination, the manufacturer supplies a table or often computer software, which can be used to derive the viscosity from the torque and the rotational speed. Thus, with this method the viscosity can be calculated directly. The method is applicable to both Newtonian and non-Newtonian fluids. By varying the rotational speed, complete rheograms can be obtained. This provides information about both non-Newtonian behaviour and thixotropy. The method is especially useful in the investigation of the stability of viscous systems.

In the second group of methods, gravity is used as a force to bring the fluid in motion. The suspended level viscometer as described in [20] is based on this principle. The Ford cup, a sort of funnel through which the fluid flows, is another example. The flow rate of a fluid per unit area of the outlet opening of, for example a capillary tube or cup is proportional to the viscosity, η, but inversely proportional to the relative density, ρ, of the fluid. The rate at which the fluid level decreases thus depends on η/ρ. Viscosity divided by density, η/ρ, we call kinematic viscosity, with m^2/s as dimension. By calibrating the device with a fluid having a known kinematic viscosity, the kinematic viscosity of the fluid can be calculated. The equipment used for these methods are usually much cheaper than those in the first group. Moreover, they are useful for designing preparations. The disadvantage of these viscometers is that they are only suitable for measuring the viscosity of Newtonian fluids. However, with these viscometers information about the pouring behaviour can be achieved which is, for example, relevant to emptying a bottle.

With an extensometer and a penetrometer, the viscosity is not directly measured but information about the flowability of materials can be achieved. In an extensometer, an ointment or cream is allowed to spread between two glass plates which yields the spreading capacity. With a penetrometer, the resistance during the penetration of a pin connected to a cone into a product is measured. This method can be used to characterise highly viscous preparations, e.g. ointments.

18.3 Interfaces and Surface Active Agents

Many pharmaceutical preparations consist of several phases. For example, a suspension consists of solid particles dispersed in a liquid and an emulsion is composed of drops of a liquid dispersed in a second liquid which is immiscible with the first. Interfaces exist between the different phases. In this section the properties of interfaces are discussed.

18.3.1 Surface and Interfacial Tension

Molecules exert attractive (Van der Waals) forces to each other. In the bulk of a liquid, this force is equal in all directions. Because fewer molecules per unit of volume are present in the air than in a fluid, the Van der Waals forces at the interface of liquid and air are smaller in the direction of air than in the direction of liquid. As a result, there is a net force (or pressure if force per unit area is considered) perpendicular to the liquid surface in the direction of the bulk of the liquid. Due to this pressure, which is called surface tension, the molecules located at the surface are in a higher Gibbs free energy state than in the bulk of the liquid. This implies that if a new surface is created, molecules are in a higher Gibbs free energy state. In other words, it takes Gibbs free energy to create a new surface. A similar situation occurs at the interface of two non-miscible liquids and the interface between a liquid and a solid. In these cases one speaks of interfacial tension. The terms surface tension and interfacial tension are often used interchangeably. The dimension of surface and interfacial tension is J/m^2 [5, 21].

Molecules consisting of a highly water soluble or hydrophilic moiety and a highly oil soluble or lipophilic moiety are called amphiphilic. These molecules accumulate at interfaces in such a way that the water soluble or hydrophilic part is oriented to the hydrophilic (aqueous) phase and the oil soluble part to the lipophilic (oil) phase. This causes lowering of the surface or interfacial tension. Therefore, the Gibbs free energy required to create a new surface or interface can be reduced by using amphiphilic substances. In the context of this application, these substances are referred to as surface active agents or surfactants. An overview of surfactants used in pharmaceutical preparations can be found in Sect. 23.6.

In order to make a proper choice of a surfactant for a specific preparation, a system has been developed in which

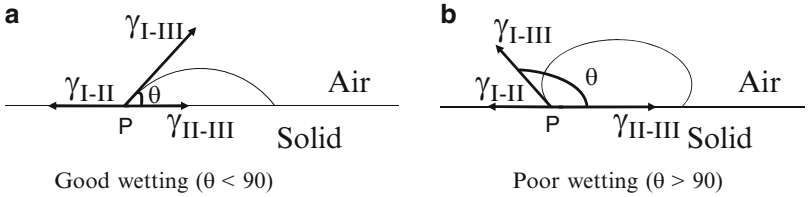

Fig. 18.7 Equilibrium of forces at the point P due to surface and interfacial tensions. The force vectors are shown as arrows for explanation see Sect. 18.3.2. Source Recepteerkunde 2009, ©KNMP

the relative contribution of the hydrophilic and the lipophilic part of the molecule is expressed as a number. This system is called hydrophilic-lipophilic balance, abbreviated as HLB. Surfactants that are equally soluble in oil and in water have an HLB value of 7. Surfactants which are more soluble in oil have a HLB-value < 7 and surfactants which are more soluble in water have an HLB-value > 7. Surfactants may have an HLB value of 1-40. In designing of a formula, the HLB value is generally used as a number to characterise surfactants.

18.3.2 Wetting

Wetting means bringing a solid in close contact with a liquid. This process is of importance for example for the preparation of suspensions and the disintegration of a tablet in the gastrointestinal tract.

When a drop of liquid is placed on a solid (smooth) surface, the drop will spread depending on the properties of the liquid and of the solid. For example, a drop of water completely spreads out on a (clean, grease-free) glass but hardly at all on a Teflon® surface. The angle formed by a liquid at the three phase boundary where a liquid, air and solid intersect as shown in Fig. 18.7, is called the contact angle θ. Young's law describes the relationship between the surface and interfacial tension of the three phases: air (I), solid (II) and liquid (III) and contact angle (θ). In equilibrium, the forces will compensate each other at the point P, so:

$$\gamma_{I-II} = \gamma_{II-III} + \gamma_{I-III} \cos\theta \qquad (18.9)$$

or

$$\cos\theta = \left(\gamma_{I-II} - \gamma_{II-III}\right)/\gamma_{I-III} \qquad (18.10)$$

When the contact angle θ is larger than 90° it is called poor wetting and when it is smaller than 90° it is called good wetting. Wetting can be improved by the addition of surfactants to the aqueous phase. As a result, the contact angle θ becomes smaller (thus cos θ becomes larger) and finally approaches to 0. In complete wetting ($\theta = 0°$) the droplet spreads out completely on the surface.

When an aqueous suspension is prepared, the air at the surface of the particles should be replaced by the aqueous phase. When a poorly wettable substance is used ($\theta > 90°$) this will not happen. The particles can float when the air is not replaced. This phenomenon is called flotation. Poorly wettable and floating particles often adhere to the wall of the bottle neck. As a result, dosing is difficult with such systems. Pharmaceutical examples of poorly wettable substances are: phenytoin, sulfur, zinc oxide and barium sulfate. By adding a surfactant, the interfacial pressure can be reduced by which wetting is improved.

To reduce the risk of foaming, surfactants that lower the interfacial pressure only moderately are mostly used.

To improve wetting, surfactants with an HLB larger than 15 are used, such as sodium dioctyl sulfosuccinate (Aerosol OT ®), ethoxylated castor oil, poloxamer, sodium salts of higher alcohol sulfates (sodium lauryl sulfate) and polysorbates, but also polymers with interfacial activity as, for example hydrogel formers as methylcellulose, hypromellose, etcetera. A further discussion of these substances can be found in Sects. 23.6 and 23.7. In practice, propylene glycol or a thickening agent will lower the interfacial tension to a sufficient extent.

18.3.3 Micelle Formation and Solubilisation

Surfactants are not only applied to reduce the surface or interfacial tension. They can also be used to increase the solubility of substances. When dissolved in water above a certain minimum concentration, aggregates of surfactants are formed, also called micelles. Lipophilic substances can be brought into solution (solubilised) using these micellar solutions. Micelles can be prepared as follows.

Consider an aqueous solution of which the surfactant concentration is gradually increased. At low concentration of the surfactant, the molecules are predominantly located at the surface. If the concentration is increased, more of the surfactant molecules will be present at the surface and the surface tension will decrease. Above a certain concentration, however, the surface will be full and the extra molecules will migrate into the bulk of the solution. When this occurs, the surface tension will not further decrease.

The surfactants molecules that migrate into the bulk of the solution form micelles. The structure of the micelles is such that the lipophilic part of the surfactant molecules is at the inside of the micelle, so that the thermodynamically unfavourable contact of the lipophilic part of the surfactant molecules with the water molecules is minimal. The minimum concentration at which micelles are formed is called the critical micelle concentration (CMC). The exact shape of the micelles and the CMC differ from substance to substance. Micelles have the size of colloids and also behave physico-chemically as such. This behaviour will be discussed in more detail in Sect. 18.4.1.

In an oil phase, micelles with the inverted structure can be formed, i.e. the hydrophilic part of the surfactant molecules is oriented towards the inside. These micelles are also called reverse micelles.

Many poorly water soluble substances can, molecularly disperse, adsorb or absorb on or into micelles. These micellar solutions are optically clear. This is called solubilisation. Examples from the Dutch formulary FNA are oral aqueous preparations with vitamin A (retinol palmitate) or D (cholecalciferol (Table 18.15)). Another example is a licensed oral mixture with ciclosporin.

Table 18.15 Cholecalciferol Oral Solution[a] 50.000 IU/mL [22]

Cholecalciferol concentrate (oily form) 2,000,000 IU/g	2.5 g
Citric acid monohydrate	0.24 g
Polysorbate 80	12.5 g
Potassium sorbate	0.3 g
Star anise oil	0.22 g
Syrup BP	12.5 g
Water, purified	75.7 g
Total	104 g (= 100 mL)

[a]This solution is actually a solubilisate

The order of mixing the components in this preparation is important in order to achieve solubilisation: first polysorbate to cover the flask with a layer, then carefully adding and mixing the cholecalciferol concentrate and star anise oil. The ratio between the amount of polysorbate and the cholecalciferol concentrate is also important.

Solubilisation may also be undesirable. Solutions containing polysorbate cannot be preserved with for example methyl or propyl parahydroxybenzoate. The preservative effect of these substances is inhibited by solubilisation or even nullified. With sorbic acid/sorbate, preservation is possible, provided that a higher than conventional concentration is used.

18.4 Disperse Systems

Many liquid and semi-liquid pharmaceutical preparations are disperse systems. Disperse systems are defined as systems in which a substance is distributed as particles (discontinuous) into a dispersion medium (continuous). Three types of disperse systems will be discussed which are pharmaceutically relevant: colloidal systems, suspensions and emulsions. In both colloidal systems and suspensions, solid particles are dispersed in a liquid. The difference is that in colloidal systems the particles do not settle, while they do in suspensions. This difference is caused by the size of the particles. In colloidal systems, the particles are so small (1 nm – 1 μm) that the Brownian motion (diffusion caused by thermal energy) is stronger than the force of gravity so that they remain suspended in the liquid and do not settle. In suspensions, the particles are larger (>1 μm) and as a consequence the force of gravity is stronger than the Brownian motion which makes them settle (if the density of the particles is larger than that of the dispersion medium). Emulsions consist of non-miscible liquids. Two types of emulsions will be discussed: oil drops dispersed in water (oil-in-water emulsion or o/w emulsion) and water drops dispersed in oil (water-in-oil emulsion or w/o emulsion). There are also more complex structures such as w/o/w emulsions and bi-continuous systems. However, these systems will not be discussed.

18.4.1 Colloidal Systems

18.4.1.1 Lyophilic and Lyophobic Systems

Colloidal systems can be divided into lyophilic and lyophobic systems. Lyophilic colloids have a strong affinity with the dispersion medium by which a solvation shell around the particle is formed. This process is called solvation and if the dispersion medium is water it is called hydration. A polysaccharide dissolved in water is an example of a lyophilic colloidal system. The solvation shell is formed by hydrogen bonds between the hydroxyl groups of the polymer molecules and the water molecules. Pharmaceutical examples are solutions of dextran, used as plasma expanders. Micelles are also lyophilic colloids. Example of such a system is the aqueous cholecalciferol oral mixture (Table 18.15). In these preparations, a lipophilic fluid is dissolved in an aqueous medium by incorporating it in micelles. Because this type of colloids falls apart on dilution to concentrations below the CMC, they are also known as association colloids. Lyophobic colloids have no affinity with the dispersion medium. Thus, in this type of colloids no solvation shell is formed around the particles. An example of lyophobic particles are colloidal gold particles (with a diameter of 1 nm – 1 μm) dispersed in water. There are no

hydrogen bonds or other interactions between the gold particles and the water molecules, so the solvation shell is missing. If the dispersion medium is water, lyophilic colloids and lyophobic are also referred to as hydrophilic and hydrophobic colloids, respectively.

18.4.1.2 Stabilisation of Colloidal Systems

Basically, colloidal systems are not thermodynamically stable. The particles have the tendency to attract each other by Van der Waals forces and aggregation can take place. Yet there are many colloidal systems that can be stored for extended periods of time without this happening. This is because two stabilising mechanisms may play a role.

Around lyophilic colloids a solvation shell is formed, which acts as a protective layer around the particles. This protective layer prevents the two particles from approaching each other too closely. In addition, the particles repel each other when they are electrostatically charged. This repulsion is not fully determined by the charge at the surface of the particle (Nernst potential) but by the charge at a small distance from the particle which is called zeta or ζ-potential. During the diffusion of the particle through the dispersion medium a layer of the dispersion medium around the particle is dragged along with it. Therefore, it is not the charge of the particle, but the charge of the particle together with this layer of dispersion medium that is relevant for the stability of the system. If the particle is charged and when ions are present in the dispersion medium, there will be more ions of opposite charge (counter ions) in the near vicinity of the particle than ions of the same charge due to electrostatic attraction. The charge of the particles is therefore neutralised to a certain extent. This neutralisation increases with increasing ionic strength. This implies that the zeta-potential is smaller than the Nernst potential and decreases with increasing ionic strength. If the dispersing medium contains polyvalent counter-ions, the zeta-potential and the Nernst potential can even have opposite charges.

The zeta-potential can also be influenced by the absorption of specific ions from the dispersion medium onto the surface of the colloidal particle. For example, if a positively charged surfactant adsorbs onto a positively charged colloidal lyophobic particle, the zeta-potential becomes larger than the Nernst potential.

Moreover, the adsorption of surfactants onto lyophobic particles has a second effect. Because only the lyophobic part of the surfactant adsorbs onto the lyophobic particle, its lyophilic part is oriented towards the dispersion medium. This lyophilic part forms a protective layer by which the particles can approach each other less easily. This effect is called steric stabilisation. Surfactants usually do not adsorb onto lyophilic particles. However, by covalently linking hydrophilic polymers to their surface, we can also achieve steric stabilisation of lyophilic colloidal particles. A detailed description of the forces of attraction and repulsion can be found in literature [5, 21].

So a lyophilic colloidal system can be stabilised by two mechanisms, namely by a solvation shell and by electrostatic repulsion. This implies that a lyophilic colloidal system with a zero zeta-potential does not necessarily have to be unstable. This is because the stabilising effects of the solvation shell may be sufficient. A lyophobic colloidal system, however, lacks a solvation shell. A lyophobic colloidal system can therefore only be stable if the zeta-potential is sufficiently high (positive or negative).

18.4.1.3 Destabilisation of Colloidal Systems

A sol is a colloidal system in which the repulsion forces between the colloidal particles dominate in such a way that they can move freely with respect to each other. Lyophilic colloidal particles can be destabilised either by making the particles more lyophobic or by reducing the zeta-potential or both. Lyophobic colloidal particles, however, can only be destabilised by reducing the zeta-potential. Lyophilic colloidal particles can be rendered more lyophobic by adding a fluid which is miscible with the dispersion medium but in which the colloidal particles are lyophobic (for example, ethanol when the dispersion medium is water). The zeta-potential of colloidal particles (lyophilic or lyophobic) can be reduced by adding an electrolyte to the system. When a sol is partially destabilised, the forces of attraction are stronger than the forces of repulsion. As a result, the particles will no longer be able to move freely with respect to each other, but they will form a continuous three-dimensional network extending throughout the dispersion medium. Such a structure is called a gel and it is called a hydrogel if the dispersion medium is water. This sol-gel transition can be observed by the flow behaviour. Because the colloidal particles in sols move more or less freely with respect to each other, Newtonian or pseudoplastic flow behaviour can be observed. Gels exhibit a yield stress because first the continuous three-dimensional structure must be broken down before flow can occur. In this case plastic flow behaviour can be observed. Because the colloidal particles in a gel cannot move freely with respect to each other, a gel can be considered as a partially or controlled destabilised sol. However, when sols are extensively destabilised a compact aggregate will be formed, which will start to float or sediment depending on the density difference with the dispersion medium. They are no longer considered as colloidal systems. This process is called salting-out when it is induced by the addition of an electrolyte.

Carbomer is a special hydrogel former. The chemical name for carbomer is polyacrylic acid. As such the polymer is poorly soluble in water. However, when monovalent bases (e.g. NaOH) are added, the carboxylic acid groups are deprotonated. By deprotonation the polymer becomes negatively charged and thereby hydrophilised and forms a hydrogel.

Carbomer in combination with monovalent bases, however, is not extremely hydrophilic as it also forms a gel in ethanol.

Addition of salts may have two effects:

1. Divalent ions such as calcium and magnesium form cross-links between deprotonated carboxylic acid groups by which the negative charge is neutralised and the hydrophilisation is counteracted. To prevent this, disodium edetate is added in (aqueous) carbomer gel pH 6.5 NRF (Table 18.16).

Table 18.16 Carbomer Gel pH 6.5 [23]

Carbomer 35000	1 g
Disodium edetate	0.1 g
Propylene glycol	10 g
Trometamol	1 g
Water, purified	87.9 g
Total	100 g

2. At high ionic strength the (absolute) zeta-potential of carbomer will decrease, which may result in precipitation and is an example of salting-out of a colloid.

Carbomer, carmellose sodium, hydroxypropylcellulose and other cellulose derivatives are examples of well-known polymers that form hydrogels. An overview of different gel formers can be found in Sect. 23.7.

DLVO-Theory

The destabilisation of colloidal systems can also be described with the DLVO (Deryagin-Landau-Verwey-Overbeek) theory. This theory has been proposed for lyophobic colloidal systems but can also be applied qualitatively to lyophilic colloidal systems. If the potential energy is plotted as a function of the distance of two particles, a curve is obtained as shown in Fig. 18.8.

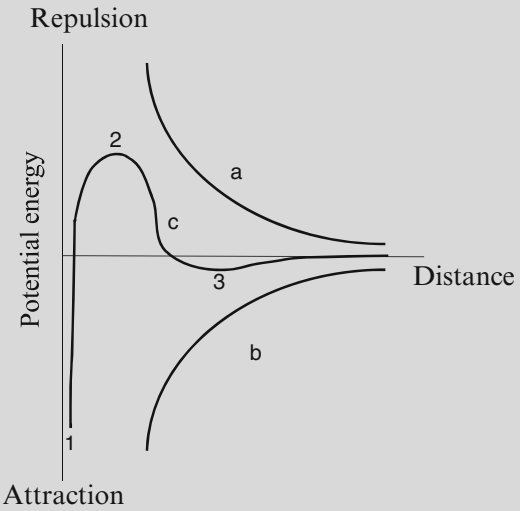

Fig. 18.8 Potential energy between two particles as a function of their distance. (**a**): repulsion due to zeta-potential; (**b**): attraction as a result of Van der Waals forces; (**c**): net potential energy curve; primary minimum, maximum and secondary minimum are indicated by 1, 2 and 3, respectively. Source: Recepteerkunde 2009, reprinted by permission of the copyrights holder

This curve is established by adding the potential energies resulting from the attraction and repulsion forces to each other (with a negative potential energy meaning attraction and a positive potential energy repulsion). Suppose that two particles approaching each other have too little thermal energy to pass the maximum. In this situation they approach each other to a distance where the secondary minimum is located and thus attract each other. Now two situations can occur:

1. The particles have sufficient thermal energy and they spontaneously diffuse away from each other. This kind of system is a sol. Such a situation is also called deflocculation.
2. The particles have insufficient thermal energy and remain at the same distance. This kind of system is a gel, because external energy (in the form of yield stress) is needed to bring the particles at a greater distance from each other. This is called reversible aggregation or flocculation.

Suppose a lyophobic colloidal system that behaves like a sol and it is destabilised by decreasing the zeta-

(continued)

potential. At a certain point, a sol-gel transition will take place. The reduction of the zeta-potential by the addition of electrolyte is expressed in the energy curve by a lowering of the potential energy in the secondary minimum. The addition of a certain amount of electrolyte will result in such a lowering of the potential energy in the secondary minimum that the particles have insufficient thermal energy to spontaneously diffuse away from each other. However, addition of electrolyte also results in a lowering of the maximum of the potential energy curve. Therefore, when a huge amount of electrolyte is added, it is possible that the particles have sufficient thermal energy to pass the maximum. The particles approach each other now to a distance where the primary minimum is located. Compact aggregates are formed and there is no longer a colloidal system. Because the attractive forces are so high, the original colloidal system cannot be restored by adding external energy. This process is called irreversible aggregation or coagulation.

A great deal of research has been performed into the use of poloxamers for the controlled release of active substances [24]. Poloxamers, also referred to as Pluronics or Lutrols, consist of triblock copolymers having a central hydrophobic polypropylene oxide block and on both sides a hydrophilic polyethylene oxide block (Fig. 18.9).

By varying the length of the blocks, polymers with different physical properties can be achieved. At low temperatures, these polymers are generally soluble in water and form sols. When the temperature is increased, however, a sol-gel transition may take place. This is caused because, with increasing temperature, the thermal energy and thus also the Brownian motion of the molecules increases. As a result, the hydrogen bonds between the water molecules and the polymer become weaker. The stabilising effects of the solvation shell will therefore decrease and the attraction forces will become dominant, resulting in gelation. The temperature at which the sol-gel transition takes place depends on the composition of the polymer (length of the three blocks) and the concentration. In addition, the sol-gel transition temperature can be influenced by the addition of other substances. For example, the sol-gel transition temperature will be greatly reduced by the addition of a small amount of carmellose sodium. This makes it possible to prepare a solution of poloxamer (and an active substance) that behaves as a sol at a low temperature, for example room temperature or lower, but transforms into a gel at body temperature. Therefore, the solution can be administered at low temperature as a free flowing liquid to a patient after which a gel is formed in situ by the increase of the

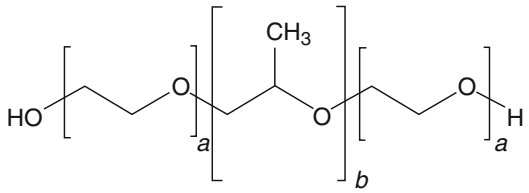

Fig. 18.9 Chemical structure of poloxamer

temperature. Because the gel slowly erodes *in vivo*, the active substance is slowly released. In principle, different routes of administration for this delivery system are possible. Preparations based on poloxamers have been studied for e.g. parenteral (subcutaneous and intramuscular injection), rectal, vaginal, nasal, ocular, and dermal administration. E.g. a poloxamer based morphine-containing hydrogel for the treatment of large-scale skin wounds has been developed [25].

18.4.1.4 Protein Solutions as an Example of Colloidal Systems

Until the beginning of the twenty-first century, in pharmacy, the particles in a colloidal system usually did not consist of active substances but of excipients, such as viscosity enhancers. The number of publications in the pharmaceutical literature on colloidal systems in which the dispersed particles solely consist of a drug substance or consist of carrier systems in which an active substance has been incorporated, however, has increased dramatically in recent years.

Important medicines within this so-called nanotechnology are therapeutic proteins. Protein solutions are becoming ever more popular within pharmacy. This is due to the fact that the unravelling of the human genome and the recent developments in the field of biotechnology offer access to a growing number of proteins that can be used for the treatment of various diseases and disorders. Due to their specific physico-chemical properties, these medicines must be handled in a different way from the classical drugs, which are usually relatively small organic molecules. The specific three-dimensional structure of proteins is essential for their therapeutic action.

The structure of proteins can be described at four levels:

1. Proteins are polymers built up from amino acids. The sequence of the amino acids is called the primary structure.
2. Parts of the protein form specific three-dimensional structures, for example alpha-helices (spiral like structures) and beta-sheets (plate like structures), which are called the secondary structure. The secondary structure is mainly stabilised by hydrogen bonds.

3. The relative orientation of the structural elements with respect to each other is called the tertiary structure. This structure is stabilised by hydrogen bonds, disulfide bonds, electrostatic interactions and hydrophobic interactions.
4. In some cases, several chains of amino acids, also referred to as polypeptide chains, form complexes. For example, insulin forms hexamers in the presence of zinc ions. The relative orientation of the polypeptide chains with respect to each other in such a complex is called the quaternary structure.

Some proteins also contain, besides amino acids, oligo- or polysaccharides. These substances are called glycoproteins.

One of the major problems with proteins is that they are usually not stable. Physical or chemical changes may lead to changes in the three-dimensional structure. This may not only cause a loss of efficacy but it can also have dramatic effects such as the induction of antibodies and severe immune responses.

Some practical advice to improve the stability of proteins is given below.

Protein solutions should not be stored at a pH which is equal to their iso-electric point. At the iso-electric point, the amount of deprotonated carboxylic acid groups and protonated amino groups are equal and thus the net charge of the particle is zero. In that situation the zeta-potential is zero and irreversible aggregation can easily occur. For the same reason, the electrolyte concentration in the solution should not be too high. A very low or high pH is not recommended because the hydrolysis of proteins is both acid and base catalysed. The oxidation of many proteins is catalysed by the divalent metal ions, in particular Fe^{2+} and Cu^{2+}. Divalent metal ion catalysed oxidation of proteins can be prevented by the addition of disodium edetate to complex these ions. However, certain divalent metal ions can also act as stabilisers for specific proteins.

Proteins can in particular irreversibly adsorb onto hydrophobic surfaces. Storage of a protein solution in polypropylene vials is therefore not recommended. In addition, protein solutions are sensitive to shear forces. The use of peristaltic pumps during the preparation of formulations should therefore be avoided. By refrigerated storage and transportation, the degradation processes of protein solutions can be slowed down, and thus their shelf life increased. However, freezing must be prevented since ice formation can damage proteins. Alternatively, proteins can be stabilised by freeze-drying them. Sucrose or other sugars are often added to the solution as a stabiliser during freeze-drying to avoid damage to the protein during the freezing and the drying phase of the process. During the reconstitution, by adding water to the freeze dried samples, vigorous shaking should be avoided. During vigorous shaking a large liquid-air surface is created at which denaturation can easily occur. For an overview of the stabilisation and formulation of proteins for pharmaceutical applications see references [26] and [27].

Summarising, physical degradation of proteins can be caused by:

- Aggregation
- Denaturation
- Adsorption onto surfaces
- Precipitation

Chemical degradation can be caused by:

- Deamidation
- Oxidation
- Hydrolysis
- Racemisation
- Reduction disulfate bridges/disulfide exchange

18.4.2 Suspensions

Suspensions are regularly used as a dosage form. Examples can be found in oral suspensions (co-trimoxazol suspension), dermatological preparations (zinc oxide or calamine lotions like Zinc oxide lotion NRF (Table 18.17)), parenteral preparations (corticosteroid injections, medroxyprogesterone injection) and a suspension in the form of a solid dispersed in a melted fat base as in the case of suppositories.

As with colloidal systems, suspensions consist of particles dispersed in a liquid. As a result, the physico-chemical properties of suspensions are, in principle, similar to those of colloidal systems. As described in the introduction to Sect. 18.4, the main difference is that the particles in a suspension are larger (>1 μm) than in a colloidal system (1 nm – 1 μm). As a result, the particles settle in a suspension (if the density of the particles is greater than the density of the dispersion medium, which is generally the case) while this is not the case in a colloidal system. Fast sedimentation of particles in a suspension has major drawbacks. Pouring out a partially settled suspension in several portions or at different times leads to too low particle concentrations in the first portions and too high in later portions. In the past this has had fatal consequences, when a 4 months old boy got a threefold dose of spironolactone [29].

Table 18.17 Zinc oxide Cutaneous Suspension [28]

Zinc oxide	25 g
Glycerol (85 %)	5 g
Ethanol (90 %) BP	25 g
Water, purified	45 g
Total	100 g

18.4.2.1 Sedimentation Behaviour

The sedimentation rate of the particles in a suspension can be calculated using Stokes' law:

$$v = \frac{2r^2(\rho_1\text{-}\rho_2)g}{9\eta} \qquad (18.11)$$

where v is the sedimentation rate, r the radius of the particle, ρ_1, the density of the particle, ρ_2, the density of the medium, g the acceleration due to gravity and, η the viscosity of the medium.

From this equation, it can be deduced that the rate of sedimentation decreases as the particle size decreases, the difference in the density of the particles and the medium decreases and the viscosity increases.

When applying this equation, the zeta-potential of the particles has also to be taken into account. Again the curve can be used in which the potential energy is plotted as a function of the distance of two particles, as discussed for colloidal systems (Fig. 18.7). The difference with colloidal systems is that the maximum in the curve for suspensions is generally higher. As a result, coagulation or irreversible aggregation almost never occurs in practice. Usual situations are either reversible flocculation or aggregation when the zeta-potential is small or deflocculation when the zeta-potential is large. The sedimentation behaviour is largely affected by whether or not flocculation or aggregation occurs, as described below.

In a deflocculated system the particles will not aggregate and therefore settle separately from each other. Because, according to Stokes' law, the sedimentation rate increases with particle size, large particles will arrive earlier on the bottom of the container than smaller particles. Because the particles do not attract each other, the voids between the large particles are gradually being filled up with the small particles. Therefore, a very compact sediment (cake) is slowly built up from the bottom of the container (Fig. 18.10a).

If the suspension also contains particles smaller than 1 μm (the colloidal fraction of the suspension), these particles will not settle but will continue to be suspended in the liquid so that the liquid above the sediment remains cloudy. The sediment exhibits dilatant flow behaviour.

In a flocculated system, the particles do attract each other and aggregates will be formed anywhere in the fluid. These aggregates have very open structures. This is because when a particle approaches an aggregate, it will be immobilised by the attractive forces at the outside of the aggregate. This makes diffusion of the particle to possible void spaces in the inside of the aggregate impossible. As everywhere in the fluid aggregates are formed, a large and loose sediment is formed (Fig. 18.10b). This typical way of settling of flocculated suspensions may be called sedimentation, but more precisely subsidencing as is suggested by [5]. Because the aggregates rapidly increase in size the subsidencing also progresses rapidly. Any further settling and compaction of the sediment is unlikely to occur. Once the sedimentation has been completed, a very open sediment is obtained due to the cavities in the aggregates. As a result, at the same volume fraction of particles, the volume of the sediment of a flocculated suspension will be much larger than in a deflocculated suspension. The liquid above the sediment is clear because particles smaller than 1 μm are included in the aggregates. The sediment exhibits plastic flow behaviour.

Both deflocculated and flocculated systems have advantages and disadvantages. In a deflocculated system sedimentation proceeds slowly but once it is completed, it is very difficult to disperse the very compact sediment. The

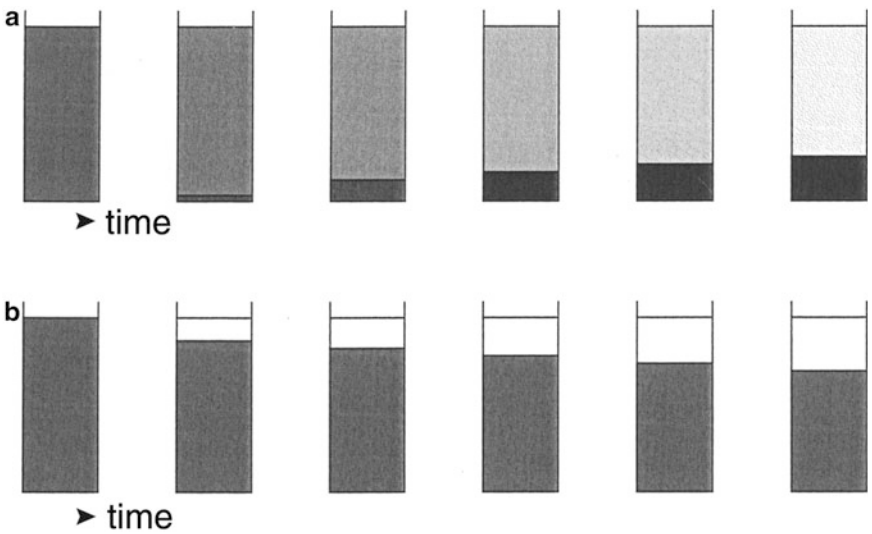

Fig. 18.10 Schematic representation of deflocculated (**a**) and flocculated (**b**) sedimentation. Source: Recepteerkunde 2009, ©KNMP

Table 18.18 Properties of a deflocculated and a flocculated suspension

Deflocculated suspension	Flocculated suspension
Sediment built up from the bottom	Subsidencing sediment
Slow sedimentation	Fast sedimentation
Compact sediment	Open sediment
Small volume sediment	Large volume sediment
Possibly cloudy fluid above sediment	Clear fluid above sediment
Flow behaviour sediment: dilatant	Flow behaviour sediment: plastic
Sediment difficult to disperse	Sediment easy to disperse

disadvantage of a flocculated system is the high sedimentation rate. The sediment, however, is easy to disperse because it has a very open structure.

In practice, therefore, the objective is to achieve an intermediate form by the addition of a controlled amount of electrolyte or surfactant. When the particles strongly repel each other, an electrolyte can be added. By decreasing the zeta-potential, the repulsive forces will decrease. When the particles attract each other too strongly a surfactant can be added. As the lyophobic part of the surfactant molecule adsorbs onto the surface of lyophobic colloids its lyophilic part will be oriented into the dispersion medium. By steric stabilisation, the attraction forces are decreased. The properties of flocculated and deflocculated suspensions are summarised in Table 18.18.

A preparation that illustrates the versatile function of a surfactant in a suspension is the Chloramphenicol Oral Suspension 33 mg/mL FNA (Table 18.19)

Table 18.19 Chloramphenicol Oral Suspension 33 mg/mL [30]

Chloramphenicol palmitate	5.75 g
Carmellose sodium M	1 g
Polysorbate 80	0.5 g
Cacao Syrup (local standard)	15 g
Syrup B.P.	15 g
Ethanol (90 %) BP	1 mL
Vanillin	0.02 g
Water, purified	ad 100 mL

In this preparation, first a gel of carmellose is prepared in a portion of the cold water using a rotor-stator mixer. Then chloramphenicol palmitate is dissolved in a mixture of hot polysorbate 80 and propylene glycol. Polysorbate 80 thus functions here as a part of the solvent mixture. The hot clear solution is added to the aqueous gel under intensive stirring with the rotor-stator mixer. During this process the chloramphenicol palmitate crystallises to form microcrystals. The size of these microcrystals is not only determined by the intensity of stirring but also by the presence of polysorbate 80, which acts as the surfactant. During storage polysorbate 80 also inhibits any crystal growth. In addition, in this suspension design, polysorbate 80 acts as a deflocculating agent and prevents, by wetting chloramphenicol palmitate, flotation and sticking of the active substance to the bottleneck.

18.4.2.2 Influencing Sedimentation Behaviour

Ideally the sedimentation rate of pharmaceutical preparations is as low as possible. On the basis of the Stokes' law, it is clear which variables can be varied to accomplish this. The gravitational acceleration cannot be reduced, nor the density of the particles. However, the particle size, the density and the viscosity of the dispersion medium may be adjusted.

A first method to reduce the sedimentation rate is particle size reduction. This can be accomplished by milling. On a small scale, this is possible by using a mortar and pestle, if electrostatic charging and agglomerating can be managed. On a larger scale, high-tech equipment has been developed for this (see Sect. 29.2.2). The precipitation method is another method to reduce the particle size. It is a useful method when no milling equipment is available or when electrostatic charging will be a problem. In the precipitation method, at first the active substance is dissolved and then its solution is brought into the supersaturated state. As a result, the dissolved substance will precipitate. The size of the precipitated particles will decrease when the degree of supersaturation increases or when the rate at which supersaturation has been achieved increases, or both. Supersaturation can be created in different ways. The solubility of many active substances is pH dependent. As described in Sect. 18.1.1, active substances with for example one or more acid groups are generally poorly soluble at a low pH but their solubility will be better at a high pH. This property can be used by preparing a solution of the active substance at high pH and then adding an acid to the solution by which it becomes supersaturated. Obviously, the opposite strategy can be used for active substances containing one or more amine groups: first the active substance is dissolved at low pH and then a base is added. Thus in both cases a solution of the active substance in ionised form is prepared. Then, the active substance in the form of its free acid or base (non-ionised form) is formed by changing the pH and supersaturation is achieved.

In another precipitation method, two different liquids are used that are miscible with each other, but in which the solubility of the active substance substantially varies. Firstly, the active substance is dissolved in the liquid in which the active substance dissolves well. Subsequently, supersaturation is achieved by adding the second liquid to the solution in which the active substance is poorly soluble.

In a third precipitation method, the fact that most substances are more soluble at a high than at a low temperature is to made use of. A saturated solution is made at a high temperature after which it is cooled until supersaturation is achieved. This last method is the least suitable because in practice it is often difficult to cool rapidly. The chloramphenicol palmitate suspension as described in Table 18.19 is an example of a suspension prepared by precipitation. Chloramphenicol palmitate precipitates when the solution in a hot mixture of polysorbate 80 and propylene glycol is mixed with the cold aqueous gel. By vigorous stirring during the final step, small particles are obtained.

A second method to reduce the sedimentation rate is to increase the density of the dispersion medium, for example, by the addition of syrups or a solution of sorbitol.

A third method to reduce the sedimentation rate is to increase the viscosity of the dispersion medium, which is almost always achieved by the application of polymers. But it must be kept in mind that accurate dosing by the patient of a specific amount of the suspension is more difficult when the viscosity increases. To avoid inadequate dosing the preparation can be delivered together with a dosing/measuring syringe instead of a measuring cup or spoon.

Most corticosteroids nasal sprays (licensed preparations) are suspensions in which croscarmellose sodium is used as viscosity enhancer. The inhalation liquids for nebulisation with the same type of active substances however only contain polysorbate and sorbitan laureate to stabilise the suspension. For atomisation in jet nebulisers, the liquid should not be too viscous, in order to prevent clogging of the nebuliser.

18.4.2.3 Particle Size Stability

The size of the particles in suspensions is not stable. During time, the particle size will increase by temperature fluctuations and by the so-called Ostwald ripening.

Because most substances are more soluble at a high than at a low temperature, small particles present in a suspension will dissolve when the temperature increases. When subsequently the temperature decreases again the solution will become supersaturated. The undissolved larger particles will act as nuclei for precipitation and grow.

Ostwald ripening is happening because the solubility of a substance in the near vicinity of small particles is greater than in the near vicinity of large particles. The relationship between the solubility and the size of the particles is given by the Ostwald-Freundlich equation:

$$C_{s,curved} = C_{s,flat} \cdot \exp\left(\frac{2 \cdot \gamma \cdot \mathrm{M}}{\mathrm{R} \cdot \mathrm{T} \cdot \rho \cdot r}\right) \qquad (18.12)$$

where $C_{s,curved}$ and $C_{s,flat}$ is the solubility near a small particle and an infinitely large particle, respectively, γ the interfacial tension between the particles and the dissolution medium, M the molecular weight of the substance, R the gas constant, T is the temperature (in K), ρ the density of the substance, and r the radius of curvature of the particles.

Due to the differences in solubility, differences in concentration in the dispersion medium arise and the dissolved molecules diffuse from the small particles to the large particles. As a consequence, the dispersion medium around the large particles becomes supersaturated and the dissolved molecules will precipitate onto these particles. Because the dissolved molecules around the small particles are diffusing away, the dispersion medium is no longer saturated and molecules from the small particles will dissolve. Thus, small particles become smaller and eventually disappear and large particles are getting bigger. A second effect is that irregularly shaped particles in suspensions become spherical.

From the above it can be concluded that by both temperature fluctuations and Ostwald ripening the particle size will increase faster when the particle size distribution is larger. It is therefore desirable that the particle size distribution in a suspension is as small as possible.

18.4.2.4 Polymorphism, Pseudo-polymorphism, Glassy State

Solids may exhibit polymorphism, which means that they can exist in different crystal modifications which differ in their physical properties [3, 20, 31, 32]. No less than eleven different crystal modifications of phenobarbital are known. It depends on the physical conditions such as temperature which crystal modification is stable. The other modifications are metastable. For substances that exhibit polymorphism, the solubility of the metastable form is higher than that of the stable form. This means that if the metastable modification is in equilibrium with the solution (i.e. saturated for the metastable form), the solution is supersaturated for the stable modification. In other words, the stable form can grow over time at the expense of the metastable form. Some fats also exhibit polymorphism [33]. The preparation method and the storage temperature will influence for example the melting behaviour of suppositories, and thereby probably also the release rate.

Besides polymorphism, pseudo-polymorphism also exists. In pseudo-polymorphism, a substance is found in

Table 18.20 Erythromycin Eye Ointment 0.5 % [34]

Erythromycin, anhydrous	0.5 g
Cetostearyl alcohol	2.49 g
Paraffin, liquid	39.8 g
Paraffin, white soft	51.2 g
Wool fat	5.97 g
Total	100 g

crystal modifications whose hydration or solvation state differs. There may therefore be crystal lattices in which more or less water or other solvent molecules are included. Similar to polymorphism, the substance in the form of one pseudo-polymorph is more soluble than in the other. Erythromycin is an example of a substance which exhibits pseudo-polymorphism. It exists in an anhydrous form and as a hydrate. In Erythromycin Eye Ointment FNA (Table 18.20) the anhydrate is used, because this form dissolves faster in the fatty ointment base.

Besides in the crystalline form, a substance may also exist in the glassy state. In the glassy state, the molecules are not oriented in a specific manner towards each other as they are in a crystal lattice, but randomly (amorphous). The aqueous solubility and thereby also the dissolution rate of a substance in the glassy state is better and higher than in crystalline form [35, 36]. Therefore, the bioavailability of lipophilic active substances after oral administration, which is limited due to their slow dissolution, can be improved by converting them into the glassy state.

18.4.3 Emulsions

Emulsions can often been found as dermatological preparations, and sometimes as injections and oral preparations. They make combinations of immiscible liquids possible, typically of fatty/lipophilic components and water. The fat/lipophilic ingredients can act as an active substance, for example, in creams to keep the skin hydrated. They can also serve as a solvent for other substances such as diazepam in Diazemuls® injection or for fat soluble vitamins in parenteral nutrition (see Sect. 13.9.2).

The physico-chemical properties of emulsions are basically similar to those of suspensions, with the essential difference that in emulsions the dispersed phase consists of a liquid instead of a solid. This difference has important consequences. Similar to a suspension, an emulsion exhibits a large interface between the dispersed phase and the dispersing medium. It requires energy input to create an interface. This implies that energy is liberated when the interfacial area is reduced. Since this is thermodynamically advantageous, the system will attempt to minimize the interfacial area. Because liquids are 'deformable' the dispersed drops in emulsions will therefore have a strong tendency to coalesce. This coalescence may eventually result in 'breaking' of the emulsion. When breaking occurs, the two phases will be present as two liquid layers. The stability of an emulsion can be improved by adding surfactants. The driving force of the dispersed drops to coalesce becomes smaller because less energy will be liberated.

Specifically applied in emulsions, surfactants are referred to as emulsifying agents. According to the rule of Bancroft, the HLB of the emulsifying agent determines which type of emulsion is obtained, water in oil (w/o) or oil in water (o/w). According to this rule, the phase in which the emulsifying agent dissolves better will be the dispersion medium. An emulsifying agent with an HLB < 7 thus gives a w/o emulsion, and an emulsifying agent with an HLB > 7 an o/w emulsion. This can be explained as follows. When an emulsifying agent is more soluble in oil than in water (HLB < 7), the lipophilic part of the molecule occupies a larger volume than the hydrophilic part. Since at the outside of a drop there is more space than at the inside, it is sterically more favourable when the (larger) lipophilic part is directed towards the outside and (smaller) hydrophilic part to the inside of the droplet. In this case a w/o emulsion will be obtained. With an emulsifying agent having an HLB > 7, the hydrophilic part occupies a larger volume and an o/w emulsion is obtained.

The stability of an emulsion increases when the emulsifying agent molecules form a more compact layer at the interface. A very compact layer can be achieved by making use of two different emulsifying agents, one of the o/w-type and one of the w/o-type. One emulsifying agent occupies the cavities in the interface that the other emulsifying agent cannot fill. Such combinations of emulsifying agents are referred to as mixed layer emulsifying agents or emulsifying agent complexes. The HLB of a two emulsifying agents can be calculated by multiplying the weight fraction of each emulsifying agents by its HLB value and adding them together. Thus the HLB of a mixture of two emulsifying agents A and B can be calculated as follows:

$$\mathrm{HLB}_{\mathrm{mixture}} = f_A \times \mathrm{HLB}_A + f_B \times \mathrm{HLB}_B \qquad (18.13)$$

where f_A and f_B are the weight fractions of the emulsifying agents A and B, respectively; $\mathrm{HLB_A}$ and $\mathrm{HLB_B}$ are the HLB values of the emulsifying agents A and B, respectively.

When two emulsifying agents are combined, one with an HLB of 4.7 and the other with an HLB of 10.3, in a weight ratio of 40/60, the HLB of the whole will become 8.1 ($HLB_{mixture} = 0.40 \times 4.7 + 0.60 \times 10.3 = 8.1$). According to the rule of Bancroft, with this combination an o/w emulsion will be obtained.

The Bancroft rule should be interpreted as a general rule. In practice, however, there are many exceptions. In addition, the type of emulsion that is formed will also depend on the volume ratio of the two phases, the method of preparation, the electrolyte concentration, etc.

18.5 Osmosis

Osmosis is the transport of water through a semi-permeable membrane as a result of a difference in the concentration of solutes on either side of the membrane. A semi-permeable membrane is only permeable to water; dissolved dissociated or undissociated substances cannot pass through it. Living cells are provided with a membrane through which water transport can take place. This must be taken into consideration when the envisaged dosage form for an active substance is a solution. If a solution is administered to a patient, water transport across the cell membrane of the cells in the near vicinity of the site of administration should be avoided as much as possible. This is because extensive water transport across cell membranes may lead to irritation and cell damage. The risks for this are, in particular, present with parenteral preparations and irrigations, but also in the case of preparations for eye, middle ear, and nose. In this section the water transport across membranes is dealt with in more detail. Methods are given to prevent net water transport across cell membranes after the administration of solutions.

18.5.1 Osmotic Pressure

When an aqueous solution and pure water in two different compartments are separated from each other by a semipermeable membrane, a spontaneously transport of water molecules across the membrane into the solution will take place. This spontaneous transport is caused by the attractive forces between the solute molecules and the water molecules. As a result, water molecules are forced through the pores of the semi-permeable membrane. By this water transport, the liquid level in the compartment of the solution will rise, while it will fall in the compartment of pure water. The rise of the liquid level in the solution compartment will, however, not continue indefinitely because the difference of the fluid levels creates a hydrostatic pressure difference that leads to a driving force for water transport in the opposite direction, i.e. across the membrane to the compartment containing pure water. At a given moment the driving forces for transport of water from the solution to pure water and from pure water to the solution are equal, and the liquid levels in the two compartments do not change anymore.

The process of transport of water through a semipermeable membrane due to a concentration difference is called osmosis and the final pressure difference between both sides of the membrane is called osmotic pressure. Basically, the osmotic pressure should be expressed in Pascal, but in practice the words osmolality or osmolarity are used to indicate osmotic pressure, both with osmole as unit.

Osmotic pressure is a colligative property. A colligative property solely depends on the concentration of the dissolved molecules or ions and is independent of the nature of the solute. Freezing point depression is also a colligative property and can be indirectly used to determine osmotic pressure. In practice, it is much more difficult to determine the osmotic pressure of a solution than to measure its freezing point depression. The freezing point of a solution can be measured and the osmotic pressure can be calculated from it.

The molar freezing point depression of water is 1.86 ° C. Blood freezes on average at -0.54 ° C. Plasma and tear fluid have the same freezing point. The osmolarity of blood, plasma and tear fluid is thus equal to:

$$\frac{0.54}{1.86} = 0.290 \text{ osmole} \quad (290 \text{ mosmole}) \qquad (18.14)$$

In literature, also a freezing point depression of blood of 0.52 °C or 0.56 °C has been reported. Based on these values, it can be calculated that the osmolarity of blood, plasma and tears will be 280 or 300 mosmole, respectively.

The osmotic pressure has the unit of Pascal (N/m^2) but in clinical practice this unit is not used as such. Measurements and calculations are performed with concentrations expressed as osmoles or milliosmoles, which are abbreviated as “osmole” and “mosmole”, respectively.

In the clinical setting 1 osmole means a concentration of 1 mol of a non-dissociable substance per kg of solvent or per litre of solution. If this concentration is expressed as mole per kg of solvent (molality) it is called osmolality. If the concentration is expressed as mole per litre of solution (molarity) it is called osmolarity.

Since the concentration of, in particular, parenteral preparations is more commonly expressed as mole per

(continued)

litre solution than mole per kilo solvent, usually the osmolarity of injections and infusions is given. The difference between osmolarity and osmolality in dilute aqueous solutions is usually not significant, because the density of water is one kilogram per litre, and the volume fraction of the solute is usually negligible. In highly concentrated solutions, however, there is a clear difference between osmolality and osmolarity. But highly concentrated solutions are clinically hardly relevant (see Sect. 18.5.2).

18.5.2 Iso-osmotic and Isotonic

If two aqueous solutions with different concentrations of dissolved substances are separated from each other by a semipermeable membrane, there is a net transport of water from the solution with a lower concentration molecules or ions to the solution with the higher concentration of molecules or ions. The solution with the lower concentration is called hypo-osmotic, while the solution with the higher concentration is hyper-osmotic in relation to the other. When the concentrations of dissolved substances in the solutions on either side of the semi-permeable membrane are equal to each other, there will be no net transport of water across the membrane. In such a case we call the two solutions iso-osmotic.

When cells are brought into contact with a solution and a cell membrane would behave as a semi-permeable membrane, the solution within the cell will try to become iso-osmotic to that outside of the cell. This water transport will cause damage to the cell. It must therefore be ensured that there is little or no net water transport from the solution into the cell or vice versa. If an active substance is administered in a low concentration solution, the osmotic value will be less than that of the blood. To achieve an iso-osmotic concentration, NaCl or glucose can be added. When the active substance has to be administered in a high, hyper-osmotic concentration, consideration should be given to reducing the concentration by dilution. If this is not possible, then, under certain conditions a solution with a hyperosmotic concentration can be administered, preferably into a vein with a good flow so dilution will take place swiftly (see Sect. 13.5.5).

The cytoplasmic membrane of an erythrocyte or a corneal epithelial cell and other physiological membranes, however, do not always behave as a semi-permeable membrane. Cell membranes are to some extent also permeable to some molecules other than water. Some molecules or ions, such as urea, ethanol, and ammonium salts, are able to pass through a cell membrane at a relatively high rate. If an erythrocyte for example is placed in an iso-osmotic solution of ammonium chloride, the transport of ammonium chloride across the cell membrane occurs quickly until its concentration in- and outside the cell is equal. For this reason, solutions containing that type of molecules may be iso-osmotic with the cell content, but nevertheless show water transport when brought into contact with cells. On the other hand, a net water transport does not necessarily occur when the cell content is not iso-osmotic with the environment. If certain ions or molecules do not stay at one side of the (cell) membrane, their contribution to the pressure difference will not be the same as in the case of a 'perfect semi-permeable' membrane. If net water transport occurs from the environment to the cell the solution outside the cell is called hypotonic. And vice versa, when a net water transport occurs from the cell to the environment the solution outside the cell is hypertonic. If no net water transport takes place, both solutions are called isotonic.

Iso-osmotic is a physico-chemical concept and only depends on the concentration of dissolved molecules and ions. Isotonicity is the concept that takes into account, as well, the properties of the biological membrane in relation to the type of dissolved substances. Thus isotonicity should be interpreted as a physiological concept. Therefore, in this context it is better to speak of selectively permeable instead of semi-permeable. For most applications or routes of administration (bio-membranes), the number of substances for which there is a difference between iso-osmotic and isotonic is limited. For this reason, terms such as hypertonic and hypotonic are commonly used while actually hyper- or hypo-osmotic, respectively, are meant.

18.5.3 Non-ideal Solutions

On the basis of paragraph Sect. 18.5.1, it would be expected to calculate as follows: if the composition of the fluid is given in millimoles, determine whether or not the dissolved substances dissociate and if so how many ions are formed. For example, a solution of 1 mmole of glucose in 1 L of water yields 1 mosmol, but a solution of 1 mmole of NaCl or 1 mmole $CaCl_2$ in 1 L of water yields 2 or 3 mosmol, respectively. After summing the contributions of all components it can be verified whether or not the total strength is approximately 300 mosmol.

This way of calculating only applies to so-called ideal solutions. In an ideal solution of substance A in a solvent B, the interactions between A and B, A and A, and B and B are equal. In practice, however, non-ideal solutions are more common. As a result, at an equal concentration of molecules or ions, the osmolarity of a non-ideal solution can be different from that of an ideal solution. This difference in

osmolarity is expressed by a correction factor f. This correction factor is specific to each substance and in dilute solutions independent of the concentration. At very high, clinically irrelevant, concentrations, the correction factor may change due to association of the dissolved components. The osmolarity of a solution can be calculated as follows:

$$\frac{G}{\mathrm{M}} \times \mathrm{f} \qquad (18.15)$$

where G is the concentration of the solute in grams per litre and M the molecular weight of the dissolved substance. The f-values are mentioned in Table 18.21 as group averages.

In a preparation, the active substance (if present in dissolved form) and the excipients (e.g. buffering agents, preservatives, antioxidants, and disodium edetate) all contribute to the osmotic value of a preparation.

If 290 mosmol is taken as the iso-osmotic value, a solution of the substances A, B, ... is iso-osmotic with blood under the following condition:

$$\frac{G_A}{\mathrm{M_A}} \times \mathrm{f}_A + \frac{G_B}{\mathrm{M_B}} \times \mathrm{f}_B + \ldots + \frac{G_H}{\mathrm{M_H}} \times \mathrm{f}_H = 0.290 \qquad (18.16)$$

where G_A, G_B, ... are the concentrations of the solutes in grams per litre, $\mathrm{M_A}$, $\mathrm{M_B}$, ... the molecular weights of the dissolved substances, and $\mathrm{f_A}$, $\mathrm{f_B}$, ... the correction factors associated with dissociation of the solutes. To make a solution iso-osmotic, an excipient can be added. In (18.16) this excipient is indicated with an H.

18.5.4 Calculation of Osmotic Value

If an active substance or excipient substantially contributes to the osmotic value, it may be necessary to calculate this contribution. This can be done in practice by three different calculation methods. The choice of the method depends on which physical characteristics of the substances are available.

Method 1: If the molecular weight and the dissociation type (f-value, Table 18.21) are known, the osmotic value can be calculated using a part of equation 18.16, namely:

$$\frac{G_A}{\mathrm{M_A}} \times \mathrm{f}_A$$

Method 1 is exemplified by the calculation of the osmotic value of betaxolol 1 % eye drops:
Suppose that no iso-osmotic concentration of the substance (betaxolol) is known. The osmotic value can then be calculated using the molecular weight and the type of dissociation. Betaxolol hydrochloride has a molecular weight of 343.9. The degree of dissociation and the $\mathrm{pK_a}$ cannot be easily found in the literature. Based on its chemical structure, however, it can be concluded that this is a salt of a secondary amine. The so-called f-value of this type of molecules is 1.8. The contribution of betaxolol hydrochloride is then (G/M) $\times$ f = (20/343.9) $\times$ 1.8 = 52 mosmol per litre. Betaxolol hydrochloride therefore contributes for (52/290) $\times$ 100 % = 18 % of the iso-osmosis. As a consequence, excipients should contribute for the remaining 82 % to make an isotonic solution.

Table 18.21 Dissociation types and f-values of various substances

Dissociation type	Molar freeze point depression (in °C/mol)	f-value	Examples
Non-dissociating	1.9	1.0	Glycerol
			Glucose
			Sorbitol
			Urea
Weak electrolytes	2.0	1.05	Alkaloids
			Bases
			Boric acid
Di-divalent electrolytes	2.0	1.05	Magnesium sulfate
			Zinc sulfate
Mono-monovalent electrolytes	3.4	1.8	Sodium chloride
			Silver nitrate
			Phenobarbital sodium
Mono-divalent electrolytes	4.3	2.3	Sodium sulfate
Di-monovalent electrolytes	4.8	2.5	Zinc chloride
Mono-trivalente electrolytes	5.2	2.7	Sodium citrate
Tri-monovalent electrolytes	6.0	3.2	Aluminium chloride
Tetraborate	7.6	4.0	Borax

Method 2: If the iso-osmotic concentration of a substance is known, the osmotic value can be easily calculated. In Martindale, these values are often specified in the description of substances [11]. In the Merck Index and in the Handbook of injectable drugs, the iso-osmotic concentrations for a large number of substances are listed in a table [6, 37].

Method 2 is exemplified by the calculation of the osmotic value of Pilocarpine Eye Drops 2 % FNA (Table 18.22):

Table 18.22 Pilocarpine Eye Drops Solution 2 % [38]

Pilocarpine hydrochloride	2 g
Benzalkonium chloride	0.01 g
Borax	0.375 g
Boric acid	0.7 g
Disodium edetate	0.1 g
Water, purified	ad 100 mL

A 4.1 % w/v solution of pilocarpine hydrochloride is iso-osmotic (293 mosmol as determined by measuring its freezing point depression). A 2 % w/v pilocarpine hydrochloride thus contributes to about 50 % of the iso-osmotic value (the osmolarity as determined at pH 6 is 147 mosmol). The other 50 % should be provided by the excipients. Iso-osmotic stock solutions (see also Sect. 10.7.1) for the preparation of eye drops could be very useful for the purpose of easy calculation. The stock solution Boric acid-benzalkonium solution FNA (see Table 10.10) is nearly iso-osmotic (boric acid is iso-osmotic at a concentration of 19 mg/mL). The contribution to the osmotic value of the benzalkonium chloride 100 mg/L is too small and can be neglected in the calculations. Without adjusting the pH, 50 % v/v of Boric acid-benzalkonium solution would be needed. But because the stability of pilocarpine is optimal at pH 6.5, the pH is adjusted with 3.75 mg/mL borax to 6.5. As 3.75 mg/mL borax contributes 15 % to the osmotic value, 35 % is left for the Boric acid-benzalkonium solution.

Method 3: If no iso-osmotic concentration is known, it can be calculated with the aid of the sodium chloride equivalent, also known as tonicic equivalent or E-value. The sodium chloride equivalent is defined as:

$$E = \frac{\text{freeze point depression per gram of compound A}}{\text{freeze point depression per gram NaCl}} \tag{18.17}$$

For each substance, the E value can be calculated if the dissociation type of that substance is known [39]. In practice, tables are used in which the E-values for a large number of substances are listed. These tables can be found in references [6, 37]. The calculation using E-values proceeds as follows. The concentration of each of the solutes, expressed as a percentage, is multiplied with the corresponding E value. The product thus obtained, gives for each substance in the amount used the amount of NaCl which corresponds to the osmotic value. The sum of the products of all individual components represents the strength in NaCl equivalents of the total solution. Because the overall strength of the solution should be 0.9 NaCl equivalents, the relative contribution of the active substance to the osmotic value is known. The amount of iso-osmotic stock solution to be added can be calculated as described above.

Method 3 is exemplified by the calculation of E value and NaCl equivalents for a thiamine-injection 25 mg/mL (Table 18.23):

Table 18.23 Calculation of E value an NaCl equivalents for a thiamine injection solution

	Per 100 mL	E	NaCl-eq
Thiamine-hydrochloride	2.5 g	0.21	0.525
Disodium edetate	0.01 g	0.20	0.002

This gives a total of at E = 0.527 sodium chloride equivalents. 0.9 g of sodium chloride per 100 mL is iso-osmotic. This means that almost 0.373 g per 100 mL should be added.

18.5.5 Importance of Osmotic Value in Dosage Forms

With the aid of the three methods described in Sect. 18.5.4 it can be calculated whether or not a pharmaceutical preparation is iso-osmotic. Hypo-osmolarity can usually be avoided as it can be compensated by the addition of excipients in calculated quantities. Hyper-osmolarity may be inevitable due to dosage reasons, for example when a high dose of an active substance has to be administered in a small volume. The extent to which hyper-osmolarity is tolerated will depend on the route of administration and administration site. The tolerance for parenteral administration, for example, increases in the order: subcutaneous < intramuscular < intravenously. This has to do with the fact that of these three routes, the intravenously administered dose spreads most rapidly, and thus dilutes most rapidly in the body and the subcutaneously administered dose most slowly. For the same reason, the tolerance is greater when the solution is injected into a large blood vessel than in a small blood vessel. The tolerance is also determined by the volume infused. In Sects. 13.5.5 and 13.6.3, more information is given about the relative importance of iso-osmosis for different types of parenterals. The osmolarity of an eye wash should be much more accurate than that of an eye drop. This is because the

eye drops, which are administered in small volumes, are rapidly diluted by tear fluid. But with an eye wash, all protective tear fluid is washed out of the eye. The osmotic value of nasal drops and aqueous ear drops should not deviate too far from the physiological value. Limits of osmolarity for various dosage forms are discussed in the chapters on dosage forms (4 – 14) of this book. These limits, however, are never absolute. Adverse effects are more readily accepted for serious indications.

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Microbiology

19

Hans van Doorne, David Roesti, and Alexandra Staerk

Contents

Abstract

Microbial contamination of pharmaceutical preparations may cause health hazard to the patient (e.g. infection, pyrogenic or allergic reaction), altered therapeutic activity of the product, or other decrease in quality (turbidity, loss of consistency, altered pH). This chapter provides a general introduction on pharmaceutical microbiology by focusing on the essential properties of micro-organisms. First of all the basic characteristics of life and the types of biological contaminants and potentially infectious agents of pharmaceutical products will be discussed: viz. prions, viruses, mollicutes, bacteria, fungi, and endotoxins. In the next section factors affecting survival and growth of micro-organisms are discussed. In addition to well-known factors such as time, temperature, and chemical and physical characteristics of the environment, attention will be paid to biofilm formation. Primary microbiological contamination is prevented by implementing an adequate microbiological quality control and quality assurance program and by following cGMPs during production.

Microbiological quality control of pharmaceutical preparations and monitoring of production areas depend on the detection and quantification of micro-organisms. The classical, growth based, methods and some of the commercially available alternative methods are discussed.

Understanding essential microbiological concepts is necessary in designing both microbiologically stable pharmaceutical products and ensuring an effective quality control and monitoring program within the manufacturing or preparation facility.

Some of the information in this chapter has been adapted and updated from: H. van Doorne, A Basic Primer on Pharmaceutical Microbiology, edited by Richard Prince, co-published by PDA DHI Publishing II, USA.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_19,

Keywords
Micro-organisms • Contamination • Hygiene • Microbiological examination • Sterility test

19.1 Characteristics of Life

Although there is no universal definition of life, scientists generally agree that living systems share all or at least the characteristics: organisation, interaction with the environment, adaptation, metabolism, growth, motility and communication.

19.1.1 Organisation

Organisms are composed of one or more cells, which are the basic units of life. Each cell must be highly organised because growth and multiplication can only occur when the individual biochemical processes are synchronised. In higher organisms, organisation within the organs, and communication with other organs are essential for the normal functioning of the body.

19.1.2 Interaction with the Environment

Cells respond to chemical and physical input from the environment. A response is often expressed by motion. Chemotaxis, the movement of a cell in response to a concentration gradient of a substance, is an example of such an interaction.

19.1.3 Adaptation

Adaptation is the accommodation of a living organism to its environment. It is fundamental to the process of evolution, by which cells change their characteristics and transmit these new properties to their offspring.

19.1.4 Metabolism

Metabolism involves the uptake of nutrients from the environment, their conversion to energy (adenosine triphosphate: ATP) and cellular components, and the deposition of waste products (e.g. carbon dioxide: CO_2) or metabolites (e.g. toxins or antibiotics) into the environment. Living things require energy to maintain internal organisation (homeostasis) and to produce the other phenomena associated with life.

19.1.5 Growth

Growth is the increase in biomass. A growing individual increases up to a point in size in all of its parts. Reproduction is the result of a series of biochemical events that result in the production of a new individual (asexually, from a single parent organism, or sexually, from at least two differing parent organisms). In microbiology growth is often used as a synonym for reproduction.

Dormancy is a state of decreased metabolic activity in which there is no growth, i.e. no increase in biomass. It may be a dynamic state in which the number of newly formed cells balances the number of dying cells. The duration of this period is relatively short (hours, days). Dormancy of bacterial spores may continue for considerably longer periods of time.

19.1.6 Motility

Many cells and organisms can move under their own power. Movement to a new location may offer the cell new resources. Motility however is not a characteristic of all living organisms. Animals are typically motile, whereas plants are non-motile. In micro-organisms motility is dependent on the type of organism and sometimes even on the stage of the life cycle the cells have reached.

19.1.7 Communication

Throughout evolution humans and animals have developed a multitude of ways for communication. Micro-organisms (bacteria, yeasts and moulds) can communicate through a process called quorum sensing. Quorum sensing is the regulation of gene expression in response to fluctuations in cell-population density.

Quorum sensing exemplifies interactive social behaviour innate to the microbial world that controls features such as virulence, biofilm formation, antibiotic resistance, swarming motility, and sporulation [1, 2]. In gram-negative bacteria, small molecules (e.g. acyl homoserine lactone (ALH) [3]) serve as signals to recognise microbial cell population size. When a signal exceeds some threshold concentration the expression of specific genes is changed [4].

If a microbial cell is introduced into a pharmaceutical preparation or onto a surface it will sense whether suitable conditions (nutrients, moisture, etc.) for growth are available (interaction with the environment). If possible the cell will adapt to its new habitat, and start to metabolise the available nutrients. Eventually growth will take place. Motility of individual cells will facilitate colonisation of other sites. Production of toxins (in case of a pathogen) is a demanding

biochemical process and will occur only when quorum sensing indicates that a sufficiently large population has developed.

Thus the interplay between all these characteristics determine whether a cell will be able to grow in a specific product, or on a surface.

19.2 Biological Contaminants of Pharmaceutical Preparations

Survival and growth of micro-organisms in pharmaceutical preparations is governed by extrinsic factors (particularly temperature) and intrinsic factors (product composition and physico-chemical characteristics). The combination of intrinsic and extrinsic factors will determine the types and number of micro-organisms that will develop in a product or on a surface.

19.2.1 Growth and Survival: Extrinsic Factors

19.2.1.1 Temperature

Temperature has a strong influence on whether an organism can survive or thrive. Temperature exerts its influence indirectly through water (which has to be in the liquid state), and directly through its influence on the organic molecules composing the living cells.

Mesophilic organisms are widespread in nature. They have the potential to grow in a temperature range of roughly 8–45 °C. At temperatures above 30 °C some contaminants of water and air including different types of bacteria and moulds will fail to grow or grow more slowly. The optimum growth temperature for pathogenic bacteria is around 37 °C with an upper range from 44 °C to 48 °C. *Legionella pneumophila* (*L. pneumophila*) is an exception; it will grow at temperatures up to 55 °C.

Geobacillus stearothermophilus is a thermophile and grows at temperatures between 50 °C and 65 °C. It is used as a test organism (biological indicator) to verify the efficacy of moist heat sterilisation processes.

For reasons of chemical stability some preparations must be stored frozen. Under these conditions (no liquid water) microbial growth is not possible. However, the majority of the preparations are either stored refrigerated (4–8 °C) or at room temperature (20–25 °C), which will allow growth of most mesophilic micro-organisms. According to European Good Manufacturing Practice (EU-GMP) regulations water for injection (WFI) should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 80 °C (see also Sect. 27.5.2).

19.2.2 Growth and Survival: Intrinsic Factors

19.2.2.1 Water

The presence of water is essential to every form of life including micro-organisms. In the late 1930s, it was recognised that water activity (or a_w), as opposed to water content, was the more significant factor in studying the relationship of water to microbial growth. The a_w value is defined as the proportion between the water vapour pressure of the product and the vapour pressure of pure water at a common temperature.

Lowering the water content has historically been a convenient method to protect foods from microbial spoilage. Examples where the available moisture is reduced are dried fruits, syrups, and pickled meats and vegetables. Low water activity will also prevent microbial growth within pharmaceutical preparations, see also Sect. 22.3.3. Water activity values supporting microbial growth of a number of representative micro-organisms are provided in the USP [5]. That chapter also suggests a strategy for microbial limit testing based on water activity.

Pharmaceutical cleaning operations usually involve a final rinse with water of suitable pharmaceutical quality. To prevent microbial growth, it is essential to dry the object as soon as possible after rinsing.

Although water is essential for microbial growth, a low a_w value does not necessarily lead to cell death. For instance, some dry raw materials, especially those of natural origin, may be heavily contaminated with both endospores and vegetative cells. Freeze drying in a suitable medium, for instance, is an excellent way to preserve pure cultures of viable micro-organisms. A water activity below 0.6 does not enable micro-organisms to grow. Solid oral dosage forms such as tablets have in general an a_w value lower than 0.5 which means that these products remain stable from a microbiological point of view over long periods of time if the product is stored in a waterproof blister that remains integral.

19.2.2.2 Nutrients

Micro-organisms require for their growth suitable nutrient sources of elements (e.g. C, H, O, P, S, N), minerals (e.g. Na^+, Ca^{2+}, Mg^{2+}) and trace elements (e.g. Cu^{2+}, Mn^{2+}, Co^{2+}). Even in a relatively nutritionally poor medium such as distilled water, the number of micro-organisms may be as high as 10^5–10^6 colony forming units (CFU)/mL, indicating that nutrients are present in sufficient quantity to allow proliferation of water-borne bacteria such as the pseudomonads. The presence of readily assimilated substances such as sugars or polyalcohols in dosage forms such as creams or syrups can lead to an increased probability of microbial adulteration of those products.

19.2.2.3 pH

A pH range of 6–7 does not exert any discernible selective influence on growth of pharmaceutically relevant types of organisms. Below pH 6, growth of many bacteria will start to be inhibited. Pathogenic and toxinogenic bacteria generally will not grow at pH values below 4.5, but they may survive long times of immersion in weakly acidic solutions. Yeasts and moulds unlike bacteria, generally tolerate acidic media quite well. Optimum pH of most fungi is about pH 5. At more alkaline conditions, pseudomonads will predominate. For example, *Ps. aeruginosa* is known to grow at a pH range of 6–9.

19.2.2.4 Redox Potential

Microbes are classified as aerobes or anaerobes. This is now defined in terms of oxidation-reduction potential (E_h). Generally, the range at which different micro-organisms can grow are as follows: aerobes +500 to +300 mV; facultative anaerobes +300 to −100 mV; and anaerobes +100 to less than −250 mV. The redox potential of a normal aerobic nutrient medium is about + 300 mV. Thioglycolate medium, which is used for growth of anaerobic bacteria has an E_h of about −200 mV. For reasons of chemical stability, the redox potential of some pharmaceutical preparations is kept at a low level by means of reducing agents such as sulfite, tocopherol or ascorbic acid. The effect of a reduced redox potential on the microbial flora of such preparations has never been studied.

19.2.2.5 Substances with Antimicrobial Properties

The number and types of micro-organisms that may develop in various pharmaceutical dosage forms is greatly influenced by the presence of substances with antimicrobial properties. Antimicrobial active substances can be divided into three groups, as follows:

- The first group consists of substances used for therapeutic or preventive antimicrobial purposes, for example: antibiotics, chemotherapeutics, and disinfectants.
- The second group consists of preservatives (see Sect. 23.8), used to guarantee the microbiological quality of the product throughout its shelf life. For example: esters of hydroxybenzoic acid, quaternary ammonium substances and sorbic acid are widely used in pharmaceutical and cosmetic preparations. Other preservatives that are used include phenol, chlorhexidine, benzoic acid and benzyl alcohol.
- The third group consists of excipients with 'collateral' antimicrobial activity that are principally added to dosage forms for reasons unrelated to their (sometimes weak) antimicrobial activity. For example, sodium lauryl sulfate is known to inactivate some gram-positive bacteria. Similarly, edetate has weak antimicrobial activity, and it confers synergistic antimicrobial properties when combined with quaternary ammonium substances. In addition, some active substances may show substantial antimicrobial activity.

19.3 Potential Biological Contaminants

19.3.1 Prions

19.3.1.1 Brief Description of Prions

A prion – short for proteinaceous infectious particle – is a unique type of infectious agent. Prions are composed of abnormal isoforms of a normal host-encoded membrane protein, termed prion protein (PrP^c). Abnormally folded prion protein catalyses the refolding of normal prions into abnormal forms. Prions are not considered life. However, their biological origin and their potential effect on animals and human beings warrant a brief discussion.

The term 'prion diseases' refers to a group of neurodegenerative disorders. These include scrapie (in sheep and goat), Kuru (prion disease endemic amongst cannibalistic tribes in Papua New Guinea), bovine spongiform encephalopathy (in cattle) and Creutzfeldt-Jakob disease (CJD) (in humans) [6]. Prion diseases are characterised by long incubation periods ranging from months to years and are invariably fatal once clinical symptoms have appeared. In all prion diseases the infectious prions are generated in the brain of the afflicted animal. In the rare cases of interspecies transmission, such as from cattle to humans a 'template assisted replication' takes place. This means that the prions that replicate in the human brain have the amino acid sequence encoded by the DNA of the host (human being) and not the sequence of the donor animal [7].

19.3.1.2 Prions as Contaminants of Pharmaceutical Preparations

BSE was first diagnosed in the United Kingdom in 1986 and a large number of cattle and individual herds have been affected. Interspecies TSE transmission is restricted by a number of natural barriers, transmissibility being affected by the species of origin, the prion strain, dose, and route of exposure.

Transmission of scrapie to sheep and goats occurred following use of a formol-inactivated vaccine against contagious agalactia, prepared with brain and mammary gland homogenates of sheep infected with *Mycoplasma agalactiae* [8]. Iatrogenic transmission of human prion disease can occur through medical or surgical procedures. An example is the injection of hormones such as gonadotropins extracted from cadaver pituitaries. Current evidence indicates that, with respect to the risk of TSE infection, urinary-derived gonadotrophins appear to be safe [9]. The risks of urine-derived fertility products could now outweigh their benefits,

particularly considering the availability of recombinant products [10].

Cases of CJD have also been attributed to the use of contaminated instruments in brain surgery and with the transplantation of human dura mater and cornea [11].

Suppliers of materials may minimise the risks of contamination of TSE by ensuring [12]:

- The source animals and their geographical origin
- Nature of animal material used in manufacture and any procedures in place to avoid cross-contamination with higher risk materials
- Production process(es) including the quality control and quality assurance system in place to ensure product consistency and traceability

Manufacturers of pharmaceutical preparations select their raw materials so they are TSE free (see also Sect. 23.1.7). This can be ensured either by purchasing materials from non-animal origin or from non-TSE relevant animal species (e.g. porcine instead of bovine). If material from TSE-relevant animal species is purchased, it should be delivered with a certificate that confirms it free of TSE. Regular audits verifying this assumption should be performed by the manufacturer at the material's supplier manufacturing site. Prions, unlike the normal PrP^c proteins, are very resistant to inactivation. The only methods that appear to be completely effective under worst-case conditions are strong sodium hypochlorite solutions or hot solutions of sodium hydroxide [13, 14]. Some cross contamination can be avoided by the use of disposable instruments, e.g. in tonsillectomy [15].

19.3.2 Viruses

19.3.2.1 Brief Description of Viruses

A virus is a non-cellular genetic element, which is dependent on a suitable host cell for its multiplication. Their size generally ranges from 20 to 300 nm. It has been argued extensively whether viruses are living organisms. The majority of virologists consider them as non-living as they lack many of the characteristics of life, such as independent metabolism. Viruses exist in various states throughout their life cycle. In the extracellular state a virus particle is called a virion.

Virions are composed of a core of genetic material, which can either be in the form of DNA or ribonucleic acid (RNA), and a protein coat or capsid. In some viruses (enveloped viruses) the capsid is surrounded by a lipid bilayer membrane. Attached to these membranes are specific proteins, which may play a role in the attachment of the virion to the host cell, or release from the host. Thus, haemagglutinin and neuraminidase are two important enzymes present in the envelope of the influenza virus.

The virions are metabolically inactive because they are devoid of a self-generating energy system, transfer RNA, ribosomes, and so forth. Many viruses do contain enzymes that become essential in rendering these agents infectious to susceptible hosts. Viruses are obligate intracellular parasites. Replication occurs only inside the cell of a suitable host.

Replication usually leads to destruction of the host cell. Sometimes the viral DNA is incorporated into the genetic material of the host. This principle is successfully used in genetic engineering, where viruses are used as vectors to incorporate a new gene in a cell.

Viruses are causative agents of many human, animal, and plant diseases. AIDS, SARS, and avian flu are viral diseases, which are nearly daily covered by the headlines in papers and by the news items on radio and television. In 1917–1919 a 'Spanish flu' pandemic killed over 50 million people. The virus involved was most probably a mutation of some avian virus. The Avian flu pandemic (caused by the H_5N_1 variant) was, by comparison very small, as it has caused 'only' about 150 fatalities. The great concern for virologists and epidemiologists is the extremely high mortality rate (over 50 %) of infections with this virus. In the form of vaccines, viruses are inactivated or attenuated so as to prevent diseases in susceptible populations.

The Baltimore classification is the preferred way of classifying viruses. Viruses are grouped into families depending on their type of genome (DNA, RNA, single-stranded (ss), double-stranded (ds) etc.) and their method of replication.

A series of important medicines is derived from animal or human sources and may potentially be contaminated with undesired virus particles. Such medicines include:

- Coagulation factors, immunoglobulins and albumin from human blood plasma
- Vaccines and monoclonal antibodies from cell cultures
- Proteins from cells altered by genetic engineering
- Homoeopathic preparations of animal origin

19.3.2.2 Viruses as Contaminants of Pharmaceutical Preparations

Vaccination is one of the most important public health accomplishments. However, since vaccine preparation involves the use of materials of biological origin, such as Chinese Hamster Ovary cells, vaccines are susceptible to contamination by micro-organisms, including viruses [16–18]. Several cases of viral vaccine contamination have been reported. For example, human vaccines against poliomyelitis were found to be contaminated with SV40 virus from the use of monkey primary renal cells. Several veterinary vaccines have been contaminated by pestiviruses from foetal calf serum [19]. In 2010 the detection of fragments of a porcine circovirus was the reason for a temporary

withdrawal of some commercial vaccines from the Spanish market [20].

Several methods are being used or in development to reduce infectivity of blood products, including solvent-detergent processing of plasma and nucleic acid cross-linking via photochemical reactions with methylene blue, riboflavin, psoralen and alkylating agents. Several opportunities exist to further improve blood safety through advances in infectious disease screening and pathogen inactivation methods [21, 22]. One potential way to increase the safety of therapeutic biological products is the use of a virus-retentive filter [23]. Plasma pools may be submitted to serological tests and/or genome amplification assays before they are released for further fractionation [24].

Multidose containers and the environment were found to be the source of a number of nosocomial viral infections [25–33].

Presence of viruses in pharmaceutical preparations may be verified by performing either *in vivo* tests by inoculating the product directly in animals (e.g. rabbits, mice) or *in-vitro* tests such as polymerase chain reaction (PCR) or cell culture safety tests.

19.3.3 Bacteria

19.3.3.1 Brief Description

Along with the Archea, bacteria belong to the prokaryotic organisms, i.e. cells that do not possess a real nucleus and that reproduce asexually. They are unicellular micro-organisms with a size in general ranging from 0.2 to 10 μm.

Their extraordinary diversity in terms of biochemical processes and metabolic characteristics enable bacteria to adapt themselves to a large variety of environments. Indeed, some species have the capacity to grow in anaerobic (absence of free oxygen in the air) environments by using other electron acceptors than oxygen, such as sulphates or nitrates or by fermentation. Other species may use energy and carbon sources for growth from not only organic substances but also from carbon dioxide and light energy. For this reason, bacteria have colonised most habitats on earth (soil, water, animals, plants) and even the most extreme environments such as deep-sea fumaroles or geysers.

Another fascinating (but critical in terms of product safety) characteristic of bacteria is their capacity to grow extremely fast if the environmental conditions in terms of nutrient availability, moisture and temperature become favourable.

During growth, an individual cells first increases in size and then the cell is divided in two parts (binary fission). In nutrient media, bacteria follow four growth phases (see Fig. 19.3). The first is the lag phase, during which the bacteria adapt to their new environment by repairing damaged structures and synthesising enzymes to catabolise nutrients in the medium. The second phase, the most spectacular, is the exponential phase during which nutrients in the medium are metabolised rapidly leading to a rapid doubling of the population of bacterial cells. The population of *Escherichia coli* cells under optimal growth conditions can multiply each 20 min. This would mean that after 8 h the population would reach one million cells and after 43 h, the volume of cells produced would be equivalent to the volume of planet earth! Once nutrients start to deplete, the exponential growth is slowed down and the amounts of cells in the overall population remains stable; this is the third phase called the stationary phase. In this phase, secondary metabolites such as antibiotics are produced in higher quantities. The last phase is when no more nutrients are available and the amount of bacterial cells starts to drop.

In the human microflora, there are at least 10 times more bacterial cells than human cells and most of them are harmless. Human bacterial infections are mainly caused by strict pathogenic species (less than 2 % of bacterial species) or by opportunistic pathogens when the immune system of the person is depleted. Bacteria may cause a large variety of infections, the most common being food poisoning, pneumonia, skin infection, urinary tract infection, throat and mouth infection, meningitis, eye infection. Depending on the infectious agent, the minimum amount of micro-organisms provoking an infectious dose varies greatly. For instance in some cases, only 10 cells of *Shigella dysentriae* need to be ingested to provoke dysentry but at least a 1,000 cells of *Vibrio cholera* to provoke cholera [34].

19.3.3.2 Mollicutes

Mollicutes, also known under the trivial name mycoplasmas, are the smallest free-living prokaryotic organisms and for years were thought to be viruses because they passed through the usual bacterial filters. They resemble protoplasts, because they lack a cell wall, but they are relatively resistant to osmotic lysis due to the presence of sterols in the cell membrane. In this respect the mycoplasmas form an exceptional group, because sterols are absent in other prokaryotic cells. Mycoplasmas are widespread in nature and many are animal, plant or human pathogens. Most mycoplasmas that infect humans are extracellular parasites. Examples of human pathogenic mycoplasmas are *Mycoplasma pneumonia* (infections of upper respiratory tract), and *Mycoplasma genitalium* (non-gonococcal urethritis) [35].

Mycoplasma contamination is a major concern for vaccine and biotechnological industries since the organisms may cause disease and may interfere with cell culture [36]. Peptones, and animal sera used as components of cell culture media may be sources of this contamination [37, 38].

Mycoplasmas can be cultured in liquid or on solid media. However, in contrast with other bacteria, their growth is slow, and a microbiological assay as described in the Ph. Eur. is time-consuming (at least 28 days). Alternative, rapid methods, based on nucleic acid technologies such as PCR, have been developed [36, 39]. Under certain conditions these methods may be used as an alternative method instead of the official, growth based method [40].

19.3.3.3 Structure

Bacteria may be composed of the following structural elements (see Fig. 19.1):

- Flagella
- Pili and fimbriae
- Capsule or slime layer
- Cell wall
- Cytoplasmic membrane
- Cytoplasm
- Spores

Cytoplasm, cytoplasmic membrane and cell wall are always present. The presence of the other components depends on the type of micro-organism, the culture conditions and the growth phase.

Flagella

Bacteria become motile by means of flagella [41]. Bacterial flagella are protein threads which originate in a defined region of the cytoplasmic membrane and protrude through the peptidoglycan layer and the outer membrane. The number of flagella per cell and their position depends on the species. *Pseudomonas aeruginosa* (*Ps. aeruginosa*) has only one (polar) flagellum at the tip of the cell, whereas *Escherichia coli* (*E. coli*) has numerous flagella spread over the entire cell surface (peritrichous). Flagella may play an important role in pathogenicity [41, 42].

Pili and Fimbriae

The surface of cells of some bacterial species is covered with many (10 to several thousands), thin (3–25 nm), and long (up to 12 µm) threads called pili, or fimbriae. They play a role in the initial adhesion of bacteria to host tissues and inanimate surfaces [43, 44]. Attachment to a surface is the first step in biofilm formation. Upon attachment on tissue cells they may trigger a number of biochemical signals from the host, which ultimately leads to the bacterial disease [45].

Capsule or Slime Layer

Capsules and slime layers – collectively called glycocalix – consist of source polysaccharide material secreted by the cell. A capsule is a rigid structure, whereas a slime layer, or loose extracellular slime, is more flexible, with diffuse boundaries. The glycocalix has several functions. It is involved in cell attachment and it may protect cells from being digested, a phenomenon known as phagocytosis. Whilst encapsulated strains of *Streptococcus pneumoniae* are highly pathogenic, non-encapsulated mutants are completely avirulent [46, 47]. Dextran, a slime layer product of *Leuconostoc mesenteroides* of relatively low molecular weight can be used as a therapeutic agent in restoring blood volume [48].

Cell Wall Constituents

The outer surface of the bacterial cell plays an important role in the adhesion of the cell to various surfaces. In addition to the factors that have been discussed, adhesion may also be mediated by so-called surface-associated adherence factors, usually designated as adhesins. Adhesion, which is the first step in a series of events leading to colonisation, biofilm formation and ultimately infection, is a specific process in which the adhesin "recognises" a receptor on the host surface. This specificity explains why micro-organisms such as

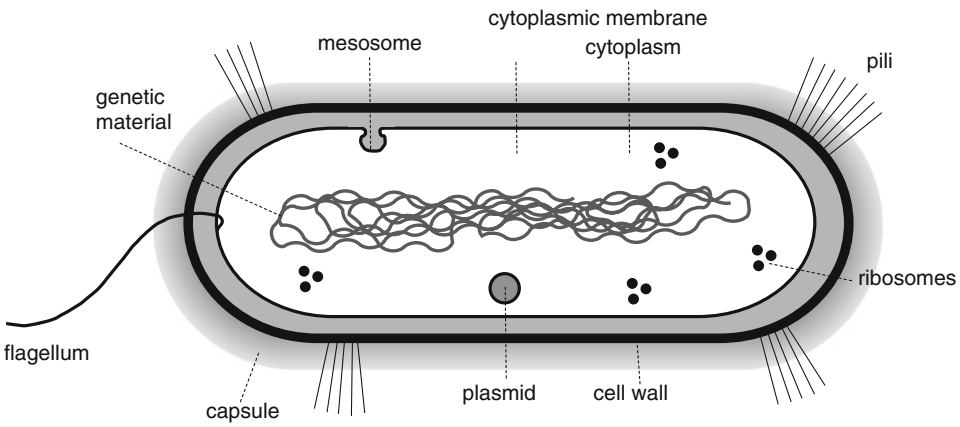

Fig. 19.1 Structural elements of the bacterial cell

Influenza or *Mycobacterium tuberculosis* can cause targeted infection of the respiratory tract but otherwise are relatively harmless when contacting other host tissues.

The cell wall gives the cell its shape and strength. The cell wall must resist the internal osmotic pressure of the cell that is estimated to be about 2 bar. The composition of cell walls of gram-positive bacteria is very different from those that stain gram-negative.

Gram-Positive Cell Wall

Peptidoglycan is the common cell wall component of bacteria (excluding mollicutes) and gives the wall its shape and strength. It is a polymer consisting of a backbone of alternating N-acetylglucosamine and N-acetylmuramic acid residues, cross-linked with small peptide bridges. Peptidoglycan accounts for about 80–90 % of the wall of gram-positive bacteria and for about 10 % of the gram-negative cell wall.

Gram-Negative Cell Wall (Outer Envelope)

The gram-negative cell wall contains only a shallow peptidoglycan layer. On the outer side of this layer is the outer membrane, a complex structure consisting of four major components: phospholipids, lipopolysaccharide, proteins (e.g., porins), and lipoprotein. Lipolysaccharide (endotoxin) is responsible for the pyrogenicity of the gram-negative bacteria.

Cytoplasmic Membrane

The cytoplasmic membrane, or plasma membrane is a phospholipid bilayer into which proteins/enzymes are embedded. The function of the cytoplasmic membrane is to act as a selective permeability barrier between the cytoplasm and the exterior environment. A mesosome is an organelle of bacteria that appears as an invagination of the plasma membrane and functions either in DNA replication and cell division, energy production, or excretion of exoenzymes. Flagella (if present) originate in a special structure in the cytoplasmic membrane (see the section on Flagella under Structure of the Bacterial Cell).

Cytoplasm

The cytoplasm is a viscous liquid, which contains all other essential elements for the living cell. The genetic material is mainly organised in the genome, a circular string of DNA. There is no discrete bacterial nucleus. The genetic code is translated into messenger RNA and then transported to the ribosomes, where the protein synthesis occurs. The building blocks of the proteins (amino acids) are transported to the ribosomes by means of transfer RNA.

Some genetic information such as antibiotic resistance may be encoded in plasmids – DNA molecules that are independent of the genome and that can replicate themselves. Some plasmids contain a set of genes (in the tra region) that enable the transfer of the plasmid by cell to cell contact (conjugation). The plasmid is replicated during this process and its genetic information (e.g. antibiotic resistance) is thus transferred to the recipient cell. There are both intra-species and inter-species plasmid transfer phenomena. The cytoplasm may also contain reserve material such as polyhydroxybutyric acid, and other substances of uncertain function (e.g. polyphosphate, volutin).

19.3.3.4 Bacterial Endospores

Some gram-positive rods such as the genera *Bacillus, Geobacillus* and *Clostridium* are capable of forming endospores that enable these genera to survive harsher conditions, such as exposure to heat, radiation, or chemicals. Bacterial spores are resistant forms of life. Some experts have suggested that they may remain viable (capable of life) for millions of years.

The bacterial spore has a complex structure, consisting of various layers, including coat and cortex, all of which play a role in long-term survival (see Fig. 19.2).

Endospore formation is a non-reproductive process: one cell produces only one spore which, after germination, produces one vegetative cell.

Bacterial sporulation occurs when growth decreases due to exhaustion of an essential nutrient. It is a complicated process requiring the participation of more than 200 enzymes. Conversion to a vegetative cell involves three steps: activation, germination and outgrowth. Activation can be accomplished by heating the spores to a non-lethal temperature. Germination can be induced by a variety of events, including exposure to nutrients (amino acids, sugars, or purine nucleosides), non-nutrient germinants (dodecylamine, lysozyme) and heating [49]. The spore loses its characteristic constituents, and heat resistance decreases dramatically. In the last stage water is taken up, and metabolism (synthesis of ATP,

Fig. 19.2 The bacterial spore. © 2003 Ricca and Cutting, *Journal of Nanobiotechnology* 2003, 1:6, doi:10.1186/1477-3155-1-6, published by BioMed Central

proteins and genetic material) resumes. Heat activation is an important factor in the occurrence of a shoulder in the survival curve of bacterial spores upon heating.

Destruction of bacterial spores is the ultimate goal of sterilisation processes. Bacterial spores are typically used in biological indicators for validation and monitoring of sterilisation processes.

19.3.4 Endotoxins/Pyrogens

Pyrogens are substances that cause a febrile reaction. Two groups of pyrogens can be distinguished: exogenous and endogenous pyrogens. The exogenous pyrogens form a heterogeneous group of substances; the most important one is lipopolysaccharide (LPS) from the cell wall of gram-negative bacteria. LPS, also known as endotoxin, has antigenic properties (O antigen) and causes fever when injected intravenously. Lipoteichoic acid, muramyldipeptide, porins, glycans and nucleic acids, are examples of non-endotoxin pyrogens originating from bacteria (gram-positive and gram-negative), yeast and moulds.

The pyrogenic activity of LPS is much higher than that of most other pyrogenic substances. This is the reason why an *in-vitro* limit test for LPS (the Limulus Amoebocyte Lysate, or LAL test) generally suffices for quality control purposes of parenteral medicines and raw materials, including water for injection.

The European Pharmacopoeia requires the rabbit pyrogen test for a number of vaccines, some antibiotics, and specific excipients including glucose, if intended for the preparation of large volume parenterals (see Sect. 32.8). These products may be contaminated with pyrogens other than LPS, or are known to inhibit the LAL test.

A third test, the monocyte activation test (MAT) is based on the *in-vitro* activation of human blood cells by pyrogens. This leads to the release of pro-inflammatory cytokines tumour necrosis factor alfa (TNF-alfa), interleukin-1 beta (IL-1beta) and interleukin-6 (IL-6) that are determined by Enzyme-Linked Immuno Sorbent Assay (ELISA). Consequently, the MAT will detect the presence of both exogenous and endogenous pyrogens in the test sample. The MAT is suitable, after a product-specific validation, as a replacement for the rabbit pyrogen test [50].

The reagent for the LAL is isolated from the blood of the horseshoe crab (*Limulus polyphemus*). The blood is collected from wild animals. Many animals do not survive (mortality rates of up to 30–50 % have been reported), and this living fossil is threatened with extinction. It is to be expected that in the near future the MAT test or other alternatives for the LAL test and the rabbit test will be more generally introduced. The development of such new methods will significantly reduce animal testing. The commercially most successful alternative method, which replaces the rabbit pyrogen test for bacterial impurities in medicines with a test using human cells, could save the life of 200,000 rabbits a year.

19.3.5 Biofilms

Biofilms are multicellular, microbial communities held together by a self-produced extracellular matrix that adhere to biological or non-biological surfaces [51]. A biofilm has a defined architecture, and it provides an optimal environment for the exchange of genetic material between cells, e.g. spread of antibiotic resistance. Cells within a biofilm may communicate via quorum sensing (see Sect. 19.1.7), which may in turn affect biofilm processes such as detachment of cells. The ability to form biofilms is a universal attribute of bacteria and many other micro-organisms.

Elimination of bacteria in this mode of growth is challenging due to the resistance of biofilm structures to both antimicrobials and host defences.

Biofilms have great importance for public health because of their role in certain infectious diseases and their role in a variety of device-related infections. Biofilm infections on indwelling devices or implants are difficult to eradicate because of their much better protection against macrophages and antibiotics, compared to free living cells, leading to severe clinical complications often with lethal outcome.

19.3.6 Fungi (Moulds and Yeasts)

Fungi are widespread in nature and have considerable economic and medical importance, because:

- They may contaminate and cause spoilage and deterioration of pharmaceutical preparations. Mould and yeasts are the second cause of FDA recalls in non-sterile pharmaceuticals [52].
- This group of organisms is used by producers of active substances, including antibiotics, such as penicillins by *Penicillium* species, or alkaloids, such as ergotamine by *Claviceps purpurea*.
- Some fungi are pathogenic to humans. They may cause infections (e.g., *Trychophyton* sp. or *Candida* sp.), or produce toxic substances (e.g., aflatoxin by *Aspergillus flavus*).

Two groups of fungi are relevant in the context of pharmaceutical products or processes: the moulds and the yeasts. Their physical differentiation is not always clear, because some fungal species (e.g., *Candida*, *Histoplasma* and *Cryptococcus*) show dimorphism, a phenomenon in which a filamentous and a yeast-like stage both exist.

Moulds are obligate aerobic micro-organisms; they grow on the surface or in the uppermost layers of the substrate. Characteristic of moulds is the filamentous body, the mycelium. Vegetative growth of moulds occurs at the tip of the individual filaments (hyphae).

Depending on the species, hyphae may be divided into compartments by means of septa (*Eumycetes*). Each septum contains a pore, which allows flow of cytoplasmic constituents from one compartment to another. The lower fungi (*Phycomycetes*) have aseptate (coenocytic) hyphae; the mycelium is a multinucleated cell.

Asexual reproduction of moulds normally occurs by means of spore formation. From the mycelium special branches reach up into the air. At the tip of these conidiophores the spores (conidiospores) are formed on a genus specific structure. The colour of mould colonies on solid substrates (e.g., different shades of green for *Penicillium* species, or black for *Aspergillus niger*) is entirely due to the massive production of these conidiospores.

Mould spores may cause significant issues in the production of pharmaceutical preparations since they survive desiccation and may be transported via air, personnel or material flow into products.

The spores are readily dispersed into the environment and may form a new mycelium. Because of mechanical forces, such as those exerted during vortexing, hyphae may break up into smaller fragments, which may also form new mycelia. Clumps of conidiospores may also break up into smaller units. Such fragmentation caused by vigorous mixing in the course of microbiological examination of pharmaceutical samples may lead to considerable uncertainty in fungal counts.

Yeasts are typically unicellular organisms. Yeast cells are spherical or oval. Growth (asexual reproduction) takes place by a process called budding. A new cell is formed as an outgrowth of the mother cell, the daughter cell enlarges and finally the two cells separate. Pathogenic dimorphic fungi usually form yeast-like cells in the human body and a mycelium at room temperature (e.g. *Histoplasma*). *Candida* sp. is an exception because it forms hyphae in the host tissue.

Sexual reproduction is associated with many yeasts and moulds. A stage in which spores are formed is always involved in the sexual process. Depending on the type of sexual spore formation four groups of moulds can be distinguished: Ascomycetes, Basidiomycetes, Zygomycetes, and Oomycetes. The spores are called ascospores, basidiospores, zygospores, and oospores, respectively.

Fungi for which no sexual reproduction has been demonstrated are classified as *fungi imperfecti* (*Deuteromycetes).* The majority of fungi thus far classified fall into this category. *Penicillium* and some *Aspergillus* species are well-known representatives of this group.

The cell wall of fungi consists of 80–90 % polysaccharides. Chitin is a common constituent of fungal cell walls, but is replaced by other substances such as mannan, galactosan or chitosan in some species. Peptidoglycan, the common constituent of bacterial cell walls is never present. This phenomenon explains why fungi are insensitive to antibiotics that inhibit murein synthesis, such as the penicillins and the cephalosporins. Sterols are essential structural components of the fungal cytoplasmic membrane. This characteristic makes fungi sensitive to antibiotics that interact with sterols, such as nystatin and amphotericin.

19.4 Fate of Micro-organisms in Pharmaceutical Preparations

In the previous sections the characteristics of potential contaminants of pharmaceutical preparations and their requirements for survival and growth have been discussed. There appears to be a complicated interplay between the type and characteristics of the micro-organisms (e.g. spore formation), their ability to form biofilms, the composition of the environment, and external factors, particularly the temperature. The fate of a micro-organism in a pharmaceutical preparation depends on this interplay. Four different curves may be observed when numbers of colony forming units (CFU) are plotted against time (Fig. 19.3).

Microbial growth follows the well-known sigmoid growth curve, with lag phase, log phase and maximum stationary phase. Microbial destruction under influences of heat, radiation or chemicals is frequently a first order kinetic process. When microbial destruction is plotted on a semi-logarithmic scale, a straight line is observed. A ‘shoulder’ is sometimes observed at the beginning of the curve. This lower death rate is attributed to the genetic repair mechanisms of the cells, e.g. when exposed to low doses of UV radiation. Bacterial spores must be ‘activated’ before they can germinate and grow out to become prototypical vegetative cells. This phenomenon may also cause a ‘shoulder’ in survival curves. At the end of the survival curve, a ‘tail’ may be observed, indicating the presence of resistant cells or clumps of cells. True dormancy is found only in bacterial endospores. Nevertheless, even vegetative organisms can produce an effective state of dormancy because of either a relatively slow death rate or growth and kill rates that offset each other.

In pharmaceutical preparations another type of curve is sometimes observed. An initial decrease in the number of colony forming units may occur, followed by an increase. This phenomenon can be observed when analysing data from preservative efficacy testing of inadequately preserved dosage forms. It is the reason why in pharmacopoeial

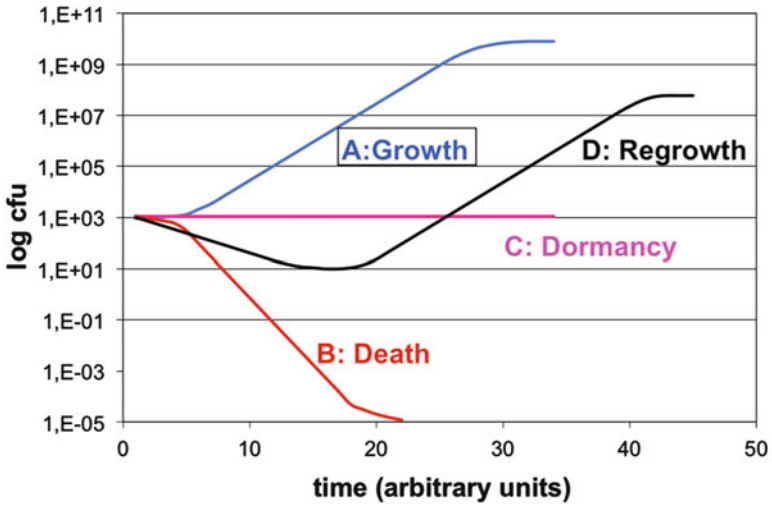

Fig. 19.3 Fate of micro-organisms in pharmaceutical preparations

preservative efficacy tests the number of viable cells must be followed for a period of 28 days (see Sect. 32.8).

19.5 Biological Contamination of Pharmaceutical Preparations

19.5.1 Impact of Microbial Contamination

Microbial contamination of pharmaceutical products may result in deterioration of the product or direct hazard to the patient.

Whether a contaminated pharmaceutical product will trigger infection or disease in the patient depends on various factors such as:

- Number of micro-organisms (CFU per g or mL)
- Ability of the contaminant to grow and metabolise components of the product
- Properties of the particular strain
- Immunocompetence of the patient, due to disease (AIDS) or use of immunosuppressiva
- Route of administration

Deterioration or spoilage of the product because of microbial growth may result in several effects including:

- Loss of texture because of metabolism of oil/fat phase
- Loss of organoleptic quality because of production of olfactory products
- Loss of preservative efficacy because of metabolism of the preservative
- Loss of package integrity because of excessive gas production
- Loss of therapeutic activity because of metabolism of the active substance(s)
- Release of toxigenic substances, including toxins (e.g. aflatoxin) and pyrogens

19.5.2 Origin of Microbial Contamination

The contamination can be primary or secondary. Primary contamination occurs at the premises or during preparation:

- *Personnel*. Personnel account for the majority of contaminations in the clean room environments. This can be explained by the high number of micro-organisms located on or in the human body. The organisms may be introduced into the environment due to inadequate gowning or hygiene, infrequent or ineffective hand washing and disinfection procedures, unqualified behaviour (non-clean room adequate) of personnel, etc. In the aseptic production of sterile pharmaceutical preparations living micro-organisms should not enter the aseptic filling area and the product should not contain any viable micro-organism. In those situations, low-level microbial contaminations of products occur mostly at critical interventions near to the product during processing. Microbial contamination of non-sterile pharmaceutical preparations may not originate primarily from the human body, but raw materials, equipment, air and packaging material may also play an important role
- *Raw materials*. Raw materials from natural origin may be highly contaminated with micro-organisms especially spore-forming bacteria and moulds and in some cases with more critical Enterobacteriaceae. Soon after a publication on salmonellosis in more than 200 persons caused by the contamination of thyroid tablets with two types of Salmonella originating from the raw material [53], proposals for the examination of non-sterile pharmaceutical preparations and acceptance criteria were published [54].
- *Water*. Water may be used to clean equipment and clean rooms as well as a product component. Water contains water-borne micro-organisms that may grow under low nutrient conditions. In a recent review of FDA product recalls, almost half (48 %) of them were due to

contamination by water-borne micro-organisms such as *Burkholderia cepacia, Pseudomonas species*, or *Ralstonia pickettii* [52].

- *Air*. Micro-organisms may be carried over from dust or soil particles and may be transported into manufacturing areas by personnel, material or airflow. Mould spores for instance were carried over from a highly contaminated source into the production room [55].
- *Equipment*. Equipment may be contaminated if inappropriate cleaning, disinfection or sterilisation procedures have been performed.
- *Primary packaging*. The microbiological quality of primary packaging material is critical for sterile preparations. Vials, ampoules and stoppers shall be sterile and free of pyrogens before filling. For non-sterile preparations the microbiological quality of the packaging material is less critical. Because of the production process, bottles, tubes etc. will have only low levels of contamination, provided they have been packed, stored and handled under appropriate conditions.

Secondary contamination may occur during storage, transport, and administration of the product. The root cause for contamination during storage and transport is mainly insufficient closure integrity (see Sect. 24.3). Contamination during administration can be avoided by suitable design of the primary package (see Sect. 24.1) and appropriate instruction of the medical staff or patient (see Sect. 37.4). Tubes are less prone to contamination than jars. In hospitals eye drops should only be used for one specific patient and preferably for one specific eye.

19.5.3 Prevention of Microbial Contamination

Microbiological quality assurance and microbiological quality control should be part of the pharmaceutical quality system of any production site. Its main aim is to prevent microbial contamination in case of products required to be sterile (e.g. parenteral medicines), or to reduce the microbial counts and avoid objectionable micro-organisms in case of non-sterile products (e.g. tablets). The elements of a Pharmaceutical Quality System (PQS) that are crucial for microbiological quality regard adequate design of premises, procedures and controls. They are discussed in this section. The principles are included in current Good Manufacturing Practices (cGMP) guidelines (see Sect. 35.5.7), which are legally binding for pharmaceutical manufacturers. Microbiological quality assurance (QA) refers to the procedures in the quality system that ensures that microbiological requirements of the product are fulfilled. Microbiological quality control (QC) refers to the tests performed to verify that the product meets the required specifications.

19.5.3.1 Procedures

The following procedures and measures concerning facilities should mitigate the risk of microbiological contamination:

- Qualified Personnel. Only trained and qualified personnel should enter areas where products are manufactured or prepared. Personnel should wear dedicated gowning which provides a physical barrier between the body and the working environment. The more critical the activity or product microbiological requirements, the stricter the gowning. Gowning may consist for instance of overalls, face masks, gloves (which are disinfected with ethanol) or even goggles in case of aseptic processing. Personnel that have apparent illnesses or infected wounds should be excluded from areas where open product is handled. Chapter Aseptic handling (Sect. 31.3.3) also discusses gowning.
- Basic hygiene. Whereas the manufacturing of the most microbiological-critical products (e.g. parenteral, intravenous products) is strictly regulated and inspected, their preparation and application in hospitals is less subject to control. Nevertheless, measures to prevent microbial contamination or proliferation are equally, if not more important in this case. Basic hygiene rules include e.g. regular cleaning and if appropriate disinfecting the hands with alcohols, wearing sterile gloves for the preparation of parenterals, disinfecting the outer surface of critical products before opening. See Chap. 31 for detailed instructions on microbiological monitoring, disinfection procedures, operator qualification and validation of aseptic handling.

For basic hygiene at the preparation of non-sterile medicines the main points are given here.

Contact between the product and the operator is to be prevented. Thus:

- Equipment and production processes shall be designed so that direct contact between operator and product is minimised.
- Under no condition shall the product be touched with bare hands. If manipulation is unavoidable use utensils, such as forceps, or wear gloves. Gloves shall be changed when appropriate, particularly at every preparation and after obvious contamination such as sneezing and wiping the nose.
- Refrain from talking above the product. Coughing and particularly sneezing are difficult to suppress. Wearing a facial mask and changing it at least every 2 h will considerably reduce the risk of contamination by this route. The operator shall inform his or her superior in case of a disease such as a cold.

(continued)

- Facial hair shall be appropriately covered; this may require the wearing of a head cover and a facial mask to cover moustaches and beards. This is also necessary from a safety point of view when operating with rotating equipment such as an ointment mill.

From a pure microbiological viewpoint wearing an overall doesn't make sense other than the promotion of an attitude of working cleanly and neatly. Already after 1–2 h the overall bears as much contamination as the personal clothing. Directions for clothing are however also necessary to promote occupational safety and health (see Sect. 26.4.3). The overall has to remain in the preparation area (thus taken off at lunch and coffee breaks) and has to be cleaned according fixed schemes, such as daily and when visibly contaminated. The overall shall have long sleeves and cover completely personal clothing.

Washing hands must always occur:

- At the start of preparation
- If hands are visibly dirty
- After using the toilets
- After sneezing and wiping the nose
- Between two different preparation processes, because of cross contamination

Nails have to be kept short and proper hand washing procedures include removal of watches, voluminous rings and bracelets (remaining off during the preparation process).

Washing hands technique requires preferably lukewarm water, soap from a dispenser, proper attention to thumbs, sufficient duration and proper drying with a towel because that will carry off micro-organisms too.

- Controlled environments. Clean rooms in which pharmaceutical preparations are prepared processed, and packed are controlled for room pressure, humidity and temperature. They are segregated from other operating areas and may be entered via separate air locks for personnel and material. The incoming air of the clean rooms is filtered using HEPA (high efficiency particulate air) filters that may retain more than 99.995 % of 0.3 µm air particles (see Table 27.4). The higher the microbiological quality of the product or the critical the process step, the higher the clean room quality criteria. For instance in aseptic processing of sterile products for critical areas where the product is exposed to the surrounding environment, the air should not contain more than 3,520 particles of 0.5 µm size per cubic metre and should be devoid of viable micro-organisms (see air classifications in Tables 27.2 and 27.3). Clean room design should ensure that air, personnel and material flow is optimal to prevent microbial contamination from a less clean area to a cleaner area. Isolators have been introduced as an alternative to conventional clean rooms for aseptic production. These may be large installations, in which complex operations such as large-scale aseptic filling of syringes can be performed.

  Controlled environments also regard to aseptic handling in pharmacies, where they are achieved using laminar flow cabinets, biological safety cabinets or isolators (see Sect. 28.4).
- Cleaning and disinfection. The procedures for cleaning and disinfection (destruction of micro-organisms – but not necessarily spores – by chemical agents, see Sect. 31.4.3) of equipment parts that are in contact with the product have to be validated. In addition, for the more critical products that are required to be sterile, the equipment parts that are in contact with the product need to be sterilised. Sterilisation (destruction of micro-organisms including spores by heat) process of the manufacturing lines has also to be validated. For products, which are required to be sterile, the aseptic status of the production line is regularly evaluated by performing media fill simulations that consist of replacing the product with a microbial culture medium and evaluating if filled-media containers remain sterile.
- Reducing bioburden. The preparation processes may reduce or even eliminate living micro-organisms. For instance on the preparation of tablets, the tableting of a granulate into a tablet may kill non-spore forming micro-organisms by the shearing forces of the interparticulate movement. Products required to be sterile are either sterile filtered (filter $\leq$0.2 µm pore diameter, see Sect. 30.6) or terminally sterilised directly in their container or package (e.g. steam sterilisation (Sect. 30.5.1), radiation (Sect. 30.5.3), ethylene oxide gas (30.5.4)).
- Water distribution system. The distribution and storage systems for water that is used for cleaning, sterilisation and preparation should be devoid of biofilms. A distribution system may be controlled by continuously circulating heated water (>80 °C) in loops, avoiding one-way systems and dead ends, and application of disinfection steps such as adding ozone to the re-circulating water (see Sect. 27.5.2). The latter processes are often called sanitisation. In addition to the physico-chemical characteristics, water is monitored for microbiological counts. For preparation on a smaller scale, the storage of water should follow strict requirements as well, see further Sect. 23.3.1.
- Standing time. Other risk mitigating actions may include defining maximum standing times for intermediate or final aqueous solutions if microbial growth is to be

expected, performing internal audits to ensure that procedures are followed, and testing the product's container closure integrity.

19.5.3.2 Tests

Microbiological testing is performed to monitor the microbiological bioburden and to ensure that the final product complies with the regulatory microbiological specifications. It comprises:

- An environmental monitoring program in order to monitor the microbiological levels of classified rooms. Air, product-contacting surfaces, working surfaces, floors and personnel are sampled. Frequency and sampling locations are defined based on a risk assessment. Maximum microbiological count levels should be defined either based on historical data or on regulatory guidelines. If they are exceeded, this may signal a deviation from normal conditions that would require an investigation and an evaluation on the impact on the respective product produced. Trending of environmental results may also be performed in order to evaluate shifts in the overall hygienic conditions over an extended period of time to define appropriate corrective actions. See also Sect. 31.6.1.
- Testing of primary packaging materials, raw materials (excipients, active substances, water) and products according to internal or official methods and specifications. Microbial limits of pharmaceutical preparations are given in relevant monographs of the European Pharmacopoeia. Section 19.6 provides a deeper insight on the European test methods of pharmaceutical preparations and acceptance criteria.
- Monitoring water distribution and storage system.
- Root cause investigation (see Sect. 35.6.15). When a test does not fulfil a microbiological acceptance criterion, this is considered as a deviation or out of specification result. This requires an investigation to determine the root cause of contamination, e.g. whether it occurred during laboratory testing, sampling or manufacturing. If a source of contamination has been found, corrective and preventive actions are put in place to eliminate and prevent re-occurrence of the contamination.

Failure to meet measures to prevent microbiological contamination of pharmaceutical preparations may have dramatic consequences. A major health issue related to microbiologically contaminated pharmaceutical preparations was the 2012 New England Compounding Center (NECC) meningitis outbreak in the USA [56]. On October 4, 2012, the CDC (US Centers for Disease Control) and the FDA (US Food and Drug Administration) issued a recall alert for pharmaceutical preparations produced by the NECC, following a multistate outbreak of fungal meningitis and other infections among patients who received contaminated preservative-free methylprednisolone acetate epidural injections. Most patients suffered infection by the fungus *Exserohilum rostratum* and in August 2013, CDC reported 749 cases and 63 deaths. After performing microbiological testing of the unopened incriminated product lots, CDC confirmed presence of *Exserohilum rostratum,* along with other fungi (e.g. *Cladosporium cladosporioide*, *Aspergillus fumigatus*) and spore-forming bacteria (e.g. *Bacillus subtilis*) [57]. After inspecting the NECC preparation area, the FDA mentions in its report [58] that moulds and bacteria were found in large numbers in many air and surface samples where the products were prepared.

19.5.4 Elimination and Destruction of Micro-organisms

A number of physical and chemical techniques to eliminate or to destroy micro-organisms may be employed in order to assure that the microbiological quality of the product complies with pharmacopoeial requirements, immediately after production and throughout its shelf life. Since these techniques are discussed in detail in other chapters, they are mentioned only briefly.

19.5.4.1 Physical Removal of Micro-organisms

Physical removal of micro-organisms (filtration, see Sect. 30.6) is applied for gases and liquids. High Efficiency Particulate Air (HEPA) filters are used to remove viable and non-viable particles from the air introduced in classified working areas (see Sect. 27.5.1). Hydrophobic membrane filters are used as vent filters on tanks and to filter production gases.

Membrane filtration of liquids is applied to reduce the bioburden of raw materials and of final products (see Sect. 30.6). In an aseptic process, membrane filtration is the final step before filling. During the production of a terminally sterilised product membrane filtration is applied to reduce the bioburden.

19.5.4.2 Physical Destruction of Micro-organisms

Micro-organisms may be physically destroyed by means of dry heat (see Sect. 30.5.2), moist heat (see Sect. 30.5.1) and ionising radiation (see Sect. 30.5.3).

Dry heat sterilisation is primarily applied for glassware and some heat stable raw materials. The standard temperature is between 160 °C and 180 °C. Ointments and some powders may be treated at lower temperatures because they are not stable enough. Higher temperatures (250 °C and above) are used for the depyrogenation and sterilisation of glass vials.

Moist heat sterilisation at 121 °C for 15 min is the method of choice for terminal sterilisation of finished products.

Sterilisation by means of ionising radiation of pharmaceutical preparations is not allowed in a number of countries. Many active substances and raw materials are decomposed by the doses required for sterilisation. Some polymers become brittle and glass may become discoloured. For these reasons there is only limited application for this sterilisation method for pharmaceutical preparations. Radiation sterilisation is however widely used in the medical device industry.

19.5.4.3 Chemical Destruction of Micro-organisms

Disinfection, sanitisation, decontamination, chemical sterilisation, are only a few terms for these processes. Disinfection, defined as removal, destruction or de-activation of micro-organisms on objects or surfaces, is the term of preference in this book.

Disinfection of surfaces (gloves, equipment, floors and walls) is done with a range of products, including isopropyl alcohol, ethanol, quaternary ammonium compounds, biguanides and amphoteric agents. If a sporicidal activity is required (as alcohols are not sporicidal), oxidising agents such as chlorine/hypochlorite, peracetic acid, or hydrogen peroxide may be used.

For medical devices a number of processes are available such as ethylene oxide and low-temperature hydrogen peroxide gas plasma sterilisation.

The objective of preservation is to assure the microbiological quality throughout storage and the period of use. A number of substances, including parabens, chlorhexidine, and sorbic acid are used (see Sect. 23.8).

19.6 Examination of Pharmaceutical Products

19.6.1 Sterility Test

Sterility tests appeared in the British Pharmacopoeia for the first time in 1932 and in the United States Pharmacopeia in 1936 [59]. Currently sterility testing is a legally binding release test for industrially manufactured sterile products. Only under specific conditions, including an excellent track record and a high level GMP, national authorities may grant a product and site-specific approval for parametric release (release without performing a sterility test) (see Sect. 32.8).

For many products prepared in hospital pharmacies or in institutions such as blood banks, the batch size is too small (one or only a few units) or the shelf life is too short (<14 days) to perform a complete sterility test as described in pharmacopoeias. In such instances, such as with radiopharmaceuticals (see Sect. 15.6.7), the pharmacist has to rely on the aseptic precautions during preparation (see Sect. 31.6). The use of rapid microbiological methods (RMMs) may also be an alternative to test products with such short shelf lives.

The objective of the sterility test is obviously to demonstrate that a batch is sterile, i.e. does not contain any viable micro-organism. There is an on-going debate on the rationale of the sterility test. The test is a destructive one and relatively small samples are taken from the batch. The results cannot be extrapolated to items that have not been examined. For terminally sterilised products a limit (Sterility Assurance Level, SAL of 10^6) has been imposed for which there is no appropriate test methodology of sufficient sensitivity. The test will only detect those micro-organisms capable of growing to detectable levels under the defined incubation conditions (media, temperatures and time). The sterility test is however the last possibility to detect any gross error in the production process. This means that applying an appropriate quality system with stable and well-controlled preparation and sterilisation processes (and not just performing a sterility test on the final product) is the key to ensure that a product that purports to be sterile remains free of microbial contamination. Regulatory initiatives strengthen the view that quality cannot be assured by final product testing, but should rather be assured by appropriate design of the manufacturing process (see Sect. 35.3). Consequently, these initiatives emphasise process understanding and monitoring over final product testing. For the way in which the process is monitored to ensure sterility during aseptic handling, see Sect. 31.6.1.

After several years of negotiation the sterility tests of the European Pharmacopoeia, The United States Pharmacopeia and the Japanese Pharmacopoeia are harmonised [59]. In the next sections the five steps of this harmonised test, as described in Ph. Eur. 2.6.1 will be discussed: sampling, sample preparation, inoculation, incubation, and interpretation. Prior to the routine application of the test, a suitability test with a range of specified test organisms shall demonstrate that growth of these organisms is not inhibited due to residual antimicrobial activity of the product.

19.6.1.1 Sampling

The monograph specifies the minimum number of items that shall be examined in relationship to the batch size,

and the minimum volume/amount that shall be taken from each container. The samples used should be representative for the whole batch. Furthermore immediately after an intervention in an aseptic filling operation (e.g. re-adjustment of a filling needle) the probability of contamination may be increased, and specific sampling for sterility testing may be justified. This has to be specified in relevant procedures.

19.6.1.2 Sample Preparation

Sample preparation includes all operations necessary before the actual examination can be performed, including opening of the primary packaging, withdrawal of the required amount and, if necessary, dilution or dissolution of the sample in a suitable liquid.

19.6.1.3 Inoculation

The technique of membrane filtration is used whenever the nature of the product permits. The membrane is transferred to the growth medium, or the medium is transferred onto the membrane. Alternatively, the prepared sample is inoculated directly into the appropriate media. This method is only used when the product (e.g. some vaccines) cannot be dissolved or diluted in a nontoxic diluent. The media used are fluid thioglycolate medium (FTM) for aerobic, micro-aerophilic and anaerobic bacteria, and Soybean casein digest broth (SCDB) for aerobic bacteria and fungi. FTM and SCDB are incubated at 30–35 °C and 20–25 °C respectively, both for a period of not less than 14 days. This relatively long incubation period seems to be justified, because an unacceptable proportion of contaminants would be missed by limiting incubation to 7 days [60].

19.6.1.4 Interpretation

The media are examined at intervals and at the end of the incubation period. If no growth is visually observed the sample passes the test. Normally the sample shall be rejected if growth is observed in at least one of the media. However under certain conditions the test may be invalidated and in that case be repeated.

19.6.2 Requirements for Non-sterile Products and Raw Materials

Sections 5.1.4 and 5.1.8 of the European Pharmacopoeia [61, 62] specifies microbiological quality criteria for non-sterile pharmaceutical preparations and raw materials. They are stated as Total Aerobic Microbial Count (TAMC) and Total combined Yeast and Mould Count (TYMC) (see Sect. 19.6.3) and requirements regarding specific micro-organisms. Limits depend on the route of administration, the nature of raw materials, the type of micro-organism, and on the fact whether an antimicrobial treatment can be given to the product (cf. Table 19.1 for a few examples).

The more stringent criteria for the aqueous preparations than for non-aqueous oral preparations reflect the greater potential for microbial growth of the former. *E. coli* must be absent from most of the preparations because this is an indicator organism for poor hygiene during production, or poor microbiological quality of the raw materials.

Products intended for inhalation must be free of *Staphylococcus aureus*, because it may cause pulmonary infections. This organism also indicates poor hygiene during production. *Pseudomonas aeruginosa* should be absent as well, because this organism may cause serious lung infections. Because of the aqueous nature of these products the presence of this organism and other bile tolerant gram-negative bacteria is a serious potential risk. Bile tolerant gram-negative bacteria form a complex group of micro-organisms comprising of the Enterobacteriaceae and many other strains (formerly Pseudomonads), including *Burkholderia cepacia* [63] and *Ralstonia pickettii* [64]. *Burkholderia cepacia* is a waterborne organism and causes great problems to the pharmaceutical industry and hospitals. It may be resistant to many commonly used disinfectants and preservatives, such as chlorhexidine, and it may cause serious lung infections, particularly in compromised hosts, such as cystic fibrosis patients. *Salmonella* must be absent from 25 g of herbal preparations. This reflects the low infectious dose of this organism and the severity of infections.

Test methods for the microbiological examination are described in Ph. Eur. Sections 2.6.12 [65] and 2.6.13 [66] respectively. Section 2.6.12 describes qualitative methods for the determination of the total aerobic microbial count and the total yeast and mould count. Section 2.6.13 describes tests for specified organisms.

19.6.3 TAMC and TYMC

The total aerobic microbial count (TAMC) is defined as the number of colonies observed on casein soya bean digest agar. The total combined yeast and mould count (TYMC) is defined as the number of colonies observed on Sabouraud-dextrose agar. The assessment consists of four steps: sampling, sample preparation/testing, incubation, and interpretation.

19.6.3.1 Sampling

In general the sample size shall be 10 g or 10 mL. An exception is made for those active substances for which the amount per dosage unit or per 1 g or 1 mL (for preparations

Table 19.1 Microbiological quality criteria of some pharmaceutical preparations

Route of administration	TAMC (CFU[a]/g or CFU/mL)	TYMC (CFU/g or CFU/mL)	Specified micro-organisms
Non-aqueous preparations for oral use	10^3	10^2	Absence of *Escherichia coli* (1 g or 1 mL)
Aqueous preparations for oral use	10^2	10^1	Absence of *Escherichia coli* (1 g or 1 mL)
Rectal use	10^3	10^2	–
Oromucosal use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
Gingival use			
Cutaneous use			Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Nasal use			
Auriculair use			
Vaginal use	10^2	10^1	Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
			Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Candida albicans* (1 g or 1 mL)
Transdermal patches (limits for one patch including adhesive layer and backing)	10^2	10^1	Absence of *Staphylococcus aureus* (1 patch)
			Absence of *Pseudomonas aeruginosa* (1 patch)
Inhalation use (special requirements apply to liquid preparations for nebulisation)	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
			Absence of bile-tolerant gram-negative bacteria (1 g or 1 mL)
Special Ph. Eur. Provision for oral dosage forms containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU/g or CFU/mL	10^4	10^2	Not more than 10^2 CFU of bile-tolerant gram-negative bacteria (1 g or 1 mL)
			Absence of *Salmonella* (10 g or 10 mL)
			Absence of *Escherichia coli* (1 g or 1 mL)
			Absence of *Staphylococcus aureus* (1 g or 1 mL)

[a]Colony forming unit (CFU): One or more micro-organisms that produce a visible, discrete growth entity on a semisolid, agar-based microbiological medium

not presented in dose units) is less than 1 mg or 1 mL. In these cases the amount to be tested shall be not less than the amount in 10 dosage units or in 10 g or 10 mL of the product.

Any sample shall be representative for the whole batch. However batch sizes may range from extremely small (e.g. for some biotechnological products) to very large (e.g. a batch of tablets). The Ph. Eur. does not describe how the samples shall be taken and this must be put down in local procedures.

19.6.3.2 Sample Preparation

If necessary the sample is dissolved and diluted in a suitable non-toxic diluent. Buffered sodium chloride-peptone solution to which an emulsifier and/or a neutraliser for antimicrobial agents may be added is widely used.

19.6.3.3 Testing/Incubation

Three methods may be used for the enumeration: membrane filtration, plate count, and most probable number (MPN) method. The advantages of the membrane filter method are its low limit of detection (LOD) of < 1 CFU/g or mL and the efficient separation of the micro-organisms from components of the product, particularly antimicrobial agents. For the pour-plate method, the sample is generally 1: 10 dissolved in the diluent, and 1 mL of the dilution is mixed with the agar. This corresponds to a LOD of 10 CFU/g or mL. The LOD is sometimes higher (e.g. 100 CFU/g or mL) if the product needs to be further diluted due to microbial inhibition, or lower in case of products with low microbial acceptance criteria. If the spread plate count technique is used the LOD is a factor of ten higher ($>$100 CFU/g or mL), because only 0.1 mL of the

dilution can be spread over the surface of the agar plate. The precision and accuracy of the MPN method is less than that of the membrane filtration and the plate count methods. Unreliable results are particularly obtained for moulds. For these reasons the MPN method is reserved for the enumeration of TAMC in situations where no other method is available.

Casein soya bean digest agar is incubated for 3–5 days at 30–35 °C. Sabouraud dextrose agar is incubated for 5–7 days at 20–25 °C. Duplicate plates are prepared for each dilution and each medium. If the MPN method is used the tubes are incubated for 3–5 days at 30–35 °C.

19.6.3.4 Interpretation

At the end of the incubation period the colonies on the plates are enumerated. The number of CFU per gram or per mL of product is calculated for each medium from the arithmetic means of the plates. Because of the relatively poor accuracy and precision of microbiological enumerations, according to the Ph. Eur. an acceptance criterion may be interpreted as follows:

10^1 CFU: maximum acceptable count is 20

10^2 CFU: maximum acceptable count is 200; etc.

19.6.4 Specified Micro-organisms

The group of specified micro-organisms is a limited group of organisms which may be either pathogenic, or are indicator organisms for lack of hygiene during production. This group includes a number of organisms that have been discussed in a previous section, viz. *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa,* and bile tolerant gram-negative bacteria. The group also includes: *Salmonella, Clostridium,* and *Candida albicans*. Tests for the detection of these organisms are described in the pharmacopoeias (e.g. Ph. Eur. 2.6.13 [65]).

Salmonella belongs to the family of the *Enterobacteriaceae*. Over 2,000 species are known. Salmonellae are differentiated by means of biochemical reactions and by serotyping. Salmonellae are pathogenic bacteria causing food poisoning. The bacterium is present in many free-living and domesticated animals. Pharmaceutical raw materials that have been contaminated include carmine, pancreatic powder and thyroid powder.

Bacteria from the genus *Clostridium* are anaerobic, sporeforming gram-positive rods. The spores are heat-resistant and can survive in foods that are incorrectly or minimally processed. The genus contains a number of dangerous pathogens, including *Clostridium botulinum, Clostridium difficile,* and *Clostridium tetani*.

Candida albicans is a fungus that grows both as yeast and filamentous cells and is a causal agent of oral and genital infections in humans. Systemic fungal infections including those by *Candida albicans* have emerged as important causes of morbidity and mortality in immunocompromised patients (e.g., patients with AIDS, cancer chemotherapy, and transplantations). *Candida albicans* biofilms may form on the surface of implantable medical devices. In addition, hospital-acquired infections by *Candida albicans* have become a cause of major health concerns.

In addition to these well-known organisms it has however been demonstrated that other organisms (e.g. *Burkholderia cepacia*, or *Ralstonia pickettii*) can cause infection when present in pharmaceutical preparations. For this reason the concept of 'objectionable organisms' was originally introduced in the USA. Objectionable micro-organisms are defined as contaminants that, depending on the microbiological species, would adversely affect product safety and product quality. So the assessment of microbial safety of a medicine has to include the examination of absence of objectionable micro-organisms as well. One approach to determine whether an organism is objectionable is to perform a risk analysis [55], see also Chap. 21. Such an analysis should address at least four issues:

- Potential level of microbial contamination (total aerobic microbial count, total yeast and mould count)
- Identity and characteristics of possible micro-organisms present (pathogenicity, ability to metabolise product components, ability to survive or even grow in the conditions of the product)
- Product characteristics (presence of antimicrobials, water activity, route of administration, container and closure design)
- Potential impact on patients (for instance: is the preparation meant for immunocompromised patients or for neonates)

The examination of pharmaceutical preparations for specified micro-organisms involves generally the following steps: sampling, sample preparation, resuscitation and enrichment, incubation on diagnostic or selective media, and evaluation. Sampling and sample preparation is basically the same as for TAMC and TYMC determination and will not be further discussed.

19.6.4.1 Resuscitation and Pre-enrichment

As a result of mild heat treatment, drying, or chemical antimicrobial treatment, cells may be sublethally injured. A cell is, by definition, sublethally injured if it is unable to grow on a selective medium that is typically suitable for normal healthy cells of that type. Sublethally injured cells may recover when transferred to a suitable non-selective medium and thus regain all their normal characteristics, including resistance to selective antimicrobial agents and pathogenicity. This recovery process is called resuscitation.

The examination of non-sterile pharmaceutical products for the presence of specified micro-organisms involves one or

Table 19.2 Media for the detection of specified micro-organisms

Specified micro-organism	Resuscitation + non-selective enrichment	Selective enrichment	Diagnostic media
Bile-tolerant gram-negative bacteria	TSB	EE broth	VRBG
Escherichia coli	TSB	McConkey broth	McConkey Agar 42–44 °C
Salmonella	TSB	Rappaport Vasiliades medium	XLD
Pseudomonas aeruginosa	TSB	–	Cetrimide agar
Staphylococcus aureus	TSB	–	MSA
Clostridia	Reinforced medium for Clostridia	–	Columbia agar
Candida albicans	SDB	–	SDA

more steps with selective media. To increase the likelihood of detecting sublethally injured micro-organisms, the product is initially incubated in a non-selective (enrichment) medium. This non-selective culture thus may serve a twofold purpose: to first resuscitate sub-lethally injured cells and, secondarily, to facilitate their growth for purposes of further isolation and identification. For some organisms a second enrichment step in a selective medium is include in the method. Table 19.2 gives an overview of the purposes of the media used for each (group of) specified micro-organisms.

If there is no growth in the selective medium, the corresponding specified micro-organism is absent and the product complies with the requirement. If there is typical growth in the diagnostic medium a confirmation of the presence of the specified micro-organism should be performed using either biochemical tests or other identification methods (e.g. 16S rDNA sequencing).

19.6.5 Alternative Methods

In the previous sections only the conventional microbiological methods, developed in the late ninetieth and first half of the twentieth century, have been discussed. All these methods are growth-based methods that have their own limitations (long incubation periods, only viable micro-organisms that also grow on the media can be recovered, variability in nutrient media quality, etc.). In the past decades many new technologies have been developed with the first aim to reduce the time to obtain results of microbiological testing.

The use of such rapid microbiological methods (RMM) is beneficial in terms of reduction of throughput time for release (especially of parenterals), early identification of product contaminations, allows for causal investigations to be carried out earlier, making it easier to find and eliminate contamination causes [67]. For short shelf life products (<14 days), rapid microbiological methods are essential for assessing microbiological safety. In addition, automation by alternative methods enables to reduce hands-on time, human error and paperless data recording.

Before microbiological testing can be performed with an alternative method, the user must demonstrate that the alternative method is suitable for its intended purpose. This validation is based on demonstrating at least equivalent performance of the RMM compared to the traditional method and is performed according to Ph. Eur. 5.1.6., USP <1,223 > or PDA TR-33 [68–70].

It is beyond the scope of this chapter to discuss all available technologies, just one example of each of three detection principles will be mentioned here, viz., a growth based method, a non-growth based method and a nucleic acid determination method. For an encyclopaedic overview the reader is referred to the literature [71].

19.6.5.1 Growth Based Method: ATP Bioluminescence

ATP is a metabolite present in all organisms (excluding viruses). The amount of ATP per cell is species-dependent and also is dependent on the metabolic state of the cell. ATP can be measured semi-quantitatively with the luciferin/luciferase system. This system (naturally occurring in the firefly) emits light in the presence of ATP. The sample is mixed with a special reagent, which causes lysis of the cells, liberating the ATP, followed by addition of the luciferin and luciferase reagents. The amount of emitted light is measured by means of a photomultiplier system and used as an indicator of the number of cells present. This principle can be applied for numerous purposes, such as the detection of micro-organisms in products or monitoring of cleaning and disinfection procedures. Its use has been suggested for microbiological examination of sterile and non-sterile pharmaceutical preparations [72, 73].

19.6.5.2 Non-growth Based Method: Solid State Laser Scanning Cytometry

A sample is filtered over a membrane filter and treated with a fluorogenic reagent. Living cells actively take up the reagent and convert it to a fluorescent substance. The filter is scanned with a laser beam and the fluorescence is measured. The system records the position of the fluorescent item, so that it can be verified microscopically that the signal was not due to an artefact. The method is able to detect a single cell within about 2 h post sample processing and testing. It is used to monitor large water systems in pharmaceutical plants [74].

19.6.5.3 Nucleic Acid Based Identification: Ribotyping

Ribotyping measures the pattern that is generated when DNA from an organism is treated with a restriction enzyme. DNA is isolated from a pure culture. The genes encoding for 16S rRNA are amplified with PCR, treated with one or more restriction enzymes, separated by means of electrophoresis and finally probed. The obtained genetic fingerprint is a stable marker that provides definitive species discrimination or even characterisation below species level.

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Statistics

20

Herman Wijnne and Hans van Rooij

Contents

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Abstract

Preparation, manufacturing, quality control and dispensing of medicinal products have always been associated with the pharmacist. Traditionally the pharmacist has therefore been trained in pharmaceutical analysis, focusing on analytical measurement of quality characteristics (identity, strength and purity) but the pharmacist was marginally trained in statistical quality control that is related to manufacturing processes.

The routine measurement of a characteristic or quantity in a dosage form by an accurate and highly precise analytical method will reduce the risk of rejecting batches when these truly comply or alternatively reduce the risk of falsely accepting batches, when batches do not comply.

The collection of analytical data or data with format go no-go is meaningless without a conclusion on rejection or acceptance of a batch. In addition, a decision is worthless when not properly based on sound scientific statistical principles: a carefully conceived sampling plan that considers issues such as sample size and variability.

The up scaling of production (batch size, numerous products in a single facility) and by consequence the up scaling of complexity within industry as well as within larger production facilities e.g. hospital pharmacies have led to the application of statistical quality control. Such an approach has been in use since the middle of the past century and is nowadays easy accessible by statistical software programs.

This chapter discusses several statistical principles that are used in pharmaceutical quality decisions, such as: normal distribution, rounding, confidence interval, standard deviation, outliers, operating characteristic curves, acceptance sampling. Examples have been embedded in a pharmaceutical context.

Keywords

Population • Sample • Confidence interval • Standard deviation • Outliers • Acceptance sampling • Content uniformity

Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_20,

20.1 Introduction

This chapter aims to refresh knowledge of basic statistical principles [1] to which other chapters may refer as well. It may also be of use in providing relevant practical pharmaceutical solutions to statistical problems. The chapter may be of interest to all involved in the preparation of medicines whether involved in large scale or small scale operations. Including but not limited to: suppliers, buyers, QC state laboratories, regulatory agencies, hospital pharmacists, qualified persons and governmental auditors.

Population and *sample* are discussed in Sect. 20.2. The properties of a population are studied in a representative random sample taken from that population. In pharmacy preparation practice populations are for instance batches of dosage units. Their properties are measured by analytical or biological assays and summarised as means, standard deviations and many other sample statistics. Some basic notions of probability distributions are briefly discussed.

Confidence intervals are presented by simple mathematical formulas in Sect. 20.3 with examples from a pharmaceutical control laboratory. Both Sects. (20.2 and 20.3) will lead the reader to the conclusion that representative sampling, sample size, variability, batch size and percentage defects are highly interconnected.

Section 20.4 explains and discusses the concept *acceptance sampling*, its practices and interpretations. Performing assays on pharmaceutical preparations in a sample is not sufficient warranty of quality, as valid conclusions with respect to the population cannot be drawn without knowledge of the sampling method. Such conclusion would be acceptance or rejection of the batch.

For example, quality may consist of the correct content of active principle in dosage units. Or quality may be questioned when glass-like particles are observed in a number of glass containers out of a large batch. The first example is referred to as *acceptance sampling by variables*; the latter is an example of *sampling by attributes*.

The expressions *producer's risk*, *consumer's risk*, *limiting quality level (LQL) and acceptable quality level (AQL)* are explained in order to understand how important these criteria are to warrant a high level of quality of medicines.

Finally, Sect. 20.5 completes this chapter by giving examples of statistical calculations and trivial numerical operations encountered in daily practice. It includes how to treat an apparent outlier.

20.2 Basic Statistical Concepts

20.2.1 Population and Sample

20.2.1.1 Population

A population is a set of elements that match a certain description, such as a batch of capsules. Usually, a specific characteristic of the elements is taken into consideration, for example the weight of the capsules. The set of all weights is also called a population. In both cases, the population is finite since the number of capsules in a batch is finite. Populations may be finite or infinite. The set of true weights of the capsules in a batch is an instance of a finite population, the set of distinct measurements of the weight of one specific capsule (in principle) forms an infinite population.

20.2.1.2 Sample

To study the properties of a (large or infinite) population a limited number of elements of the population are chosen at random. This subset of the population is called a sample.

The methods of drawing a sample from a population should be such that the sample is representative for the population. In a random sample every element of the population has a defined (often an equal) chance of ending up in the sample.

A stratified sample is a sample where sets of elements with certain characteristics are over- or under represented in a planned way. For example the first 500 suppositories in a large production batch may be twice over represented with the purpose of detecting starting up instability earlier in the process. Sample statistics should of course be corrected for this over- or under representation.

Functions on the sampled observations such as the sample mean, the sample standard deviation and many others (see Sect. 20.2.2) are called (sample) statistics. They are random variables, which have a probability distribution. Observations from subsequent samples vary due to at least three sources of variation: deviations reflecting the variation in the population (e.g. variation of the true weights of the capsules in the batch), sampling error (deviations due to differences between subsequent samples) and measurement errors.

A sample statistic ideally is an unbiased estimator of the corresponding population parameter. An *estimator* is a random variable and is said to be unbiased, if upon an infinitely large number of independent determinations its mean can be proved to equal the true value of the parameter being estimated.

20.2.2 Central Value and Measures of Variation

The arithmetic mean is a measure of the central value of a population. It is defined as:

$$\mu = \frac{1}{n}\sum_{i=1}^{n} x_i \qquad (20.1)$$

i.e. the sum of the values of the variable (x_i) considered, divided by the number (n) of elements in the population. If the population is very large or infinite, its mean can only either be estimated from a random sample taken from the population, or its value can be derived from probability

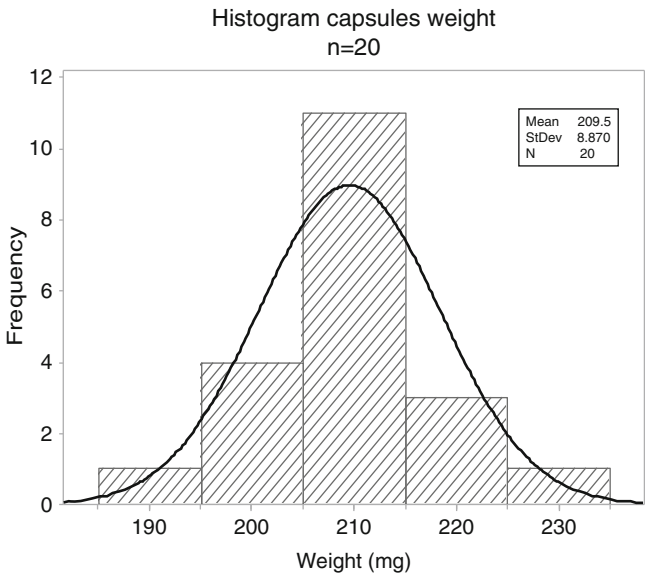

Fig. 20.1 Histogram of capsule weights (n = 20)

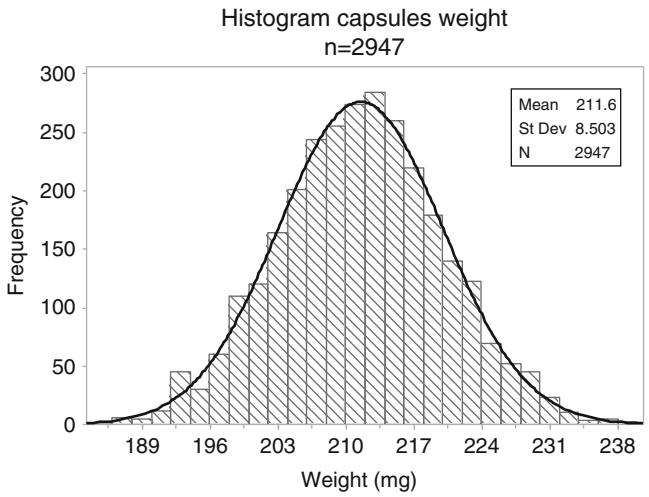

Fig. 20.2 Histogram of a large sample or population

theory e.g. the mean of the standard normal distribution is by definition zero. The calculated sample mean (m),

$$m = \frac{1}{n}\sum_{i=1}^{n} x_i \qquad (20.1a)$$

is an unbiased estimate of the true mean (μ) of the population.

Observed values of a population or sample show as a rule a certain degree of variation around the mean. There are a number of options to quantify this variation.

Observations or measurements are said to be accurate if they are unbiased estimates (Sect. 20.2.1) of the corresponding true value, and are said to be precise (or reproducible) if their replicated measurements have low variation. See Fig. 29.1 in chapter Basic Operations for a schematic representation of accuracy and precision.

The term accuracy often is incorrectly used as precision is meant and sometimes accuracy means accuracy and precision together. To avoid misunderstandings, it is recommended to use the terms accuracy and precision in their proper meaning (see Sect. 32.16.6).

One option to quantify variability is to draw a graphical representation of the frequency of certain values of the property concerned, called a histogram. The values are divided into classes.

Figure 20.1 Histogram of capsule weights (n = 20) shows the weight distribution of a number of capsules in a histogram. It is a sample of 20 capsules with average 209.5 mg. The class interval size is 10 mg. The height of a bar is a measure of the frequency.

When the number of observations is increased and the class interval size is reduced (Fig. 20.2 Histogram of a large sample or population), the histogram appears to become smoother. At an infinitely large number of observations and an infinitesimally small class interval size a *probability density* curve appears. Well known is the so called Gaussian or normal distribution, that applies to numerous situations in science e.g. the distribution of measurement errors, of genetic variation or, generally, of the sum of a large number of random variates, see Fig. 20.2. Other distributions are the binomial distribution and the Poisson distribution.

A quantitative measure of variation is the range, i.e. the difference between the highest and the lowest value (if existing) in the population or in the sample. The significance of this parameter is limited because only two elements in the sample determine the degree of variation making it unreliable.

A more reliable measure of the variation of a population distribution is the standard deviation (σ):

$$\sigma = \sqrt{\left[\sum_{i=1}^{n} (\mu - x_i)^2 / n\right]} \qquad (20.2)$$

i.e. the square root of the mean of the squared deviations of the population values (x_i) to the population mean (μ).

Equation 20.2 is appropriate when the n elements form a population, e.g. a batch consisting of 30 divided powders. If the n elements form a sample taken from a larger population then Eq. 20.3 applies.

The standard deviation of the sample (s) when the population mean (μ) and standard deviation of the population (σ) are unknown is computed as:

$$s = \sqrt{\left[\sum_{i=1}^{n} (m - x_i)^2 / (n - 1)\right]} \qquad (20.3)$$

where m is defined in Eq. 20.1a and division is by n − 1, the number of *degrees of freedom*.

The sample variance (s^2) is an unbiased estimate (see Sect. 20.2.1) of the population variance (σ^2), because it can be proved that for $k \rightarrow \infty$:

$$\left(s_1^2 + s_2^2 + s_3^2 + \ldots + s_k^2\right)/k = \sigma^2 \qquad (20.3a)$$

Note that division in Eq. 20.3 by n instead of by $n - 1$ produces a biased, too small, estimate of the population variance.

The population standard deviation of an analysis method will often be estimated from two or more duplicates, i.e. samples with $n = 2$, taken from different populations:

$$s = \sqrt{\left[\sum_{i=1}^{k} d_i^2/2k\right]} \qquad (20.4)$$

where d_i = the difference of two duplicate values, $i = 1, 2, \ldots, k$; k = the number of duplicates; s has k degrees of freedom, since each independent duplicate attributes one $(2 - 1)$ degree of freedom.

The standard deviation has the same dimension as the mean to which it relates, e.g. 20 capsules, weighing 215.2 mg on the average may have a standard deviation amounting to 8.4 mg.

To compare standard deviations the *relative standard deviation (rsd)* or coefficient of variation, may be useful:

$$rsd = s/m \qquad (20.5)$$

The relative standard deviation is dimensionless and is expressed in proportions or percentages.

The standard deviation of a sample (Eq. 20.3) is an estimate of the standard deviation of the corresponding population distribution.

Quite a different notion is the distribution of a sample statistic such as the sample mean or the sample standard deviation. For instance samples taken from a population with parameters μ and σ^2 have themselves a distribution with mean μ and variance $\sigma_m^2 = \sigma^2/n$, where n is the sample size. The square root of σ_m^2 is often called the standard error of the mean or SEM:

$$\sigma_m = SEM = \sigma/\sqrt{n} \qquad (20.6)$$

If σ is unknown, it can be replaced by s, the sample standard deviation (Eq. 20.3). The equation expresses the well-known fact, that the sample mean becomes more precise with the reciprocal of the sample size. This 'law of the large numbers' implies that for obvious reasons the standard error of the mean becomes zero if the sample size approaches infinity.

More generally the standard deviation of any statistic is called a standard error of that statistic being a measure of the imprecision with which the statistic is determined.

20.2.3 Random and Systematic Errors

Both random and systematic deviations may refer to the actual properties of the elements in a population, but frequently also to errors occurring during the manufacturing process or errors occurring in the QC laboratory. The weights of individual suppositories in a lot will exhibit random variation around the average, and when the wrong mold is used, the weights are systematically too high or too low.

Another source of random or systematic deviations may be the measurement process itself. When running a series of six assays of the active substance in an oral solution, the observed variability solely is caused by the analysis, provided the active substance is completely dissolved in the solution and the solution is homogeneous.

Uncorrected background absorption in a spectrophotometric UV–determination is an example of a systematic error, caused by the measuring process. However, background absorption may also be caused by components from the matrix in an unpredictable way and may then be random.

The effect of random deviations on the determination of the population mean can be eliminated by increasing the number of samples or the sample size. As a result the observed mean approaches more and more the true mean of the population. The effect of systematic deviations is independent of the number of samples or the sample size, and can only be eliminated by taking away the cause (the correct suppository mold) or in case of the UV-determination by correction for background absorption.

20.3 Confidence Intervals

20.3.1 Probability and Confidence Intervals

When the population distribution is known, for example X is normally distributed with mean μ and variance σ^2, we may calculate the probability of X being equal to or larger than x ($X \geq x$). We use that principle for e.g. process control by control charts. The production process has known targets for μ and σ^2 and when an uncommon value of variable $X \geq x$ is observed, the production process should be adjusted.

Very often the population is only known or assumed to have a normal (or other type of) distribution and we want to estimate the unknown values of μ and σ^2. To do that, we take a sample from the population and determine the sample mean, m, and the variance of the sample, s^2 (with $n - 1$ degrees of freedom). Both are unbiased estimates (see Sect. 20.2.1) of the corresponding population parameters μ and σ^2, meaning that, if we repeat the determination numerous times, the mean

of all sample means approaches μ and, equally, the mean of all sample variances approaches the true value σ^2.

In practice, only one or a few determinations are performed leaving us with uncertainty in the estimates of the population parameters.

A confidence interval is then the interval of values of m (or s^2), that comprises the true value of μ (or σ^2) in, say, 95 of 100 cases. The latter is called the confidence level and can be varied at will. In other words when we repeat the determination a large number of times, we are sure that, in about 95 % of the repetitions the true value of μ (or σ^2) is captured by the confidence interval.

An example is the assay of dexamethasone capsules using a sample of six capsules with observed mean m = 97.4 % and standard deviation s = 4.0 %.

The 95 % confidence interval is (for details see Sect. 20.3.2):

$$97.4 - t_{5,0.975} \times 4.0/\sqrt{6} < \mu < 97.4 + t_{5,0.025} \times 4.0\sqrt{6} \quad (20.7)$$

where $t_{5,0.025}$ (= 2.57) is the value of the t-distribution with 6 − 1 = 5 degrees of freedom and an upper tail probability of 2.5 % and $t_{5,0.975}$ (= −2.57) the lower tail probability of 97.5 %.

The lower limit of the 95 % confidence interval is 93.2 % and the upper limit equals 101.5 %.

Mark that, when the determination is repeated again and again, the confidence interval will change each time, because calculation of the upper and lower limits requires the values of the sample mean and standard deviation whose values will vary from sample to sample.

The result should be interpreted carefully. We have only an estimate of the value of the population mean and we know that each time the limits of the confidence intervals change.

However, we can be confident that upon repeating the assay sufficiently often, we approach the true value of μ more and more and that μ is within the calculated confidence intervals in say 95 % of the cases.

Confidence intervals provide a method of stating both how close the value of a statistic (e.g. the sample mean) is likely to be to the value of a parameter (μ) and the probability of its being that close. Mark that the confidence level 95 % is not the probability that the statistic is equal to the population parameter. It is a statement about our confidence in the method we use to estimate the true value and to how close we can come to it. Also the population parameter, μ, is a fixed value and has no probability distribution.

The normal distribution is known as a bell shaped curve of x against its probability density, f(x), and is characterised by two parameters: the average, μ, and the variance, σ^2, see Fig. 20.3. The area under the probability density curve, f(x), between two values, say x_1 and x_2, is equal to the chance of finding a value between x_1 and x_2, $P(x_1 < X < x_2)$, in the population. If $x_1 = -\infty$ and $x_2 = +\infty$ the area is equal to 1.

If $\mu = 0$ and $\sigma^2 = 1$ the normal distribution is called the *standard normal distribution*. Any normally distributed variable, X, can be transformed to the variable Z that has the standard normal distribution through equation:

$$Z = (X - \mu)/\sigma \quad (20.8)$$

Z can easily be seen to have the standard normal distribution with $\mu = 0$ and $\sigma^2 = 1$.

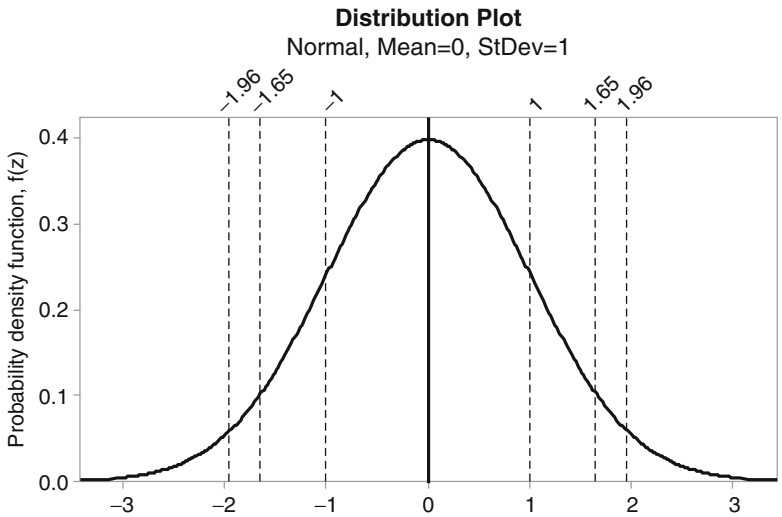

Fig. 20.3 Probability density function of the standard normal distribution with $\mu = 0$, $\sigma^2 = 1$.
Note:
68 % of the elements are between μ + σ and μ – σ
90 % of the elements are between μ + 1.65σ and μ – 1.65σ
95 % of the elements are between μ + 1.96σ and μ – 1.96σ

Table 20.1 Upper tailed probabilities of the standard normal distribution. More extensive tables for the standard normal distribution can be found in books and on the internet

z	P ($z < Z < \infty$)
0.50	.3085
1.00	.1587
1.50	.0668
1.645	.050
1.96	.025
2.00	.023
2.576	.005
3.00	.0013

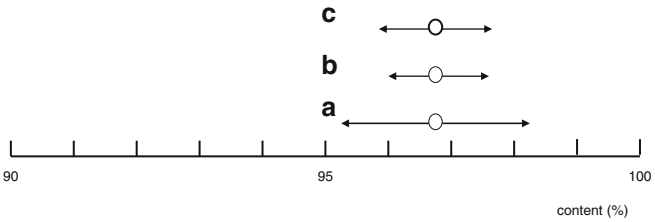

Fig. 20.4 Confidence intervals (95 % confidence level). (**a**): $\mu = 96.8$, $\sigma = 0.8$, $n = 1$; 95 % confidence interval $= 96.8 \pm 1.6$. (**b**): $\mu = 96.8$, $\sigma = 0.8$, $n = 4$; 95 % confidence interval $= 96.8 \pm 0.8$. (**c**): $\mu = 96.8$, $s = 0.6$, $n = 4$; 95 % confidence interval $= 96.8 \pm 0.95$

Values of P ($z < Z < \infty$) of the standard normal distribution are called upper tail (or one-sided) probabilities. Since the normal distribution is symmetric, the lower tail probabilities P ($-\infty < Z < z$) have the same values as their upper tail equivalents. They are usually tabulated as a function of z in books and on internet sites, see Table 20.1 for a small sample.

Thus from Table 20.1 it can be read that for the standard normal distribution a proportion of $1 - 2 \times 0.1587 = 0.683$ or 68.3 % of the population is found between plus and minus one standard deviation, σ, from the mean μ. The abscissa of the standard normal distribution is calibrated in standard deviation units, see Fig. 20.3.

Also for the standard normal distribution 2.5 % of the elements is larger than 1.96, 2.5 % of the elements is smaller than −1.96 and the remaining 95 % is between −1.96 and +1.96. Back transforming using Eq. 20.9 to the corresponding normal distribution with parameters μ and σ^2, 2.5 % of the elements is larger than $\mu + 1.96\,\sigma$, 2.5 % of the elements is smaller than $\mu - 1.96\,\sigma$ and 95 % of the elements is between $\mu - 1.96\,\sigma$ and $\mu + 1.96\,\sigma$, i.e.

$$\mu - 1.96\,\sigma < x < \mu + 1.96\,\sigma \qquad (20.9)$$

comprises 95 % of the values of X, when X is normally distributed with parameters μ and σ^2, see also Fig. 20.3. So, if $\mu = 100$ and $\sigma = 5$, X is between $100 - 1.96 \times 5 = 90.2$ and $100 + 1.96 \times 5 = 109.8$.

20.3.2 Confidence Interval of μ if the Standard Deviation of the Population is Known

Equation 20.9 can be converted to:

$$x - 1.96\,\sigma < \mu < x + 1.96\,\sigma \qquad (20.10)$$

Equation 20.10 is one version of the confidence interval defined in the introduction of this section. The real value of μ will be located in 95 out of 100 cases in the confidence interval. This is the double-sided 95 % confidence interval of μ, the right-tailed form of the 95 % confidence interval is:

$$-\infty < \mu < x + 1.645\,\sigma \qquad (20.11)$$

which says that the real value of μ will in 95 out of 100 cases be smaller than $x + 1.645\ \sigma$. The value $z_{0.95} = 1.645$ corresponds to the upper tail probability of 0.05 in Table 20.1. The left tail confidence interval is analogous to the upper tail interval.

The sampling distribution of the mean of n independent observations has mean μ and standard error equal to $\sigma_m = \sigma/\sqrt{n}$, see Eq. 20.6.

Assuming normal distribution of the sample mean, m, we obtain for the 100(1−α) % confidence interval:

$$m - z_{\alpha/2}\,\sigma/\sqrt{n} < \mu < m + z_{\alpha/2}\,\sigma/\sqrt{n} \qquad (20.12)$$

where α/2 is the upper tail probability and $z_{\alpha/2}$ can be found in Table 20.1. For instance $z_{\alpha/2} = 1.96$ if $\alpha/2 = 0.025$, giving the 100(1 – 0.05) % = 95 % confidence interval.

The width of the confidence interval is inversely proportional to $\sqrt{n}$, which implies that if the sample size increases, the sample mean is a more precise, but not necessarily a more accurate estimate of the population mean, see Fig. 20.4 Confidence intervals (95 % confidence level).

Worked Example: See Fig. 20.4 sub a. A control laboratory for pharmacy preparations knows by experience that the standard deviation of the determination of noscapine hydrochloride in an oral solution by means of U.V.-measurement equals 0.8 %.

When the outcome is 96.8 %, the true content of the oral solution is with 95 % confidence $96.8 \pm 1.96 \times 0.8$, i.e. between 98.4 % and 95.2 %. Or, the true content is with 95 % confidence above $96.8 + 1.645 \times 0.8 = 98.1$ % (down to 0 %, which is in this example of course unrealistic).

Note: when calculating the confidence interval please check that the standard deviation, and not the relative standard deviation is used.

The choice of the confidence level is arbitrary. We could have chosen 99 % instead of 95 % confidence by replacing 1.96 with 2.58. A wider interval will have a higher probability of including μ, but the statement loses precision.

Worked Example: See Fig. 20.4 sub b. The determination of noscapine hydrochloride in the oral solution, see previous example, will be quadruplicated. The mean of the four observations is 96.8 %.

The true content of the oral solution with 95 % confidence is between $96.8 \pm 1.96 \times 0.8/\sqrt{4}$ i.e. between 96.0 % and 97.6 %.

20.3.3 Confidence Interval of μ if the Standard Deviation of the Population is not Known

If the standard deviation of the population (σ) is unknown, confidence statements have to be based on the sample standard deviation, s. In the equation for the confidence interval (Eq. 20.12) the value $z_{\alpha/2}$ is replaced by the corresponding value $t_{\nu,\alpha/2}$ of Student's t-distribution. The result is:

$$m - t_{\nu,\alpha/2}\, s/\sqrt{n} < \mu < m + t_{\nu,\alpha/2}\, s/\sqrt{n} \qquad (20.13)$$

The value of $t_{\nu,\alpha/2}$ depends on the number of degrees of freedom (ν) and the desired confidence level, $(1 - \alpha)$. Student's t-distribution and *t*-test have been invented by Gosset (his pen name was Student) as early as 1908.

The number of degrees of freedom is $n - 1$, if the sample standard deviation, s, is obtained from one sample. It may eventually be obtained from a series of K samples by pooling s_i, $i = 1, 2, \ldots, K$ with degrees of freedom ν_i, $i = 1, 2, \ldots, K$:

$$s_p^2 = \sum_{i=1}^{K} s_i^2 / \sum_{i=1}^{K} \nu_i \qquad (20.14)$$

Values of t for different numbers of degrees of freedom and upper tail probabilities can be looked up in a t-distribution table such as Table 20.2. More extensive tables can be consulted in books and on the internet.

Worked Example: See Fig. 20.4 sub c. The assay of noscapine hydrochloride in the oral solution, see previous example, has been run in fourfold but now the standard deviation of the population is unknown and estimated by the sample standard deviation $s = 0.6$ with $\nu = 4 - 1 = 3$ degrees of freedom. The sample mean is 96.8 %. The upper tailed $\alpha/2 = 0.025$ t-value with $\nu = 3$ is $t_{3,\ 0.025} = 3.182$.

According to Eq. 20.13 the two-sided 95 % confidence interval of the true content, μ, is $96.8 - t_{3,\ 0.025} \times s/\sqrt{4} < \mu < 96.8 + t_{3,\ 0.025} \times s/\sqrt{4} = 96.8 - 3.18 \times 0.6/2 < 96.8 + 3.182 \times 0.6/2 = 95.8 < \mu < 97.8$.

20.3.4 Confidence Interval of the Variance σ^2, and the Standard Deviation σ

The sample variance, s^2, is an unbiased estimate (see Sect. 20.2.1) of the population variance, σ^2, with ν degrees of freedom. The statistic νs^2 has the chi-square distribution with ν degrees of freedom. The 100(1–α) % two-sided confidence interval is:

$$\nu s^2/\chi^2_{\nu,\alpha/2} < \sigma^2 < \nu s^2/\chi^2_{\nu,(1-\alpha)/2} \qquad (20.15)$$

The square roots of the upper and lower limits give the confidence interval of the standard deviation, σ. Values of $\chi^2_{\nu,\alpha/2}$ and $\chi^2_{\nu,(1-\alpha)/2}$ can be obtained from tables of the chi-square distribution. See Table 20.3 for a small selection of frequently occurring upper and lower tail probabilities and degrees of freedom. More extensive tables for the chi-quadrate distribution can be found in books and on the internet.

Worked Example. The Control Laboratory determines the content distribution of a batch of capsules on six capsules. The estimated standard deviation is computed as is 3.7 or

Table 20.2 Values of $t_{\nu,\alpha/2}$ for selected upper tailed probabilities, α/2, and degrees of freedom, ν, of the t-distribution

	Degrees of freedom					
α/2	2	3	5	10	20	∞
.50	0.000	0.000	0.000	0.000	0.000	0.000
.30	0.617	0.584	0.559	0.542	0.533	0.525
.20	1.061	0.978	0.920	0.879	0.860	0.839
.10	1.886	1.638	1.476	1.372	1.325	1.279
.05	2.920	2.353	2.015	1.812	1.725	1.645
.025	4.303	3.182	2.571	2.228	2.086	1.960
.010	6.965	4.541	3.365	2.764	2.528	2.327
.005	9.925	5.841	4.032	3.169	2.845	2.576

Table 20.3 Values of $\chi^2_{\nu,\alpha/2}$ for selected upper tailed probabilities, α/2, and degrees of freedom, ν, of the chi-quadrate distribution

	Degrees of freedom, ν					
α/2	2	3	5	10	20	100
.975	0.050	0.220	0.830	3.25	9.59	74.22
.95	0.103	0.352	1.145	3.94	10.85	77.93
.90	0.211	0.584	1.610	4.87	12.44	82.36
.10	4.61	6.25	9.24	15.99	28.41	118.50
.05	5.99	7.82	11.07	18.31	31.41	124.34
.025	7.38	9.35	12.83	20.48	34.17	129.56

$3.7^2 = 13.69$ for s^2 with 6–1 = 5 degrees of freedom. From Table 20.3 $\chi^2_{5,\,0.025} = 12.83$ and $\chi^2_{5,\,0.975} = 0.83$ giving for the 95 % confidence interval of σ^2: $5 \times 13.69/12.83 < \sigma^2 < 5 \times 13.69/0.83$ or $5.34 < \sigma^2 < 82.5$. The 95 % confidence interval of the standard deviation σ, is $2.30 < \sigma^2 < 9.08$.

If the sample size had been 11 capsules, then σ (the standard deviation of the population) with 95 % confidence is between 2.6 and 6.3 (α = 0.05 and ν = 10).

The example illustrates that the confidence interval of s is relatively large, especially if the number of degrees of freedom (ν = n − 1) is small.

20.3.5 Outliers

An outlier is an element in an observation series with a value that deviates from the other values in the series in such a way that the value cannot be from the same population as the other observations in the series.

Outliers occur due to numerous causes, for instance an outlier might occur due to unnoticed irregularities during the execution of a measurement (wrong filling up to the mark, bubble in pipette, reading errors, spelling mistakes, etc.). In principle, the outlier presumed must not be removed unless it can be identified as caused by an error in the process that produced the observation.

To prove that the outlier is outside the expected range of observations a statistical test may be of help. A common statistical approach may be to apply the Q-test of Dixon. Q is defined as the ratio of the deviation of the discordant value from its nearest neighbours with respect to the range of the values.

The procedure for testing suspected outcomes is as follows:

1. If the suspected outcome does not affect the final conclusion, then the observation is not deleted.
2. If it does, then an outlier test is performed, for example Dixon's Q-test:
   (a) sort all values to size ($x_1, x_2, \ldots x_{n-1}, x_n$)
   (b) check whether the suspected value is now x_1 or x_n
   (c) calculate Q with Eq. 20.16 if x_1 is the suspect value, or with Eq. 20.17 if x_n is the suspected value

Table 20.4 Dixon's Q-test limit values (Gardner-version)

Test criterion	n	Limit values	
		α = 0.05	α = 0.01
Eq. 20.16 or	3	0.970	0.994
Eq. 20.17	4	0.829	0.926
	5	0.710	0.821
	6	0.628	0.740
	7	0.569	0.680
$\frac{x_2 - x_1}{x_{n-1} - x_1}$ or $\frac{x_n - x_{n-1}}{x_n - x_2}$	8	0.608	0.717
	9	0.564	0.672
	10	0.530	0.635
	11	0.502	0.605
	12	0.479	0.579
$\frac{x_n - x_{n-2}}{x_n - x_3}$	13	0.611	0.697
	14	0.586	0.670
	15	0.565	0.647
	16	0.546	0.627
	17	0.529	0.610
	18	0.514	0.594
	19	0.501	0.580
	20	0.489	0.567
	21	0.478	0.555
	22	0.468	0.544
	23	0.459	0.535
	24	0.451	0.526
	25	0.443	0.517
	26	0.436	0.510
	27	0.429	0.502
	28	0.423	0.495
	29	0.417	0.489
	30	0.412	0.483

   (d) when the value of Q is greater than the value from the Q-table (see Table 20.4) belonging to the correct value of n and the desired alpha level, then the suspected value will be deleted.

$$Q = \frac{x_2 - x_1}{x_n - x_1} \tag{20.16}$$

or

$$Q = \frac{x_n - x_{n-1}}{x_n - x_1} \tag{20.17}$$

The Eqs. 20.16 and 20.17 apply from n = 3 to n = 7. For larger values different equations are used, see Table 20.4.

Worked Example. Four replicates during an assay were found: 100.5, 98.3, 92.3 and 101.6 %.

Is the third value an outlier?

Q-TEST:

The values are ordered by size:

$x_1 = 92.3$, $x_2 = 98.3$, $x_3 = 100.5$ and $x_4 = 101.6$

Applying Eq. 20.16 gives Q = 0.65. This value is smaller than the value (0.829) in the Q-table at n = 4 and $\alpha = 0.05$. The hypothesis that x_1 is an outlier can be rejected.

20.4 Acceptance Sampling

20.4.1 Introduction

Producers of medicines (pharmaceutical industry, hospital pharmacies and others) warrant their customers a definite content of active substance as agreed upon or required by established specifications. This section discusses compliance with release specifications. End control by inspection or by taking samples for chemical and biological assays provides some quality guarantee that is however limited by the random errors, inherent in the sampling procedure and in the analytical method. Each release method, if executed according to a predefined sampling plan offers a statistical guarantee computed as an Operating Characteristic (OC) function and displayed as the OC curve as will be shown in Sect. 20.4.2 in detail.

The confidence in the efficacy and safety of a medicine by a consumer (patient), the latter represented by inspection or regulatory agencies, is based partly on the warranty by the producer and further on requirements laid down in pharmacopoeias and other documents such as the marketing authorisation. The correct interpretation of the results of this system, called statistical quality control [2] or SQC is crucial to understand the character of the guarantee, when provided or asked for. In Sect. 20.4.3 the significance of this system will be discussed more in depth.

Sections 20.4.4 and 20.4.5 present two types of analyses and their OC Curves, respectively called Acceptance by variables and Acceptance by attributes, illustrated with pharmaceutical examples. Section 20.4.6 on Content uniformity of dosage forms shows how the determination of uniformity of content or mass of individual units can be performed, when needed.

20.4.2 Operating Characteristic (OC) Curves

Requirements as to the content of medicines are formulated traditionally by pharmacopoeias: Product A contains not less than 95 % of active substance a.

Product or Population-Orientation. The requirement for content is mandatory for any batch of the active substance or the finished medicinal product, in statistical terms the population. Quality control (QC) department has to check whether the batch complies with specifications by taking a sample from the population. The requirements are formulated product or population-oriented. This is an impossible mission, strictly speaking, as the results by QC are by definition subject to random fluctuations. QC will guarantee the patient-consumer that the batch does comply although a small chance of non-compliance exists; meaning the content of the product is less than (say) 95 %. On the other hand, QC will guarantee the producer that there is a small chance of rejecting batches as being not complying, although the actual content is (say) 98 %. However, QC selects the sample size and other statistical parameters and will determine the chances. These parameters are in principle not laid down precisely in pharmacopoeias.

Analysis or Sample-Orientation. The formulation of requirements for Content Uniformity (CU) however is chosen the other way around. The pharmacopoeia has formulated in every detail, how the sampling plan has to be performed and what outcome will lead to rejection or approval of the batch investigated. These requirements are formulated analysis or sample-oriented. The requirements and the influence on consumer's risks (the chance that the consumer gets a safe product) as well as on producer's risk (the chance that a batch is incorrectly rejected) can be derived from the procedure and laid down in the Operations Characteristic (OC). The chances of acceptance are of course dependent on quality characteristics of the investigated batch such as mean content, standard deviation of the assay and percentage outliers. The OC does not formulate quality specifications, but is only a listing of chances, either to reject or to accept, as a function of a quality characteristic.

The product or population-orientated formulation of a claim compels QC to find out how the analysis will be set up to guarantee that the requirements of the pharmacopoeia are met as good as possible for the population/batch involved. What "as good as possible" exactly means is not stated, but it is clear that the chance a patient will get a product 100 % compliant with specification, is not 100 %.

The second pharmacopoeial strategy (analysis or sample-oriented) in principle does not provide the QC department freedom to determine or to adjust the precision of the analysis apart from the error of the assay. The pharmacopoeia has laid down requirements for analysis and sample size. Precision is fixed by the analytical protocol and is mainly determined by the sample size prescribed. The test procedure provides information on the chance that a batch will be accepted, given a certain combination of quality characteristics of the units in the batch: mean content,

standard deviation of the individual contents, percentage outliers. The set of acceptance probabilities of a batch as a function of all possible combinations of quality characteristics of the batch is called the operating characteristic of the procedure. The operating characteristic as a rule takes the form of a graph or series of graphs (OC curves), in which the probability of acceptance of the batches is displayed on the y-axis against e.g. the population central value μ or proportion of defectives π.

The OC provides a complete but complex summary of the requirements for the population to comply with. The protection of patient or consumer against the risk of receiving a low quality product is the primary objective of regulatory bodies and inspectorates and efforts should be aimed at maintaining low acceptance probability values of batches with a relatively inferior quality.

The chance that a batch of inferior quality will be released is called consumer's risk. A consumer's risk of 10 % is in general widely accepted. Inferior or unacceptable quality is defined as the Limiting Quality Level (LQL).

High acceptance chances of good quality batches are on the contrary predominantly in the interest of the producer. The chance that a complying batch (good quality) will be rejected and not released is called the producer's risk. Good quality is called Acceptable Quality Level (AQL). The producer may set himself an acceptable quality level, giving regard to costs of manufacturing, stock position and customer service level (i.e. complaint rate).

Specifications, AQL, LQL and an example of an OC curve will be presented in the next subsection.

20.4.3 Acceptance Plans

The system of statistical end control, as mentioned in the previous section is called Acceptance Sampling. Elements are diverse parameters such as AQL, Producer's Risk, LQL, Consumer's Risk, the method of inspection or analytical procedure and the OC curve derived from them. Typically a plan contains not only the maximum and minimum limits of the content of product or batches but also the relative frequencies by which the outcome on content may be passed (or not) and what should be done: accept or reject.

Unfortunately this type of acceptance sampling is not always applied. One reason is without doubt that just stating the content alone as requirement is not sufficient. A detailed procedure for the assay method is required from which the margins follow or a tolerance interval is given from which the details of the assay method can be derived. Mixing up of these two approaches leads to an unclear situation. In the following subsections the second approach will be followed as it is mostly used in the Statistical Quality Control (SQC) and Statistical process control (SPC) community.

A consistent statistical quality control system is of critical significance for the protection of the patient, who has regulatory bodies and the health care inspection on his side, and for a transparent control of the products of the pharmaceutical industry and other medicines producing parties.

The following definitions of quality parameters have been taken partly from the site Six Sigma Glossary [3]:

- The Acceptable Quality Level (AQL) is the maximum percentage of defectives or the maximum deviation from label claim that is acceptable as a long-term average. It is the poorest quality level for the supplier's process that a consumer would consider to be acceptable as a process average. AQL is a property of the supplier's manufacturing process, not a property of the sampling plan.
- Producer's Risk is the probability that a batch with a quality equal to, or better than, the AQL will be rejected. It is equivalent to the Type I Error in statistical hypothesis testing and is often denoted with α.
- The Limiting Quality Level (LQL) is the proportion of nonconforming items or the percentage content associated with the consumer's risk. It can be regarded as the minimum quality that the customer would not want to accept, even for a single batch. The Lot Tolerance Percent Synonyms for LQL often encountered are lot tolerance percent defective (LTPD) and rejectable quality level (RQL), the latter two used as a level of protection against individual lots of poor quality. LQL is a level of lot quality specified by the consumer, not a characteristic of the sampling plan.
- Consumer's Risk is the risk that a consumer will accept a batch of worse quality than the LQL. It is equivalent to a Type II Error in statistical hypothesis testing and is often denoted with β.
- The Operating Characteristic function and curve represent the probability of accepting a product over a range of nonconforming items or proportions.

Two different types of acceptance plans are frequently used: Sampling by variables and Sampling by attributes.

Sampling by variables refers to inspection based on measurements on a continuous scale. The key parameter is the mean content (μ) of the population. The concept of Sampling by variables is presented in Sect. 20.4.4.

Sampling by attributes refers to 'go-no go', 'good or bad' inspection. The outcome variable is discrete, usually binary, and the key parameter is the proportion (π) of units with a specified property in the population. The concept of Sampling by attributes is presented in Sect. 20.4.5.

20.4.4 Acceptance by Variables

If the outcome variable is continuous, sampling by variables is the method of choice to construct an acceptance plan.

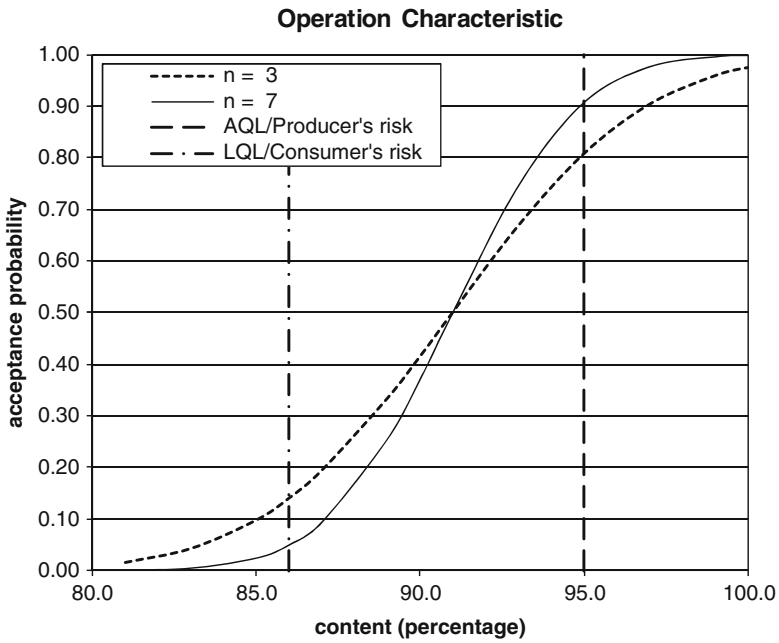

Fig. 20.5 OC-curves for two sample sizes (n = 3 resp. n = 7) of the spectrophotometric determination of noscapine hydrochloride with σ = 0.8 % and fixed limiting quality levels of LQL = 86 % and β = 5 %, and AQL = 95 % with α = 10 %. The OC-curve for sample size n = 7 complies with the predefined conditions

Compared to discrete variables, continuous variables have a large information content so that small or moderate sample sizes are sufficient for a powerful test. The probability distribution of the sample mean should be known and preferably normal, either because the population distribution is normal, or the sample is large enough to let the distribution of the sample mean approach normality (central limit theorem).

Worked Example. A regional supplier of pharmacy preparations routinely prepares an oral solution of noscapine hydrochloride. The label claim is 100 % and the standard deviation of the spectrophotometric determination for the release decision, σ = 0.8 %, is known from historic data. The limiting quality levels for this product have been fixed at LQL = 86 % with a consumer's risk, α, of about 5 %, and the AQL is set to 95 % with a producer's risk, β, of about 10 %.

Figure 20.5 shows OC-curves for two sample sizes (n = 3 resp. n = 7) of the spectrophotometric determination of noscapine hydrochloride.

The supplier's laboratory has to design the assay and the respective OC curve in such a way that the OC curve fits between the points (0.05, 86) and (0.90, 95) as presented in Fig. 20.5. This can only be done by manipulating the number of replicates of the assay, because this is the only degree of freedom. The OC curve inclusive the number of replicates are derived from the limiting values LQL and α, AQL and β and not the other way around.

The OC function is the cumulative distribution function of the standard normal distributed variable Z:

$$Z = (x - \mu)/(\sigma/\sqrt{n}) \qquad (20.18)$$

where x is the value of the content and μ is the value of x for which the acceptance probability equals 0.5, as in this example μ = 51 %. We assume a normal distribution of Z with $\sigma/\sqrt{n}$ as the standard error (see Eq. 20.6) of the assay.

Deviations above label claim, 100 %, will be neglected in this example, but can be calculated in an analogous way by mirroring.

The OC curves in Fig. 20.5 are for two sample sizes, n = 3 and n = 7. The first generates too large a consumer's risk (0.14) and a producer's risk of 0.09. The second (n = 7) provides the values asked for: consumer's risk 0.05 and producer's risk 0.09. Since the number of replicates is discrete, the producer's risk 0.09 is somewhat smaller than the required value of 0.10. For the same reason LQL equals only approximately the left-tailed limit of the one-sided 95 % confidence interval of μ.

The significance of acceptance sampling is not principally to take a decision about the release of individual cases. If the LQL is passed the respective product has to be rejected. An OC curve is not necessary for that decision, as the LQL is fixed externally by agreement or by regulations. The OC curve supports the policy of the producer and controlling laboratories and their mutual discussions. The LQL defines an inferior product, not fit for its intended use that should not be handed out to the patient. The consumer's risk indicates the chance that a borderline product still reaches the patient. The AQL is meant as a kind of long term average in the manufacturing of the product, a kind of state of the art quality stamp. It is not meant as a criterion to allow individual batches to pass QC. The associated producer's risk is not the chance that a product will be rejected, as is often thought. It is the relative frequency

that the state of the art quality (the AQL) will be met. As such AQL and producer's risk are a quality seal for the producer's production process, not for any incidental product. From this perspective acceptance sampling is not only a tool to block unwanted products, not fit for use, but it can be used to support and manage the quality policy of the company and governmental institutions. Producer's risk could better be named producer's ambition.

Industry has accepted a default release specification for the active substance of the label claim ± 5 %. This would imply that in the long run, given a label claim of 100 %, a real content between 95 % and 105 % is warranted in a pre-specified proportion of the products at release. This proportion is called producer's risk and should be between 5 % and 10 % (in the example 10 %) as is usually accepted within the Statistical Quality Control (SQC) community. The corresponding content limits are thus identical to the acceptable quality level or AQL as defined above. The producer may propose to loosen these limits, when the active substance is e.g. hygroscopic, electrostatic or otherwise difficult to handle, or when the active substance is degrading considerably within the shelf life permitted.

Batches below the Limiting Quality level (LQL) conversely are not acceptable for the consumer/patient or buyer and should not be released. The LQL represents the consumer's risk. The AQL is closer to the label claim (content stated on the inner and outer label) and could be identical to label claim ± 10 % with a consumer's risk of 5–10 %, in the above example 5 %.

Content specifications of medicinal products in industrial practice are twofold: specifications at release and specifications at end of shelf life (EOS). Specifications at release apply to the finished product at the time of leaving the production plant. Specifications at end of shelf life apply to the product until the date of expiration. Both types of specifications can be included in (separate) OC curves. The establishing of specifications is not a statistical problem, but the task of parties, such as buyers/suppliers, controlling institutions and so on. Obviously, they have to take statistical possibilities and limitations into account. For example, by bringing LQL closer to AQL one may expect that non compliance with AQL will lead to more rejects. A steeper OC curve can be realised by increasing the number of replicates of the analysis or by decreasing the standard deviation of the assay method or both.

Preparation in (hospital) pharmacies of products with a short period between production and administration or use may require other approaches, especially when the batch size varies between 20 and 1,000 and where sample size is a limiting condition.

20.4.5 Acceptance by Attributes

If the outcomes of the inspection of the units of a sample are binary, e.g. approve or reject, Acceptance by attributes is the method of choice to design acceptance plans. Such data or in general discrete variables contain much less information than continuous variables resulting in larger sample sizes and sometimes complex sampling plans in order to get sufficient statistical power. Military Standard (MIL-STD-105A) [4] and ISO 2859–1 [5] are often used standards for acceptance by attributes plans. Binary data occur in the investigation of content uniformity of individual dosage forms, where the aim is to test for large deviations of content, see also Sect. 32.7.2.

Since the sample sizes are large, up to n = 1,000, the inspection of the individual units should be cost-effective and not be time-consuming. Examples are the visual inspection of defective packaging materials, including labels or closure of containers. It is not so easy to establish errors in preparation that can have serious consequences, e.g. microbiological contaminations.

Figure 20.6 shows a number of OC-curves for a population with an unknown percentage of defectives sampled with three different sample sizes (n = 30, 50, 100).

Defective units are counted as 'no-go'. Acceptance criterion, c, is c = x = 0 in this case, meaning that the batch is accepted if no defectives are found. For binary data (go, no-go) the probabilities of x = 0, 1, 2, . . ., n defectives are calculated using the binomial distribution:

$$P(x) = \binom{n}{x} \pi^{n} (n - \pi)^{n-x} \qquad (20.19)$$

where:

$\binom{n}{x}$ is the binomial coefficient, $\frac{n!}{x!(n-x)!}$,

π is the proportion defectives in the population (the batch),

n is sample size.

If the population is limited in size, sampling without replacement leads to exhaustion of the population. Then the hypergeometric distribution is applied to calculate the chances P(x). However differences are mostly small or negligible and will not be further be discussed here.

The values of AQL = 1 % respectively LQL = 5 % are established or agreed upon by producer and buyer of the product and can be read from the graph, while 10 % is assumed to be the target for producer's risk and consumer's risk. As explained in the previous Sect. 20.4.4 the OC has to be designed in such a way that the curve passes through points (1, 0.90) and (5, 10) as best as possible.

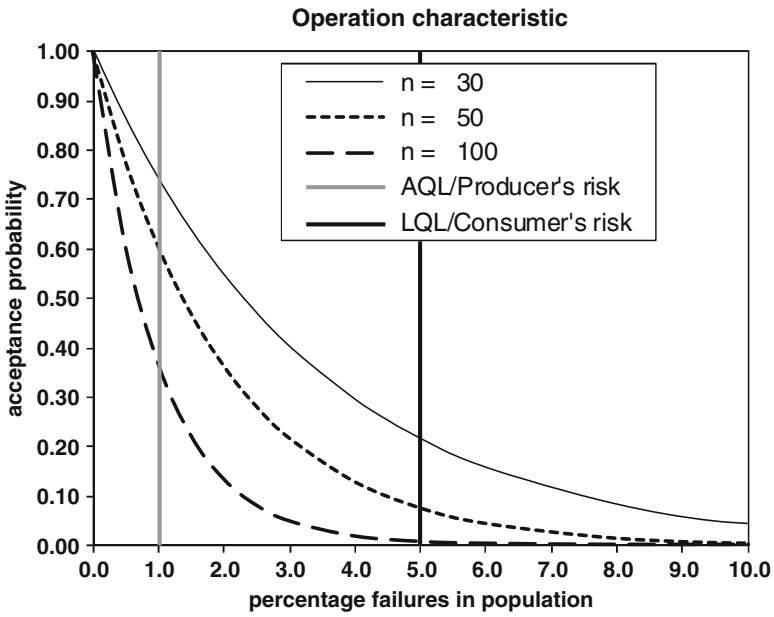

Fig. 20.6 Operation characteristics of samples of three different sizes from the same population

The OC curves of the three different sampling plans with sizes n = 30, 50 and 100 are presented in Fig. 20.6. Using a sample size of n = 50 the producer can guarantee an LQL of maximal 5 % defects in the population with a chance of 8 % (consumer's risk) of exceeding that percentage. A sample size of n = 100 provides a much lower risk and a stricter LQL could have been agreed upon.

An AQL of 1 % defects in the population has been chosen in this example. The producer's risk is then extremely high, namely about 25 % for a sample size n = 30 and will increase even more for larger sample sizes. Apparently it is not possible to obtain the desired acceptance plan by manipulating the sample size. The following example shows how to improve the characteristic and get a better result by changing the acceptance criterion as well.

We would like to find an OC curve in which the consumer's risk remains small, while the producer's risk decreases. Possibly, around the AQL of 1 % defectives in the population the acceptance chance can be increased by accepting 0 or 1 defects in the sample while staying at an AQL level of about 1 %.

Figure 20.7 shows the OC curves of five different sampling plans of which the acceptance criteria are:

1. x = 0, no defects in the sample: acceptance of the batch; whereas x > 0, one or more defectives in the sample: batch not accepted.
2. x = 0 or x = 1, zero or 1 defect in the sample: acceptance; whereas x > 1, two or more defective units in the sample: no acceptance.
3. x = 0, 1 or 2, 2 defectives at the most in the sample: acceptance; whereas x > 2, three or more defective units in the sample: no acceptance.

Finally, a fourth and fifth sampling plan are possible in which two steps lead to a decision (two steps, 1 and 2 in Fig. 20.7).

4. x = 0: acceptance of batch; x > 1: no acceptance of the batch; x = 1: sample again, size identical or different and count number of defective units x'. If x' = 0: acceptance of the batch, else no acceptance.
5. x = 0 or x = 1: acceptance of batch; x > 2: no acceptance of the batch; x = 2: sample again, size identical or different and count number of defective units x'. If x' = 0: acceptance of the batch, else no acceptance.

Relaxing the acceptance criterion (n = 50) appears to be disadvantageous for the consumer's risk and of advantage for the producer's risk. Acceptance at 0 or 1 defective units in the sample instead of only 0 defects increases the consumer's risk to 28 % from 8 % in the first example. At the same time the producer's risk decreases from 40 % to 9 %. This approach is obviously not acceptable. The stepwise approach is much better, but unfortunately not good enough. A second sample of 50 units, drawn when the first sample contains one and not more than one defective unit (plan 4 above) does not change the consumer's risk much compared to that in plan 1 (only acceptance at zero defective units in the sample): 8 % changes to 9 % and reduces the producer's risk from 40 % to 21 %.

This (21 %) is still above the acceptance probability of 10 % agreed upon, but more options are not available in this particular case. If an AQL of 0.5 % instead of 1 % would have been agreed upon, the producer's risk would have been 7 % instead of 21 %, which complies with the original agreement. But then the producer would in the long run have been obliged to supply a product with maximal 0.5 % defective units. Probably he did not consider this a wise option. These kinds of considerations will not be addressed

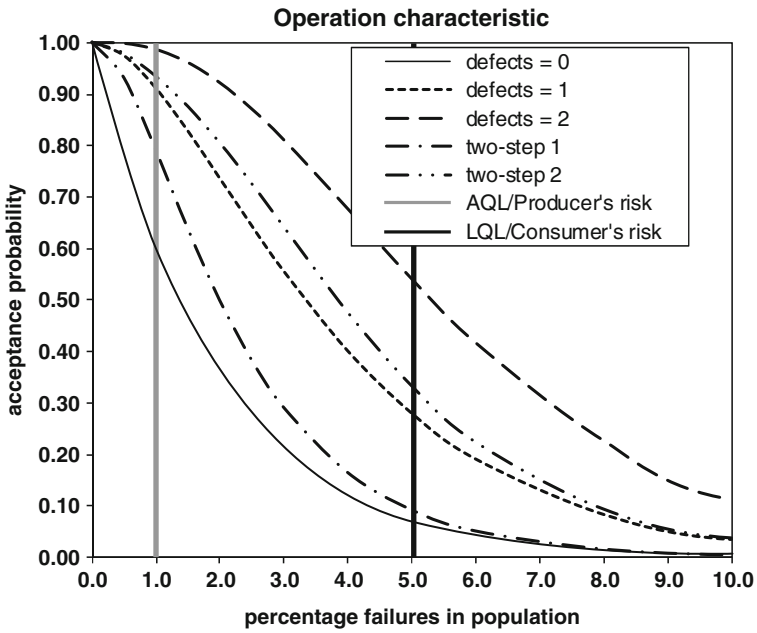

Fig. 20.7 OC curves of five different sampling plans for the same population, n = 50

here. The consequences of exceeding consumer's or producer's risk are difficult to oversee as well. If the consumer's risk of 10 % is exceeded, this will not immediately lead to the destruction of the batch, when e.g. the defects are in the packaging materials. The defective units can simply be removed or replaced. On the contrary if the defective units are posing a safety hazard for human health, e.g. a microbiological contamination on a part of a batch of ampoules, then statistics settles the matter and the whole batch has to be destroyed, because it is not possible to find all contaminated ampoules without destroying them all. If however the producer's risk is exceeded, there is no direct consequence for the release of the batch: just release the batch. The producer and an inspecting authority should consider that as a signal to review the production process more closely and when needed or possible to improve that process.

The design of an acceptance plan is therefore not only a statistical exercise, but requires a review of all potential options and interests. The options have a technical character: what is feasible from a technical and economical point of view and will give a reliable outcome; interests are in guaranteeing a safe and efficacious medicine and are in the interests of the producer.

20.4.6 Content Uniformity of Dosage Forms

This section provides basic knowledge to understand the current requirements of the Ph.Eur. as described in Sect. 32.7.2.

The examination of the distribution of active substance across individual dosage forms (content uniformity) implies the determination of the content of each single unit. The mean and the relative standard deviation are then calculated. The variation observed is caused by:

- Variation of weights across the individual unit
- Variation in mixing (non-homogeneity)
- Random error due to the analytical method

If the last component of variation is indeed negligible relative to the other two sources of variation, in a next step the variations due to weight and due to mixing can be split up. This is important if corrective or preventive actions have to be taken, when commonly accepted requirements for content uniformity are not met (see also Sect. 4.6.5).

To this end, both content of each unit and its weight are determined. If the observed distributions of weight and content are in the same order of magnitude, then this is an indication that the content distribution will be caused mainly by differences in weight of the capsules. If alternatively the weight distribution is considerably smaller than the spread in content, then mixing probably contributes significantly to variation. Mixing is never perfect in suspensions of a solid in a liquid or in mixtures of two solids. In addition, physical segregation may occur.

The net amount of the active substance in a separate unit corrected for random deviation of the weight of the unit, g, may be calculated from:

$$g = m \times d \tag{20.20}$$

where m is the sample mean of the weights of all units divided by the weight of a single unit, and d is the measured content of the same unit.

Table 20.5 Content uniformity analysis of a sample of six dexamethasone capsules

Capsule	Weight (mg)	Assay %	Corrected assay % (content)
1	161.6	103.5	100.9[a]
2	155.9	93.5	94.5
3	154.5	95.7	97.6
4	156.9	91.5	91.9
5	154.3	100.5	102.6
6	162.7	99.7	96.6
Mean	157.6	97.4	97.4
Standard deviation	3.6	4.6	4.0
s/m (percent)	2.3	4.7	4.1
s^2/m^2 (percent^2)	5.3[b]	22.1[c]	16.8[d]

[a]Calculation of content of this capsule: (157.6/161.6) × 103.5 = 100.9
[b]Variance due to differences in weight
[c]Total variance
[d]Variance due to imperfect mixing

The variation in g is then calculated from two measured components i.e. the total variance of the content of the units, d, and the variation in the weights of the units, m, with the aid of the modified Eq. 20.22 from Sect. 20.5.3:

$$\sigma_g^2/\mathrm{g}^2 = \sigma_m^2/\mathrm{m}^2 + \sigma_d^2/\mathrm{d}^2 \qquad (20.22a)$$

σ_g^2 represents the variance due to (de-)mixing which is the total variance of the dosing unit, σ_d^2, corrected for the variance due to differences in weights, σ_m^2.

The variances σ_m^2 and σ_d^2 will be estimated by the corresponding sample variances s_m^2 and s_d^2. The denominator of m, i.e. the sample mean of the weights, is assumed to be a constant and precise estimate of the population mean leaving the numerator, the individual weight of each unit, as the chance variable. It is assumed that the analysis and other errors are either negligible, or are included in one of the other components of variation, though it makes sense to include these explicitly in the equation, if estimates are available.

For example, six capsules of a batch of dexamethasone capsules are weighed and the content of dexamethasone in each capsule is determined. Weights and contents are listed in Table 20.5 and further calculations are presented there.

In accordance with Eq. 20.22 the last row of the table states 5.3 (for weight) and 16.8 (for corrected assay) sum up to 22.1 (for corrected assay). The conclusion is that 5.3/22.1, or 24 % of the total variation in the content of the capsules is due to variation in the weights of the capsules and 16.8/22.1, or 76 % of the total variation is due to mixing. In conclusion a first step would be improvement of mixing in order to improve content uniformity.

20.5 Statistical Calculations and Numerical Operations

20.5.1 Effect of More than One Deviation in a Process

If an outcome is a function of two or more measurements (or steps in a measurement or a manufacturing process) every step contributes to the variation of the final outcome. The variation may be calculated using the squares of the standard deviations, i.e. the variances of the individual measurements.

To calculate the total variance there are two possibilities:

1. The outcome is the sum or difference of measurements
2. The outcome is the product or quotient of measurements

Application of the Eqs. 20.21 and 20.22 assumes independence of the errors in the measurements, i.e. x and y should be uncorrelated in the underlying population.

20.5.2 The Outcome is the Sum or Difference of Measurements

If the final outcome, z, equals the sum or difference of two or more measurements (x, y, ...) then the variance of the outcome is equal to the sum of the variances of the individual measurements. So, if z = x + y or z = x − y, then:

$$\sigma_z^2 = \sigma_x^2 + \sigma_y^2 \qquad (20.21)$$

Worked Example. An example is the weighing of a tube with sterile eye ointment base during the aseptic process of

preparation of a suspension-eye ointment. The first weighing of the tube is 100 g with a standard deviation $\sigma_x = 0.5$ g and after sampling the desired amount from the preparation, the second weighing of the tube results in 95 g with a standard deviation of also $\sigma_y = 0.5$ g. The standard deviation of the sample (5 g eye ointment base) σ_z can be calculated from Eq. 20.21:

$$\sigma_z^2 = 0.5^2 + 0.5^2 = 0.50$$

The standard deviation $\sigma_z = \sqrt{0.50} = 0.71$ g. This example shows immediately that outcomes based on measurements of a difference are more unfavourable than single measurements. The relative standard deviation amounts to $0.71/5 = 0.14$ g or 14 %, while the standard deviation of separately weighing 5 g of eye ointment base is about 0.5/5 or 10 %.

In this example, the smaller standard deviation in direct weighing would however not compensate for the disadvantage of less secure aseptic processing conditions.

Standard deviations of two or more variables are always added up as their variances, even if the result is calculated as the difference between two observations.

20.5.3 The Outcome is Obtained by Multiplying or Dividing Measurements

If the final outcome, z, equals the product or quotient of two or more measurements (x, y, . . .), so if $z = x \times y$ or $z = x/y$, then:

$$\sigma_z^2/z^2 = \sigma_x^2/x^2 + \sigma_y^2/y^2 \qquad (20.22)$$

Equation 20.22 is an approximation, since it is derived using Taylor's series expansion.

Worked Example. An example is the preparation of one litre of saline. The content is the quotient of the weighed amount of NaCl and the measured quantity of water.

0.9 g of NaCl has been weighed with a standard deviation of 5 %, so $\sigma_x = 0.045$ g. The container is filled with water up to 1,000 mL with a relative standard deviation of 5 %, then $\sigma_y = 50$ mL. The standard deviation of the content of the physiological salt solution, calculated with Eq. 20.22 is:

$$\sigma_z^2/z^2 = 0.045^2/0.9^2 + 50^2/1{,}000^2 = 0.005$$

Hence the relative standard deviation is: $\sigma_z/z = \sqrt{0.005} = 0.07$ or 7 %. The concentration (z) is 0.9 g NaCl per 1,000 mL water, so that the absolute standard deviation σ_z equals $0.9 \times 0.07 = 0.063$ g NaCl per 1,000 mL of water.

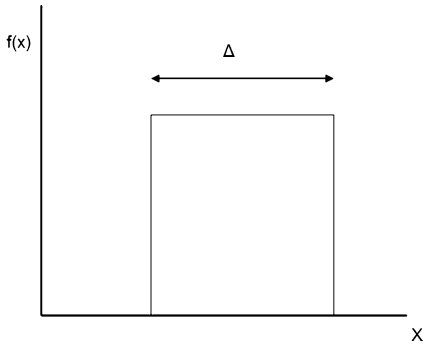

Fig. 20.8 Density, f (x), of the uniform probability distribution of the values, x, in the rounding interval Δ

20.5.4 Rounding

When finalising an outcome on a limited number of decimal places we add a random error to that outcome. By rounding off an outcome to one decimal place, e.g. 5.136 into 5.1, all values in the interval 5.150 into 5.050 are represented in the rounded value 5.1.

We designate the rounding interval with the Greek letter Δ. In this example $\Delta = 0.1$. Because all values in the interval are equally likely, the uniform distribution is the probability distribution of these values, see Fig. 20.8. The uniform distribution has as variance $\sigma_a^2 = \Delta^2/12$. When rounding to one decimal place, the standard deviation will be $\sigma_a = 0.1/\sqrt{12} = 0.03$.

The original, not rounded outcome contains a random error by itself. For example, if $\sigma_o = 0.05$, the total standard deviation in the rounded outcome using Eq. 20.21 is:

$$\sigma^2 = \sigma_0^2 + \sigma_a^2$$

In our example, the standard deviation of the total rounded outcome $\sigma = \sqrt{(0{,}05^2 + 0.03^2)}$ equals 0.06, not much larger than the standard deviation in the original, not rounded outcome.

If we would have rounded one decimal place more, 5.136 will become 5, we would have generated an additional $\sigma_a = 1/\sqrt{12}$ equals 0.288 and the standard deviation in the final result would be $\sigma = \sqrt{(0.05^2 + 0.288^2)}$ equals 0.294. By rounding so roughly, the standard deviation is nearly completely determined by the rounding procedure.

If we want however no more than a 1 % increase in σ, we must ensure that:

$$\sigma_a/\sigma_0 = \left(\Delta/\sqrt{12}\right)\sigma_0 < 0.01 \qquad (20.23)$$

In conclusion, the rounding interval Δ should be $< 0.035\,\sigma_0$. So rounding to one decimal place is only allowed if $\sigma_0 > 3$. Rounding off to two decimal places is allowed when $\sigma_o > 0.3$, and so on.

In some cases, we apply an observation method that in a similar way leads to the introduction of a random error in the final outcome. For example, we always read 0.1 mL if we use a 10 mL measuring pipette, calibrated in tenths of a millilitre. Actually we round off the observation to one decimal place without mentioning or realising that.

The same thing happens when weighing 10 g. The weighing program and the printer report as weighing result 10 g, if the reading is between limits ± 1 % (see also Sect. 29.1.6), or between 9.9 and 10.1 g.

All values in the interval of 0.1 g are then equally likely and their distribution is uniform. We introduce a standard deviation of $\sigma_a = 0.1/\sqrt{12} = 0.03$ g, solely as a result of reading the pipette or due to the reporting routine of the balance. All such errors should, according to Eqs. 20.21 and 20.22 in Sects. 20.4.2 and 20.4.3, be added to other variances, when calculating or assessing the random error in the final result.

Rounding off is in practice applied according to the following rules:

1. Decide which is the last digit to keep
2. Leave it the same if the next digit is less than 5 (this is called rounding down)
3. But increase it by 1 if the next digit is 5 or more (this is called rounding up)

So:

36.4584 rounded in 2 decimals becomes 36.46
56.8734 rounded in 2 decimals becomes 56.87
89.6651 rounded in 2 decimals becomes 89.67
89.665 rounded in 2 decimals becomes 89.68
29.335 rounded in 2 decimals becomes 29.34

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Quality Risk Management

21

Yvonne Bouwman-Boer and Lilli Møller Andersen

Contents

Abstract

Firstly the chapter approaches risk management in a general sense, including the phases of risk assessment (risk identification, risk analysis and risk evaluation), risk control (risk reduction or mitigation, and risk acceptance), risk documentation and communication, and risk review. Then some methods for risk assessment are explored further, such as matrix type and Failure Mode Effect Analysis (FMEA) using risk priority numbers (RPN).

Quality risk management (QRM) is illustrated by practical examples about logistics, equipment, pharmaceutical care on the wards and clinical pharmacy.

QRM finds its way into medicines regulations as it is seen as a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. A structured and documented management of risks is a requirement in EU GMP as well as in the European Pharmacopoeia (Ph. Eur.). A guideline with a description of QRM elements together with appropriate tools is to be found in ICH Q9, mainly directed at manufacturing. Finally implementation of QRM in the Pharmaceutical Quality System is briefly elaborated.

Keywords

Quality • Risk management • Risk assessment • ICH Q9 • Risk analysis

21.1 Orientation

Pharmacists will, in their work, reflect on all processes for which they are responsible, with the purpose of improving quality and availability of medicines and hence to minimise any risk of harm to patients. Quality risk management (QRM) offers a structure and tools for a systematic approach to these efforts. The process usually consists of the phases risk assessment (Sect. 21.3.1) (with sub processes risk identification, risk analysis and risk evaluation) and risk control

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_21,

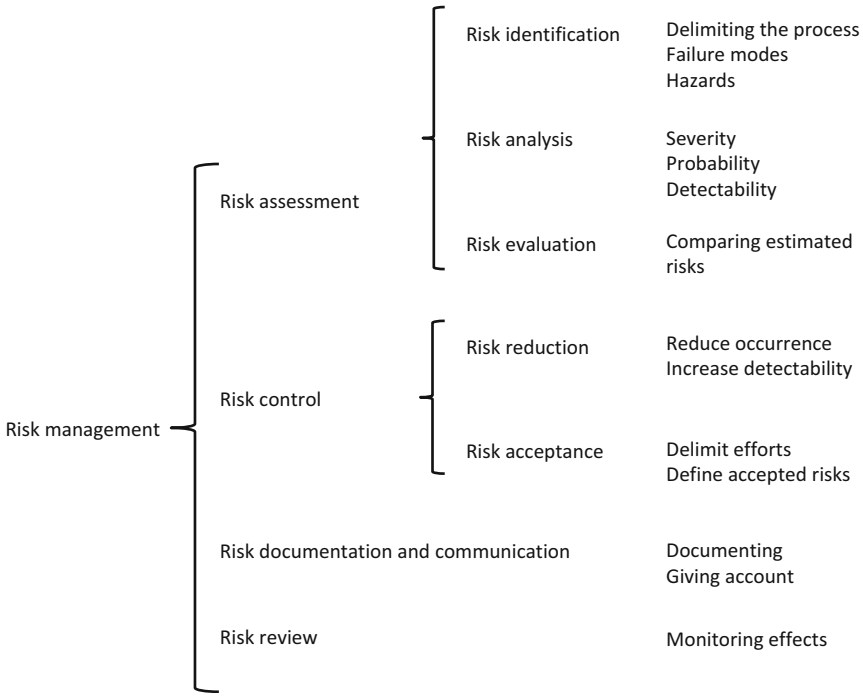

Fig. 21.1 Elements of the risk management process and companion activities or topics

(Sect. 21.3.2) (with the sub processes risk reduction and risk acceptance), see Fig. 21.1.

This structured approach helps to substantiate considerations and decisions. It eases documentation, and thus may help to communicate about them.

This chapter explains the basics of Risk Management applying it to the field of preparation and product care in pharmacies, that is from logistics to prescription assessment, from production to pharmaceutical care on the wards (Sect. 21.5). Essentials of frequently used methods will be described (Sect. 21.4). QRM aimed at quality of medicines has found its way to regulations (Sect. 21.6), for large-scale manufacturing as well as for preparation in pharmacies. Some guidance is given for implementation of QRM in pharmaceutical quality systems (Sect. 21.7).

21.2 Definitions

ICH Guideline Q9 is the reference document on quality risk management for pharmaceutical preparations [1]. Therefore in this chapter mostly ICH Q9 definitions are used. Many of them are identical to those of the International Standards Organisation (ISO, see also Sect. 35.7.2).

The definitions are tabulated in Table 21.1.

21.3 Risk Management Process

Risk management basically implies risk assessment (with subsequently risk identification, risk analysis and risk evaluation), risk control (with subsequently risk reduction and risk acceptance), risk communication and risk review. Figure 21.1 shows consecutive elements of the risk management process and keywords indicating companion activities or topics.

This section explains these elements and illustrates them with a simple example case of small-scale filling capsules with a powder mixture.

21.3.1 Risk Assessment

Risk assessment consists of the identification of hazards (Risk identification), followed by the analysis (Risk analysis) and evaluation (Risk evaluation) of risks associated with the occurrence of those hazards. As a simple illustration the extemporaneous preparation process of capsules according to a standard formulation is taken as to illustrate the principles involved.

21.3.1.1 Risk Identification

At first the process for which the risks have to be assessed is defined and delimited as well as its hazards that have to be focused upon.

> As said the process to be assessed is limited to the extemporaneous preparation process of capsules according to a standard formulation. Let the focus be on a quality defect that will lead to not meeting the requirements for content uniformity.

Secondly the separate process steps are identified and coupled to possible deviations or ‘failure modes’ (What

Table 21.1 Risk management definitions

Harm	Damage to health, including the damage that can occur from loss of product quality or availability
Hazard	The potential source of harm
Quality risk management	Risk management directed at the quality of the (medical) product
Risk	The combination of the probability of occurrence of harm and the severity of that harm
Risk management	The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk.
Risk acceptance	The decision to accept risk
Risk analysis	The estimation of the risk associated with the identified hazards
Risk assessment	A systematic process of organising information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
Risk communication	The sharing of information about risk and risk management between the decision maker and other stakeholders.
Risk control	Actions implementing risk management decisions.
Risk evaluation	The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.
Risk identification	The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.
Risk mitigation	Risk reduction
Risk reduction	Actions taken to lessen the probability of occurrence of harm and the severity of that harm
Risk review	Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk
Severity	A measure of the possible consequences of a hazard

might go wrong?) as well as to the consequences (harms or effects) of these.

> The process of the preparation of capsules is composed of several steps or unit operations. One step concerns mixing the active substances and excipients, giving the powder mixture. Another step is filling empty capsule bodies with the powder mixture. Possible deviations are: insufficient mixing and uneven filling respectively. The effect in both cases is insufficient content uniformity.

21.3.1.2 Risk Analysis

Risk analysis estimates the risk of every deviation that has been identified. The estimation consists of three aspects:

- The severity of the consequences of the deviation
- The probability of its occurrence
- Its detectability (before it can lead to any consequences)

> Insufficient mixing may be estimated (in a specific situation: operator, equipment, pharmacy setting) as a risk that probably will occur and not be detected by an in-process control. Whereas uneven filling seems a little less probable and may be noticed by the operator or easily measured by in-process control of the capsule weights. Both deviations will lead to insufficient content uniformity. Both severities are assumed to be equally large.

21.3.1.3 Risk Evaluation

Risk evaluation is the comparison of the estimated risks.

> It can be concluded that insufficient mixing poses a larger risk than uneven filling.

Risk evaluation will make risk prioritising possible. The use of a (semi-) quantitative scale can make risk evaluation more sophisticated. The determination of a risk criterion for risk acceptance is another addition. See Sect. 21.4.2.

21.3.2 Risk Control

The purpose of risk control is the reduction of the risk to an acceptable level, followed by a check to consider if any new risks, introduced by the introduction of the control of identified risks, are acceptable. Risk control consecutively exists of the elements: risk reduction (some sources use the term: risk mitigation) and risk acceptance.

21.3.2.1 Risk Reduction

Risk reduction investigates all critical process steps to draw up measures that reduce the occurrence of the risks or improve the detectability. But any measure should not lead to the introduction of new risks.

For the reduction of the risk of an inhomogeneous powder mixture, the mixing process needs more attention. The operator can be taught to perform mixing correctly (see Sect. 29.4 about mixing quality), monitor their way of operating from time to time by observation or by assaying content uniformity of pilot batches, or introduce personal qualification and requalification for the preparation of capsules. In large-scale preparation an in-process control by Near Infra Red (NIR) is used to detect inhomogeneity (see Sect. 17.7), however for small-scale preparation NIR is not commonly used.

For the improvement in the capsule filling technique, teaching, observation and monitoring may be used as well. An in-process control on capsule weights after filling will increase detectability substantially. Ultimately each batch may be analysed before release.

Would these measures introduce new risks? Probably any interruption of an operation for an in-process control can lead to mix-ups. And weighing may cause a risk of cross contamination.

21.3.2.2 Risk Acceptance

Risk acceptance requires decisions about how much effort to reduce risks is feasible in terms of cost and benefit.

Analysis of each batch will take too much time and money (excess active substance needed) to be an option for extemporaneous preparations. The qualification of operators for the preparation of capsules, by validation and monitoring may be feasible. This may lead though to specialisation of operators and thereby to a decrease of flexibility.

The amount of effort used for risk control should be proportional ("commensurate" is the Q9 terminology) to the significance of the risk. In pharmacy preparation it will generally lead to more quality investments in stock preparation compared with extemporaneous preparations due to the higher number of patients that will be exposed.

In pharmacy preparation other elements will contribute to the balance that has to lead to acceptance (or not) of specific risks. These elements are, for instance, availability and the pharmacologic qualities of the active substance.

The standard operating procedure for extemporaneous preparation of capsules should reflect the decisions on quality risk management of that process. The level of quality risk management should be accounted for in the quality manual of the pharmacy.

21.3.3 Risk Communication and Documentation

Communication with stakeholders about the risk assessment's results is important to give account of one's professional decisions. By ensuring that key stakeholders are engaged in both the data collection process for the risk assessment and the decision-making for risk control, the decision-maker will get commitment and support for his QRM. Documentation will make communication easier. There should be a report for every risk assessment, of which the level is proportional to the level of risk.

Section 2.2.3. depicts models for a structured risk assessment of a prescription for extemporaneous preparations. The physician and the patient will be the most important stakeholders in that situation, the latter also represented by the competent authority. But the insurance company may be stakeholder as well because of the resources.

21.3.4 Risk Review

The experience and results of measures taken to diminish risks should be monitored and reviewed to decide if the chosen approach works. As with other elements of QRM, the level and formality of the review should be proportional to the level of risks.

Knowledge about mixing and filling being critical steps in capsule preparation are well known from professional education or literature and the effects of the efforts can be anticipated. Monitoring the actual effects however may confirm knowledge or sometimes may reveal unforeseen aspects. Moreover it will usually contribute to the motivation of the operators.

21.4 Methods

More can be said about methods for risk identification, risk analysis and risk evaluation. In Sect. 21.3 these phases were defined, and, as the capsule preparation example, executed in an informal, rather simple way. That section was meant as an introduction to the phases of risk management and the terminology. It also meant to convey the idea that defining and delimiting the process steps and thinking about risks with all staff concerned will already lead, halfway, to a proper result.

If risk management applies to a more complex or a less well-known process, some experience and methods may be helpful for a more formal risk assessment. They will be discussed following the sequence of: risk identification, risk analysis, risk evaluation. They also facilitate proper documentation, which is essential for being transparent about decisions.

21.4.1 Risk Identification

For any risk assessment method it is crucial that the problem or risk issue is well defined, described and understood. A common mistake is to start the risk analysis before the process to be analysed is well defined and well delimited. Such an approach is easy to imagine because a problem often creates a sense of urgency that tempts one into action though the framework is not yet understood. This mistake will most likely result in waste of time and personnel frustration.

A risk assessment can be performed retrospectively or prospectively. If an adverse event – whether a complaint, a deviation or adverse effect – happens it will be analysed retrospectively. Staff will be convinced about the necessity for any action. When staff do not report incidents however or do not qualify them as important the improvement process may be missed. For risk assessment a blame-free culture in the organisation is very important.

Prospective methods look at which risks may occur and assess the severity of these risks, in order to subsequently choose which actions should be taken to prevent errors and deviations. In the preparation of medicines prospective methods can be used for the initiation of new activities or purchasing a new equipment (see Sect. 21.5.2), as part of change control (see Sect. 35.6.10) and in planning of qualification and validation activities (see Sect. 34.14).

In practice a mixed approach of a retrospective and prospective method is often encountered. The capsule-filling example in Sect. 21.3 may appear to be a pure prospective method but by using process knowledge it also has, in fact, retrospective elements.

A 'brainstorm' is a useful technique to start risk identification. This may start with a presentation of a problem using preliminary information or already processed data. A preliminary evaluation of the possible harms to the patients may be presented to increase motivation. The brainstorm may be rather informal or more structured depending on the issue, the participants and traditions in the organisation. The goal is achieving, within short time, as many ideas as possible and engaging and focussing the participants.

Any risk identification may include a compilation of observations, trends and other available information. For more complex issues, a suitable presentation of background information and relevant data together with a targeted review of literature is advisable. Collecting and depicting this knowledge in a way that also can be used by other professionals may be very helpful in an expected rather long QRM process. Furthermore, depictions as these may facilitate handling of new knowledge or understanding. For listing and depicting the results flowcharts and process mappings are commonly used, if possible with marking of already known critical steps. As easy to use tools the Fishbone/Ishikawa diagram, flowcharts and mind maps are mentioned. Reference is made to [2] for further information about these tools.

21.4.2 Risk Analysis and Evaluation

When the problem or risk issue is well understood an appropriate tool for risk analysis has to be chosen. For the hazards identified during the brainstorm the associated risks has to be estimated. This may be a qualitative description eventually using semi-quantitative descriptors, as "high", "medium" or "low" or it may be a quantitative analysis with scores according to a pre-defined scale. The estimation of risks in Sect. 21.3 occurred following a qualitative method. It enabled the prioritisation of two risks within a rather simple process and no comparison to a fixed value was felt to be necessary.

The numerical scores to be used in a (semi-) quantitative risk analysis have to apply to the factors severity, probability and detectability. The scale may be linear or non-linear, for instance logarithmic. Addition or multiplication of these scores will lead to risk scores. These can be put in a priority sequence: the harm with the highest scores should be dealt with the highest priority (efforts and formalities). And the score can also be compared with a fixed limit, for instance in case of a decision if any action has to be taken at all.

In this way a quantitative method may improve the practicability of the outcomes (by putting priorities) and it may help documentation and communication. This may apply to

situations when the process to be analysed consists of a large number of steps or if many different measures have to be considered.

Qualitative methods are suitable in relation to relatively simple issues where as quantitative methods may be necessary for more complex or comprehensive issues.

Many tools for risk analysis are in use. ICH Q9 Briefing Packs [2] describes many of them. The best-known method might be the Failure Mode Effect Analysis (FMEA). FMEA is basically done in the following way:

- Draw a schematic representation of the process and name in a 'brainstorm session' the ways in which the process could possibly fail (failure mode).
- Name the effect of every failure mode and classify the *severity* of that effect on a scale.
- Classify the *probability* of each failure mode and rate it on a scale.
- Classify the chance of each failure mode to be *detected* after occurrence and before leading to consequences and rate this chance on a scale.
- Calculate for each failure mode a risk priority number (RPN) by multiplying the ratings for severity, probability and chance of detection.
- The failure modes with the highest RPN should be addressed first, preferably by eliminating them or reducing the frequency of occurrence. A final possibility for improvement is increasing the detection chance. The alternative is accepting the risk.

An example of this method is given in Sect. 21.5.2. A very complete and dedicated description of the FMEA method, executed as a RPN mode, is to be found in the ICH Q9 Briefing Packs [2]. It also contains, for instance, a list of severity scores coupled to resources.

Instead of RPNs a matrix may be used to visualise risks, especially if risks are diverse and difficult to compare, using a single tool. The use of matrices is exemplified in Sects. 21.5.1 and 21.5.3.

21.4.3 Risk Acceptance

Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best risk control might not entirely eliminate risk. In these circumstances it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis. For in every case specific measures are created for diminishing the risks, for instance in-process controls may contribute significantly to decrease the risks of extemporaneous preparation, see Sect. 34.6. Examples of parameters that can play a role in accepting a residual risk are: no alternative clinical treatment, the exposure limit to genotoxic substances (see Sect. 26.3.3), financial investments in quality control measures, or harm to a patient through loss of availability.

21.4.4 Risk Documentation and Communication

Documentation of a qualitative method may be a simple description of the issue dealt with, including assessment of associated risks and a conclusion regarding necessary action, if any. Though simple, such a QRM process should also be documented: which risks were defined and balanced and who accepted the residual risk.

Again it should be emphasised that the use of informal risk management processes could be acceptable if the risk assessment and the conclusion are well documented.

As an example: documented decision about whether or not fulfilling a physician's requirement for a pharmacy preparation is a first step in giving account of or even in involving stakeholders in responsibilities (see Sect. 2.2.3).

21.5 Practical Examples

This section discusses some applications of risk assessment in preparation and pharmacy practice. In this book more examples can be found: see Sect. 34.14.2 on parametric release at autoclaving; Sect. 2.2. on prescription assessment; Sect. 26.7.3 on occupational safety and health risk matrix.

21.5.1 Evaluation of Distributors

A hospital pharmacist has to decide how often it is necessary to evaluate the suppliers of licensed medicines. The team starts to enumerate elements and qualities of the supply process: timeliness, clinical need of the medicine, uniqueness of distributor, distributor's quality assurance system, business relation with the supplier etc.

It is decided to focus the risk assessment on two qualities: clinical need of the medicine and uniqueness of distributor. Each quality may be scored as: acceptable, relevant or critical.

For the quality 'clinical need of the medicine' the team decides to score as follows:

- Clinical need is low: non-deliverability of medicine is not really important for the patient; patient care is not at risk or the medicine is easily substituted (risk score: acceptable).
- Clinical need is moderate; non-deliverability of medicine does not directly affect the patient; patient care may suffer discomfort (risk score: relevant).

Table 21.2 Risk matrix for the assessment of audit frequency of distributors. Darker shades reflect higher priority

	Uniqueness of distributor →		
Clinical need ↓	Acceptable	Relevant	Critical
Acceptable	*Assessment not necessary*	*Once per 3 years*	*Once per year*
Relevant	*Once per 3 years*	*Once per 3 years*	*Once per year*
Critical	*Once per year*	*Once per year*	*Once per year*

- Clinical need is high: non-deliverability directly affects the patient; patient care is at risk (risk score: critical).

For the quality 'uniqueness of distributor' the team decides to score as follows:

- Other distributors are available (risk score: acceptable).
- Access to other distributors is doubtful (risk score: relevant).
- No other distributor (risk score: critical).

The pharmacist puts the combination of the qualities in a risk matrix system and connects the scores to the frequency of assessing the distributors (Table 21.2).

A risk assessment is always temporary. For instance the elements Distributor's own quality assurance system and business relation with the supplier will probably appear to be much more important and determine the way of evaluating the suppliers. Furthermore the scores will have to be changed for instance at a risk review after 2 years.

In a matrix only two effects can be combined. If more effects have to be considered, subsequent matrices can be created.

21.5.2 Equipment – Washing Machine

A risk assessment can be used quite naturally in the process of drafting a User Requirements Specification (URS) for equipment utilities. By clarifying the intended use of the equipment and investigating the hazards, their possible causes and ways to control them in the actual context, the URS will be a fine starting point for purchasing and for the subsequent qualification. The risk assessment is to be updated as soon as actual brands and types of a specific piece of equipment have been chosen. As a conclusion a 'level of risk' can be determined for specific equipment, placed in specific locations and used for well-defined purposes. If such a 'level of risk' is determined for several pieces of equipment in a department, it may serve other purposes as well, for instance prioritising validation and frequency of maintenance or determination of the replacement period for specific equipment.

The responsibility for the QRM is consequently and unambiguously placed at the user of the equipment. For a rather complex piece of equipment – e.g. a washing machine to be used in the Aseptic department of a large hospital pharmacy for washing utensils and other materials that will be sterilised subsequently – a risk analysis could be executed with a RPN mode of a FMEA (see Sect. 21.4.2). The risk score is the result of the multiplication of the scores on Severity, Probability and Detectability.

A Risk Assessment document may consist of a descriptive part reflecting the logic and an attached table listing hazards, possible causes and controls, scores and comments. Table 21.3 reflects only a part of such a table for the risk assessment of the washing machine.

From the risk analysis it is concluded that risks related to the washing machine are low when compared to other equipment and will only indirectly affect patients. Critical aspects and critical parameters are identified and will be part of the URS. The most critical aspects are related to ineffective washing process or contamination of utensils or materials by the chamber.

21.5.3 Aseptic Handling on Wards

The aim of this example of risk assessment is to assess the risks in order to prioritise measures to improve safety of reconstitution on the ICU ward [3]. Two hazards of reconstitution of parenteral medicines admixtures are focussed upon: microbial contamination (in fact: loss of sterility) and faulty composition. The probability of microbial contamination and faulty composition is related to the number of steps during the process that are critical for microbial contamination (see Sect. 31.3.2) or faulty composition respectively. The number of critical steps are multiplied by 2 if the medicine is mentioned in the Institute for Safe Medication Practices' (ISMP) list of high-alert medications [4]. In this way the severity in case of faulty composition is taken into account.

For prioritising actions both hazards (microbial contamination and faulty composition) were related to the frequency of administration. The top 10 of both frequency lists are taken into the risk assessment. The risk matrix puts the frequency of administration against the risk of contamination or the risk of faulty composition respectively (= Tables 21.4 and 21.5). These matrixes visualise which products have to be improved first. Risk reduction can be achieved by decreasing the number of steps, for example by pharmacy preparation of premixed preparations or prefilled syringes.

Table 21.3 Risk analysis (part) of a washing machine

Hazard	Potential causes	Controls	Severity	Occurrence	Detectability	Risk S × O × D	Comments
Contamination of chamber	Contaminated air or unintended use of the washing machine	Washing machine is placed in class C room	1	1	5	5	Severity and occurrence is low as only well trained employees will have access to the room. Furthermore no other activities take place near to the washing machine
Microbiological contamination	Stagnant water in chamber or tubes	The chamber and drain will be controlled for dryness and disinfection with alcohol after use Wash with empty chamber if more than 8 h empty standing Control of surfaces in chamber as part of routinely Environmental control	1	1	5	5	Low severity: Washed utensils and materials will be autoclaved within defined timespan after wash (maximum for standing clean) Low occurrence: Washing and final rinse takes with +80 °C WFI + controls High detection score because detection is not possible URS requirements (among others): • Effective drainage of tubes, pipes, surfaces • No remaining water in drain • Easy to clean, dry and inspect • Tubes for water easy to disassemble, the same for pneumatic valves for inlet of water. Effectiveness of drain and management of valves have to be documented in the Operational Qualification (OQ) Surfaces in direct contact with materials of pharmaceutical grades should be very smooth stainless steel (low Ra) Preventive maintenance has to be defined
Contamination from the washing machine	Chemicals or particles from surfaces or installation of the washing machine	Preventive maintenance	1	3	3	9	Occurrence level 3 as final wash and rinse are with +80 °C WFI. Utensils and materials in contact with WFI of pharmaceutical grade. Preventive maintenance is necessary due to the aggressiveness of purified water. The equipment is approved for the intended use e.g. in accordance with ISO DS/EN ISO15883. All parts in direct contact with utensils and materials are of pharmaceutical grade steel (A316L). Other parts such as tubes, gaskets and packaging materials have to be dedicated for pharmaceutical purposes
Ineffective washing process	Wrong temperature or time Clogged nozzles Too low water pressure Program changed or interrupted with or without intention	Alarms for functioning, temperature and time Visual control of nozzles before start of washing Impossible for users to interrupt or change program	5	1	3	15	Severity is scored high (5) especially due to risk for blocked nozzles. URS requirements (among others): • Well defined alarms with informative text in display • After an alarm the washing process will be restarted from the beginning • Accuracy for critical measuring equipment and certificates for calibration as appropriate. • Alarms for blocked nozzles or easy visual control • At least three user-levels (user, supervisor, technical service) • Supplier will train users as well as Technical Service

Table 21.4 Microbiological contamination hazard as risk factor for prioritising the improvement of reconstitution of parenteral medicines on wards (data from [3] with permission). MC: number of critical steps related to microbiological contamination; p = perfusor syringe; i = injection/short infusion. Darker shades reflect higher priority

Score *MC* → Frequency ↓	0 or 1	2	3	≥ 4
Seldom (1)		phosphate (p)	morphine (p)	prednisolone (p) amiodaron (p)
Frequent (2)		amoxicillin + clavulanic acid (i) meropenem (i) ketanserin (i)	dopamine (p) midazolam (p) morphine (i)	bupivacaine + fentanyl (p)
Often (3)		pantoprazole (i)	magnesium sulfate (i)	enoximone (p) metoclopramid (i)
Very often (4)		insulin (i)	erytromycine (i)	

Table 21.5 Faulty composition hazard as risk factor for prioritising the improvement of reconstitution of parenteral medicines on wards (data from [3] with permission). F = number of critical steps related to a faulty composition; S = severity factor (1 or 2, see text); p = perfusor syringe; i = injection/short infusion. Darker shades reflect higher priority

Score F x S → Frequency ↓	1 or 2	3 or 4	5 or 6	≥7
Seldom (1)			prednisolone (p) morphine (p) phosphate (p)	amiodaron (p)
Frequent (2)	amoxicillin + clavulanic acid (i) meropenem (i)	ketanserine (i)	dopamine (p) midazolam (p)	morphine (i) bupivacaine + fentanyl (p)
Often (3)	metoclopramide (i) pantoprazole (i)	magnesium sulfate (i) enoximon (p)		
Very often (4)	cefotaxim (i)	erytromycin (i)	insulin (p)	

Generally the reconstitution of perfusion syringes (p) takes more process steps and is carried out, mostly, on high-risk medicines but they are used less frequently than injection solutions and short infusions (i). Insulin and bupivacaine/fentanyl perfusor syringes have the highest scores.

21.5.4 Risk Management in Clinical Pharmacy

QRM may also be applied to clinical pharmacy, which is easy to suggest when the example of 21.5.3 would be extended to processes such as the prescription and administration of the medication. Apart from the pharmacy staff also other disciplines (physicians, nurses) will be involved in the risk assessment.

The ICH Q9 strategy and tools can be adapted for a framework for clinical pharmacy, such as described in [5]. The very start of a QRM process is again the description of the work process. As an outcome of their study the team list a series of decisions that have to be made and specified, for instance by creating SOPs. In this way the priority in creating SOPs is led by the risk analysis. The team realise that QRM may contribute to the protection of the clinical pharmacist who is aware that the risk of patient hazard never can be excluded but who is held to reduce that risk to an acceptable level.

Another framework for QRM for clinical pharmacy can be taken from the ISO 9001 for healthcare: EN15224, especially from the practical implementation guide Sect. B.4.2. Risk management [6]. In this way QRM of clinical pharmacy can be integrated into the existing QRM of the pharmacy and the hospital.

21.6 Regulations and Standards

21.6.1 QRM Evolving

The field of QRM in pharmacy is very much evolving as experiences and knowledge is obtained in individual enterprises as well as by authorities and professional bodies. QRM has found already its way into several medicines regulations and standards:

- Good Manufacturing Practice (GMP see Sect. 35.5.7)
- Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (PIC/S GPP see Sect. 35.5.5)
- Pharmaceutical Preparations Monograph of the European Pharmacopoeia (Ph. Eur.) (see Sect. 35.5.3)
- Resolution CM/ResA P(2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients (CoE Resolution see Sect. 35.5.4)

EU GMP Chap. 1 on Pharmaceutical Quality System highlights the inter-relation of the basic concepts of Quality Management, Good Manufacturing Practice and Quality Risk Management and emphasises their fundamental importance to the production and control of medicinal products.

QRM as described in EU GMP and related guidance provides a framework as well as common definitions and terminology. So it is possible to express risk assessments and explain appropriate actions in this relation. This facilitates an effective and constructive dialogue with stakeholders, competent authorities included, in relation to prospective as well as retrospective quality-related issues.

21.6.2 GMP and ICH Q9

EU GMP defines QRM as "a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. All efforts in QRM are aimed at minimising any risk for the patients due to inappropriate quality of the products". QRM is elaborated in EU GMP in Part III as ICH Q9 Quality Risk Management.

ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality, most of them directed to complex manufacturing situations. Very useful Briefing Packs [2] offer an explanation as to how to use the QRM tools as well as training.

Application of QRM principles and its elements are to be found in chapters and annexes of GMP Part I (Basic requirements for Medical Products). Within GMP it helps to find the cause of an adverse event, which enables the efficient reduction of the chances of recurrence of the event.

Executing a retrospective risk assessment is compulsory for licensed medicines in relation to potential recalls, complaints and non-conformities. The main issue is to ensure the immediate application of effective standard work procedures so that any risks to patients are dealt with, with due diligence. The authorities expect documentation of QRM in relation to acknowledged product errors in cases reported as complaints. Also reported adverse events are to be included in the group of events that require a comprehensive QRM. For deviations the consequential risks are in general easy to manage, as the affected products are not yet released. A fast and effective limitation of an acknowledged production error is crucial anyhow in order to decide whether the error may also be present in released products that may be used by patients. After the assessment of the acute needs for corrective actions, retrospective methods examine which causes have led to an actual error or deviation, in order to prevent the recurrence of it. As tools in connection with complaints and non-conformities GMP requires that "an appropriate" level of Root Cause Analysis (RCA, see Sect. 35.6.15) is applied. Usually followed by a corrective and preventative action (CAPA, see Sect. 35.6.15).

> The pharmacist not only has to manage risks of insufficient product quality or loss of availability, but also other risks, such as health risks of his personnel or financial risks. EU GMP focuses on the risks to product quality. QRM is an element of the Quality Management System in parallel to requirements of EU GMP Chap. 1 (see Sect. 21.6.1). Even though e.g. health and safety of the operators and environmental risks are equally important in a societal perspective, these considerations, from a GMP viewpoint, have to be taken care of in other ways. For an illustration of this opinion, compare the warning for pharmaceutical inspectors: "Inspectors should be cautious when reviewing assessments which include other business-related risks (e.g. environmental, occupational health &safety) in addition to quality risk assessments. As whilst these factors are important in a holistic sense there is a danger that they may compromise quality" [7].

21.6.3 Regulations for Pharmacy Preparation (Ph. Eur. and CoE Resolution)

In pharmacy preparation, management of risk, whether structured or not, is used on many occasions within the lifecycle of the medicine (see Sect. 35.4). QRM starts with the assessment of the physician's request for pharmacy preparation (see Sect. 2.2). The scientific and professional knowledge of a pharmacist has to be used to decide whether the

required medicine can be produced. The Ph. Eur. monograph Pharmaceutical preparations acknowledges this situation:

> In considering the preparation of an unlicensed pharmaceutical preparation, a suitable level of risk assessment is undertaken. The risk assessment identifies:
> – the criticality of different parameters (e.g. quality of active substances, excipients and containers; design of the preparation process; extent and significance of testing; stability of the preparation) to the quality of the preparation; and
> – the risk that the preparation may present to a particular patient group.

The CoE resolution directs QRM to the quality management system for preparation stating:

"Before preparation, a risk assessment should always be carried out in order to define the level of the quality assurance system which should be applied to the preparation of the medicinal product." And: "The Product dossier should therefore state the considerations about the risk of pharmacy preparation versus unavailability of the product and should contain more information for products with a higher risk." The Risk Assessment should refer to:

- Dosage form and administration route
- Amount prepared
- Pharmacological effect
- Pharmacotherapeutic window
- Type of preparation process
- (Way of) supply

For a risk assessment in line with these recommendations, the following list of parameters may be useful for the risk definition phase (see also Sect. 2.2.3 especially for forms framing the balancing of such risks against the benefits):

- Active substances and excipients. Assessment may include questions such as:
  - Are the substances well known (maybe described in a pharmacopoeia) or is it e.g. a chemical substance never used in pharmaceutical preparations before?
  - Is the manufacturer of the active substance and critical excipients audited and certified and well known or is little known about that company?
  - Will the active substance be stable during the shelf life of the products or will degradation take place?
- Containers. Assessment regards whether it is possible to find suitable containers
  - Able to protect the product during its shelf life
  - Not providing a risk of leachables or in other ways introduce a risk to the suitability for the intended method of administration
- Design of the product and method of preparation. Important elements are related to:
  - Dosage form; suppositories and other dispersions are more difficult to prepare than solutions; preparation of parenterals without terminally sterilisation provide a higher level of risk than e.g. cutaneous preparations.
- Preparation process
  - Type of preparation process; generally risk is considered to increase with the preparation types:
    - Reconstitution
    - Extemporaneous preparation of products for one or a few patients
    - Stock production

    Each of these groups can be further subdivided in different levels of risks. For example a simple reconstitution of a well-known sterile product in closed systems has a lower risk profile than reconstitution in excess of instructions in the SPCs.
  - Feasibility of preparation. Considerations may include questions such as:
    - Are the pharmacy facilities and equipment suitable for this kind of preparation?
    - Does the pharmacy have previous experiences with similar types of preparation so systems and personnel is ready for production?
  - Potential risks for cross contamination and mix-ups (will cause risks for other patients)
- Testing. Is it possible and feasible to introduce tests and thereby reducing risks:
  - In-process controls of critical steps
  - Assay of the active substance
  - Test of the finished product
- Stability of the medicine
  - Can labelled shelf life be justified, for example based on analytical data or literature references?
  - The risk due to instability is especially relevant for stock batches; for extemporaneous products that are immediately administrated to a single patient at least physical stability and a short term chemical stability has to be guaranteed.
- Patients: Ph. Eur. requires that considerations should be given to particular groups of patients. Important elements are, among others:
  - Identification of any identical or similar licensed medicine; licensed medicines provide a lower risk level due to the comprehensive requirements for authorisation
- The expected benefit for the patient, including the consequences of getting no medication;
  - How many patients will be medicated with the preparation; The level of efforts and documentation is expected to increase with the number of patients exposed to the medicine.

21.7 QRM and Pharmaceutical Quality Systems

It is neither always appropriate nor always necessary to use a formal risk assessment using the tools given by ICH Q9. The use of informal risk assessment (using empirical tools and/or internal procedures) can be acceptable, as is illustrated by Sect. 21.3 and by the several forms discussed in Sect. 2.2.3 applied to small-scale preparation. However QRM should be part of the local pharmaceutical quality system (PQS) (see Sect. 35.6.8).

For the inclusion of QRM in the PQS it has to be listed which areas of the pharmacy activities, organisation and processes have to be assessed, always including the initial prescription assessment and the ultimate goal to benefit the patient.

As for other elements of the PQS also for QRM the implementation should be traceable, for instance when in dialogue with the authorities. Responsibilities for initiating QRM processes and for acceptance of any remaining risks have to be described clearly. The governance of documentation has to be established, as templates, including guidelines for filling them out, have to be available before performing the risk assessment.

QRM procedures can establish useful functions within a PQS such as providing the basis for training.

The output and associated risk analysis justifying the approach should be documented and endorsed by the organisation's quality unit and senior management. Additionally, this information should be communicated to stakeholders for their information and to ensure their support. Again reference is given to Sect. 2.2 for an example how to perform this for pharmacy preparations.

A system of change control requires the repetition of risk assessments because of new knowledge or if other relevant changes have happened. A Risk Review is therefore a natural part of a quality system. WHO [8] states: "Appropriate systems should be in place to ensure that the output of the QRM process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original QRM decision. Examples of such changes include changes to control systems, changes to equipment and processes, changes in suppliers or contractors and organisational restructuring." For pharmacy preparation foreseeable changes also apply to the therapeutic alternatives or new information on adverse effects (see also Sect. 35.4.2).

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Stability

22

Daan Touw and Jean Vigneron

Contents

Abstract

After manufacturing or preparation and during use, medicines are subject to changes. Examples are a decline of the content, formation of degradation products, changes in appearance and microbiological contamination. In this chapter, physical degradation, chemical degradation and microbiological aspects of the stability of pharmaceutical preparations are discussed. The section on chemical stability not only concerns hydrolysis, oxidation, isomerisation and photolysis but also structural changes of proteins. This basic knowledge leads to general advice on how to improve the stability of pharmacy preparations. This is not only relevant for the formulation of medicines, but also for reconstitution and for the storage in the pharmacy of licensed pharmaceutical preparations. If degradation reactions are sufficiently understood, the pharmacist may be able to solve every day's stability problems. Examples are given.

When performing stability studies on medicines to determine shelf-life and usage periods, it is shown that chemical degradation may be fairly predictable but shelf life and usage periods may be influenced by less predictable causes. Changes that can be observed by the patient offer another perspective. The last section of the chapter provides advice on storage conditions, shelf life and usage periods of pharmacy preparations.

Keywords

Stability • Chemical degradation • Microbial degradation • Shelf life • Storage • Hydrolysis • Oxidation • Photolysis • Stability testing • Usage period

Based upon the chapter Stabiliteit by Yvonne Bouwman-Boer and Herman Woerdenbag in the 2009 edition of "Recepteerkunde".

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_22,

22.1 Physical Degradation

Physical degradation is seen as a change in physical characteristics without a change of the active substance molecule itself. Physical changes usually concern the dosage form: resuspendability of suspensions, viscosity, phase separation of emulsions, capsules getting sticky, alterations of friability, disintegration, or dissolution rate of tablets. But taste, colour, smell or appearance of solutions of medicines can also alter. Changes may also mean the appearance of agglomerates and particles or, crystallisation. These changes usually negatively affect the usability and efficacy of medicines.

The subvisual physical degradation is an important aspect that cannot be ignored when studying the stability of injectable medicines. An interesting example is the stability of pemetrexed. The chemical stability has been evaluated by various authors [1, 2] who observed little change by HPLC after 1 month. However, the turbidity measurement shows an increase of the NTU value (Nephelometric Turbidity Measurement) when the solution is stored at low temperature (refrigerator or freezer) [3]. This phenomenon can provoke the occurrence of a visible precipitate.

As a rule, medicines need to comply with their physical characteristics during their shelf life.

Physical changes probably indicate a problem with the robustness of the design of the medicine. Another reason could be that the pharmacist fails to realise the importance of a special container of the medicine. The latter may occur when the pharmacist repacks for automated medicines dispensing systems. Insufficient information to the patient on how to handle the medicine can also be the reason for physical instability. When the patient usually stores his medicines in a refrigerator, this habit may be the cause of the crystallisation of the active substance in an oral solution which should not be stored below room temperature.

Physico-chemical instability of emulsions (e.g. creams), can be predicted with a test where the temperature is changed with short cycles.

To get an idea of the stability of an extemporaneous preparation the only possibility is to keep a part of the preparation in the pharmacy in order to be able to recall if necessary or to have some information in case of a second prescription. For background information on the instability of disperse systems (suspensions, emulsions) and the ways to overcome those stability problems, see Sect. 18.4. For a useful review about the changes in dissolution rate during shelf life and how to prevent them, reference is made to [4].

Physico-chemical degradation can be limited by a robust design, a suitable container, correct storage conditions and good patient information.

22.2 Chemical Degradation

Upon storage of medicines, chemical reactions inevitably occur. These reactions may proceed with a noticeable speed or unnoticeably slow. Degradation products of active substances are usually inactive, although toxic degradation products are sometimes formed.

Isoniazid degrades into hydrazine, which has carcinogenic properties.

When primaquine degrades under the influence of light (photodegradation) degradation products may be formed that are more toxic than primaquine itself [5].

Under the influence of light chloramphenicol degrades into *p*-nitrosanilline, which is carcinogenic.

Paracetamol (acetaminophen) hydrolyses into aminophenol, which in turn oxidises into toxic chinonimines. These processes may occur in the raw material [6].

Hydrolysis and oxidation are the most frequently occurring degradation reactions, in addition to isomerisation and photolysis. For pharmaceutical proteins, degradation processes may lead to alteration of the tertiary and quaternary structure.

The development of a new medicine requires knowledge about these degradation reactions, about the rate with which they occur, and about the factors that influence these processes. Formulation, production conditions, container and storage conditions should be optimised to minimise the degradation of the active substance within the medicine.

Section 22.6 describes how data on chemical stability at a certain temperature and basic knowledge of reaction kinetics can be used when in daily practice a product's stability has to be re-estimated, because of a different storage temperature or of a change in medium.

22.2.1 Hydrolysis

Hydrolysis is the cleavage of an ester, carbon amide or lactam bond by water. Therefore, hydrolysis of substances can occur in aqueous solutions, but also in solids when the relative air humidity is sufficiently high. The hydrolysis of amide bonds in proteins is called proteolysis.

Generally speaking, a fixed percentage of a substance is hydrolysed per unit of time when dissolved in water (a first

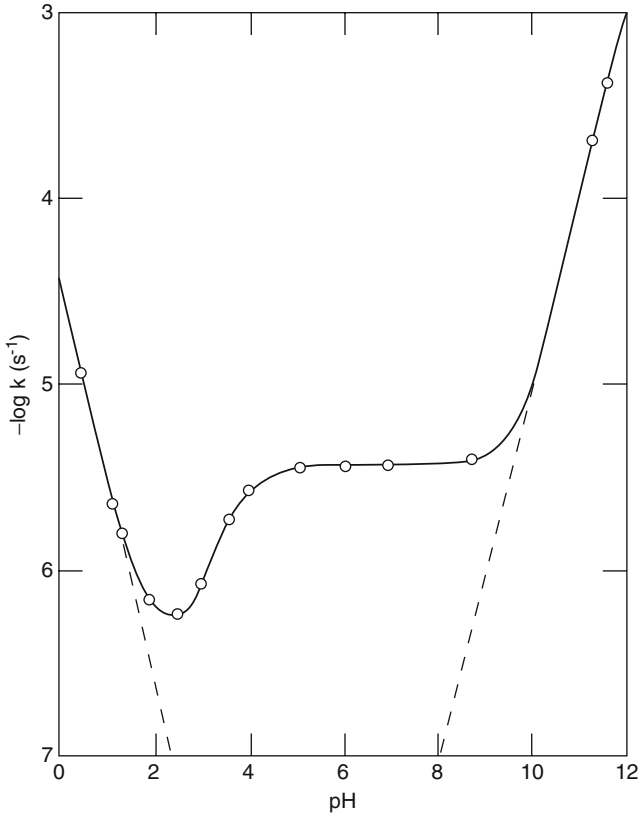

Fig. 22.1 pH stability relationship for acetylsalicylic acid solution [11]

order reaction, see Sect. 22.5.7). The absolute amount thus depends on the concentration of the substance. This is in contrast to the process of oxidation, for which a fixed quantity of the substance degrades per unit of time (a zero order reaction).

Hydrolysis is a pH-dependent process, which usually proceeds more rapidly in either acidic or alkaline conditions. Therefore, substances that are prone to hydrolysis have a pH optimum. For example, the rate of hydrolysis of indomethacin is the lowest at pH 4.9 and increases with higher and lower pH values [7–9]. For isoniazid, the stability optimum regarding hydrolysis is pH 6 [10], and also here, hydrolysis increases with higher and lower pH values. A classic example of an investigation of the influence of pH on hydrolysis is that for acetylsalicylic acid [11]. Figure 22.1 shows the pH stability relationship for acetylsalicylic acid that resulted from that investigation.

Hydrolysis is not only dependent on the pH (catalysis by H^+ or OH^- ions), but may also be catalysed by certain ions, such as phosphate and acetate. In general, higher ion concentrations promote hydrolysis reactions [12]. In a buffered solution, hydrolysis thus depends on the pH, the type of buffer and the concentration of that buffer.

Hydrolysis rates increase by 2–3 times for every 10 °C temperature increase. Note that the pH of a buffered solution may shift when the temperature changes [13]. Heating of a solution may thus influence the hydrolysis rate both through temperature and pH. Changes in pH may also be important during freezing and freeze-drying. Gradual freezing of an aqueous solution results in the formation of ice crystals and a concentrated salt solution, in which hydrolysis rates can be increased due to a higher concentration or a pH shift, or both. Therefore, freezing should be done as fast as possible.

Borate buffers show a minimal pH shift when the temperature increases (e.g. during heating or sterilisation) or decreases (freezing) and the concentration that is required to achieve an isotonic solution is relatively low. These two factors contribute to this buffer's suitability for ophthalmic solutions (see Sect. 10.6.1).

Hydrolysis of an ester can result in a substance with reduced aqueous solubility; possibly leading to precipitation even when relatively little degradation has occurred. An example is the hydrolysis of prednisolone disodium phosphate and the formation of the poorly soluble prednisolone.

Examples of substances that are prone to hydrolysis are: acetylsalicylic acid, ampicillin, barbiturates, chloramphenicol, chlordiazepoxide, cocaine, corticosteroid phosphate or succinate esters, proteins, folinic acid, indomethacin, local anaesthetics, paracetamol (acetaminophen), pilocarpine, tropa alkaloids (atropine, scopolamine), xylomethazoline and the antimicrobial preservatives methyl and propyl parahydroxybenzoate. In the field of oncology, melphalan and bendamustine hydrochloride are highly susceptable to hydrolysis with a shelf life of 1.5 h for melphalan and 3.5 h for bendamustine at room temperature.

Cocaine Eye Drops

The hydrolysis of cocaine strongly depends on pH and temperature. To minimise degradation, the pH should not exceed 5.5. Therefore, a boric acid – benzalkonium solution is suitable for the preparation of iso-osmotic solutions, with a pH of 4.5–5 (see Table 22.1).

Table 22.1 Cocaine Hydrochloride Eye Drops 5 % [14]

Cocaine hydrochloride	5 g
Benzalkonium chloride	0.01 g
Boric acid	0.4 g
Disodium edetate	0.1 g
Water, purified	ad 100 mL

Cocaine may degrade into benzoylecgonine and subsequently into ecgonine and benzoic acid [15]. The

(continued)

degree of degradation that results from heating the solution has been investigated. The unheated solution (pH 5.0) contained 1.3 % benzoylecgonine, expressed as percentage of the cocaine content. After 30 min of heating the solution at 100 °C, the benzoylecgonine content had increased to 2.1 % and after 15 min at 121 °C to 2.7 %. Due to the weak buffer in the solution, the degradation resulted in a pH decrease to approximately 3.

The process of hydrolysis can be inhibited by using the right pH, by reducing the storage temperature, or by processing the active substance in the solid state. Solid state active substances and medicines should be stored under dry conditions to prevent hydrolysis.

The pH of a prednisolone oral solution (Table 22.2) is set at 7–7.5 to limit the hydrolysis of prednisolone disodium phosphate. After 12 months of storage, no degradation is measurable. However, hydrolysis of the preservative methyl parahydroxybenzoate limits the shelf life to 12 months, as the amount of preservative has then been decreased by 25 %.

22.2.2 Oxidation and Reduction

Oxidation is a chemical reaction during which a substance loses (donates) electrons, whereas during reduction an electron is taken up (accepted) by the substance. Active substances are decomposed more often by oxidation than by reduction. Typical oxidation processes involve organic molecules that react with oxygen molecules that are dissolved in water or present in the air. The process usually consists of a cascade of reactions through the formation of free radicals, which are molecules or atoms that are highly reactive, due to the presence of one or more unpaired electrons. Free radicals exist as the superoxide anion (•O = O-), hydroxyl radicals (•OH) and carbon (chain) radicals (•R). Many oxidation reactions are catalysed by traces of heavy metals.

Table 22.2 Prednisolone Oral Solution 1 mg/mL (as disodium phosphate) [16]

Prednisolone sodium phosphate	0.146 g
Bananas flavouring (local standard)	0.1 g
Disodium edetate	0.1 g
Disodium phosphate dodecahydrate	1.9 g
Methyl parahydroxybenzoate	0.15 g
Sodium dihydrogen phosphate dihydrate	0.21 g
Sorbitol, liquid (crystallising)	25.8 g
Water, purified	77.5 g
Total	106.8 g (= 100 mL)

The mechanisms and kinetics of oxidation reactions are very complex, which makes it difficult to predict whether oxidation reactions of organic molecules will occur and how to prevent them from happening.

The oxidation reaction rate is usually not dependent on the concentration of the substance (see Sect. 22.5.7). Therefore, the content of low-dose preparations decreases relatively faster by oxidation than that of high-dose preparations. This is in contrast to the process of hydrolysis, during which the percentage of the substance that degrades is more or less constant per unit of time. Like all chemical reactions, oxidation proceeds more slowly at lower temperatures. However, oxygen molecules dissolve better in water and fats at lower temperatures, which implies that more oxygen will be present in the formulation to initiate oxidation reactions. The degree of oxidation of many substances in aqueous solutions is dependent on the degree of ionisation of the substance. Lowering the pH will lead to protonation of nitrogen atoms in amines and blocking of easily excited electrons in several organic molecules [17]. Those molecules will therefore be protected by a low pH. This is only the case for basic substances.

An example of a simple oxidation reaction is the conversion of Fe^{2+} into Fe^{3+}. Examples of active substances that are prone to oxidation are acetylcystein, adrenaline, apomorphine, clioquinol, dithranol, dobutamine, ergotamine, hydroquinone, isoniazid, mesalazine, naloxone, neomycin, oxycodone, paracetamol, peptides, salbutamol, phenothiazine derivatives (promazine, promethazine, chlorpromazine), phenylephrine, physostigmine, tetracycline, tretinoin, the vitamins A and D, and the excipients: flavouring agents, fragrances and unsaturated fats (vegetable oils, suppository bases).

Reduction of active substances occurs more infrequently than oxidation. Some examples are:

- The conversion of hydrogen peroxide into oxygen
- The reduction of methylthionine (in the solution for injection) into its leuco-form, which may be the active form anyway
- The formation of metallic silver in an aqueous solution of silver nitrate that is exposed to light and that contains a trace of an organic substance to prime the reaction

Oxidative reactions often proceed into polymerization reactions, resulting in large molecules of which the complex structures can be difficult to determine. A well-known pharmaceutical example is the brown discolouration of adrenaline solution.

Upon degradation, adrenaline solution first turns into pink, then red, and finally brown. Adrenaline is first oxidised into adrenochrome, which is consecutively oxidised into the fluorescent adrenolutin and brown melanin products [18]. The oxidation rates increase with increasing pH. The stability is the best at pH 3.2–3.6, by virtue of the relatively low reaction rate of the first step at this pH [19]. At pH 7.4, the rate of the second step is relatively high, whilst at pH 6.9, accumulation of adrenochrome occurs [18].

The raw material paracetamol may hydrolyse into aminophenol at high relative humidity. Subsequently, aminophenol is oxidised into toxic quinonimines and related substances [6]. This process causes a discolouration of the powder from white to pink, brown, and black. Discolouration of a paracetamol solution may imply that the raw material was stored under humid conditions. To be able to be aware of toxic degradation products, it is advised not to add a coloured flavouring agent, like caramel, to a paracetamol solution.

Oxidation processes can be inhibited by limiting the availability of oxygen and sometimes by the addition of antioxidants.

22.2.2.1 Limiting the Availability of Oxygen

An effective way to prevent oxidation is to remove oxygen from the water that is used in the formulation and to prevent the influx of oxygen after preparation. It is nearly impossible to completely remove oxygen from water, oil or fat. Preventing the influx of oxygen is only possible if the preparation is packed separately per dose. For injectable, oxygen sensitive substances, in ampoules, flushing with and packaging under an inert gas is a common and effective method to decrease the oxygen content. However, the transfer of a solution for injection from an ampoule into a syringe allows oxygen to dissolve in the water. Therefore, it is usually not possible to prepare the syringes far ahead when dealing with oxidisable active substances (for example at the Centralised Intra Venous Additives Service (CIVAS)).

In multidose containers, the ingress of oxygen can only be prevented marginally. For aluminium tubes, squeezing them and rolling them up helps to a certain extent. For bottles, limiting the empty volume in the top may increase the shelf life of the unopened container. By substituting a part of the water in an aqueous solution for a concentrated sugar solution, glycerol or propylene glycol, the solubility of oxygen is diminished, and thus oxidation. However, in many situations it is essential to add antioxidants, substances that reduce oxidation.

22.2.2.2 Antioxidants

Oxidation reactions can be inhibited by three types of antioxidants [20]:

1. True antioxidants: these are thought to block chain reactions by reacting with free radicals. The agent (e.g. DL-alpha-tocopherol, butylhydroxytoluene) donates electrons and hydrogen atoms, which are accepted by free radicals, more easily than the active substance itself.
2. Reducing agents: these have a lower redox potential than the active substance or excipient they are protecting. The agent (e.g. sodium metabisulfite, sodium formaldehyde-sulfoxylate, ascorbic acid) is oxidised more easily than the active substance.
3. Antioxidants synergists: these enhance the effects of antioxidants. For instance by the binding of copper or iron ions, which catalyse the oxidation reaction. Usually, complexing agents are used for this purpose (e.g. disodium edetate, citric acid).

The mechanism of action of a substance that is oxidised more easily than the active substance can be explained by Nernst's law:

$$E = E_0 + \frac{0,059}{n} \log \frac{[ox]}{[red]} \qquad (22.1)$$

in which E = redox potential
E_0 = standard redox potential
n = number of electrons in the redox equation
$[ox]$ = concentration of substance in oxidised form
$[red]$ = concentration of substance in reduced form

This equation can be used for both the active substance and the antioxidant. The active substance is protected when the redox potential of the antioxidant is several units lower than the redox potential of the active substance, which is the case when both the standard redox potential of the antioxidant is lower than that of the active substance and the antioxidant is mainly present in its reduced state. For a given oxygen load, protection against oxidation lasts longer when the initial concentration of the antioxidant is higher. Some active substances have a very low standard redox potential, which renders protection by the usual antioxidants ineffective. In these cases, elimination of oxygen is the only way to prevent oxidation.

The Nernst equation can only be applied when the redox potentials of both the active substance and the antioxidant are known.

Generally, the choice for an antioxidant or combination of antioxidants and the required concentration are determined experimentally. This choice is also dependent on the phase that should contain the antioxidant, either the water phase or the oil phase. The antioxidants that act via the first mechanism are fat-soluble; those that act via the second and third mechanism are water-soluble. Some examples follow showing the importance of actually testing the anticipated effect of an antioxidant.

Example 1. Blocking the Oxidation of Tretinoin

Butylhydroxytoluene decreases oxidation of tretinoin both in an ethanol/propylene glycol mixture (Table 22.3) and in cetomacrogol cream (Table 22.4).

Table 22.3 Tretinoin Cutaneous Solution 0.05 % [21]

Tretinoin	0.05 g
Alcohol denaturated 95 % V/V (local standard)	40.4 g
Butylhydroxytoluene	0.05 g
Propylene glycol	52 g
Total	92.5 g (= 100 mL)

Table 22.4 Tretinoin Cream 0.05 % [22]

Tretinoin	0.05 g
Alcohol denaturated 95 % V/V (local standard)	12 g
Butylhydroxytoluene	0.04 g
Cetomacrogol cream FNA[a]	88 g
Total	100 g

[a]Cetomacrogol emulsifying wax (BP) 15 g, sorbic acid 200 mg, decyl oleate 20 g, sorbitol, liquid (crystallising) 4 g, water, purified 60,8 g. Total 100 g

On the contrary, a different antioxidant, DL-alpha-tocopherol, increases oxidation in cetomacrogol cream. This phenomenon is caused by peroxides, which originate from DL-alpha-tocopherol oxidation in the oil phase. The peroxides generate free radicals that initiate the oxidation of tretinoin.

Example 2. Instability of Acetylcysteine

Acetylcysteine decomposes in aqueous solution by hydrolysis and oxidation. The oxidation into N,N-diacetylcystin is said to be predominant [23, 24]. Furthermore, hydrogen sulfide and other sulfur containing substances can be formed. The shelf life of the medicine is not only limited by the requirement of a maximum of 10 % decomposition of acetylcysteine, but also by the unpleasant smell of the sulfur-containing degradation products. By HPLC the effects of antioxidants on the formation of N,N-diacetylcystin in acetylcysteine eye drops (Table 22.5) could be determined.

Table 22.5 Acetylcysteine Eye Drops 5 % [25]

Acetylcysteinum	5 g
Benzalkonium chloride	0.01 g
Disodium edetate	0.1 g
Trometamol	5.3 g
Water, purified	ad 100 mL

It appeared that ascorbic acid, sodium metabisulfite or sodium formaldehyde sulfoxylate had no effect or even increased the amount of N,N-diacetylcystin and potentiated the smell of sulfur containing substances.

Example 3. Dithranol Cream

Ascorbic acid has been added to a dithranol cream (Table 22.6) following research results with similar preparations [27, 28]. According to the literature [28] the combination of ascorbic acid and salicylic acid protects dithranol in a cetomacrogol cream better than salicylic acid alone. If ascorbic acid and salicylic acid are omitted, the degradation of dithranol amounts up to 40 % instead of 10 % within 1 month at room temperature.

Table 22.6 Dithranol Cream 0.05 % [26]

Dithranol	0.05 g
Ascorbic acid	0.1 g
Salicylic acid (90)	1 g
Lanette cream I FNA[a]	98.85 g
Total	100 g

[a]See Table 12.34

The concentration of the antioxidant is related to the total volume of the preparation instead of the active substance content, since the volume determines the oxygen content. When a preparation that contains an antioxidant has to be diluted, caution should be exercised to ensure that the end concentration of the antioxidant is not too low to be effective.

Table 22.7 Antioxidants with their E-number, ADI and Usual Concentrations

Antioxidant	E-number	ADI (mg/kg body weight)	Usual concentration (%)
Ascorbic acid	E 300	No limit	0.01–0.5
Butylhydroxyanisole (BHA)	E 320	0.5	0.01–0.02, but less in i.v. injections
Butylhydroxytoluene (BHT)	E 321	0.3	0.01–0.02, but less in i.v. injections
Sodium metabisulfite (sodium pyrosulfite, sodium hydrogen sulfite)	E 223	0.7	0.01–0.2
Sodium formaldehydesulfoxylate	[a]		0.1
DL-alpha-tocopherol	E 307	2	0.05–0.1

[a]Not allowed in food

'True' antioxidants (type 1, see above) and reductants (type 2, see above) are used up during the shelf life, which implies that their content is much lower at the end of the shelf life than when the preparation was released.

Other aspects of antioxidants should be considered:

- Sodium metabisulfite reacts with oxygen with the formation of sulfate, which results in a pH drop
- Sodium metabisulfite may bind to certain active substances, such as prednisolone disodium phosphate and adrenaline tartrate

Adrenaline reacts in equimolar proportions with sodium metabisulfite and is thereby inactivated [29a]. Because of the equimolarity of this reaction, changing the concentration of either adrenaline or metabisulfite may change the shelf life of the preparation quite drastically. It is supposed that metabisulfite at first reacts with oxygen. Therefore, the availability of any metabisulfite that is left for the reaction with adrenaline also depends on the amount of oxygen in the preparation. Moreover, this reaction is influenced by the pH, with a maximum rate at pH 2–3 [30].

To add to the complexity of the preparation, bisulfite has a negative effect on the stability of adrenaline in presence of light. Therefore, it may be necessary to avoid the use of bisulfite if the solution is exposed to light during the administration, especially during continuous infusion [31].

Oxidation of ascorbic acid causes a yellow discolouration. A preparation that contains this substance can turn yellow, whilst the active substance may still be unaffected. Therefore, masking the discolouration of ascorbic acid in a promethazine syrup with caramel is defendable.

Many of the antioxidants and complexing agents that are used in pharmaceutical preparations are also used in food products. Since food can be taken daily, limits have been established for these substances. These limits are called Accepted Daily Intake (ADI) in the EU and Recommended Dietary Allowance (RDA) in the US. In many countries, these limits also apply to pharmaceuticals. Table 22.7 summarises the antioxidants, their European identification number, their ADI, and their usual concentrations in pharmaceutical preparations according to [32, 33].

22.2.3 Isomerisation

Isomerisation is the transition of one isomer of a molecule into another isomer. During this transition, the configuration (spatial arrangement of molecular groups) around an asymmetric carbon atom changes. Two types of isomerisation can be distinguished: racemisation and epimerisation. In the case of racemisation the molecule has one centre of asymmetry. In case of epimerisation the molecule has two or more centres of asymmetry, of which one is involved in isomerisation. Isomerisation is a reversible process; eventually equilibrium between both configurations is established. A solution of one of the configurations is optically active. Racemisation results in a racemic mixture without optical activity. On the contrary, for epimerisation the optical activity remains in equilibrium. In many cases pH influences the rate of isomerisation.

A well-known example of isomerisation is the conversion of ergotamine into ergotaminine and, if the other carbon atom also is affected, in aci-ergotamine. Other active substances that degrade by isomerisation are adrenaline, colecalciferol, ergometrine, pilocarpine and tetracycline.

Racemisation of L-adrenaline is accelerated by light and acid. At pH 4.5, racemisation is minimal. Temperature has a large influence: $Q_{10} = 2.8$ (see Sect. 22.5.7). The leftward rotating isoform is 15–20 times more active than the rightward rotating isoform, so racemisation results in loss of activity.

22.2.4 Photolysis

Photolysis is chemical degradation facilitated by light. The standard reference on this topic is the book Photostability of drugs and drug formulations [17].

Light is a form of energy. When a molecule absorbs this energy, its energetic state is increased and in some cases, ionisation can occur. The molecule may return to its original stable state, or it may degrade. In principle, all types of degradation can follow the absorption of light, but most often oxidation occurs. This combination of events is called photo-oxidation. Light can also be absorbed by excipients that subsequently transfer a different kind of energy to the active substance, which in turn may degrade. This process is called photo-sensitisation. Examples of excipients that can act as sensitizers are the antioxidant metabisulfite and furfural, which is the degradation product of glucose that is present in trace amounts in glucose 5 % infusion solutions [34].

The light spectra that can be absorbed by a substance can be determined from the substance's absorption spectrum. Coloured active substances absorb visible light; the light spectrum that is absorbed is complementary to the colour of the active substance. White organic substances absorb UV light, corresponding to their UV spectrum. The presence of conjugated double bonds or an aromatic ring are an indication of the ability of the substance to absorb UV light and thereby be susceptible to photolysis.

The most reactive part of the spectrum is UV-B (280–320 nm), which is responsible for most direct photochemical degradation reactions of active substances. UV-A (320–400 nm) is more likely to induce photo-sensitisation. Infrared light is only relevant in the sense that it transfers heat, and may thus increase the reaction rate of degradation processes. Sunlight has a very broad light spectrum. Glass blocks most UV-B light present in sunlight, but still enough may pass through to induce degradation of active substances in glass containers, for example in a container that is kept on the window sill, or in an infusion bottle hanging from the bed of a hospitalised patient. Fluorescent light, in some countries known as tube luminescent (TL-)light, contains a fraction of UV light.

Some well-known photochemical degradation reactions of active substances are:

- The formation of *p*-nitrobenzaldehyde from chloramphenicol
- The formation of lumi-derivatives from ergotamine
- The separation of a side chain from methotrexate

Also the oxidations of chlorpromazine, cyanocobalamine, dithranol, nifedipine, tretinoin and primaquine are accelerated by light. In oncology, carmustine, fotemustine and dacarbazine are examples of active substances that are very sensitive to light. Moreover, the degradation products of dacarbazine are suspected of being toxic to the patient.

Photolysis can be prevented or reduced in the following ways:

- Prevent the light from reaching the medicine product.
- Exclude oxygen or add radical scavengers or UV absorbing substances.
- Reduce the exposure to light during manufacturing.
- Administer the medicine in subdued light or cover the skin with clothes after administration of a dermal medicine.

A coating or protective secondary packaging can be used to prevent light from reaching the active substance.

A tablet coating can protect the core against photolysis if this coating is not light transmissive, for example because it contains pigments. Suitable non-light transmissive secondary packagings are carton boxes and aluminium tubes. Brown glass may provide enough protection for its contents, but not always.

> For coloured, light-protective glass, the Ph. Eur. contains requirements on the transmittance of light with a wavelength of 290–450 nm. These requirements provide a certain standardisation of coloured glass, but they do not guarantee that coloured glass protects against all kinds of photolysis. For example, phytomenadione in oily solution, colchicine tablets and tretinoin solution are not protected sufficiently by brown glass or opaque plastics. In addition to the brown bottles in which they are packaged, these products should be stored in the dark.

The disadvantage of an overwrap is that the patient or nurse may want to take it off and not put it back on, which may result in problems in the following situations:

- For parenteral medicines that should be prepared for administration and subsequently administered, wrapping the medicine conflicts with the desire to continuously check the solution for clarity and volume. If a light-sensitive active substance is to be administered, the duration of the administration should be limited. A nicardipine intravenous infusion can be exposed to light for up to 8 h, which is sufficient time for administration [35]. A furosemide intravenous infusion can even be exposed to light for up to 24 h [36].

- Repackaging of solids in automated medicine dispensing systems should be done in such a way that the light protective capacity of the original container is met. In practice however, the new packaging material is often more transmissive to light than the original packaging material. Still, it is generally assumed that in most cases, the shelf life in the dispensing bag is long enough to cover the storage period of such bags, which is usually 1 week. An example of an active substance that requires specific attention in these situations is nifedipine.

Oxygen is usually involved in many photochemical reactions, thus the elimination of this substance is an effective means of protection against these reactions in many cases. Radical scavengers can be used to reduce the reactivity ("quench") of radicals or oxygen singlets. Ascorbic acid, DL-alpha-tocopherol and butylhydroxytoluene are used for this purpose. Also lactose, mannitol, saccharose, starch and povidone can have a quenching effect [17b]. Another strategy is to add UV-absorbing substances, such as p-aminobenzoic acid, benzophenones or vanillin, to a light sensitive active substance [17c].

Some active substances are so sensitive to light that light must be excluded to the highest possible extent during preparation. In practice, this means that the preparation should not be done in the vicinity of a window and that artificial lights should be switched off. Examples of pharmaceutical preparations for which this may be necessary are dithranol cream, phytomenadione oral solution and tretinoin solution.

The final question that should be raised is would it be necessary to protect light sensitive active substances if the patient uses the preparations on his skin or in the eye. The answer is that it depends on the rate of degradation and on the toxicity of the degradation products.

As an example, the photodegradation products of chloramphenicol (nitroso-compounds and paranitrobenzaldehyde) are considered carcinogenic. These products will be formed *in vitro* and *in vivo* and can reach the bone marrow in rats [37]. Chronic use of chloramphenicol has been connected with bone marrow depression, not caused by chloramphenicol itself. Apart from the question if this risk is estimated well [38], it can be avoided completely if the patient covers his skin if a dermal preparation has been applied and only use chloramphenicol as eye ointment 1 % at night. See also Sect. 10.5.

If a light sensitive substance is administered via an infusion administration system, this should be covered, or made from opaque or completely light-resistant material.

22.2.5 Degradation of the Protein Structure

Many of the newly licensed medicines are biopharmaceuticals, which either are proteins or contain protein groups. Such pharmaceutical proteins are expected to become more and more available in the near future.

Examples of pharmaceutical proteins are: insulin, glucagon, somatostatin and analogues, erythropoeietin and analogues, interferons, interleukins, monoclonal antibodies, gonadorelin and analogues, colony stimulating factors, antithrombotic medicines, vaccines.

Proteins can be described by a primary, secondary, tertiary and quaternary structure, all of which can be affected by degradation processes. See also Sect. 18.4.1.

The primary structure of a protein consists of the arrangement into chains of amino acids. The number of amino acids per chain can vary from a few dozens to many hundreds.

The secondary structure is created by hydrogen bonds between the carbonyl group of one amino acid with the amine group of another. This structure manifests itself as an alpha helix or in a beta sheet. Within one protein, both alpha helixes and beta sheets can occur.

The tertiary structure is formed by the folding of peptide chains. Covalent and non-covalent bonds result in the positioning of the secondary structures in relation to each other. Covalent bonds are disulfide bonds between two cysteine units in the protein. Examples of non-covalent bonds are hydrogen bonds, ionic bonds and hydrophobic bonds in the protein. Which type of bond is formed, depends on the length of the peptide chain, pH, electric charge, polarity, and lipophilicity of (secondary) structural elements of the protein.

A quaternary structure is the arrangement of two or more protein subunits into a complex. These subunits may be identical but may also differ from each other. Interactions between subunits determine the three-dimensional orientation towards each other and therewith the structure of the whole protein (dimer, trimer, tetramer). The three-dimensional structure of proteins is essential for their biological efficacy and is highly sensitive to degradation.

The chemical bonds in proteins can be disrupted by:

- Hydrolysis of amide bonds (proteolysis)
- Deamination (cleavage of an unbound amino group of an amino acid)
- Disulfide exchange (breaking of disulfide bonds and formation of new disulfide bonds with other cysteine units)

These degradation reactions are influenced by pH, temperature, and the presence of light and oxygen.

The spatial structure of proteins (tertiary and quaternary) can be disrupted by:

- Aggregation (coagulation of proteins)
- Denaturation (unfolding of proteins)
- Precipitation
- Adsorption (binding of lipophilic parts of the protein to surfaces)

Many factors influence the disruption of the spatial structure. Changes in temperature and pH can induce aggregation. The pH and ionic strength influence the charge of the amino acids and therewith the bonds and tertiary structure. In general, the higher the ionic strength, the greater the influence is on the structure. However, the effect of specific ions on the structure may vary.

In addition, the concentration of the pharmaceutical protein and the processes that they are subjected to, such as dissolving, suspending, and diluting, can be of influence. Shaking a vial can cause foam formation and denaturation. Shearing stress, as with the use of peristaltic pumps, can cause aggregation. Certain packaging materials are more absorbent than others.

Degradation of proteins can be prevented by not changing the composition of the solution of the protein, by not repackaging, by not shaking but gentle swirling of the solution, by not using peristaltic pumps, by avoiding large temperature differences, and by not heating the solution. Processes in the pharmacy in which proteins are involved are for example dissolving a freeze-dried pharmaceutical protein before use, or the preparation with a protein raw material like polymyxin.

Stability studies have demonstrated that monoclonal antibodies are chemically stable in daily practice. Rituximab and trastuzumab infusion are stable for 6 months when stored between 2 °C and 8 °C [39, 40]. Bevacizumab repackaged in syringes is stable for at least 3 months [41].

22.3 Microbiological Stability

Medicines must have a low micro-organism content and for some administration routes, the products have to be free of micro-organisms (sterile). The requirements are described in Sect. 19.6.2. The microbiological quality of a preparation can worsen after preparation despite a good starting quality. This happens when micro-organisms that are present grow (see Sect. 19.2) or when micro-organisms from the environment contaminate the preparation during storage in the pharmacy or at home, and during use by the patient. The microbiological shelf life of a medicine depends on:

- The initial degree of contamination
- The probability of contamination from the environment
- The suitability of the preparation for growth of micro-organisms (see Sect. 19.4)

A good microbiological quality can be achieved by using starting materials of the right quality, by working hygienically, by using germicidal treatments, and by using clean or sterile packaging material (see Sect. 19.5.3).

The construction and volume of the stock packaging, the patient packaging, and the hygiene during repackaging from stock packaging to patient packaging determine the chance and amount of contamination. The formulation of the medicine and the storage conditions (temperature, humidity) determine the suitability for growth of micro-organisms. This is called the microbiological vulnerability (see also Sect. 22.3.3).

The factors packaging, hygienic handling, microbiological vulnerability, and storage conditions are discussed separately in the next paragraphs, but for the determination of a safe shelf life concerning the microbiological stability the interdependence of these factors should be considered. When for example a medicine is microbiologically vulnerable, the requirements for the construction of the container and the storage conditions must be stricter.

22.3.1 Packaging Material

For the storage of medicines in the pharmacy, storage in the primary container (as dispensed to the patient) is preferred over packaging in stock containers. The reason for this is obvious, since a primary container will not be opened before dispensing. Stock containers are frequently opened for repackaging the contents, and thus subject to contamination by the hands of the operator, utensils, and possibly by airborne micro-organisms.

When the use of stock containers is inevitable, the volume should be restricted to limit the number of times that the stock container will be opened. As a general rule, a stock container should contain no more than ten times the amount that is dispensed to an individual patient.

A multidose container should also ensure a minimum chance of contamination. This is especially important when the preparation is microbiologically vulnerable, or has stricter microbiological requirements (eye drops, creams) than preparations that are less vulnerable, such as water-free dermatological preparations.

22.3.2 Hygienic Handling

Hygienic handling means that contact of the medicine with sources of microbiological contamination are minimised.

Relevant sources of micro-organisms for pharmacy preparations are the human body, dirty utensils, and moist

surfaces. These are more likely sources of contamination for medicines than airborne contamination.

The operator's hands are an important source of microbiological contamination, as such, but also as a medium for transferring contamination coming from other body parts. This can be limited by wearing gloves during preparation. However, a study into the contamination of hard gelatine capsules via handling with bare hands showed that the contamination may be minimal in practice [42]. Despite these findings, the use of gloves becomes more and more common practice, not only from a microbiological perspective but also from an occupational health and safety perspective (see Sect. 26.4.3).

Hygienic handling is the most important factor for good aseptic handling, both in the pharmacy and during reconstitution on hospital wards (see Sect. 31.3.3).

Proper hygienic handling by the patient can be improved with a well-constructed container, such as a tube for a cream, a Gemo® dropper bottle for eye drops, or a pump sprayer for nose drops that uses air from the surroundings. In addition, the patient should be informed clearly and sufficiently about the importance of hygienic handling of the medicine (see Sect. 37.7.4).

22.3.3 Microbiological Vulnerability

A preparation is microbiologically vulnerable when it facilitates microbiological growth. Microbiological vulnerability can be investigated with a challenge test, a test for the effectiveness of the preservative. In this test, the degree of growth or eradication of micro-organisms in a formulation is investigated. The predominant reason to perform challenge tests is to test the effect of varying the formulation on the microbiological vulnerability. However, firm statements on microbiological vulnerability are difficult to make. Only a limited number of strains are tested and the question arises whether a single inoculation with a large number of micro-organisms is representative for a real contamination. Still, the Ph. Eur. contains requirements [43] for the minimal and recommended eradication rate, depending on the dosage form.

It is advised to test the microbiological vulnerability without the addition of a preservative. That way, it may be proven that the addition of a preservative is not always necessary. An example is a diacetylmorphine injection for multiple uses for heroin addicts. A solution of 150 mg/mL diacetylmorphine without preservative complied with the Ph. Eur. test [44].

Especially from research with food microbiology, knowledge is available of the factors that influence the microbiological vulnerability of medicines. The most important factors are the presence or absence of water, the presence or absence of antimicrobial agents, pH, environmental temperature and relative humidity. These factors are discussed separately.

22.3.3.1 Water

The presence of water is a prerequisite for the growth of micro-organisms (see Sect. 19.2). This implies that in dry pharmaceutical preparations no growth of micro-organisms is to be expected, as spore forming micro-organisms reside in their spore form, whereas non-spore forming micro-organisms die. A trace of water, e.g. condensed water, may be sufficient for revival of spores. For this reason, a preservative agent is sometimes added to tablets that are used in tropical areas [45]. The chances of survival for various micro-organisms are dependent on the water content in the preparation. Some micro-organisms can only survive in a wet environment, whereas others are able to resist high salt concentrations or even grow in a (moist) powder. This knowledge is important for the investigation of the microbiological vulnerability of medicines. Preferably, those micro-organisms with the highest chance of survival in the product are used in studies.

A measure for the water content in a preparation is the water activity, as defined in the Ph. Eur. [46]. The water activity is the ratio between the water vapour pressure of a preparation at a certain temperature and the water vapour pressure of pure water at the same temperature. Therefore, water activity is the reciprocal of the osmotic value. Table 22.8 gives an overview of micro-organisms that can grow at a certain water activity, with pharmaceutical examples.

Micro-organisms cannot grow in a pharmaceutical preparation with a water activity below 0.5. Concentrated solutions, for example of saccharose, sorbitol, sodium chloride and urea, give micro-organisms little chance to grow, due to their low water activity. Simple syrup and sorbitol solution basically need no preservation, but nevertheless this is done for two other reasons. The first reason is that when simple syrup is used in oral mixtures, it is diluted. Preservation then gives an extra microbiological protection of the mixture. The second reason is that in the stock bottle of simple syrup condensed water can be formed at the surface and the vacant sides of the bottle, in which micro-organisms can grow.

Besides the water activity, the size of the water droplets in the water phase of an ointment can be important. Butter, which is not preserved, contains small water drops in which micro-organisms hardly grow, perhaps because the amount of food for the micro-organisms is limited. However, this theory does not apply to pharmaceutical preparations as well. In w/o ointment, growth of micro-organisms can occur when contaminated water is used (see Sect. 12.5.3).

Table 22.8 Water activity, micro-organisms and pharmaceutical preparations (From [47] with permission)

Water activity	Micro-organisms that can grow at this water activity	Examples of pharmaceutical preparations with this water activity
1.00–0.95	Gram-negative rods, bacterial spores, some moulds	Eye drops, water containing creams
0.95–0.91	Most cocci, *Lactobacillus* species, vegetative forms of bacillaceae, some yeast	
0.91–0.87	Most moulds	Simple Syrup
0.87–0.80	Most yeasts, *Staphylococcus aureus*	Sorbitol 70 % solution
0.80–0.75	Most halophile bacteria	
0.75–0.65	Xerophile yeasts	
0.65–0.60	Osmophile moulds	Starch with 18 % water
0.50		Extractum glycirrhizae crudum
0.40		Sodium lactate 60 % solution
0.20		Milk powder
0.0		Dried lactose

22.3.3.2 Substances with an Antimicrobial Effect

Some active substances or excipients have an antimicrobial effect not only through reducing the water activity, but also through a specific antimicrobial mechanism. The best-known example is propylene glycol, but also ethanol, local anaesthetics, chlorpromazine hydrochloride, promethazine hydrochloride and essential oils exhibit a specific antimicrobial effect. In addition, the combination of weak antimicrobial effects of disodium edetate, borax, and boric acid appeared to justify prolongation of the shelf life of non-preserved eye drops over the standard limit of 24 h [48].

22.3.3.3 pH

Micro-organisms exist in numerous forms and shapes, so for every (extreme) pH value, types can be found that are able to survive and replicate under those specific conditions. However, micro-organisms that are commonly encountered during the preparation and use of pharmaceutical preparations do not grow outside the pH range of 3–9. There are a few examples of preparations with a pH outside this range, for example a ferrous chloride oral solution (pH 1.5) (Table 22.9) and a theophylline oral solution 30 mg/mL (pH 9.5) (Table 22.10). Such preparations thus require no preservation.

The pH is important for the preservative effect of sorbic acid and parahydroxybenzoic acid esters. These substances are most effective at pH <5. Since sorbic acid decomposes faster at low pH, pH 5 is used as a compromise (see Sect. 23.8.6). At a pH above 5.5–6.0, sorbic acid is not effective at all. At pH 7–8.5, the effectiveness of the parahydroxybenzoic acid esters is strongly reduced, in part due to their chemical instability. This implies that for dermatological preparations with a pH > 7, or in case of hypersensitivity for parahydroxybenzoic acid esters already > 5, the pharmacist has to resort to propylene glycol or probably phenoxyethanol. In case of an oral liquid with such a pH, in fact no suitable preservative exists; only the use of high concentrations of parahydroxybenzoic acid esters may give some level of preservation.

Table 22.9 Ferrous Chloride Oral solution 45 mg/mL [49]

Ferrous chloride tetrahydrate (local standard)	7 g
Citric acid monohydrate	0.42 g
Sorbitol, liquid (crystallising)	10.6 g
Syrup BP	105 g
Water, purified	8 g
Total	131 g (= 100 mL)

Table 22.10 Theophylline Oral Solution for Children 30 mg/mL [50]

Theophylline-ethylenediamine, anhydrous	3.5 g
Lemon spirit BP	0.5 mL
Saccharin sodium	0.25 g
Sodium hydroxide solution 2 M (local standard)	2.5 mL
Water, purified	ad 100 mL

22.3.3.4 Storage Temperature and Humidity

Most micro-organisms replicate more slowly in a refrigerator than at room temperature. Storage at a low temperature generally improves the microbiological stability and slows down chemical degradation processes. Under freezer conditions, no growth takes place at all. A preservative only has an antimicrobial effect when micro-organisms actually grow. When a patient uses preserved eye drops, room temperature is therefore preferred over the refrigerator for storage: micro-organisms that contaminate the eye drops should be killed as quickly as possible.

Another concern is the effect of changes in temperature. Changes in temperature may lead to condensation of moisture from the air, which can form a thin layer of water on top of the pharmaceutical preparation. Micro-organisms that were initially suppressed in the preparation can now grow

in this water layer. In addition, following adaptation to the preservative, they may eventually be able to grow into the preparation itself. This effect is for example observed during storage of syrups. Another, especially notorious, example is the growth of micro-organisms in tablets that are packed in a strip impermeable to water, through which condensed water cannot evaporate. Upon cooling of a tablet that was produced under heated conditions, condensed water is formed. Covering during cooling and mixing after cooling are therefore necessary precautions. Ideally, non-preserved pharmaceutical preparations should be stored as cool as possible and preserved preparations should preferably be stored at room temperature, large temperature fluctuations should be avoided.

22.3.3.5 Summary

This paragraph can be summarised as follows:

- All preparations that contain water are microbiologically vulnerable. Dry formulations are therefore preferred from a microbiological perspective.
- High percentages of propylene glycol, ethanol or sugar can reduce the microbiological vulnerability of a preparation.
- For the preservation of oral liquids and dermatological preparations at pH <5, sorbic acid or methyl parahydroxybenzoate is used, at pH 5–7 methyl parahydroxybenzoate, and at pH >7–8.5 methyl parahydroxybenzoate, even though its preservative effect is weak. It is therefore advised to reduce the pH or pay extra attention to the prevention of contamination.
- The chance of microbiological contamination is reduced by limiting the amount of the preparation that is dispensed to the patient, by use of containers and dosage devices with better protection against micro-organisms, or by reducing the shelf life after dispensing and opening.
- Non-preserved preparations are stored in the refrigerator, preserved preparations are stored at room temperature.

22.4 Content Limits During Storage

How much can a medicine be altered by instability before it cannot be used anymore?

For medicines that show a gradual decline in content, a limit can be determined for the decline of the active substance. Limits can also be determined for toxic degradation products that are formed during storage. Such limits are dependent on the toxicity of the degradation product. The shelf life of a medicine can be determined by investigating the stability of the medicine under standardised and realistic conditions. This paragraph discusses the norms for the decline in active substance content, as well as the design of stability studies required for determination of the shelf life of the medicine.

Physical or microbiological changes usually lead to the immediate expiration of the medicine but it is hard to predict when these, occur. Estimations can be made on researched microbiological vulnerability of the product or by reasoning by analogy, such as: if the maximum storage time for a chemically stable all-fatty ointment is 2 years, then a water-containing ointment should not be stored that long. In fact the storage times for dosage forms given in Table 22.15 are mainly based on analogy reasoning.

22.4.1 Limits for Decline of Content

It is common practice to accept a decline of 5 % or 10 % of the active substance. At the start of the shelf life, the content of the active substance is between 95 % and 105 % relative to the declared content. At the end of the shelf life, the content should thus be between 90 % and 105 % [51]. These limits are hardly attainable for the pharmaceutical industry, as often an overage is needed to comply to the limits [52]. If too much of a toxic degradation product is formed or the appearance has unacceptably changed before the limit of the active substance has been reached, the shelf life of the product should be shorter.

For pharmacy preparations, limits of 90–110 % apply to the entire shelf life (see Sect. 32.6). As an example: the shelf life of the Dutch standardised preparations in the FNA is based on a maximum content decline of 5 %. When 10 % decline would be allowed, the chance on the active substance content falling below the lower limit of 90 % would be unacceptably high. If setting the limit for decline of content at 5 % would result in unacceptable storage conditions or an unacceptably short shelf life, it can be reasoned to accept a decline of 10 %.

During the preparation of medicines, content decline of the active substance can occur, especially by heat sterilisation. To compensate for this loss, an overage can be added to the preparation, which means that more of the active substance is put in the preparation to obtain a content of 100 % relative to declared content in the final product. In general, the application of an overage is unattractive for pharmacy preparations. The amount to be weighed must be recalculated and the chance of preparation errors increases.

22.4.2 Limits to the Amount of Toxic Degradation Products

A general approach, to determine limits to the concentration of toxic degradation products, can be found in a CHMP guidance on impurities [53]. This directive states that if the maximum daily dose is <1 g, impurities are limited to <0.1 %. At a daily dose of >1 g, impurities should be no greater than 0.05 %. The EMA requires a toxicological

evaluation on limits greater than these for licence applications. For genotoxic impurities (see Sect. 26.3.3), other limits apply. The applicable CHMP Guideline [54] states that if a limit is available, such as the Permitted Daily Exposure (PDE) or the No Observed Adverse Effect Level (NOAEL), these can be used. If no limit is available, the Threshold of Toxicological Concern (TTC), which is related to a life-long intake, can be used. A TTC value of 1.5 micrograms/day of a genotoxic impurity is defined as leading to an acceptable risk for a given medicine, because it is weighed against the benefit: the disease is considered to be worse than the risk from the impurity in the medicine. With this value and the expected daily dose, the maximal percentage can be calculated for genotoxic impurities. Higher values than the TTC can be justified if:

- The therapy with the medicine is of short duration
- A life-threatening condition is treated
- The expected survival is <5 years
- A person is exposed to the same impurity from other sources in higher quantities
- The genotoxic impurity is also a metabolite formed in the body

Since many medicines are used for only a short period of time, the TTC concept has been expanded [55]. The amount of 1.5 micrograms/day is applicable for an exposure >12 months. For an exposure <1 month, the TTC limit is 120 micrograms/day.

A limit to hydrazine in Isoniazid Oral solution (Table 22.11) and Injection solution (Table 22.12).

Table 22.11 Isoniazid Solution for Injection 200 mg = 2 mL (100 mg/mL) [56]

Isoniazid	10 g
Disodium edetate	0.01 g
Hydrochloric acid (local standard)	q.s.
Water for injections	ad 100 mL

Table 22.12 Isoniazid Oral Solution 10 mg/mL [57]

Isoniazid	1 g
Disodium edetate	0.1 g
Glycerol 85 %	20 g
Methyl parahydroxybenzoate	0.15 g
Sodium citrate	0.075 g
Water, purified	82.8 g
Total	105 g (= 100 mL)

An example is the establishment of the shelf life of an Isoniazid injection solution. Isoniazid when dissolved in water, may hydrolyse and oxidise. Upon hydrolysis, isonicotinic acid, isonicotinamide, di-isonicotinoylhydrazine and hydrazine are formed [10, 29b]. The increase in hydrazine does not match a decrease of isoniazid content. Since hydrazine is genotoxic, the shelf life of the product is limited to the formation of hydrazine, which is measurable even before the degradation of isoniazid is measureable.

Neither the USP nor the BP give limits to the amount of hydrazine in isoniazid oral solutions or isoniazid injection solutions. The amount in the starting material is limited to 0.05 % by the Ph. Eur. as hydrazine sulfate relative to isoniazid, which equals to 0.012 % hydrazine. Hydrazine may be present in the starting material following the synthesis.

A PDE for hydrazine can be calculated from the NOAEL [58], which is 1 microgram/day for life-long exposure.

Using the general TTC approach, an acceptable percentage of 0.00005 % or 0.5 ppm for long-term use and of 60 ppm for short-term use can be calculated as isoniazid injection solutions usually contain 100 mg/mL isoniazid and the daily dose is 300 mg. Since 3 mL is allowed to contain up to 1.5 micrograms and 120 micrograms of hydrazine respectively, the maximum allowable concentration in the injection is 0.5 microgram/mL equalling 0.00005 % or 0.5 ppm and 60 micrograms/mL equalling 0.006 % or 60 ppm.

Isoniazid injection solution FNA (Table 22.11) is sterilised by autoclaving, which increases the amount of hydrazine in the solution, for example from 0.02 % (relative to isoniazid in the starting material) to 0.1 % (after autoclaving). During storage at 25 °C, the amount of hydrazine increases with 0.1 % every 3 months. These percentages are higher than calculated with the TTC concept, also if a higher limit is applied because of short duration of the intravenous therapy.

However, based on the justifications described above, an exception to the general rule can be made for isoniazid as an injection. Firstly, the injection is given as a treatment to a life threatening condition to very weak tuberculosis patients. Moreover, hydrazine is also formed in the body upon the metabolism of

(continued)

isoniazid in larger quantities than are formed during storage of the injection solution [59, 60].

Should the limit be decreased, this means that the injection cannot be autoclaved, which results in less certainty about sterility in the situation of small-scale preparation. Storage in the refrigerator would reduce the degradation rate, but then the concentration of the injection has to be lowered to prevent precipitation. This would result in a larger volume to be administered, which would be burdensome to the already weakened patient.

It is clear that Isoniazid injections should only be given if there are no therapeutic alternatives. Even Isoniazid oral solution FNA (Table 22.12) is a better alternative from a toxicological perspective.

22.5 Stability Studies

The following types of stability studies are described:
- Accelerated
- Long term or real time
- In use
- Ongoing

All types of stability studies require an analytical method that is specific for the active substance (stability indicating) to allow for determination of the stability of the preparation. The parameters to be determined should be defined beforehand.

22.5.1 Method of Analysis

The method of analysis (assay) should allow for determination of the content of the parent active substance and, if necessary, the amount of degradation product that is formed. Therefore, the assay should be specific, which means that it is able to quantify the parent substance in the presence of degradation products and excipients (stability indicating). The method has to be validated.

For the validation of analytical methods, an international guideline applies [61] that has been elaborated by EDQM, see Sect. 32.16.2. For stability studies on pharmacy preparations, where there may be neither the equipment nor the time available to develop and validate an analytical method, as an alternative approach [62–64] can be used.

The reduced reliability of the results of stability studies on pharmacy preparations compared to the stability data of licensed medicines can be compensated with a relatively short shelf life.

22.5.2 Stability Parameters and Number of Samples

Directly at the start of a stability study, the parameters to be determined and their limits for storage should be established. Some parameters should always be determined (see further Chap. 32):
- Active substance content
- Content of toxic degradation products
- Appearance (colour, clarity, phase separation)
- Dissolution time and disintegration time of tablets and capsules
- pH of aqueous solutions
- Resuspendability of suspensions

In addition, determination of the content of the preservative can be useful to detect degradation and adsorption. The determination of the antioxidant may be useful in certain cases, but a decrease of this substance is to be expected and does not necessarily mean that the product cannot be used anymore.

Since it is not always known beforehand which changes occur, it is better to monitor a few parameters more instead of less.

The same holds true for the number of samples. This number depends in the first place on the accuracy of the assay [51], see also Sect. 20.4.4. However, to allow for repetition of assays or to determine samples at extra time points that turn up during the study, it is advised to have an ample number of samples.

For a stability study of a parenteral medicines samples are scheduled at t = 0, t = 3 months, t = 6 months, t = 12 months, t = 18 months, t = 2 years and t = 3 years. It was calculated that per sample point 5 vials should be tested. That makes 35 vials. Because of loss, more sample points or extra tests it is advised to store at least 42 or 49 vials (1 or 2 extra vials per sample point).

22.5.3 Accelerated Stability Testing

During the design phase of a medicine, stability studies are performed, to investigate the influence of variations of the formulation and to determine under which circumstances the final stability study should be performed. To limit the time awaiting for the results, degradation reactions can be accelerated by increasing the temperature. According to ICH guidelines (see Table 22.13), the standard conditions

Table 22.13 Guidelines for long-term stability testing

ICH guidelines (www.ich.org):	
Q1A (R2)	Stability testing of new drug substances and products
Q1B	Photostability testing of new substances and products
Q1C	Stability testing, requirements for new dosage forms
Q1D	Bracketing and matrixing designs for stability testing of new substances and products
Q1E	Evaluation of stability data
Q3A	Impurities in new drug substances
Q3B	Impurities in new drug products
Q5C	Stability testing of biotechnological/biological products
WHO guidelines (www.who.int/en/):	
WHO guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms (http://whqlibdoc.who.int/hq/1994/WHO_PHARM_94.565_rev.1.pdf)	
European CPMP guidelines (www.ema.europa.eu/ema/):	
Stability testing for applications for variations to a marketing authorisation	
Stability testing of existing active ingredients and related finished products	
In use stability testing of human medicinal products	
Maximum shelf life of sterile products of human use after first opening or following reconstitution	
Annex: declaration of storage conditions for medicinal products particulars and active substances	

for an accelerated stability study are 40 °C ± 2 °C at 75 ± 5 % relative humidity.

However, the recalculation of the rate of degradation under accelerated conditions to the rate at the final storage temperature has its limits. This approach usually does not apply well to heterogeneous systems like emulsions or suspensions. An increase in temperature may result in a change of the nature of this kind of preparations, such as the dissolution of dispersed ingredients, or the breaking of the emulsion. Moreover, at higher temperatures interaction with the primary packaging material can take place in a different way. Also for solutions, a rise in temperature can lead to important changes. The pH shift of buffer solutions is being discussed in Sect. 22.2.1, but also the activation energy of a degradation reaction can change, meaning that the Arrhenius equation (see Sect. 22.5.7) cannot be used to interpolate over large temperature intervals.

Another example of an accelerated stability study is the acceleration of the rate of phase separation in emulsions by changing the temperature. To compare the stability of different formulations of emulsions, they are subjected to temperature cycles, for example 24 h refrigerator, 24 h room temperature, 24 h refrigerator, etc.

22.5.4 Long-Term Stability Testing

Long-term stability testing is used to determine the shelf life of the medicine. Long-term stability studies should thus show the latest time point on which the product still complies with the specifications.

For the execution of long-term stability studies, worldwide ICH guidelines, WHO guidelines and European CPMP guidelines are followed. Table 22.13 gives an overview of the most important guidelines. These guidelines include the following directions:

- Storage conditions for storage at room temperature are 25 ± 2 °C at 60 ± 5 % relative humidity, for storage in the refrigerator 5 ± 3 °C, and for storage in the freezer −20 ± 5 °C.
- Sampling times are every 3 months for the first year, every 6 months for the second year and once yearly thereafter.
- At least three independent batches should be investigated in their final package, which are produced according to the final method of preparation.
- The batch size should relate to the final batch size.
- Stability testing should be based on knowledge of the behaviour of the active substance and the dosage form.

From the experience with stability testing of the Laboratory of Dutch pharmacists some advice can be added:

- Pharmacy preparations usually have a short shelf life; therefore, sampling times should be adjusted accordingly.
- Keeping a constant temperature during long-term stability studies is important, not only to comply with the regulations, but also for repeatability and interpolation of the results. Refrigerators and incubators with temperature monitoring are therefore required.
- Studies of preparations that are packed in water (semi)-permeable packaging material should be performed at constant relative humidity too. Ideal for such studies are climate cabinets in which both the temperature and the humidity can be controlled. Alternatively, saturated aqueous solutions of salts can be used to control the relative humidity in air-tight cabinets [65, 66].
- Preparations that are packed in water (semi)-permeable packaging material should be checked for evaporation of water by regular weighing.
- Up to a shelf life of 3 years the so-called half-time rule can be applied. When after 1.5 years of stability testing the extrapolation of the results demonstrates that a shelf life of 3 years is justifiable, a shelf life of 3 years can then be attributed after 1.5 years.

22.5.5 In-Use Stability Testing

For certain dosage forms, it is necessary to collect stability data whilst the patient is using them. This is especially important for:

- Medicines that are dispensed in packages for multiple use
- Medicines that require reconstitution or dilution prior to use

When the primary packaging of a preparation has been opened, oxygen, micro-organisms, water, and sometimes also light can enter. An in-use stability study thus focuses on medicines that are sensitive to (photo-)oxidation and microbiological contamination. When the actual use is simulated, relevant circumstances should be taken into account. For example, for a preparation in a 300 mL bottle that is sensitive to oxidation, 10 mL should be taken, three times a day, from that bottle, over a period of 10 days, to simulate the influence of the remaining volume on the available amount of oxygen. Guidelines exist [67] for this type of studies. However, the simulation of the expected behaviour of the patient has its limitations.

22.5.6 Ongoing Stability Testing

Even when the shelf life has been established stability testing should be continued. This is called ongoing stability testing. A practical approach is to investigate the active substance at the end of the shelf life. It can be questioned whether the preparation always complies with the end-of-shelf life requirements during routine production. Small deviations in the production process, starting materials, or packaging materials may influence the stability of the preparation.

22.5.7 Reaction Kinetics

Stability studies on degradation rate by chemical reactions usually also include the investigation of the reaction kinetics. It not only matters if a hydrolysis or an oxidation reaction is taking place but also at which rate and which dependency on pH or temperature is valid: reaction kinetics. This science is only very modestly dealt with in this book, just to serve practical purposes in case that a shelf life has to be roughly re-estimated. Examples of those practical situations are a patient who wants to take his medication with him on a holiday to a tropical country, medicines in a doctor's bag, or parenterals to be prepared for use for which stability data have to be interpreted from the product information. Such examples are dealt with in Sect. 22.6.

This chapter deals briefly with equations for the degradation rate and their dependence on the temperature. For further study of this topic, reference is made to the textbooks of Grimm [51] and Tønnesen [17].

22.5.7.1 Reaction Rate

In pharmaceutical practice, most degradation reactions occur following a first order equation:

$$-\frac{dC_t}{dt} = kC_t \tag{22.2}$$

In which C_t is the concentration of the degrading active substance at any time point t and k is the reaction constant.

Suppose C_0 is the concentration at time point 0, then integration of Eq. 22.2 gives:

$$\frac{C_0}{C_t} = k\,t \tag{22.3}$$

and:

$$\log\frac{C_0}{C_t} = \frac{kt}{2.303} \tag{22.4}$$

This implies that a linear relationship exists between the logarithm of the content and time. This is important, because it leads to a better interpolation and to more reliable results than non-linear interpolation of concentration-time data. In addition, measurement of the content on only two time points is necessary to estimate the degradation (see Fig. 22.2).

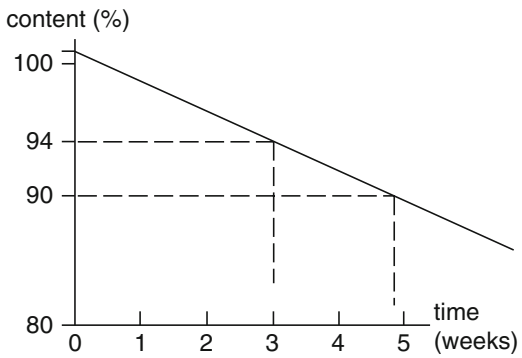

Fig. 22.2 Determination of t_{90} by extrapolation from 102 % at t = 0 and 94 % at t = 3 weeks. t_{90} is almost 5 weeks

For t_{90} (the time point that 90 % of the content is still present) Eq. 22.5 follows on Eq. 22.4:

$$t_{90} = \frac{2.3\log\frac{100}{90}}{k} = \frac{0.105}{k} \tag{22.5}$$

22.5.7.2 Temperature Influence

The influence of the temperature on reaction kinetics has been described by Arrhenius:

$$k = \mathrm{Z.e}^{-E/R.T} \tag{22.6}$$

In which Z is a constant, E is the activation energy of the degradation reaction, R is the gas constant and T is the temperature in Kelvin (= °C + 273).

The logarithmic Eq. 22.6 is:

$$\log k = \log \mathrm{Z} \frac{E}{2.303.\mathrm{R}} \quad \frac{1}{T} \tag{22.7}$$

The logarithm of the reaction constant k, plotted against $\frac{1}{T}$ gives a straight line. This way the reaction constant at a certain temperature can be calculated when it is already known at two different temperatures. It is also possible to plot the logarithms of t_{90} against $\frac{1}{T}$. Then t_{90} at the desired temperature can be read easily from the plot.

From the Arrhenius equation and the activation energy for various reactions, the following general rule is derived: with every 10 °C temperature increase the reaction rate increases 2–4 times. This factor is called Q_{10}.

When the reaction rate has to be estimated at an increased temperature, a Q_{10} value of 4 is safe. On the contrary, when the reaction rate has to be estimated at a lowered temperature, a Q_{10} value of 2 is safe. It is also possible to make calculations using t_{90}; a rise of the temperature with 10 °C results in a t_{90} that is four times shorter, whilst a lowering of the temperature with 10 °C results in a t_{90} that is twice as long.

For any change in temperature ΔT the following equation can be used:

$$k_{T_2} = k_{T_1}\, \mathrm{Q}_{10}^{\Delta T/10} \tag{22.8}$$

or:

$$t_{90(T2)} = t_{90(T1)}/\mathrm{Q}_{10}^{\Delta T/10} \tag{22.9}$$

22.6 Stability Data in a Pharmacist's Daily Practice

In the pharmacy, shelf life is often only based on a specific temperature. For licensed medicines shelf life may be traced from the product information by the manufacturer or investigated by the pharmacist for pharmacy preparations. Many situations in practice however require stability data at different temperatures, different concentrations, solvents or containers. A justified extension of a shelf life could be very helpful for the patient or the pharmacy's logistics as well as saving a lot of money.

This section at first deals with examples of a different storage temperature and secondly with the extension of shelf lives for reconstituted parenteral solutions.

22.6.1 Storage at a Different Temperature

Calculations to estimate a shelf life at a different temperature can only be made when the active substance is not subject to degradations other than chemical degradation, such as physical or microbiological degradation. In addition, calculations are only possible for relatively small differences in temperature. Data from stability studies that have actually been performed are preferred over estimations. Moreover, the equation for a first-order reaction can only be used for the first 10 % degradation for any other type of reaction.

22.6.1.1 Patient Going on Holiday

A patient plans to go on a holiday with a backpack (without a cool box) to a country with an average temperature of 30 °C. The medicine he uses has a shelf life of 3 months in the refrigerator due to chemical degradation. How long can the patient use the medicine on his holiday when the medicine is freshly prepared?

Suppose: a refrigerator has a temperature of 5 °C and the shelf life is based on a maximal degradation of the active substance of 10 %. Because there is a rise of the temperature, a Q_{10} of 4 is used:

$$\text{Then } \mathrm{Q}_{10}^{\Delta T/10} = 4^{25/10} = 32$$

From Eq. 22.9 $\left(t_{90(T2)} = t_{90(T1)}/\mathrm{Q}_{10}^{\Delta T/10}\right)$ it can be calculated that storage in a backpack results in a shelf life that is

32 times shorter than storage in a refrigerator, which is only 3 days.

Calculated in another way: from Eq. 22.5 $\left(t_{90} = \frac{2.3\log 100/90}{k} = \frac{0.105}{k}\right)$ a $k_{5°C}$ of 0.001154 per day can be calculated.

From Eq. 22.8 $\left(k_{T_2} = k_{T_1}\, Q_{10}^{\Delta T/10}\right)$ the $k_{30°C}$ can be calculated: $k_{30°C} = 0.001154 \times 4^{25/10} = 0.001154 \times 32 =$ 0.037 per day.

For t_{90} in the backpack it follows then (Eq. 22.5): $\frac{0.105}{0.037} = 3$ days

It is clear that both the pharmacist and the patient have to consider other options in this situation.

When the shelf life of a medicine is at least 3 years, a journey of less than 6 months to a country with a warmer climate usually gives no stability issues for that specific medicine.

22.6.1.2 Doctor's Bag

The temperature in a doctor's car may fluctuate between rather extreme values: heat as well as freezing. The required storage conditions for the medicines in the doctor's bag will possibly not be met and the expiry date of many medicines may not be valid anymore. In the Netherlands the doctors are advised:

- Not to leave their bag in the car, to avoid extreme temperatures (and to prevent theft)
- To refresh the medicines once a year, preferably just after summer season
- To check the expiry dates and the appearance twice a year

22.6.2 Shelf Life when Packaging has been Changed

If medicines are repackaged, especially into a medicines dispensing system, the new primary package should protect from degradation at least as well as the original package . This requirement will seldom be met. The new packaging of a medicines dispensing system will usually be more transparent to light and humidity for instance. The pharmacist who repackages the medicine has to evaluate stability and decide on the maximum storage period in the new package. Parenteral infusion solutions can be put into infusion bags of different type of plastic (PE, PVC) which may lead to an unexpected adsorption of the active substance.

22.6.3 Extension of the Shelf Life

Very short shelf lives limit the time frame for reconstitution, aseptic handling, transport and administration of the medicine or do not allow for the preparation in advance for the weekend. Using specific information sources [68–71] can be very helpful to find justification for longer shelf lives. Some examples:

22.6.3.1 Melphalan Injection Solution

For example, the stability of melphalan injection solution is 90 min at room temperature according to the manufacturer, as the active substance rapidly degrades by hydrolysis. However stability has been demonstrated for 4 h at 2–8 °C and then 90 min at room temperature, provided that the preparation is performed by diluting with an infusion solution in a bag taken from the refrigerator [69]. The results were based on a $t_{90\%}$ value of melphalan content and the evaluation of all degradation products. However, it has also been shown [69] that a shelf life of 5 h and 30 min instead of 90 min is possible and would be much more convenient for the preparation, transport, and administration.

22.6.3.2 Clorazepate Injection Solution

Dipotassium clorazepate is available as Tranxene® containing 50 mg and the additives mannitol and potassium carbonate. According to the product information, the powder should be dissolved in a phosphate buffer until a concentration of 20 mg/mL at a pH of 6.7–7.2 is reached. How long can the reconstituted solution be kept before administration as injection solution? How long can a diluted solution as infusion be kept before administration?

Dipotassium clorazepate degrades to nordazepam following a pseudo-first order reaction that accelerates when the pH is reduced and when the temperature rises [72]. Florey [73] gives the relationship between reaction rate and pH. Using Eq. 22.4 $(t_{90} = 0.105/k)$ it can be calculated that t_{90} at 22 °C and pH 7 is 12.5 h. For pH 6 t_{90} is 1.3 h. When knowing the t_{90} at 22 °C, an estimation can be made for the t_{90} at storage in the freezer. This can be done by using the Q_{10}. A freezer temperature of 4 °C is about 2 x 10 °C lower than 22 °C. Assuming a Q_{10} of only 2 (worst case) for 10 °C temperature difference, would mean the reaction rate at 4 °C being 2 x 2 times slower compared to 22 °C. Then t_{90} at pH 6 will be estimated at about 5 h and at pH 7, t_{90} is estimated at about 2 days. In this way shelf lives for several usual clorazepate preparations can be calculated, see Table 22.14.

Table 22.14 Chemical stability of dipotassium clorazepate preparations

		Chemical stability	
	Concentration	Room temperature	Refrigerator
Reconstituted, undiluted	20 mg/mL	8 h	2 days
Diluted with NaCl 0.9 %	0.1–0.4 mg/mL	8 h	2 days
Diluted with glucose 5 %	0.1–0.4 mg/mL	2 h	8 h

22.6.3.3 Azacitidine Injection

Azacitidine is an active substance that is very sensitive to hydrolysis. According to the SmPC, azacitidine has a 45 min stability at room temperature after reconstitution, an 8 h stability after reconstitution and storage at 2–8 °C, and a 22 h stability if the reconstitution takes place with Water For Injections at 2–8 °C and storage in the refrigerator. An 8 days stability of azacitidine at −20 °C followed by an 8 h stability at 2–8 °C would allow the advanced preparation for the weekend [74]. Furthermore an extended stability of 23 days has been demonstrated when the suspension is frozen [75].

22.6.3.4 Patient Comfort at the VAD Regimen

The VAD regimen combined vincristine 0.4 mg/day (V) and doxorubicin 9 mg/m^2/day (Adriamycin®: A) as a continuous IV for 4 days with oral dexamethasone (D). This regimen was a common treatment for multiple myeloma. The patient had to stay in the hospital to receive two continuous infusions a day. To avoid this, studies were performed to demonstrate the stability of the mixture (vincristine and doxorubicin with sodium chloride) to allow for it to be given on an outpatient basis [76–78]. Today, this regimen is less often prescribed, but these stability studies were of great importance for the quality of life of the patient for many years.

22.6.3.5 Facilitating Administration on the Ward

Knowing that mixtures such as cyclophosphamide and mesna [79] or cytotoxic and antiemetic medicines [80] are stable enough for a suitable period (for instance several days) to facilitate administration for nurses and patients.

22.6.4 Preventing Wastage and Saving Money by an Extended Shelf Life

Many expensive parenteral medicines have to be dosed individually and have to be reconstituted for only one patient. From the SmPC medicines usually are advised to be prepared immediately before use. Usually some of the preparation will be left over and has to be discarded. This can lead to a waste of precious active substances and inefficiency.

If the shelf life can be extended, for instance to 2 or 3 months, preparation in advance will become possible, thus also decreasing waste. As example, extended stability has been demonstrated for carboplatin infusions (84 days) [81], rituximab (6 months) [39], oxaliplatin (3 months) [82].

A successful example is also the study on the stability of bortezomib. Bortezomib is available in lyophilised form in vials each containing 3.5 mg (Velcade®). However, the dose is 1.4 mg/m^2. For a patient with a body area of 1.8 m^2, the dose is therefore 2.5 mg. The wastage will be 1 mg which represents almost 30 % of the cost of one vial of the medicine. Stability studies have demonstrated stability for at least 1 month for the 1 mg/mL or the 2.5 mg/mL solution [83, 84]. This makes pooling of preparations for different patients possible, and thereby diminishing wastage.

> Dose Banding is an important way of diminishing those losses as well. Certain cancer chemotherapies are now more and more carried out with standardised doses instead of with individual doses. This concept of Dose Banding has been developed in the early 90s in United Kingdom. If standardised doses can be prepared in advance, many advantages occur such as: immediate availability for the patient, diminished workload and occupational exposure for the pharmaceutical staff, possibility of quality control, less wastage of precious products.

22.6.5 Searching Information about Stability and Compatibility for Practice

Stability studies on medicines are often published in pharmaceutical journals. Other sources for stability data could be useful as well, such as the Pharmaceutical Codex [29], Kommentar zur Europäisches Arzneibuch [72] (see Sect. 39.4.8), Martindale [85] (see Sect. 39.2.4), Ophthalmika [86], Connors [15] and Trissel's Stability of Compounded Formulations [70] (see Sect. 39.4.14). Additional information can be found in Analytical and International Pharmaceutical Abstracts. These can be retrieved by the search engine OvidSP [87]. The German collection DAC-NRF [88] (see Sect. 39.4.2) also provides much information on stability.

The stability of parenteral medicines is of great importance for practice, as explained in Sect. 22.6.3. For those dosage forms stability data for numerous medicines have been collected in specialised databases: Trissel's Handbook on injectable drugs [71], the King Guide® to parenteral admixtures [68] and Stabilis® [69], see Sect. 39.2.6. The last one is most explicit about the effect of various factors (solvent, container, light, temperature, concentration, pH, filters) and most reliable as to the quality of the studies it referenced. These databases are a considerable help for the hospital pharmacist but are not the total solution. The user can consider them a tool but should have sufficient background knowledge of the design and applicability of stability studies to make an informed decision about their applicability to the user's particular circumstances. A particular aspect of information about stability of parenteral admixtures is whether or not a distinction between instability and incompatibility has been made. Chemically, if two substances are incompatible in solution they will form a precipitate sooner or later (see Sect. 18.1.6). When the precipitate will form, is difficult to predict. Basing a decision regarding stability on say, 2 h without a precipitation, of two substances, is not justified. See further Sect. 13.8.

Lawrence Trissel has written in the preface of his handbook: "Users of the Handbook information should always keep in mind that the information in the Handbook must be used as a tool and a guide to the research that has been conducted and published. It is not a replacement for thoughtfully considered professional judgement."

The users should particularly compare the differences between the preparation as it was studied and the preparation as it occurs in their daily practice.

As examples:

- Is the same licensed product used to prepare the infusion solution? Are there differences in the excipients? Caution: the same licensed product can have different formulations in time. This is the case with Fluorouracil, which was alkalised with trometamol but is now alkalised with sodium hydroxide, which leads to a different stability profile.
- Is the concentration identical or comparable or are there big differences? A higher concentration can cause precipitation at low temperature.
- Is the same material used for the container? Polyvinyl chloride (PVC) containers can cause sorption of the molecule to the plastic or the leaching of plasticizers. The stability data for non-PVC containers cannot always be used for PVC containers, especially if there are lipophilic excipients in the formulation.
- Is the same solvent used? Differences in pH or in chloride ion concentration can be responsible for large stability differences.

22.7 General Instructions for Storage Times

For each medicine the storage conditions should be indicated, as well as the shelf life and the beyond-use-date after opening. In this section it is explained how storage times are determined in general[1]. Secondly, a system is introduced that can be used especially for pharmacy preparations. Finally storage conditions are dealt with.

22.7.1 Shelf Life and Usage Period

The label of any medicine meant for dispensing should contain an expiry date, stating month and year, and storage conditions (see Sect. 37.3). This applies to licensed medicines as well as pharmacy preparations.

A maximum of 5 years seems to be a sensible maximum shelf life or turn-around time for licensed medicines [89]. For pharmacy preparations the quality of design and of production is less well controlled than in industrial production. For this reason for pharmacy preparations a maximum shelf life of 3 years has become an acceptable limit in many Countries. But for many preparations the shelf life will be less than 3 years, because they are unstable in one way or another.

For industrially manufactured preparations the stability of the product in its (closed) package leads to an expiry date (exp.). This is the date after which the product is not to be used. The product information does not always make clear whether this date still applies after the package has been opened. The indication "do not use later than ..... after opening" would give a decisive answer but is not very common, except for certain categories of medicines (e.g. eye drops).

In a number of preparations the package is of a type that makes storage after opening difficult or impossible (ampoules, infusion bags, single-use vials). For this type of (sterile) unpreserved preparations a Note for Guidance of the CPMP [90] states, that the shelf life after first opening or reconstitution should not exceed 24 h at 2–8 °C. This is an example of a storage period determined by microbiological factors. A longer shelf life is allowed if justified.

However also in many non-sterile medicines discrimination between stability in the intact package and after opening is necessary, because by opening the package, in particular a multidose package, certain conditions will undergo great

[1] This section has been supplied by Suzy Dreijer-van der Glas, Royal Dutch Pharmacists' Association KNMP, The Hague, The Netherlands. e-mail: smdreijer@gmail.com.

change. These are conditions that can strongly influence stability: moist air, day light, oxygen, micro-organisms, evaporation of volatile solvents, etc.

Thus a great deal of pharmacy preparations will have a shelf life after opening that is shorter than in the intact package, for two main reasons. A relatively large part of pharmacy preparations are vulnerable to microbiological contamination, and caution in determining the shelf life is the consequence of the often limited amount of research on this subject.

In assigning shelf lives there are two possible situations:

- Preparations that are chemically stable, but can only be stored for a limited period after opening, for the risk of microbiological contamination or evaporation of volatile solvents, or due to the influence of oxygen, moist air or day light
- Preparations that are not chemically stable, where it does not make any difference for the (short) shelf life whether the package is opened or not

22.7.2 Assignation System for Pharmacy Preparations

In this section a general system is described for the assignment of shelf lives, both for the intact package and after opening. In this system shelf lives are given which apply to specified types of package and storage conditions. The system has been used for about 25 years in Germany and the Netherlands [91, 92]. The section starts with an outline of the logic used followed by the starting points together with a flow chart to decide about maximum storage times for each preparation and situation.

22.7.2.1 Definitions and Labelling

The shelf life of a preparation is usually constructed of two consecutive components: shelf life in the intact package and the usage period after opening of the package. Their definitions are:

Shelf Life of the Intact Package

The maximum shelf life in the intact package is the shelf life of that medicine (in the original intact package) with respect to the chemical, physical and microbiological quality. This shelf life is the same as that which applies to industrially manufactured preparations (time up till the expiration date, the "not to be used after. . ." date.)

Usage Period

The usage period is the time that a medicine, after opening of the package, can be used regarding the chemical, physical and microbiological quality. For an individual patient this applies to the period after opening of a package. It is the time till the in-use date. In some cases these periods will differ from one setting to the other.

The clearest way of indicating the end of a storage period for the patient is an actual date. On ampoules and other small packages there is no room to print or write, for instance, a sentence "Not to be used after. . .". In these situations the term "exp." may be used. If the patient does not open the package immediately after it is dispensed, both a shelf life for the intact package and a storage period after opening are needed on the label. Examples are situations where several packages of the same medicine are delivered to the patient. In those cases the following text can be used: "Do not use later than . . ... after opening, opened at. . .".

Chemical, physical and microbiological factors are explicitly mentioned in the definitions of the storage periods, indicating that therapeutic aspects have not been taken into account. These aspects are no less important, but demand quite different considerations. The active substance will normally be the main factor, and not the dosage form.

Administration Period

The maximum time from start to the end of the administration, especially used with parenteral medicines.

22.7.2.2 Starting Points and Flow Chart

The constructs of shelf life of the intact package and the usage period have been elaborated into concrete starting points:

- The shelf life of a pharmacy preparation is 3 years at maximum.
- Maximum usage periods for patients after opening the package, for medicines in multidose containers, with a standardised formula, are given in Table 22.15. These maximum usage periods are only valid *within* the shelf life of the preparation.
- At the time of dispensing in the pharmacy, the maximum usage period must be sufficient for the duration of the prescribed therapy.
- Medicines with limited stability have a specific shelf life, often distinguished between before and after opening of the package. After passing a renewed quality test, an extended shelf life can be specified.

Table 22.15 Assigned usage periods for dosage forms

Dosage form	Maximum usage period for the patient
Sterile forms	
Bladder irrigation	Do not store
Dusting powder, sterile	24 h
Ear drops for middle ear, preserved	1 month
Eye drops, not preserved	24 h
Eye drops, preserved, at home	1 month
Eye drops, preserved, at the ward	1 week
Eye ointment, anhydrous	1 month
Eye ointment, containing water	1 month
Eye wash, not preserved	24 h
Eye wash, preserved	1 month
Intravesical solution	Do not store
Irrigation, sterile (apart from bladder irrigations)	24 h
Solution for injection, not preserved	24 h
Solution for injection, preserved	1 month, refrigerated
Solution for intravenous infusion	1 week
Solution for nebuliser, not preserved	24 h
Solution for nebuliser, preserved	1 month
Dosage forms without water, not sterile	
Capsules in tablet container	12 months, keep dry
Collodium	6 weeks
Dusting powder	12 months
Ear drops without water	6 months
Ovules, fatty base, not in strip	12 months
Paste, anhydrous, in jar	6 months
Powders for oral use, (un)divided	12 months, keep dry
Suppositories, in strip	12 months
Suppositories, not in strip	12 months
Tablets	24 months, keep dry
Dosage forms containing water, not sterile	
Cream, not preserved, in jar	1 month
Cream, not preserved, in tube	3 months
Cream, preserved, in jar	3 months
Cream, preserved, in tube	12 months
Cutaneous emulsion, not preserved	2 weeks
Cutaneous emulsion, preserved	6 months
Cutaneous solution, not preserved	2 weeks
Cutaneous solution, preserved	6 months
Cutaneous solution, with alcohol >15 % m/m	3 months
Cutaneous suspension with alcohol >15 %	3 months
Cutaneous suspension, not preserved	2 weeks
Cutaneous suspension, preserved	6 months
Dental solution	6 months
Ear drops for external ear	6 months
Enema, not preserved	Do not store
Enema, preserved	Do not store
Gargle, not preserved	2 weeks
Gargle, preserved	6 months
Gel for dental use	3 months
Gel with alcohol >15 % m/m, in tube	3 months
Hydrogel, in jar	1 month
Hydrogel, in tube	3 months
Mouth paste	6 months
Mouth wash, not preserved	2 weeks
Mouth wash, preserved	6 months
Nasal drops, not preserved	2 weeks
Nasal drops, preserved	3 months
Nasal gel, in tube	3 months
Nasal ointment, in tube	6 months
Nasal spray, not preserved	2 weeks
Nasal spray, preserved	3 months
Oral drops, not preserved	2 weeks
Oral drops, preserved	6 months
Oral solution, not preserved	2 weeks
Oral solution, preserved	6 months
Oral suspension, not preserved	2 weeks
Oral suspension, preserved	6 months
Oromucosal solution, preserved	6 months
Ovules, hydrogel base, not in strip	1 month
Paste containing water, in jar	1 month
Shampoo	6 months
Syrup, not preserved	2 weeks
Syrup, preserved	6 months
Vaginal solution, preserved	6 months
Vapour with alcohol >15 % m/m	3 months
W/o cream, not preserved, in jar	1 month
W/o cream, not preserved, in tube	3 months
W/o cream, preserved, in jar	6 months
W/o cream, preserved, in tube	12 months

- Extemporaneous preparations, with unknown or uncertain chemical or physical stability, cannot be kept on stock in the pharmacy. They have a maximum usage period according to Table 22.15, but this period is not more than 1 month for liquid and semisolid preparations, and not more than 6 months for dry forms. If the formula is similar to a standardised one, the maximum shelf life of that standardised formula can be used.
- The length of the administration period depends on the conditions under which the medicine has been reconstituted or adapted for administration (see Sect. 31.3.6).

In Table 22.15 actual usage periods are given for the most popular dosage forms and their containers. Depending on the dosage form, these usage periods may vary between 24 h and 24 months. The flow chart (Fig. 22.3) makes it easier to determine a usage period, depending on the dosage form and the nature of the preparation.

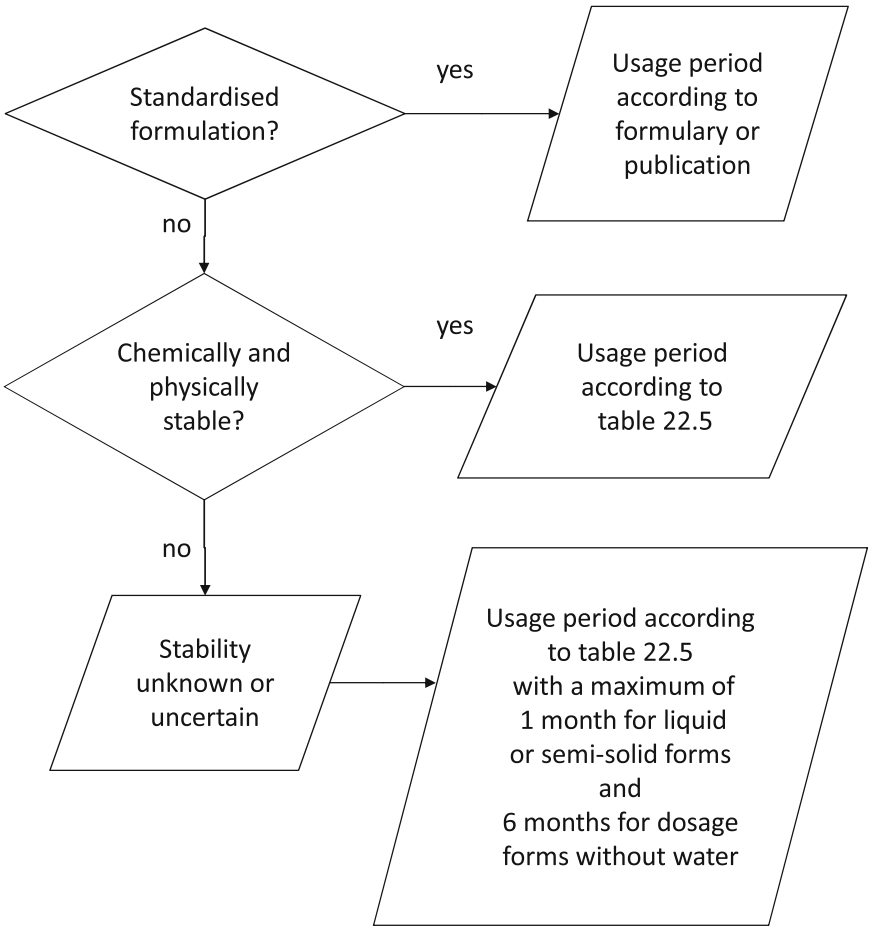

Fig. 22.3 Flow chart for the assignation of usage periods of dosage forms in multidose containers

22.7.2.3 Storage of Semi-Finished Products

Starting materials in pharmacy preparation sometimes are semi-finished products, e.g. cream bases for cutaneous preparations, concentrated solutions of preservatives or triturations of active substances. Usually this type of products will be kept in stock in jars. They may be prepared in the pharmacy, or bought from a wholesaler. These products can be considered as raw materials for a preparation.

In both cases there will be an expiry date on the label for the intact package. But also for these preparations the conditions of storage will change after opening the package, more or less in the same way as discussed above for packages for the patient. Therefore the shelf life of these semi-finished products after opening will often be shorter than that of the intact package. Microbiological factors play an important role, in particular in water containing preparations. In concentrated solutions evaporation of solvent may be the reason for a short usage period. Apart from the time, the number of openings of the stock package may influence the quality of its content.

In general it is recommended to choose the volume of the 'stock jar' in such a way that it only has to be opened about ten times before it is empty. When a semi-finished product is used as the starting material for a stock preparation in the pharmacy, it should be taken from a new package, thus not from a jar that has been opened before. In that case the shelf life of the pharmacy stock preparation will be the same as if it had been prepared from raw materials only.

Usage periods (in the pharmacy) of stock packages for different types of cutaneous bases are given in Table 22.16.

Table 22.16 Usage periods in the pharmacy of Stock packages of cutaneous bases

Type of semi-finished product	Usage period in pharmacy
Ointment bases not containing water	
Bases with mainly paraffins, pastes	3 years
Bases containing wool fat	2 years
Hydrophobic cream bases (w/o bases, not preserved)	3 months
Hydrophilic ointments (macrogol)	3 years
Hydrophilic cream bases (preserved)	6 months (in jar)
	12 months (in tube)
Hydrophilic emulsions (preserved)	6 months
Hydrophilic gels (preserved)	3 months (jar)
	12 months (tube)

The periods given by [93] have been used. In these cases the usage period must lie within the shelf life.

For concentrated solutions or triturations the maximum usage period depends on the type of preparation. For instance, if the solvent is water, the risk of microbiological contamination will play a role. In case of volatile solvents evaporation is the most important factor. When defining maximum usage periods for this kind of preparations, the pharmacist has to keep in mind the factors that influence the storage conditions after opening the stock package.

22.7.3 Storage Temperature

The following labelling statements are required for licensed preparations:

- Store in a freezer (below −15 °C).
- Store in a refrigerator (2–8 °C).
- Store below 25 °C (if necessary with the additional statement: do not refrigerate or freeze).
- Store below 30 °C (if necessary with the additional statement: do not refrigerate or freeze).
- This medicinal product does not require any special temperature storage conditions.

The formerly used "Keep cool" has disappeared from the list. Cold or cool is defined by the Ph. Eur. as: 8–15 °C. A statement like that would not make much sense to the patient any more, as most people do not have the possibility of storage in a cool place. When large quantities of products have to be kept on stock in a pharmacy however, a cool place could be more convenient than a refrigerator. In those cases the pharmacist should decide how long the shelf life can be under these conditions (see Sect. 22.5.7).

The labelling statement "below 25 °C (or 30 °C), do not refrigerate or freeze" may be used for preparations that could show crystallisation at low temperatures, or for preparations that should not be administered when cold.

It should be noted that some clinical trial material now requires storage at −40 °C.

22.8 What Should a Patient Know?

During storage of a medicine changes in appearance may occur, that are noticeable with the naked eye, or the nose or the tongue. Examples are:

- Changes in taste, colour and smell
- Decreasing resuspendability of suspensions
- Changes in viscosity
- Phase separation in emulsions
- Capsules getting sticky
- Solutions turning turbid
- Changes in the disintegration time of tablets
- Microbial growth, resulting in decay

Patients will often notice these changes and return the medicine to the pharmacy. In some cases the changes are such that the medicine cannot be used any more. But sometimes changes in appearance do not mean that the content of the active substance has decreased. Any change in appearance may undermine patients trust in the medicine, which is sufficient reason to consider them unacceptable. If such changes are unavoidable and harmless, it is better to inform and reassure patients in advance.

Patients should also be instructed on the importance of refrigerating some kinds of medicines: maintaining the cold chain, see Sect. 37.5.

References

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Raw Materials

23

Roel Bouwman and Richard Bateman

Contents

Abstract

Raw materials for pharmaceutical preparations are either active substances (or active pharmaceutical ingredients: APIs) or excipients. The choice of excipients and the quality of all raw materials determine the quality of a medicinal product. In addition to purity and content, physical properties such as particle size can influence the manufacturing process and the therapeutic effectiveness. Changes in quality can have unforeseen consequences.

Active substances have to be manufactured according to EU GMP. When manufactured outside the European Union, USA, Japan, Australia or Switzerland, they need a 'written confirmation' from the manufacturing country's authorities that they are manufactured in compliance with the EU-GMP.

Based upon the Chap. 20 Grondstoffen by Roel Bouwman and Suzy Dreijer in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_23,

The general properties of raw materials will be discussed: identity, physical, chemical and microbiological quality, nomenclature, labelling, stability and shelf life. Main excipients and groups are discussed, for their quality properties as well as their applications: solvents such as water, ethanol, glycols, fatty oils, filling agents for capsules and tablets, surfactants, viscosity enhancers, preservatives, antioxidants, complexing agents and herbal raw materials.

Keywords

Active substances • Quality • Excipients • Application • Raw material • Labelling • Pharmacopoeia • FRC • Solvents • Surfactants • Viscosity enhancers • Preservatives • Colouring agents • Herbal

23.1 Label, Identity and Quality

The structural formulas of substances not shown in this chapter, can be found in the monographs of the Ph. Eur. or Clarke's [1] or Florey [2]. Data on excipients and substances that are not included in the Ph. Eur. can be found in references [3–5].

23.1.1 Pharmacopoeial Designation

Each substance in a pharmacy preparation must meet the requirements of the latest edition of the Ph. Eur. For the monograph Pharmaceutical Preparations states: "Active substances and excipients used in the formulation of pharmaceutical preparations comply with the requirements of relevant general monographs."

When a raw material is not described in the Ph. Eur., a raw material may be used with reference to the British Pharmacopoeia (BP), the German Pharmacopoeia (DAB), the Deutsche Arzneimittel Codex (DAC) or, if that is not possible, a recent edition of a well-known non-European Pharmacopoeia, such as the Japanese Pharmacopoeia (JP) or United States Pharmacopoeia (USP). Sometimes an older edition of the European Pharmacopoeia or the other pharmacopoeias may be the sole reference.

In any case, the raw material has to comply with the general monograph Substances for pharmaceutical use of the Ph. Eur.; this monograph applies to all raw materials intended for processing in pharmaceutical preparations, regardless of whether they have a monograph in the Ph. Eur. or not. However the requirements of this monograph on related impurities, residual solvents and microbiological quality are too general as well as too detailed to be implemented in daily practice of pharmacy preparation. For the use of a raw material that is not described in one of the mentioned pharmacopoeias therefore it may be necessary for the preparing pharmacist to take personal responsibility for the use of a raw material, without being able to establish that it fully complies with the monograph Substances for pharmaceutical use. This is acknowledged by a statement in the section Active substances and excipients of the monograph: "Where no specific monographs exist, the required quality must be defined, taking into account the intended use and the involved risk".

Most raw material suppliers indicate the source of the quality specifications on the label. However, it may occur, that despite there being an entry in the Ph. Eur., suppliers, perhaps due to market conditions, will sell substances that meet the requirements of a foreign pharmacopoeia or other standard. Some suppliers may allow the download of a certificate from their website or supply a certificate with each delivery. In other cases it may be necessary to contact the supplier to request the certificate to be sent. Such a certificate should refer to which pharmacopoeia or standard the raw material complies. It should also list the pharmacopoeial analytical data of the raw materials including relevant quantifiable impurities such as bacterial endotoxins. A certificate of analysis is signed, or refers to the authorisation by the quality officer of the supplier.

23.1.2 Sources

Active substances should be manufactured in accordance with the GMP guidelines (part II) [6]. In industry, when using raw materials in a licensed product, the qualified person releasing the final product is also responsible for ensuring that the active substances used are manufactured in accordance with the GMP guidelines. EU-legislation that came into force in July 2013 [7] prescribes that each delivery of an active substance that is manufactured in a country outside the European Union must be accompanied by a declaration of the authorities of that country that the substance is manufactured according to the European GMP (a "written confirmation"). Excluded from this obligation are the 'third countries', that have proven to have a legislative framework for the inspection and enforcement of GMP-compliant production of active substances. So far these countries are: United States, Japan, Australia and Switzerland. The implementation of this system in the quality system of community and hospital pharmacies is problematic. In the (hospital) pharmacy raw materials are bought from wholesalers and for the individual hospital pharmacist it is often difficult to find out the manufacturer of the raw material. Since many raw materials are now manufactured in China or India, monitoring the GMP compliance is very difficult to achieve, so the declaration of the authorities is

Table 23.1 Different Forms of Codeine

Substance	Bruto formula	Molecular mass	1 mg substance = base (mg)
Codeine (pure substance)	$C_{18}H_{21}NO_3$	299.4	1
Codeine. H_2O (Ph. Eur.)	$C_{18}H_{21}NO_3.H_2O$	317.4	0.94
Codeine phosphate.½H_2O (Ph. Eur.)	**$C_{18}H_{24}NO_7P.½H_2O$**	**406.4**	**0.74**
Codeine phosphate. 1½ H_2O (Ph. Eur.)	$C_{18}H_{24}NO_7P.1½H_2O$	424.4	0.71
Codeine HCl.2H_2O (BP)	$C_{18}H_{21}NO_3Cl.2H_2O$	371.9	0.81

indispensable. On occasion it will be necessary to balance, based on a risk assessment, the benefits of providing a product to a patient with the level of assurance of GMP compliance of the raw material. The risk assessment should consider both the clinical consequences of not supplying the product and the degree of knowledge of the manufacture and supply chain of the raw material and its degree of compliance with EU GMP.

An example of what can happen with raw materials that are insufficiently controlled by foreign authorities occurred in China with heparin. The raw material was intentionally adulterated with over-sulfated chondroitin sulfate (OSCS). Heparin injections prepared from this raw material in the United States have led to severe hypersensitivity reactions in patients [8]. The Ph. Eur. monograph has been revised with a test to detect this impurity, on recommendation of the EMA/CHMP assessment report about this topic [9]. In June 2013 the FDA issued a Note for Guidance for Industry about this subject to manufacturers taking steps to ensure that the heparin supply chain is not contaminated with OSCS [10].

23.1.3 Other Designations

Some raw materials such as for clinical research or experimental treatments, are not available by the regular pharmaceutical chains. In such cases, it may be necessary to buy them from wholesalers in chemicals [11]. Such a trader often puts the phrase on the label “not for human use”. The pharmacist himself must, either on the basis of a Pharmacopoeia monograph, or on the basis of his in house quality system, assess whether the raw material is suitable for pharmaceutical application.

The analytical grade designation that is sometimes given to this category of substances is not a formalised quality indication in pharmaceutical meaning, but substances with this quality designation are often sufficiently pure for use in pharmaceutical preparations.

23.1.4 Water Content

Some raw materials are described with different water content. Different Pharmacopoeias may use the same name for raw materials with different water content. This is found between different editions of the subsequent Ph. Eur. The historical changes are described in the introduction of each edition of the Pharmacopoeia under ‘Hydrates’.

For example, if codeine phosphate sesquihydrate, codeine hydrochloride or codeine base is processed instead of codeine phosphate hemihydrate, this leads at standard formulations to a different codeine content. Table 23.1 exemplifies this. Therefore, it is advised to use in preference the form of codeine phosphate hemihydrate, as this is the form that is used in most standard formulations.

In addition to water of crystallisation, where the water molecules are in stoichiometric proportion to the substance, water also appears as adsorbed water, such as in the case of prednisolone disodium phosphate.

23.1.5 Salt-and Ester Forms

Many substances appear either as unconjugated or as salt or ester form. If the substance is a salt or an ester of the substance to be processed, it will be seen from the dosage specified whether or not there is a need for a conversion factor to be applied.

Exchanging a base/acid with the corresponding salt, or an alcohol/acid with an ester almost always has biopharmaceutical, pharmacokinetic or pharmacodynamic consequences of clinical importance. Sometimes these are desirable, but most often they are not. Be guided by the biopharmaceutical information in reference books (such as Martindale [3]) or the composition of the licensed medicine. Some examples:

23.1.5.1 Corticosteroids

The esters of monovalent fatty acids (triamcinolone acetonide) are usually used in cutaneous preparations. Free corticosteroids can usually be administered orally. When a solution in water is needed the esters of a multivalent acid in the salt form (-disodium phosphate, disodium succinate) should be used. This also applies to processing corticosteroids in a lipid based suppository.

23.1.5.2 Excipients

It is also important, with regard to excipients as to what chemical form is used. DL-alfa-Tocopherol acts as antioxidant in an alcohol-water mixture; the esters have no effect.

23.1.5.3 Label Claims

In many cases the labelling of the strength indication is clear, but errors can easily occur. Some examples to illustrate how label claims should be interpreted:

- Garamycin® ampoule: according to the label it contains 10 mg per mL gentamicin base as sulfate. Thus the ampoule contains gentamicin sulfate and the indication of the strength relates to gentamycin ion.
- Erythrocin® -suspension and tablets: according to the label the content is related to erythromycin base.
- 'Ritalin capsules'; when these are to be prepared from methylphenidate hydrochloride it is simple, since the strength of Ritalin® tablets relates to methylphenidate hydrochloride.
- Bethamethason cream: in this case however there is firstly the choice between valerate and dipropionate, each of which represents a different corticosteroid activity class. Then in both cases the desired concentration in relation to the amount of free betamethasone has to be calculated. The strength of the authorised products is specified respectively as valerate or dipropionate.
- Iodinated povidone is a colloidal complex and problems can arise with the content indication of iodinated povidone solution. Betadine® contains 10 % iodinated povidone complex, corresponding to a concentration of approximately 1 % iodine.
- Neomycin: Still more unclear is the issue of the interpretation of label claims with neomycin sulfate. Neomycin sulfate Ph. Eur. is "a mixture of sulfates or substances". The sulfate content may vary between 27 % and 31 % calculated on the dried substance and the water content can be up to 8 %. It is therefore not possible to derive an exact conversion factor when a neomycin preparation is prescribed. In practice no difference is made between prescribing neomycin or neomycin sulfate, as neomycin as such is not available and the dose cannot be based on experience with that substance. So it turns out from the context that there is no need for conversion.

An important point can be the difference in application of certain salts. An example is chlorhexidine digluconate, that is available as 20 % solution (Hibitane®). Chlorhexidine chloride is not water-soluble and is available as dry powder (under the same brand name Hibitane®). If in the doctor's request the brand name is used, it will be seen from the context what salt is intended and, in the case of the gluconate, whether the strength indication relates to the digluconate as such or to the 20 % solution. To complicate the matter even more, a third variant is available, i.e. chlorhexidine acetate that is insoluble in water but soluble in propylene glycol.

23.1.6 International Units

International units are used for the strength indication of raw materials where this is not possible with units of mass. This will be the case, for example, if the raw material consists of a long chain with a varying number of functional groups, if the raw material consists of a mixture of substances with different mass per functional group or if for any other reason the mass is not strictly proportional to the strength of the raw material. Often the content of such substances must be determined with biological methods.

If a substance that is prescribed in international units (IU) needs to be weighed, the amount of substance is calculated with the conversion factor that is listed on the label or in the analytical report. For vitamins A and D the number of international units per gram is standardised. Other well-known examples are polymyxin and vitamin E. Prescribers often continue writing in units, even when, for the relevant active substance, a known chemical content has existed for a long time.

In some cases, the number of international units is indicated per packaging unit, for example, per ampoule of benzylpenicillin sodium. In that case, dilute the contents of the vial to a known volume and take back a calculated volume.

In Table 23.2 are some commonly used raw materials listed with, as far as is known, the equivalent amount of mass per unit.

23.1.7 Microbiological Purity

23.1.7.1 Micro-organisms

For a number of raw materials Ph. Eur. has microbiological quality criteria for Total Aerobic Microbial Count (TAMC) and Total combined Yeast and Mould Count (TYMC) (see Sect. 19.6.3) and for absence of specific micro-organisms (see Sect. 19.6.4). Theoretically it would be logical to apply one requirement for all substances which are used in non-sterile preparations, but the approach should take into account the use of the final product. The General monograph Substances for Pharmaceutical use applies a general recommendation with regards to the microbiological contamination of the raw material and the microbiological requirements for the finished product. This contamination mainly refers to substances of vegetable, animal or mineral origin (see also Table 9.1 in Sect. 19.6.2). Even if such substances are not listed in the pharmacopoeia, it is recommended that microbiological contamination should

Table 23.2 Substances of which the strength is expressed in IU

Substance	1 IU =	1 mg =	Remarks
Bleomycin	0.00067 mg (Ph. Eur.)	1500 U (Ph. Eur.)	Clinical damage has been published [12]
	0.67–0.5 mg (USP)	1.5–2 U (USP)	
Heparin	0.0057 mg	173 IU	Theoretical value
Heparin calcium/sodium Ph. Eur.	For parenteral use: <0.0066 mg	≥150 IU	1. The exact amount of conversion should be mentioned on the label;
			2. Other standards apply for low molecular heparins;
			3. Values apply to dried substance;
			4. The tolerance in comparison to the declaration is 90–111 %;
	Not for parenteral use: <0.0083 mg	≥120 IU	5. IU are not the same as USP units; However, the difference is not clinically relevant [4]
Neomycin sulfate Ph. Eur	<0.00154 mg	≥680 IU	Value applies to dried substance
Nystatin	Not oral: <0.227 microgram	≥4400 IU	Value applies to dried substance
	Oral: <0.20 microgram	≥5000 IU	
Polymixin B	0.1 microgram	10,000 IU	Theoretical value
Polymixin B sulfate	0.12 microgram	8304 IU	Theoretical value
Polymixin B sulfate Ph. Eur, commercially available	<0.167 microgram	≥6000 IU	1. Value applies to dried substance
			2. Ph. Eur. no longer applies IU
Protamin sulfate	0.01 IU heparin	100 IU heparin	1. Theoretical value
			2. Usually, the value is expressed in amount percentage
Vitamin A as all-trans Retinol	0.3 microgram	3333 IU	1. Theoretical values
Vitamin A as all-trans Retinol palmitate	0.55 microgram	1818 IU	2. The format in IU has already been left in 1956
Vitamin A as all-trans Retinol propionate	0.36 microgram	2786 IU	
Vitamin A concentrate synthetic (oily form) Ph. Eur. (Vitaminum A densatum oleosum)	<0.002 mg	≥500 IU	The format in IU has already been left in 1956
Vitamin A concentrate synthetic (powder form) Ph. Eur. (Vitaminum A pulvis)	<0.004 mg	≥250 IU	
Vitamin A concentrate, synthetic, solubilisate/emulsion Ph. Eur. (Vitaminum A in aqua dispergibile)	<0.01 mg	≥100 IU	
Vitamin D as Cholecalciferol (D3) or Ergocalciferol (D2)	25 ng	40,000 IU	Theoretical value
Cholecalciferol concentrate (oily form) Ph. Eur. (Cholecalciferolum densatum oleosum)	<0.002 mg	≥500 IU	
Cholecalciferol concentrate (powder form) Ph. Eur. (Cholecalciferolum densatum pulvis)	<0.01 mg	≥100 IU	
Cholecalciferol concentrate (water-dispersible form) Ph. Eur. (Cholecalciferolum in aqua dispergibile)	<0.01 mg	≥100 IU	
Vitamin E as d-alfa-Tocopherol	0.67 mg	1.49 IU	The format in IU has already been left in 1956
Vitamin E as dl-alfa-Tocopherol	0.91 mg	1.1 IU	
Vitamin E as d-alfa-Tocopheryl acetate	0.74 mg	1.36 IU	
Vitamin E as dl-alfa-Tocopheryl acetate	1.00 mg	1.00 IU	
Vitamin E as d-alfa-Tocopheryl hydrogen succinate	0.83 mg	1.21 IU	
Vitamin E as dl-alfa-Tocopheryl hydrogen succinate	1.12 mg	0.89 IU	
Vitamin E as d-alfa Tocopheryl polyethylenglycole-1000- succinate	2.58 mg	0.39 IU	

be investigated; especially with herbs which can often be heavily contaminated. Examples of substances of which batches with questionable microbiological quality have been found are tragacanth gum, corn starch, kaolin and alginic acid [13].

Since vegetable raw materials with a sufficient microbiological quality are sometimes difficult to obtain, methods to sterilise them have been investigated. Gamma radiation, ethylene oxide or microwaves have been used. Viable organisms are successfully killed but spore-forming

bacteria especially may remain intact when radiation doses are used that do not adversely affect the active substances.

The microbiological quality requirements of water are described in Sect. 23.3.1.

23.1.7.2 Bacterial Endotoxins and Pyrogens

Microbiological contamination of raw materials can lead to a finished product that does not meet the requirements for microbiological purity and in addition a high endotoxin level can be found leading to a pyrogenic response after intravenous injection.

> The terms pyrogens and endotoxins (bacterial) are often used interchangeably. However, the Ph. Eur. makes a clear distinction between them:
> - Pyrogens are substances that cause a febrile reaction.
> - Endotoxins are lipopolysaccharides of the cell wall of gram-negative bacteria that causes fever when injected intravenously.
>
> So not all pyrogens are endotoxins, see Sect. 19.3.4. Endotoxins are however the most common cause of toxic reactions that are attributed to contamination of pharmaceutical products with pyrogens; their pyrogenic activity is much greater than that of most other pyrogenic substances.

For approximately 80 raw materials the Ph. Eur. has set limits for endotoxin levels if they are intended for parenteral dosage forms. These include among others: dextran, sorbitol and mannitol, sodium chloride, trometamol, water for injections.

23.1.7.3 Prions

Raw materials especially of animal origin, or produced using reagents of animal origin, can be infected with prions, some of which are the cause of transmissible spongiform encephalitis (TSE). See Sect. 19.3.1 for information about the nature and pathogenicity of prions. Examples of raw materials that may be infected with prions are gelatin and fatty acids and fats of animal origin: oleic acid, magnesium stearate, glycerol, sorbitane esters, polysorbates and wool fat.

The deactivation of prions, if it can be achieved, requires aggressive interventions on the material, see also Sect. 19.3.1. Therefore it is essential to obtain the raw materials from a supplier that delivers a certificate, certifying that the raw material is free from TSE risk material. One can consult the EDQM site by the material name (through the field *Databases* and the *Certification* button) where manufacturers can display a TSE certificate for the requested substance [14].

23.1.8 Physico-chemical and Functionality-Related Characteristics

The Ph. Eur. monograph Pharmaceutical Preparations states: "When physico-chemical characteristics of active substances and functionality-related characteristics (FRCs) of excipients (e.g. particle-size distribution, viscosity, polymorphism) are critical in relation to their role in the manufacturing process and quality attributes of the pharmaceutical preparation, they must be identified and controlled."

Ph. Eur. contains a monograph on FRCs. The chapter is not mandatory, neither is the FRC-section in specific monographs. But that does not mean that FRCs are unimportant. Especially in pharmaceutical development FRCs determine the design space of a medicinal product. Many excipients are manufactured by industries other than the pharmaceutical industry, so in many cases the excipient manufacturer has little knowledge about the pharmaceutical use of an excipient. Several methods to determine FRCs are described in Ph. Eur. e.g. Particle-size determination, Specific surface area by gas adsorption, Powder flow, Bulk density and tapped density, Wettability of porous solids including powders.

Two FRCs will be dealt in more detail: particle size and viscosity.

23.1.8.1 Particle Size

Particle size is an important physical quality property of raw materials. With regards to particles in this section a distinction is made between firstly loose crystals (primary particles) and secondly agglomerates: coagulated small particles (secondary particles) that have such a strong cohesion that they resist normal dispersion techniques and therefore are not easy to disperse in the production process.

The particle size determines to a large extent the dissolution rate and later in the use of the final product may determine the bioavailability of poorly soluble compounds. The stability of suspensions and the homogeneity of powder mixtures may also be influenced. For a detailed description of the importance and reduction of particle size we refer to Sect. 29.2. If a substance does not have the required degree of fineness for the intended process then it will be necessary to bring it to that degree.

The Ph. Eur. sets requirements for the particle size of raw materials in eye ointments and suspensions for injection. When the particle size is important for a raw material, it is common to display it in micrometres between parentheses after the name of the substance. The Ph. Eur. states in the monograph Sieve test that the fineness of a powder is

Table 23.3 Terminology concerning the degree of fineness of raw materials

Ph. Eur.:	≥95 % m/m smaller than	≤40 % m/m smaller than
Coarse	1,400 μm	355 μm
Moderately fine	355 μm	180 μm
Fine	180 μm	125 μm
Very fine	125 μm	90 μm
In BP [15] additionally:		
Moderately coarse	710 μm	250 μm
Microfine	≥90 % m/m smaller than 45 μm	
Superfine	≥90 % m/m smaller than 10 μm	

expressed by the two sieve numbers, where at least 95 % of the powder passes the higher sieve size and not more than 40 % the lower sieve size (see Table 23.3), unless otherwise prescribed in the monograph. In the case of a single number, the Ph. Eur. means that at least 97 % of the powder passes the sieve size.

The monograph *Sieves* of the Ph. Eur. has a table with sizes and tolerances of a series of 18 sieves. The smallest sieve has (square) holes with sides of 38 μm, the largest holes with sides of 11.2 mm. The result of a sieve analysis is indicated as the percentage by weight of the substance that passes the sieve. Many raw materials are naturally fine (talc, starch) or will be delivered in the required degree of fineness, such as paracetamol (45) and salicylic acid (90).

Highly active substances are in most cases available sufficiently fine. The designation 'micronised' is not standardised, but a very good description is given by Møller [16]: 90 % of the number of particles <5 μm and all <25 μm. In this area of fineness, the given 'particle size' depends strongly on the method of measurement.

The particle size measurement of the raw materials is usually done by the supplier or the manufacturer. For the interpretation of those results it is necessary to know the principles of some methods. In the design phase, during in-process controls and at final testing, it is important to choose the particle size measurement method that is relevant to the property for which the particle size is investigated. Next to the determination of the particle size, a description of the nature of particles (crystals, agglomerates or aggregates) may be recommended.

As with all methods caution must be exercised to take a representative sample, both in terms of sampling location and size, for both the raw material and the product. A good overview of the different sampling methods is available in the literature [16].

With microscopy both the form (crystal, agglomerate) and the dimensions of a particle can be determined. The microscope must be equipped with ocular micrometers. With a normal light microscope dimensions can be determined for crystals or agglomerates of 5 μm to a few 100 μm.

It is possible but not easy to describe semi-quantitatively the particle size of a raw material by a microscopic method [16]. But generally other methods are used for the characterisation of powder fineness like sieving, air permeability or gas adsorption.

Sieving gives a visual check of the size by what passes through the sieve holes, in dry form or suspended in a liquid (wet sieving), under the influence of gravity or possibly using vacuum. The sieving result and its reproducibility not only depends on the particle size but also on the crystalline form, the degree and strength of agglomeration, the shape of the sieve openings, the flow properties, the sieve technique, the duration of the sieving process and the sample size.

In addition to the afore mentioned methods there are still special instrumental techniques applied such as the laser diffraction method for the determination of the particle size and the gas permeability method for the determination of the specific surface of a powder [17]. A further discussion of these methods is beyond the scope of this book. More information is available in textbooks [18].

Some substances are available in several degrees of fineness. The raw material triamcinolone acetonide is available as a micronised powder, to be used if triamcinolone acetonide is dispersed in a base. The micronisation may increase dissolution rate and hence bioavailability. It has, however, a strong agglomeration tendency and therefore cannot be processed as such. The 1 to 10 dispersion with rice starch contains micronised triamcinolone acetonide, whose particles don't agglomerate any more due to the presence of rice starch and it may be preferred for the preparation of creams. Triamcinolone acetonide (crystalline form) as such can be used if it is dissolved in propylene glycol (for ointments) or in ethanol (for ear drops).

To improve the absorption and bioavailability, paracetamol in suppositories is processed as particles < 45 μm. In powders because of the greater density and better flow properties paracetamol (500–90) is used and for solutions either product can be used.

Microcrystalline tetracycline hydrochloride in micronised or microcrystalline form is applied in ointments,

creams and eye ointments, while the coarser ('heavy') tetracycline hydrochloride is applied in capsules because of the greater density and in suspensions because of the greater chemical stability.

Microcrystalline cellulose (Avicel®, Pharmacel®) also exists as many variations of particle size. See Sect. 23.4.1.

Lactose has many variations in terms of particle size as well, each with their specific application in the food industry. The products for pharmaceutical use reflect only a small portion of the total volume of lactose produced by multinational companies worldwide. These multinationals indicate the particle size by using mesh seizes, as is usual in the food industry. The mesh size gives the number of openings per linear inch on a screen, see Table 23.4. Suppliers of pharmaceutical grade lactose usually specify their products based on sieve analyses, so expressing the result in μm.

23.1.8.2 Viscosity

Chemical quality indications are for instance important for cellulose derivatives. The quality depends on the length of the polymer chain and is usually indicated by the viscosity that is achieved in a 2 % solution. An example is hypromellose 4000 mPa.s. This quality is a highly viscous form. A 2 % solution of medium viscous forms of the cellulose derivatives usually have a viscosity of some hundreds and the low viscous quality of 10–100 mPa.s.

Table 23.4 Conversion table suitable for some commonly used lactose types

Mesh size	Approximate size of opening
80	177 μm
100	149 μm
200	74 μm
325	44 μm
400	37 μm
450	32 μm

23.1.9 Mix-Up of Names

If names of substances are similar they can easily lead to mistakes. Well-known examples are: promazine and promethazine, salicylic acid and acetylsalicylic acid, sorbic acid and ascorbic acid, xylocain and xylometazolin, tetracycline and tetracain, Aerosil® and Avicel®, Oleum soya emulgatum and Oleum soya raffinatum etc.

A notorious source of confusion and ambiguity are the phosphates and their different ways of naming. Mistaking one for another in buffer solutions will lead to unexpected pHs. Mistaking the calcium phosphates may lead to wrong strengths in preparations. A short overview of the structural formula, name in Ph. Eur. and much used other names is given in Table 23.5.

New names in the Ph. Eur. also provide for confusion such as the two known forms of Cera lanette N and SX. Cera lanette N is now called Cetostearyl alcohol (type A) emulsifying (Alcohol cetylicus et stearilicus emulsificans A). Cera lanette SX is now called Cetostearyl alcohol (type B) emulsifying (Alcohol cetylicus et stearilicus emulsificans B). The mix-up is easily made with Cetostearylalcohol (Alcohol cetylicus et stearilicus, a mixture of equal parts cetyl-and stearyl alcohol).

Ph. Eur. will change names from time to time. Sometimes it is quite obvious and there is no ambiguity between the old and the new name, just a shift in the alphabetical order (examples are sodium diclofenac which has become diclofenac sodium, ethyl parahydroxybenzoate sodium that has become sodium ethyl parahydroxybenzoate). But sometimes, especially with hydrates (ferrous sulfate is now ferrous sulfate heptahydrate), the substance is a different one and sometimes the name will change completely but the substance remains the same e.g. Glycerol triacetate becomes Triacetin, Chloramine becomes Tosylchloramine sodium.

Differences in numbers and figures in the name can cause confusion. Cetostearyl alcohol (type A) differs from

Table 23.5 Overview of phosphates used in pharmaceutical practice

Structural formula	Name in Ph. Eur	Synonyms
$CaHPO_4$	Calcium hydrogen phosphate anhydrous	Calcium phosphate, dibasic anhydrous
$CaHPO_4.2H_2O$	Calcium hydrogen phosphate dihydrate	Calcium phosphate, dibasic dihydrate
$Ca_3(PO_4)_2$	Calcium phosphate	Calcium phosphate, tribasic
		Calcium orthophosphate
KH_2PO_4	Potassium dihydrogen phosphate	Potassium phosphate, monobasic
K_2HPO_4	Dipotassium phosphate	Dibasic potassium phosphate
$NaH_2PO_4.2H_2O$	Sodium dihydrogen phosphate dihydrate	Sodium phosphate, monobasic
Na_2HPO_4	Disodium phosphate anhydrous	Disodium hydrogen phosphate
$Na_2HPO_4.2H_2O$	Disodium phosphate dihydrate	Sodium phosphate, dibasic (anhydrous, dihydrate, dodecahydrate)
$Na_2HPO_4.12H_2O$	Disodium phosphate dodecahydrate	
$Na_3PO_4.x$H2O	–	Tribasic sodium phosphate

Cetostearyl alcohol (type B) concerning the emulsifier (type A: sodium cetostearyl sulfate; type B: sodium lauryl sulfate). The macrogols are followed by a number, which indicates the average molecular mass of the chain.

Vitamin A (Retinol) and Vitamin A acid (Tretinoin) are different substances and cannot be used instead of each other because they have a different pharmacotherapeutic application. Folic acid (Acidum folicum) and Folinic acid (Acidum folinicum) are closely related substances but differ significantly in effective strength. Tocopherol esters are applied as vitamin E; tocopherol itself is especially applied as antioxidant.

It is necessary to be alert to the existence of different esters or ethers of a substance and different amounts of water of crystallisation. The availability of two or three different forms of a raw material can easily lead to mix-ups. For examples refer to Table 23.1 and to Sect. 23.1.5.

Sometimes the name of a raw material is incomplete and therefore not unambiguous. Polymyxin can be polymyxin B or polymyxin E (colistin). If the designation vitamin D is used, it may be assumed that cholecalciferol, vitamin D3, is meant and not the less effective ergocalciferol, vitamin D2.

23.2 Quality, Stability and Shelf Life

Some raw materials degrade or otherwise lose quality. This may be the result of:

- Hygroscopicity; for example calcium chloride, docusate sodium
- Efflorescence, which is losing crystal water; it occurs especially with sulfates and in particular with zinc sulfate, and with substances with a high crystal water content such as disodium phosphate dodecahydrate
- Oxidation: for example cholecalciferol, ferro compounds, tretinoin, and catecholamines, fatty oils
- Microbiological spoilage: for example water, starch, paracetamol, amphotericin

The purity of the raw material will affect the active substance content of the finished product and requires factorisation. This means: correcting the quantity of a raw material to be weighed for the active substance content deviating from 100 % in the raw material. The content requirements of the finished product and the recommendations concerning factorisation can be found in Sect. 32.4.

The pack sizes of raw materials are often such that the contents will not be used in its entirety, but in parts. Along with the substance's properties, its packing, storage and use determine the shelf life of the raw material in the pharmacy. The shelf life of a raw material is displayed on the package by an expiration date. This applies to the shelf life at the standardised storage conditions for this raw material, in an unopened packaging. If these storage conditions are not maintained in practice, or when the packaging is opened frequently, it is likely that the label claim is no longer applicable for the content. This phenomenon occurs especially in efflorescing or strongly hygroscopic substances and also substances sensitive for oxidation such as fatty oils with many unsaturated fatty acids.

Prednisolone sodium phosphate and dexamethasone sodium phosphate are examples. They always contain a quantity of water and ethanol which is factorised in the standardised worksheets. Both substances can attract more moisture than specified according to the label. In addition, the attracted moisture accelerates the decomposition. For small scale preparation raw materials suppliers sell these substances in small quantities in a well closed container, sometimes filled under a nitrogen atmosphere, in order to remain compliant to the specifications during the listed shelf life. Within a few weeks after opening the container in the pharmacy the substance will no longer meet the specifications as a result of degradation, unless the substance is stored in a desiccator in the fridge. It is therefore recommended to process the whole pack into the final product at one time.

The water content of zinc sulfate.$7H_2O$ can decrease by efflorescence. The water may condense at the top of the container and to the inside of the lid. This water can be reabsorbed by shaking well.

Both forms of calcium chloride ($CaCl_2.6H_2O$ and $CaCl_2.2H_2O$) can attract water by hygroscopicity and subsequently dissolve in the attracted water.

Water is able to evaporate from chlorhexidine digluconate solution 20 %. This may lead to a high content in chlorhexidine creams and mouthwashes. An use-by period of 1 year is therefore recommended for this raw material.

Caution must be exercised with these kinds of substances and they need to be stored properly and not being used if the expiry date is exceeded. The influence of light should not be underestimated. The Ph. Eur. states for many substances, for example tretinoin, phytomenadione, corticosteroids and benzodiazepines that they must be protected against light. In oils and fats oxidation and peroxide formation is increased by light. Sorbic acid in solution (so also in preparations) is sensitive to light.

Proteins is a group of active substances that will be used increasingly in the future. Proteins are large vulnerable molecules with a complex structure. Their many functional

groups render proteins very sensitive to chemical and physical degradation. These can lead to disintegration of the molecule or may cause a change in the tertiary structure. In both cases, the biological activity is lost, see Sect. 18.4.1. The chemical processes that can play a part are: oxidation, hydrolysis, desamidation, disulfide conversion, beta-elimination, racemisation. Physical processes that may occur are: precipitation, adsorption, absorption, aggregation and denaturation. This means, that many factors can influence the stability of proteins. Acidity, oxygen and light are known factors or catalysts of degradation reactions. Temperature plays a part in many of degradation processes. Freeze-thaw cycles may greatly affect the material. In addition, the type of degradation reaction will depend on the temperature.

23.3 Solvents

23.3.1 Water

Various water qualities that are used in the preparation or reconstitution of medicinal products are described in the Ph. Eur. and in an EMA Note for Guidance [19]. See for the overview Table 23.6. The production of water for pharmaceutical purposes is described in Sect. 28.3 and storage and distribution in Sect. 27.5.2.

23.3.1.1 Potable Water

Potable water (Tap water, Aqua, Aqua communis, Water for human consumption) is as such a raw material for purified water in small-scale preparation and it may be used for the early stages of cleaning pharmaceutical equipment. It has the advantage that, if there is a good flow rate through the pipes, in most European countries it usually has a reasonable microbiological quality.

Potable water contains as additives sodium, calcium, magnesium, chloride and carbonate ions and a number of other ions in very low concentrations. The bivalent ions of calcium and magnesium are the cause of hardness in water. The hardness of water is specified as hardness degrees, see Table 23.7.

Hard water will form precipitations of calcium and magnesium salts of the anions that are dissolved in the water. The hardness can be subject to regional differences. The water company should be consulted (or the internet searched) for the hardness of the water it is providing.

Among the trace ions, the heavy metals ions are of particular pharmaceutical interest. For instance copper and lead can occur in potable water, since pipes can be made of these materials. To limit the electrolytic formation of these ions, the pipes are now often made of plastic (PVC) and the earth wire is no longer connected to the water pipe.

The common air gases, carbon dioxide, oxygen, and nitrogen, are also dissolved in water. The dissolved oxygen

Table 23.6 Constituents and impurities which, as a result of the preparation method and storage conditions, may be found in the different types of water

Type of water	Subcategory	Minerals	Heavy metals	Gases	Micro-organisms	Organic substances*
Potable water (tap water)		+	+	+	+	+
Water, purified Ph. Eur. (Aqua purificata) in two forms:	Demineralised water	–	+(−)	+	++	+
Purified water in bulk	Distilled water	–	–	+	+	+
Purified water in containers	Reverse-osmosis water (RO-water)	–	–	+	+	+
Water, highly purified Ph. Eur. (Aqua valde purificata)		–	–	+	–(+)	–
Water for injections Ph. Eur. (Aqua ad iniectabile) (WFI)	Water for injections in bulk	–	–	–	–(+)	–
	Sterilised water for injections	–	–	–	–	–

*incl. pyrogens
+ and – will indicate the presence or absence of the concerned materials

Table 23.7 Water hardness and corresponding calcium salt concentration

mg Ca/L	mg $CaCO_3$/L	English degrees	French degrees	German degrees	Hardness
<30	<75	<5.3	<7.5	<4.2	Very soft
30–50	75–125	5.3–8.8	7.5–12.5	4.2–7.0	Soft
50–100	125–250	8.8–17.5	12.5–25.0	7.0–14.0	Moderately hard
100–150	250–375	17.5–26.3	25.0–37.5	14.0–21.0	Hard
>150	>375	>26.3	>37.5	>21.0	Very hard

may decrease the stability of oxidisable active substances. Carbonic acid will form poorly soluble carbonates with many bivalent positive ions.

Fresh draught potable water meets the following microbiological quality requirements, provided that it flows well through the pipes and that there is no holding tank: not more than 100 micro-organisms per mL, and *Escherichia coli* <1 per 100 mL. In practice the contamination of fresh potable water will not exceed 10 CFU/mL (CFU = colony forming units[1]). This means that fresh draught potable water in microbiological terms is suitable for the manufacture of non-sterile medicinal products; the Ph. Eur. limit for these products being 100 CFU/mL. Do not use hot water from the tap, because it might come from a holding tank; prepare it by cold potable water and heat if necessary.

It is necessary to check occasionally the quality of potable water. Especially in hospital pharmacies one should anticipate the presence of still water, due to the presence of holding tanks. In those circumstances, germ growth will occur such that the limit value of 100 CFU/mL may be exceeded. Pharmacy should have access to water supplied directly from the mains supply. Nevertheless the quality of the water supplied by the water company is not under the control of the pharmacy.

Potable water can be used for the various antibiotic oral mixtures that are reconstituted from the dry granulate.

23.3.1.2 Purified Water

Purified water is water that has been purified from the hardness minerals by one of the methods mentioned by Ph. Eur. Ph. Eur. has two types of Purified Water: Purified Water in bulk and Purified Water in containers. It is used in the pharmacy in several ways: as a raw material for the manufacture of non-sterile medicines, sterile medicines that are not necessarily free of endotoxins, in water baths, as cooling water for steam sterilisers, and sometimes for rinsing glassware or packaging material. For Highly purified water Ph. Eur. the microbiological and endotoxin requirements are the same as for Water for injections.

Chemical Purity

The monograph Water, purified of the Ph. Eur. set limits for total organic carbon (TOC) or oxidisable substances, endotoxins (if intended for dialysis solutions), conductivity and the following ions: nitrates, aluminium (if intended for dialysis solutions) and heavy metals. In addition it is necessary to perform microbiological monitoring during production and storage. For purified water in containers, the Ph.Eur. adds limit tests for acidity or alkalinity, chlorides, sulfates, oxidisable substances (mandatory, no choice of TOC), ammonium, calcium and magnesium, residue on evaporation and microbiological contamination. The Ph. Eur. also requires that the conductivity is measured. At 20 °C the conductivity may not exceed the value of 4.3 microS.cm^{-1}. The measurement may be in-line or off-line. In-line measurement (see Sect. 27.5.2) enables a quick and permanent monitoring of the removal of sufficient minerals. If the water complies with the requirement for the conductivity for Water for Injections (1.1 microS.cm^{-1}) the test for heavy metals does not need be carried out.

Measuring the pH with a pH meter is only possible if the conductivity is increased by the addition of a little potassium chloride. Distilled water has a low pH, which quite often is caused by dissolved carbon dioxide. This is removed during the distillation process but it can re-enter by diffusion. This is a strong acid with a limited solubility. It is partly the cause of distilled water's aggressiveness towards base metals (beware with aluminium). Dissolved gases may also be found in demineralised water since the process is not designed to remove them. neither is the demineralisation process designed to remove heavy metals, so also these can be found.

> Carbon dioxide dissolves mainly in the form of the carbon dioxide monohydrate ($CO_2.H_2O$) which is in equilibrium with carbonic acid (H_2CO_3). The balance, however, lies predominantly to the hydrate side. Insofar as carbonic acid is formed, this is fully split into ions and thus a strong acid. However, it usually behaves as a weak acid because of the natural shift to the hydrate side.

Microbiological Purity

In the monograph for Water, purified a specification for the microbiological quality is included: not more than 100 CFU/mL (TAMC, see Sect. 19.6). This corresponds to the strictest requirement for the microbiological contamination of preparations. In general the requirements for raw materials are stricter than those for the preparations, but not in this case. The absence of *E. coli* is essential, but the starting material (potable water) has been checked already and the growth of these organisms in the systems of water purification is unlikely. For measuring the microbiological quality of water the method (the nutrient medium and the temperature), should be chosen, see Sect. 19.6. The requirement of microbiological purity is to be met at start of production by distillation but if this water is prepared by demineralisation or is kept longer than 24 h after production, then a

[1] Colony Forming Unit = One or more micro-organisms that produce a visible, discrete growth entity on a semisolid, agar-based microbiological medium.

Table 23.8 Guidelines for keeping water for non-sterile medicines

Method of preparation + way of storage:	Storage temperature:	Storage period:
Distillation		
Storage in closed bottle	2–8 °C	2 weeks
Bottle after opening	15–25 °C	24 h
Vessel from which it is tapped	15–25 °C	24 h
Demineralisation plus boiling	15–25 °C	24 h
Demineralisation with membrane filtration	15–25 °C	None: use immediately
Sterile purified water		
Closed bottle	15–25 °C	3 years
Bottle after opening	15–25 °C	24 h
Sterilised water for injections		
Closed bottle, sterilised	2–30 °C	3 years
Bottle after opening	2–30 °C	24 h

microbiological reducing treatment by heating or filtration is necessary.

A test on bacterial endotoxins is also included in the Ph. Eur. because of water for the production of dialysis preparations.

For applications requiring water of high microbiological quality the Ph. Eur. includes the monograph Water, highly purified. The 'requirement' (the pharmacopoeia states an action limit to production) is 10 CFU/100 mL. This requirement corresponds to that of Water for injections; yet Highly Purified Water is considered unacceptable for use as Water for Injections. It can be used when medicinal products administered by nebulisation are required to be sterile and non-pyrogenic and for the final rinse of equipment, containers and closures for sterile products [19]. The Pharmacopoeia lists it as one of the types of water that can be used in gene transfer.

23.3.1.3 Water for Injections

Water for injections is prepared according to the Ph. Eur. by distillation of potable or purified water from a device of neutral glass, quartz or a suitable metal. The device must be fitted with an anti-splashing device to prevent contamination of distilled water with non-distilled water.

Water for injections in bulk must comply with the requirements as formulated for Purified water. It must also be produced free of bacterial endotoxins and stored such that it remains free of them. It can be used for parenteral products and irrigations that are terminally sterilised. Water for injections, sterilised, must meet the requirements of sterility (sterility test) and the bacterial endotoxin content must not exceed 0.25 IU per mL. This is used for parenteral products and irrigations that are not terminally sterilised and for dissolving powders for injection immediately before use.

Purification should therefore only take place in this case by distillation because demineralisation and reverse osmosis, as purification processes, are considered too risky from a microbiological point of view and because of the risk of developing bacterial endotoxins. However, in the Japanese Pharmacopoeia reverse osmosis is now an accepted method and in Europe there are ongoing discussions to accept reverse osmosis after all [20].

When collecting and storing water, the growth of microorganisms and the increase of endotoxins as bacterial waste products must be prevented. That means it is either collected and kept at a temperature higher than approximately 70 °C until it is processed (Water for injections in bulk), or it is sterilised, either directly or after filling into vials or ampoules (Sterilised water for injections, Aqua ad iniectabile sterilisata). See further Sect. 27.5.2.

Purified water can also be purchased. In that case Sterile purified water or Sterilised water for injections is recommended because of the insecure shelf life and usage period of non-sterile water. Table 23.8 provides practical, not official, guidelines for keeping water in small-scale situations without a storage and distribution installation.

A special quality of water is described in addition in the Ph. Eur.: Water for the dilution of concentrated haemodialysis preparations. This monograph is included for information purposes and does not have the same legal force as the other pharmacopoeial monographs. Nephrology associations may have elaborated supplementary guidelines, such as in the UK [21] and ISO13959:2009. See also Sect. 14.5.

Special technical demands are applied to water which is used as cooling water for sterilisation equipment and other devices used in health care.

23.3.2 Ethanol

In pharmacy ethanol is usually used as a solvent and sometimes as a preservative. It can also be used as a disinfectant, mainly in a concentration of 70 % V/V in water. The excess use of alcohol as a cleaning agent has been reduced after it was registered as being mutagenic on inhalation. Although the Occupational Exposure Limit (OEL) of ethanol is rather high in many European countries: about 1,000 mg/m^3 as Time Weighted Average (TWA)-8 h and 1,900 mg/m^3 as TWA-15 min, this level can be easily exceeded in a small room, see Sect. 26.7.2.

The concentration of ethanol in water is still given in volume/volume percentage. When adding *a* mL ethanol to *b* mL of water the final volume of the solution is smaller than the sum of $a + b$. This phenomenon is called contraction. The alcoholimetric tables of the Ph. Eur. provide sufficient information to prepare a variety of concentrations. Next to the described concentrations in Ph. Eur. (absolute and 96 %), ethanol 70 % V/V (62.4 % m/m) is used for preparation purposes.

Ethanol as such is not automatically sterile. 50–70 % V/V ethanol/water is maximally bactericidal. Higher concentrations can cause some micro-organisms to transform into spores, which are able to survive. If the ethanol concentration of a liquid is higher than 15 % (V/V) in combination with a pH lower than 7, or if the concentration is higher than 18 % (V/V) in combination with a pH higher than 7, no preservative needs to be added. These conditions make the liquid self-preserving. Alcohol 96 % V/V can be sterilised by distillation. Filtration by ethanol-resistant membrane filters with pore size 0.2 μm will reduce the number of micro-organisms considerably. Mixtures with sufficient water content can be sterilised by autoclaving. Hydrogen peroxide may be added as a sporicide.

23.3.2.1 Denaturated Ethanol

In most countries excise duty must be paid on pure ethanol. Therefore in some countries alcohol that is intended for external application or disinfection purposes (including disinfection of skin) is usually denaturated: rendered unsuitable for consumption. When denaturated, the duty can (partly) be exempted. The exemption of duty may be bound to licenses stating the amount of ethanol that is bought through the year and the agents used to denaturate.

In Netherlands a usual way of denaturating alcohol is the addition of 5 mL of methylethylketone, 25 mg denatonium benzoate and 2.5 mL of synthetic bergamot oil to 1 L alcohol 96 % V/V. The methylethylketone renders the solution azeotropic thereby making re-distillation of pure ethanol impossible. Denatonium benzoate has an intensely bitter taste, thus creating an unpalatable drink. A similar method of denaturating ethanol with methylethylketone and sometimes addition of a dye occurs in Switzerland, Poland, Norway, and Czech Republic. In Kosovo and Turkey denaturating is not common nor is it carried out in Croatia, where ethanol used in pharmacies is free of tax.

After denaturation the alcohol is of course unfit for use in oral preparations.

The alcohol denatured with methylethylketone cannot be used as a solvent for iodine spirit because methylethylketone, like acetone, will complex with iodine. This complex irritates the eyes of people using it or applying it on the skin.

The addition of 5 % methanol may be considered by authorities to be sufficient to denaturate ethanol. Ethanol denaturated with 5 % methanol is commonly used in cosmetics despite the fact that methanol (and also methylethylketone) is, according to the H-statements (see Sect. 26.3.2) considered to be too toxic when regularly applied to the skin of workers.

23.3.3 Glycols and Glycerol

Glycols are diols (alcohols with two hydroxyl groups). Ethylene glycol has no pharmaceutical application. It is toxic because it strongly binds calcium.

Propylene glycol is a diol (propane-1, 2-diol). It is in use in cutaneous preparations, dissolved in the aqueous phase, as a humectant, to slow down a dehydration process. Other applications are the use as softening agent and as vehicle for ear drops intended for the external auditory meatus (see Sect. 9.5.3).

In mixtures with ethanol and water it is a solvent for active substances with low water solubility such as digoxin, diazepam, barbiturates and phenytoin (see also Sect. 18.1.3). The ratio water - ethanol - propylene glycol (or glycerol) depends on the substance to be dissolved. Propylene glycol concentrations higher than approximately 15 % are self-preserving. Depending on the formulation of the preparation, concentrations from 13 % may be sufficient for preservation. Mixtures with water can be sterilised by steam sterilisation. Propylene glycol is toxic in (chronic) oral use by children and patients with poor renal function [22].

In 1937 the Elixir Sulfanilamide disaster occurred, one of the most consequential mass poisonings of the twentieth century. This tragedy occurred when propylene glycol was used as the diluent in the formulation of Elixir Sulfanilamide. More than 100 patients died. At that moment premarketing toxicity testing was not required. In reaction to this calamity, the U.S. Congress passed the 1938 Federal Food, Drug and Cosmetic Act, which required proof of safety before the release of a new drug [23]. The FDA was established.

Glycerol is a triol (propane-1,2,3-triol) and very hygroscopic. Glycerol 85 % is less hygroscopic and thus less perishable. The applications are similar to those of propylene glycol. When used in oral liquid preparations the taste is slightly sweet and better than that of propylene glycol. Glycerol is more hydrophilic than propylene glycol; self-preserving concentration is higher than approximately 30 %, so significantly higher than that of propylene glycol. Glycerol/water mixtures are sterilised by steam sterilisation.

23.3.4 Macrogols

Macrogol (polyethylene glycol, PEG) is a polymer of ethylene oxide, see Fig. 23.1.

The chain length and the molecular mass depend on the polymerisation degree n. Macrogol 400 has a molecular mass of 400 in a polymerisation degree n = 8. Below a molecular mass of 700 the macrogols are liquid, above 1000 they are solid. Macrogols are used as a basis for hydrophilic ointments (Sect. 12.7.8) and as water-soluble suppository bases (Sect. 11.4.5). During storage macrogols can be slightly oxidised by oxygen from the air. For that reason they are incompatible with oxidisable active substances, especially if those are applied in low concentrations (e.g. ergotamine).

Macrogols with a low degree of polymerisation(<2000) are hygroscopic [5].

Fig. 23.1 The formula of macrogol

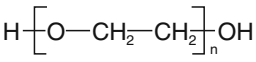


Table 23.9 Some commonly used fats and oils

Vegetable, unsaturated, liquid	Almond oil
	Arachis oil
	Olive oil
	Rapeseed oil
	Sesame oil
	Soya-bean oil
Vegetable, unsaturated, solid	Cocoa butter
Animal, saturated,[a] solid	Lard
Synthetic, saturated, liquid	Triglycerides, medium chain (Miglyol 812®)
Synthetic, saturated, solid	Hard fat

[a]Read the concept of saturated as saturated or nearly saturated

23.3.5 Fatty Oils, Fat, Waxes and Paraffin Waxes

Oils and fats are triglycerides (esters of glycerol with three fatty acids, mainly palmitic acid, stearic acid and oleic acid). The melting point and consistency decrease with decreasing degree of saturation and increase with larger chain length. The melting point of a saturated substance is higher than that of the corresponding unsaturated substance.

Esterification of glycerol with saturated short chain fatty acids and unsaturated short-and medium chain fatty acids usually results in (at room temperature) liquid oils; longer fatty acids give hard fats. Table 23.9 shows several examples of natural and synthetic oils and fats.

Rapeseed oil and sesame oil, given their sensitising properties, are no longer applied in cutaneous preparations. They can cause contact allergy. Groundnut oil is made from peanuts and may cause, when in non-purified form, peanut-allergy. When using the purified, pharmaceutical form, allergic reactions will not occur [24].

Hard Fat consists of a mixture of mono-, di- and triglycerides. It is used as a lipid suppository base. More information can be found in Sect. 11.4.4.

Ph. Eur. contains assays, for acid, hydroxyl, iodine and peroxide values, to determine the qualities of oils and fats.

The acid value is a measure of the amount of free fatty acids in the fat. An appropriate acid number, so a correct amount of free fatty acids, of groundnut oil is important in the preparation of Zinc oxide calcium hydroxide weak paste FNA (see Table 12.39). The

(continued)

ideal is 0.25–0.5. If the acid value is low (e.g. 0.06, for a just opened package) then free oleic acid must be added. At too high an acid number the emulsion breaks.

The hydroxyl value is a measure of the number of acylable places and thus the content of mono-and diglycerides. A suppository base (Hard fat) with a low hydroxyl value (<15) is less damaging to the stability of acetylsalicylic acid and ergotamine tartrate than bases with a higher hydroxyl value. Witepsol H15 has a sufficiently low hydroxyl value (5–15) for this preparation. Bases with a high hydroxyl value (up to 50) have a better emulsifying ability and can include aqueous systems in the form of a water-in-oil-emulsion.

The iodine value is a measure of the number of double bonds. For Hard fat the Ph. Eur. requires a value $\leq$ 3.0.

The peroxide value is a measure of the number of peroxide bridges in the fat. Fats or oils with a low peroxide number ($\leq$0.5) are used for the processing of easily oxidisable substances. Examples are ergotamine tartrate and chlorpromazine hydrochloride in fatty suppositories.

The saponification value is a measure of the number of available saponifiable ester bonds. Also the unsaponifiable matter may still be used as a property.

For each fatty oil or fat the requirements are specified in the relevant monograph.

Unsaturated fats (high iodine value: >4) are sensitive to oxidation by peroxides; becoming rancid. Adding antioxidants (radical scavengers, examples: butylhydroxyanisole and butyl hydroxytoluene, see Sect. 23.9) will prevent this.

In addition to long chain triglycerides, liquid medium chain triglycerides may also be used. These are available under the brand name Miglyol®, of which the most important are Miglyol 810 and 812. They differ slightly in composition and viscosity. Miglyol 812 (Medium chain triglycerides, Triglycerida media saturata Ph.Eur.) is added to Hard fat in zinc oxide suppositories (see Table 23.10) to obtain a suppository that melts as soon as it is inserted, creating a soothing layer for haemorrhoids. This liquid fat can also be used for the preparation of oily injections, for cutaneous and for oral preparations.

Table 23.10 Zinc Oxide Suppositories 10 % [25]

For a suppository mold of any volume	
Zinc oxide (90)	10 g
Triglycerides, medium chain (Myglyol 812)	20 g
Hard fat	70 g
Total	100 g

Waxes are esters of higher fatty acids and fatty alcohols. Pharmaceutically important examples are the liquid Decyl oleate (unsaturated; Cetiol V®), the semisolid Wool fat (Adeps lanae) and the solids Yellow wax (Cera flava), Bees wax, white (Cera alba, white wax) and Cetyl palmitate (Cetaceum). The solid waxes are mainly used to increase the consistency of semisolid skin preparations (see Sect. 12.5.2). Waxy liquid compounds are ethyl oleate, isopropyl myristate and benzyl benzoate. In the first two cases the fatty acid is esterified with a short-chain alcohol.

Decyl oleate is used as lipid phase in hydrophilic cream bases (see Sect. 12.7.7).

Wool fat (Adeps lanae; this is a wax and not a fat) is used in ointments and in eye ointments and increases the penetration ability of lipophilic ointments. A drawback is the chance of contact allergy. Due to the presence of free surface active lanolin alcohols Wool fat has a greater power to absorb water than the other waxes. Lanolin (Adeps lanae cum aqua) is an emulsion of 25 %water in 75 % Wool fat.

Cetyl palmitate (Cetaceum) is no longer used because of the endangered status of the sperm whale from which it originates. There is a little used synthetic variant on the market. It consists of a mixture of cetylesters with fatty acids in the order size C_{14} to C_{18}.

Paraffin waxes are hydrocarbons with short ($<C_{15}$) and long ($>C_{15}$) carbon chains. In pharmacy preparation the solid (Hard paraffin), liquid (Liquid paraffin and Light liquid paraffin) and soft type (White soft paraffin and Yellow soft paraffin) are used. They have a role in cutaneous preparations (see Sects. 12.7.9, 12.7.12, and 12.7.13) and eye ointments (see Sect. 10.7.3).

The liquid paraffin waxes are distinguished by viscosity. Liquid paraffin has a viscosity between 110 and 230 mPa.s, Light liquid paraffin between 25 and 80 mPa.s. In small-scale preparation liquid paraffin is mainly used.

Soft paraffin behaves rheologically as a gel (plastic). In a physical sense it is described as a colloidal system (hydrocarbon gel) of long chains colloidally dispersed in shorter chains.

Oil for injections originates from olive oil, sesame oil or another suitable oil. The oil must be acid-free, dry and sterile. To achieve this, in the past, the olive oil was shaken with magnesium oxide and water (binding of the free fatty acids) and then filtered and dried on anhydrous sodium sulfate. The

current commercially available oil is sufficiently acid-free and dry. The general monograph Vegetable fatty oils Ph. Eur. states that vegetable oils may be used only in parenteral preparations when they are alkali purified (no physical purification). The oil can be sterilised by dry heating or by filtration. Ethyl oleate and some other liquid waxy compounds are also in use as a solvent for oil-based injections.

23.3.6 Acetem

Acetem (E472a) is a mixture of acetylated monoglycerides of fatty acids, an oily substance, which is mainly used in the food industry. Acetem is allowed in food, also for babies, and there is no restriction on the daily intake [26] Acetem can be used as a solvent for non-water soluble substances in oral preparations if ethanol or propylene glycol is not advisable (for example, in case of paediatric use). For phenobarbital in a liquid oral dosage form, acetem seems an option. In Netherlands acetem is used for dissolving phenobarbital in a liquid oral dosage form for children (see Table 5.7), as an alternative to an alkaline solution, an alcoholic solution or a suspension in water. Be aware of huge pharmaceutical availability differences and hence unexpected pharmacodynamic effects of active substances dissolved in acetem, compared with their suspension in water. Acetem is incompatible with PVC, so it cannot be used with feeding tubes.

Acetem is available under the brand name Myvacet. There are two qualities, Myvacet 9–08 and 9–45, both of which are useful. Myvacet 9–08 has a lower solidification point, which in practice can be helpful. A disadvantage is that the substance is not explicitly described in any pharmacopoeia, which makes quality control difficult. There is only a fairly general monograph Mono-and diglycerides in the USP/NF [27]. Another drawback is the unpleasant taste.

23.4 Filling and Disintegration Agents

Filling agents are inert substances to be added to increase the mass of solid and semisolid preparations. Disintegration agents promote the disintegration of tablets and capsules.

23.4.1 Starch and Microcrystalline Cellulose

Starch (Amylum) and cellulose are polysaccharides. Starch consists of amylose, chains of glucose units: –1,4-α-glucosidic connected, long unbranched chains with a polymerisation degree of 800–3000, and of amylopectin: 1,4-α-glucosidic connected chains branched with 1,6-α-sidechains. There are starches of different origins with different particle sizes and other properties. The Ph. Eur. lists (in descending order of fineness): Rice starch (Oryzae amylum), Corn starch (Maydis amylum), Wheat starch (Tritici amylum) and Potato starch (Solani amylum). In the monographs many other characteristics, for example the grain sizes, are described. Starch is used as a filling agent for capsules and tablets, as a disintegration agent in tablets and as a moisture-absorbent ingredient in cutaneous pastes. Wheat starch can contain gluten, which makes the medicines unsuitable for coeliac patients (who are prescribed a strict gluten-free diet). For this reason, corn starch is favourite for processing in solid oral dosage forms.

Sodium starch glycolate (Carboxymethylamylum natricum) is the sodium salt of the carboxymethylether of potato starch. The Ph. Eur. describes three variants: type A and B contain 2.8–4.2 % sodium and type C 2.8–5.0 % sodium. In small-scale preparation the A type is mainly used (trade name Primojel®). The starches are used as filling agents and as disintegration agents. Sodium starch glycollate variants are, in a concentration of 2–8 %, almost exclusively used as disintegration agent.

Cellulose is beta-glucosidic polymerised glucose with a polymerisation degree of approximately 3000, see Fig. 23.2. Microcrystalline cellulose is crystalline, partially depolymerised cellulose. It is available in different qualities with particle sizes ranging between 20 and 200 µm. The most suitable quality for the production of tablets, capsules and powders has an average particle size of 100 µm and is available under various brand names including Pharmacel 102® and Avicel PH102®. It is a chemically inert substance, has reasonably favourable flow properties and is almost insoluble. The particle size of 100 µm corresponds to that

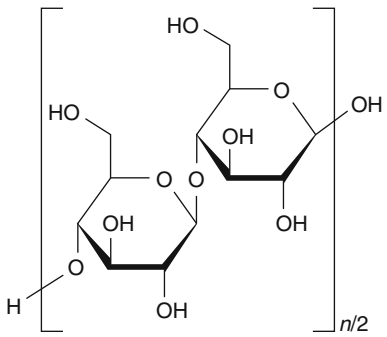


Fig. 23.2 The formula of cellulose, powdered

of many active substances being processed, which promotes good and stable mixing.

23.4.2 Polyols

The most important polyols used in the small-scale preparation are the hexoles sorbitol and mannitol, (see Figs. 23.3 and 23.4). They are obtained by reduction of the corresponding keto- or aldomonosaccharides with corresponding steric configuration. They have a sweet taste.

The absorption of polyols is slow and incomplete. High doses, administered orally, therefore have a laxative effect. They find an application as oral laxatives. The use of more than 20 g per day for adults is undesirable unless an osmotic laxative effect is required.

Besides the use as filling agents and laxatives the hexoles are used as humectants (e.g. sorbitol in creams), for taste correction (e.g. sorbitol in oral liquids), to get iso-osmotic solutions (e.g., mannitol in eyewashes, see Sect. 10.6.2), as diuretics in parenterals and as a cake stabilising agent in freeze drying.

The Ph. Eur. describes two qualities of the 70 % solution of sorbitol: Sorbitol, liquid (crystallisable) and Sorbitol, liquid (non-cristallisable). The solution is supersaturated (see Sect. 18.1.6). The crystallisable solution has the disadvantage that during storage sorbitol may crystallise. The non-crystallisable solution has a higher percentage of allowed impurities. Therefore the crystallisable form is preferable for pharmaceutical preparations. The solution can only be used after any crystals have been redissolved by gentle heating.

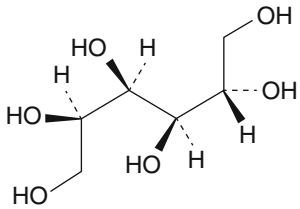


Fig. 23.3 The formula of sorbitol

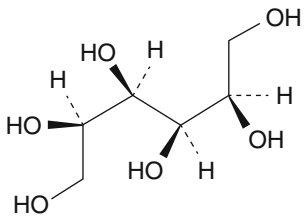


Fig. 23.4 The formula of mannitol

23.4.3 Calcium Hydrogen Phosphate Dihydrate

Calcium hydrogen phosphate dihydrate is a neutral and water-insoluble substance, which in its non-ground form is used as filling and binding agent for directly compressed tablets. It is available under the proprietary names Emcompress and Di-Cafos DC92. It is also known as 'heavy' calcium hydrogen phosphate dihydrate. It is, in case where the more universal filling agents cannot be used, also used as filling agent for capsules. Capsules containing calcium hydrogen phosphate dihydrate do not disintegrate spontaneously, despite the hydrophilic character of the substance, so the addition of a disintegration agent is necessary. This is contrary to capsules containing microcrystalline cellulose, lactose or mannitol as a diluent that disintegrate easily. The Dutch Formulary FNA uses a Primojel capsule diluent for processing corticosteroids (see Sect. 4.4.3). This diluent contains, in addition to calcium hydrogen phosphate dihydrate, sodium starch glycolate A (Primojel®) as disintegration agent and colloidal anhydrous silica as lubricant, see Table 23.11.

23.4.4 Sugars

In the group of the sugars mainly lactose and sucrose are used as filling agents. Both are disaccharides, respectively galactose-glucose and glucose-fructose. Lactose is much less sweet and less hygroscopic than sucrose. These sugars are soluble and lactose is used as filling agent in powders, tablets and capsules. If suppositories contain less than 50 mg active substance, then 100 mg lactose monohydrate (180) will also be added to improve processing. Sucrose is especially used to correct the taste, in oral mixtures for instance as sugar syrup, and in chewable tablets. For the latter xylitol can also be used. It has a sweetness value comparable with sucrose but it does not cause a pH dip in the mouth.

When using an effective mixer sugars can be dissolved in water without heat. Dissolving by heating is faster and has the advantage that the vegetative micro-organisms, which may be present in the raw materials, may be killed. Constantly stirring during heating prevents local overheating, and thus yellow discolouration (caramellisation) [29].

Table 23.11 Primojel Capsule Diluent [28]

Calcium hydrogen phosphate dihydrate, heavy[a]	94 g
Silica, colloidal, anhydrous compressed	1 g
Sodium starch glycolate (type A),[b] compressed	5 g
Total	100 g

[a]Di-Cafos® DC 92-14
[b]Primojel®

Sucrose in solution is converted by hydrolysis into the reducing sugars fructose and glucose (inversion). There are several reasons to set a limit to the degree of inversion of sugar syrup. The most important seems to be the formation of these reducing sugars which have an aldehyde group and are thereby much more reactive than sucrose. Because sugar syrup is mainly used as part of other preparations this reducing activity can be a problem. However if a high concentration of glucose and fructose is required just because of their reducing properties, then invert sugar syrup or glucose syrup, with known levels of fructose and glucose may be used intentionally.

The inversion may also reduce the syrup's ability to inhibit the growth of micro-organisms due to the decrease of the sucrose content. This is controversial as sugar syrup inhibits growth due to the high osmotic value, which increases due to inversion. Micro-organisms that are able to survive under these circumstances can generally use both sucrose and glucose or fructose as carbon source. The inversion will also reduce the sweetness of the product.

Fast heating and cooling limits the inversion. Research has shown that in the preparation of 500 g Sugar syrup, heating caused no additional inversion. Heating at 100 °C for 1 h caused about 1 % inversion. Decreasing the pH, for example by carbonic acid in using water that has been boiled for too short a time, accelerates inversion.

Lactose occurs in several forms: alfa-lactose monohydrate Ph. Eur., (see Fig. 23.5) and water free beta-lactose (Lactose anhydrous Ph. Eur.). In small-scale preparation only alfa-lactose monohydrate is used. This is usually called just lactose or lactose monohydrate. It is available in different qualities (sieved, milled, spray dried) and in a variety of particle sizes. For most small-scale pharmacy preparations, lactose monohydrate (180) is used. Lactose is functioning as a filler and binder in tableting applications; the applied process (wet granulation, dry granulation, direct compressing) may require a choice for more specialised grades. In formulation of dry powder inhaler preparations very specific lactose products are used as a carrier for the active substance.

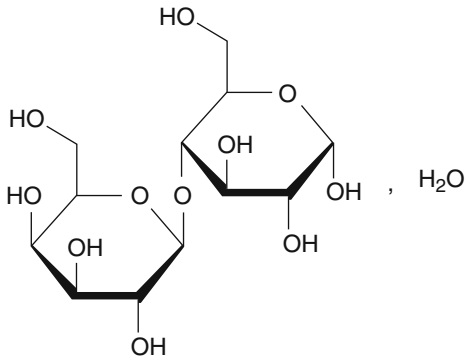


Fig. 23.5 The formula of alfa-lactose monohydrate

Lactose for pharmaceutical preparations is supplied by, for instance, Meggle and DFE Pharma. The website of both firms provide extensive decision trees for helping you to choose the optimal form of lactose (sieved, milled, spray dried, anhydrous) for your application. In some countries the original substance may be supplied by brokers, whereas you have to ask for the source of it.

Aldehyde-sugars (glucose) and derived disaccharides of it (lactose) in solid form are, in contrast to the keto-sugars (fructose), incompatible with strongly alkaline compounds and primary amines (ethylenediamine). A brown discolouration (caramellisation) takes place. In the case of primary amines is this called the Maillard reaction. In mixtures of solid (anhydrous) substances these reactions proceed very slowly and they occur only on the surface of the sugar particle. Thus they may be irrelevant in practice. However, because of this incompatibility the WHO formulation for the oral rehydration salts prescribes anhydrous glucose, which moreover is not combined with sodium bicarbonate but with sodium citrate. It is preferable not to use lactose in capsules with primary aliphatic amines. A more recently reported Maillard reaction is that between lactose and fluoxetine [30].

In solutions (intravenous solutions) the yellow discolouration is more manifest. An intermediate in the reaction is a furan derivate (5-hydroxymethylfurfural) that is toxic (see Sect. 13.6.4). In glucose containing intravenous solutions the Pharmacopoeia specifies a limit test for this impurity.

23.4.4.1 Syrups

Syrups are mentioned in Ph. Eur. as a dosage form, but in this book they are considered a raw material.

Syrups are a very commonly used form of sugars. They contain approximately 45–65 % of sugar, water and a preservative. Sometimes a flavouring is added. The preservative is most often methyl parahydroxybenzoate 0.1–0.15 %. Syrups can be very useful for improving the taste of oral liquid preparations and sometimes they can be used to stabilise a solubilisate of oil and polysorbate, e.g. in a vitamin A micellar solution (Table 23.12).

Table 23.12 Vitamin A Oral Aqueous Solution[a] 50,000 IU/mL [31]

Vitamin A concentrate (oily form), synthetic 1,000,000 IU/g	5 g
Citric acid monohydrate	0.24 g
Polysorbate 80	12.5 g
Potassium sorbate	0.3 g
Star anise oil	0.22 g
Syrup BP	12.5 g
Water, purified	73 g
Total	104 g (= 100 mL)

[a]This solution is actually a solubilisate

This stabilising effect is achieved by the following preparation method:

- Dissolve while heating potassium sorbate in 50 mL purified water and citric acid in 15 mL purified water.
- Cover the inside of the mortar or bottle with polysorbate 80.
- Mix vitamin A and anise oil with the polysorbate 80.
- Solubilise the vitamin A mixture by mixing with sugar syrup.
- Mix this mixture with potassium sorbate solution in one go and with the citric acid solution in parts.
- Add purified water and mix again.

When a syrup is used in a formulation, it must be taken into account that syrups already contain a quantity of methyl parahydroxybenzoate.

Syrups can be prepared by dissolving sucrose and methyl parahydroxybenzoate in purified water with heating (but mind inversion) but they are usually bought as such, as an intermediate.

23.5 Lubricants

Colloidal anhydrous silica (colloidal silicon oxide) and magnesium stearate are used as lubricants in the preparation of capsules, tablets and powders (see Sect. 4.4.3). Addition of lubricants in the preparation of capsules, powders and tablets usually leads to a smoother fill of the capsules, or the moulds. An additional advantage is the reduction of the losses as a result of the elimination of the static charge of the powder mixture.

In the preparation of powders and capsules colloidal anhydrous silica (Aerosil®) is used as lubricant. There is a water containing and an anhydrous type Aerosil. There is discussion about the possibility that Aerosil causes silicosis. The occupational disease silicosis is as a result of long-term inhalation of siliceous dust. But in [5] it is concluded: "Inhalation of colloidal silicon dioxide dust may cause irritation to the respiratory tract but it is not associated with fibrosis of the lungs (silicosis), which can occur upon exposure to crystalline silica" [5]. The main issue appears to be whether the silica is crystalline or not. Colloidal anhydrous silica Ph. Eur. is however amorphous. The irritation of the throat, eyes etc. is an issue though and because of lesser dust generation at weighing and processing the 'pressed' anhydrous form (Aerosil 200 V®) is preferred.

Magnesium stearate can adversely affect the disintegration time and dissolution rate and should therefore be used only if these properties can be checked.

Lubricants can counteract the formation of agglomerates of small particles and disperse pre-existing agglomerates. Colloidal anhydrous silica is added for this purpose in the preparation of suppositories (see Sect. 11.4.6) and in the preparation of oral suspensions (see Sect. 5.4.6).

23.6 Surfactants

Surfactants is the name given to those substances whose surface activity is the main reason for their use. Surfactants (see also Sect. 18.3) are used to stabilise emulsions and suspensions, as wetting agents (see Sect. 5.4.6) as micelle makers for the preparation of solubilisatesons (see Sect. 5.5.6 and Table 23.12) and to influence the flocculation- and deflocculation behaviour of dispersed systems (see Sect. 18.4.2.2). Orally they can only be used in small quantities or low concentrations because of their irritating properties and bad taste.

Many other excipients and active substances that are mainly used for another purpose, also exhibit surface activity. Examples can be found in the group of viscosity enhancing substances (see Sect. 23.7). In particular the low viscous methylcellulose is used for this purpose. Examples of active substances that have surface activity are the tricyclic antihistaminics and antidepressants, and the local anaesthetics (e.g. lidocaine).

Another term for surfactants is emulsifiers. This designation is functional but has a limited distinctive character. Viscosity enhancing substances, which also stabilise emulsions and suspensions (see Sect. 18.4) are also associated with this term. The preferred name in this book is the physical qualities characterising 'surfactants'.

The next sections deal with four types of surfactants: anionic-active, cationic-active, amphoteric and non-ionic. More information on surfactants is to be found in Sect. 18.3, in Martindale and other literature [3, 4, 32]. Table 23.13 gives an overview of the main surfactants that are used in small-scale preparation.

Table 23.13 Main surfactants

Type of surfactant	Subtype	Substances used in pharmacy preparations
Anionic-active substances	Alkali and amine soaps	Sodium stearate
		Ammonium oleate
		Triethanole amine stearate
		Trometamol stearate
	Earth alkali soaps (w/o)	Calcium oleate
		Magnesium stearate
	Alkyl sulfates (o/w)	Sodium lauryl sulfate
		Sodium cetostearyl sulfate
	Alkyl sulfonates (w/o)	Sodium dioctyl sulfosuccinate
Cationic-active substances	Quaternairy ammonium salts	Benzalkonium chloride
		Cetrimonium bromide
Amphoteric substances	Betain compounds	–
	Phospholipids	Lecithin
Non-ionic substances	Higher alcohols	Cetylalcohol
		Stearylalcohol
		Cetostearylalcohol
		Cholesterol
	Esters of fatty acids (w/o)	Glycerol monostearate (monostearin)
		Glycerol mono oleate (monolein)
		Sorbitan mono oleate (Span 80)
		Triglycerol diisostearate
	Macrogol fatty alcohol ethers (o/w)	Cetomacrogol 1,000
	Macrogole sorbitan ethers (o/w)	Polysorbate 20 (Tween 20)
		Polysorbate 80 (Tween 80)
	Aliphatic aromatic macrogol ethers (o/w)	Nonoxynol-9
		Octoxynol-9
	Poloxamers	–

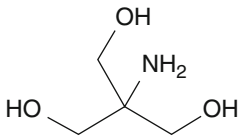
23.6.1 Anionic-active Substances

The main anionic-active components are the alkali, earth alkali, ammonium and amine salts of fatty acids, and the sulfated and sulfonated components. The first four types are also called soaps. Soaps are created by alkaline hydrolysis of natural fats and oils (saponification). This results in producing palmitic, stearic and oleic acid as fatty acids and sodium (hard soap) and potassium (soft soap) as alkali-ions.

The univalent alkali-, ammonium- and amine soaps dissociate completely in water and are therefore predominantly hydrophilic. As a result they create oil-in-water (o/w-, high HLB-) systems (HLB = hydrophilic lipophilic-balance, see Sect. 18.3.1). The bivalent earth alkali- or polyvalent metal soaps dissociate little in water and are therefore predominantly lipophilic. The earth alkali soaps form water-in-oil (w/o-, low HLB-) systems, see Sect. 18.4.3. and [4].

Trometamol and tri-ethanolamine stearate are amine soaps, formed from stearic acid and separately added tri-ethanolamine or trometamol (see Fig. 23.6). The use of amines is often avoided because of the association with nitrosamine creation [33, 34]. Primary amines are however not associated with nitrosamine creation. Secondary amines can create nitrosamines, as can tertiary amines as they always contain a small amount of secondary amines. For most preparations in which amine soaps are used they can be substituted. Experts don't consider substitution relevant for administration routes other than the oral one [35].

Fig. 23.6 The formula of trometamol

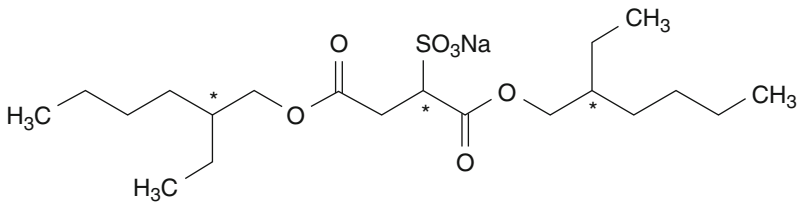


Anionic-active substances are incompatible with strong acids (pH $\leq$ 4) because the hydrophilicity of the acid group will decrease due to lower dissociation. There is also the risk of insoluble ion pairs when anionic-active substances are combined with cationic-active ones such as neomycin sulfate.

23.6.1.1 Examples with Anionic-active Substances

In the Zinc oxide calcium hydroxide weak paste FNA (see Table 12.39) a calcium soap and a zinc soap is created from

Fig. 23.7 The formula of docusate sodium



lime water and zinc oxide and the free fatty acids in the oil used. By these soaps the (lime) water is emulsified in the oil to create a cream.

Sodium cetostearylsulfate and sodium lauryl sulfate forms, both in a concentration of 10 % with 90 % cetostearyl alcohol the so-called self-emulsifying waxes Alcohol cetylicus et stearylicus emulsificans A and Alcohol cetylicus et stearylicus emulsificans B (see Sect. 12.5.4). Both are emulsifying agents in which the excess of cetostearylalcohol is also the lipophilic phase. There are many other representatives of this group with industrial applications.

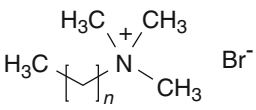
The sulfonates possess, as the reactive part, a sulfone group. Also this group of substances has many examples with industrial applications.

Docusate sodium (Sodium dioctyl sulfosuccinate, see Fig. 23.7) is used as laxative in a 0.1 % concentration.

23.6.2 Cationic-active Substances

In small-scale preparation the quaternary ammonium compounds containing an alkyl chain are the most important. Cetrimide (Cetrimonium bromide, see Fig. 23.8) is used in a concentration of 0.5–2 % as emulsifier in creams. Quaternary ammonium compounds of this type are used from a concentration of 0.004 %. They also exhibit antiseptic and preservative properties. Notably benzalkonium chloride, as well as being a surfactant of the oil-in-water emulsifying type, is also important as a preservative in for example eye and nose drops. Cationic-active compounds are often incompatible with anionic substances such as sulfobituminose ammonium due to the risk of the formation of insoluble ion pairs. Since it is often difficult to estimate this risk, it is better to avoid these combinations.

Fig. 23.8 The formula of cetrimide



23.6.3 Amphoteric Substances

Amphoteric surfactants possess both an anionic and a cationic function. In small-scale preparation they are little used but their role may increase in the future. Examples are long chain betains and phospholipids (e.g. lecithin). Phospholipids play an important role as emulsifiers and micelle formers for parenteral emulsions (see Sect. 13.5.7) and micellar solutions and also in liposome technology.

23.6.4 Non-ionic Substances

The group of the non-ionic compounds includes the aliphatic alcohols, the polycyclic alcohols, mono-and diglycerides, the sorbitanesters, the macrogol compounds and the poloxamers.

Cholesterol and lanolin alcohols are examples of alcohols with cyclic carbon structures (w/o). Cholesterol is used as such. It is suitable in combination with the phospholipids as an emulsifier for the preparation of parenteral emulsions and in liposome technology. The lanolin alcohols are found in wool fat (Adeps lanae) and Eucerinum® anhydricum. They are present as w/o-emulsifier in cutaneous preparations.

The monoglycerides of fatty acids (monostearin, monolein) and diglycerides are examples of partially substituted glycerol esters (w/o-type). These substances are found in the synthetic suppository bases Hard fat (see Sect. 11.4.4). The hydrophilic part of the molecule consists of the non derivatised OH-groups. The presence of mono-and diglycerides explains the emulsifying function of some forms of Hard fat. The polyglycerol derivate triglycerol diisostearate is used for example in a concentration of approximately 5 % as w/o emulgator in hydrophobic creams (see Table 12.26) [36].

The fatty acid sorbitan esters, are often used cyclic polyol esters (w/o). The best known example is sorbitan monooleate (Span 80) (Fig. 23.9).

The main characteristic of non-ionic o/w emulsifiers is a macrogol group (= polyethylene glycol, PEG-group) in the molecule. This group makes the molecule predominantly hydrophilic (high HLB).

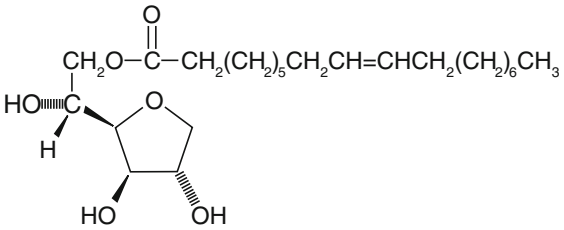


Fig. 23.9 The formula of sorbitan mono-oleate

Fig. 23.10 The formula of cetomacrogol 1000, x = 15 or 17, y = 20–24

Cetomacrogol 1000 is a cetyl-macrogolether, see Fig. 23.10.

The name includes the average molecular mass of the chain length: 1,000 (corresponding with approximately 20 glycol units). Cetomacrogol emulsifying wax is an emulsifier (see Sect. 18.4.3) and consists for 80 % of cetostearyl alcohol and 20 % from cetomacrogol 1000. The substance is incompatible with phenolic compounds (phenol, resorcinol) but low concentrations may be tolerated (see Sect. 12.5.7).

Polysorbates (Tweens) are esters of fatty acid macrogol-sorbitanethers with as main representative Polysorbate 80 (see Fig. 23.11).

These substances have a high HLB value, i.e. they are predominantly hydrophilic by the prominent role of the macrogol-sorbitan-group. So they cause the formation of o/w-systems and are in use as emulsifiers, wetting agents and also as solubilisators.

The aliphatic-aromatic ethers are represented with the macrogol-octyl-and nonylphenyl ethers (octoxynols: Triton-X® and nonoxynols). Nonoxynol-9 has a macrogol chain of 9 units. These substances are used as powerful detergents in, for example, cleaning fluids for contact lenses and as germicidal substances in spermicide gels and pessaries (see Sect. 11.14.3). These kinds of compounds also have a powerful antimicrobial and antiviral effect. Surfactants with a macrogol group (PEG-chain) in the molecule have a limited compatibility with phenols, tannins and heavy metals. Generally it is better to avoid such combinations.

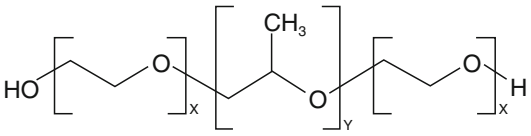


Fig. 23.12 The formula of a poloxamer

Poloxamers are copolymers and consist of a core of relatively hydrophobic polypropylene oxide surrounded by more hydrophilic polyethylene oxides; their molecular weight is about 12,500 (see Fig. 23.12).

The substances have unique properties that show up especially well in pharmacy preparations and dosage forms with sustained release characteristics. For application possibilities see Sect. 18.4.1. The waxy, white and free flowing granules are almost odourless and tasteless and are soluble/miscible in aqueous, organic polar and nonpolar solvents.

23.7 Viscosity Enhancing Substances

23.7.1 Overview

Gel formers (viscosity enhancers, thickeners) are primarily used for their viscosity enhancing effect in liquid preparations. In low concentrations they stabilise suspensions and emulsions and in high concentrations they are used for gel formation.

> In the nomenclature for pharmaceutical preparations such as standardised in the Ph. Eur. the term of gel is reserved for higher concentrations of hydrogel formers, with a semisolid consistency. But in practice the concept of gel is also used if hydrogel formers are used in lower concentrations as thickener in suspensions and emulsions for oral use.

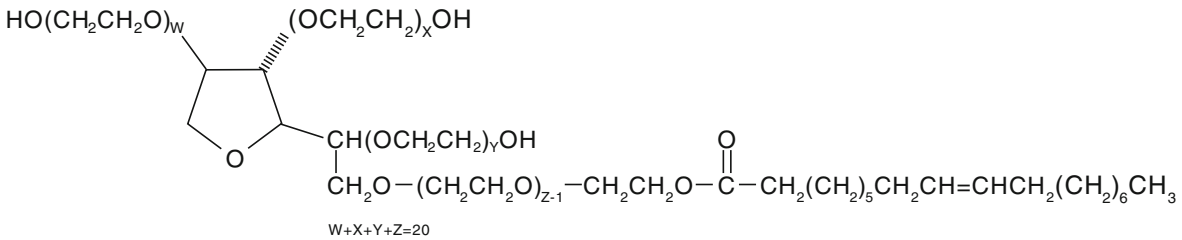


Fig. 23.11 The formula of polysorbate 80, W + X + Y + Z = 20

Table 23.14 Viscosity enhancing substances

Origin	Non-ionic	Anionic	Amphoteric
Natural	Starch species	Acacia	Gelatin
		Agar	
		Carrageenan	
		Pectin	
		Sodium alginate	
		Tragacanth	
Semi-synthetic	Hypromellose	Sodium carmellose	
	Hydroxylethylcellulose		
	Methylcellulose		
	Xanthan gum		
Synthetic	Polyvidone	Carbomer salts	
	Polyvinyl alcohol		
Mineral	Bentonite		
	Colloidal aluminium magnesium silicate		
	Colloidal anhydrous silica		

Some gel formers, for instance some of the cellulose derivatives, also exhibit a degree of surfactant activity. Others, particularly mineral viscosity enhancing substances, can also show dispersing (see Sect. 18.4.2) characteristics through the release of ions (aluminium-magnesium silicate) that improve dispersion by influencing the zeta-potential.

This group consists of linear macromolecules of natural, semi-synthetic or synthetic nature and of inorganic colloids. A further subdivision is that of non-ionic, anionic and amphoteric substances (Table 23.14).

For pharmacy preparations the (half) synthetic gel forming agents are generally preferred. Caution should be exercised with natural gel forming agents due to the varying quality and the presence of micro-organisms.

The ionic viscosity enhancing substances are usually much more sensitive to pH-changes than the non-ionic. However, the addition of electrolytes, and also of acids and bases, affect thickeners as a result of increasing ionic strength or influencing the zeta potential (see Sect. 18.4.2).

Viscosity enhancing substances not only increase the viscosity but also introduce rheological qualities such as (pseudo) plastic, dilatant and thixotropic behaviour (see Sect. 18.2.1).

Further details on substances are given in Sect. 23.7.3.

A problem with the processing of hydrogels or viscous systems is that many substances get slower wetted than they form gels. This can easily lead to lump formation which has to be taken into account in the method of preparation. Physico-chemical means or mechanical methods may be necessary to slow down gel formation and thus to avoid formation of lumps. The main gel preparation methods in small-scale preparation are dealt with in Sect. 23.7.2.

23.7.2 Gel Preparation Methods

Several different gel preparation methods exist, based on specific qualities of viscosity enhancing substances. Six of them that are most used are described in this section: dispersing by hand in hot water, dispersing by hand in a viscous fluid, pH change, dispersing mechanically, use of classic hydrogel formers and the 'corpus emulsi' (specific emulsifying) method.

23.7.2.1 Disperse by Hand in Hot Water

The physico-chemical method of temperature change uses the fact that many hydrogel formers are hydrophobic in hot water and therefore form no gel but still get wetted. The gel former is sprinkled on hot water and stirred for only a short time. After wetting and spontaneously cooling down the gel is formed and homogenised. After that the gel often has to rest in the fridge for further gelling. The method is used for substances that form no or bad hydrogels in hot water, such as the cellulose derivatives and Al-Mg-silicate. The preparation of a lidocaine hydrochloride gel 2 % (see Table 23.15) illustrates this method.

Preparation method:

- Dissolve the sodium monohydrogen phosphate dodecahydrate and the lidocaine hydrochloride in a part of the purified water.
- Mix in the glycerol 85 %.
- Dissolve, whilst heating, the methyl parahydroxybenzoate and the propyl parahydroxybenzoate in the main part of the purified water.
- Disperse the hypromellose in the hot solution.
- Mix the hypromellose dispersion with the lidocaine-glycerol solution.
- Keep the dispersion homogeneous during cooling down.
- Supplement to weight with purified water and mix.
- Dissolve the hypromellose by placing the gel at 2–8 °C for 12 h and mixing at regular intervals.

23.7.2.2 Disperse by Hand in Viscous Fluid

The physico-chemical method of changing the solvent uses the property that many hydrogel formers do not form a hydrogel in a non or slightly aqueous environment such as ethanol, a di-, tri, or poly-ol or a syrup. Triturating the

Table 23.15 Lidocaine Hydrochloride Gel 2 % [37]

Lidocaine hydrochloride	2 g
Disodium phosphate docecahydrate	0.1 g
Glycerol (85 %)	20 g
Hypromellose (4000 mPa.s)	3 g
Methyl parahydroxybenzoate	0.0875 g
Propyl parahydroxybenzoate	0.0125 g
Water, purified	74.8 g
Total	100 g

Table 23.16 Tetracycline Mouthwash 5 % [38]

Tetracycline hydrochloride	5 g
Methyl parahydroxybenzoate	0.1 g
Sodium citrate	6.5 g
Sorbitol, liquid (crystallising)	65.5 g
Tragacanth	0.5 g
Water, purified	40.6 g
Total	118.2 g (= 100 mL)

Table 23.17 Carbomer Gel [39]

Carbomer 974P	1 g
Disodium edetate	0.1 g
Propylene glycol	10 g
Trometamol	1 g
Water, purified	87.9 g
Total	100 g

hydrogel former with the non-aqueous, though water-dilutable, fluid moistens it. After that the resultant mixture can be diluted with water, which starts gel formation. The method is applicable to substances that do not form a gel with the mentioned fluids, e.g. cellulose derivatives. The method has the disadvantage that it takes quite some time to reach the final viscosity (Al-Mg-silicate). The preparation of a tetracycline mouthwash 5 % illustrates this method, see Table 23.16.

Preparation method:

- Dissolve the methyl parahydroxybenzoate in the purified water and cool down.
- Dissolve the sodium citrate in the methyl parahydroxybenzoate solution.
- Mix the tetracycline hydrochloride with the tragacanth.
- Disperse in an equal volume of sorbitol solution.
- Mix with the remaining part of the sorbitol solution.
- Mix the sodium citrate solution in portions with the tetracycline suspension.
- Add purified water to volume if necessary.

23.7.2.3 pH Change

The chemical method of pH change: some hydrogel formers are wettable at a pH where the hydrogel is not formed. After changing the pH the hydrogel forms. Polyacrylic acids (carbomers) for example have to be wetted with water and then neutralised with a base. If in ethanol they have to be neutralised with an amine. The preparation of a carbomer gel is given as an example, see Table 23.17.

Preparation method:

- Dissolve the disodium edetate in the largest portion of the purified water.
- Mix the disodium edetate solution with the propylene glycol.
- Disperse (preferably with a mixer) the carbomer in the solution.
- Dissolve the trometamol in 10 times the amount of purified water.
- Mix, with a spoon, the trometamol solution with the carbomer suspension.
- Mix in the remaining purified water.

Table 23.18 Sulfasalazine Oral Solution 100 mg/mL [40]

Sulfasalazine	10 g
Aluminium magnesium silicate	0.54 g
Carmellose sodium M	0.54 g
Citric acid monohydrate	0.63 g
Methyl parahydroxybenzoate	0.07 g
Raspberry essence (local standard)	0.3 g
Sodium citrate	4.7 g
Syrup BP	30 g
Water, purified	66.2 g
Total	113 g (= 100 mL)

23.7.2.4 Dispersing Mechanically

The mechanical method, such as with a rotor-stator mixer, is performed by dispersing the hydrogel forming agent in the vortex of the solution (water). The method is generally applicable especially for diluted hydrogels. However this method is, as a result of foaming, less suitable for hydrogel formers that also have surfactant properties such as many cellulose derivatives, and there is a risk of air being incorporated. Some (long chain) hydrogel formers are sensitive to mechanical shortening of the chains. In that case, the resulting viscosity might be lower than with other methods. In small-scale preparation practice this phenomenon has not proved to be relevant. This method is exemplified by the preparation of a sulfasalazine oral solution 100 mg/mL, see Table 23.18.

Preparation method:

- Use a rotor-stator mixer.
- Dissolve, whilst heating, the methyl parahydroxybenzoate in 50 mL purified water.
- Disperse the colloidal aluminium magnesium silicate in the hot solution.
- Disperse the carmellose sodium in this suspension.
- Mix with the sugar syrup.
- Dissolve the citric acid monohydrate and the sodium citrate in about 15 mL purified water, heat if necessary.
- Mix this solution and the suspension.
- Disperse the sulfasalazine.
- Mix the raspberry essence with the suspension.
- Add purified water to volume and homogenise.

23.7.2.5 Classic Hydrogel Formers

Some classic hydrogel formers (starch and gelatine) can be dissolved in hot water and form the hydrogel after cooling down.

23.7.2.6 Specific Emulsifying Method

A specific method was used with some classic hydrogel formers such as tragacanth and Acacia. By using a specific and exactly defined ratio of hydrogel agent to water, a thick gel was created. By further diluting with water the desired gel was obtained. This method is largely abandoned.

23.7.3 Details of Viscosity Enhancers

Table 23.14 gives an overview of the main groups of viscosity enhancers. In this section the following groups are discussed in detail: natural gel formers, cellulose derivatives, povidone, carbomers, mineral viscosity enhancers.

23.7.3.1 Natural Gel Formers

Acacia (Gum Arabic) consists of the K-Ca-Mg-polyarabinic acid salts. It may contain peroxidases which can be inactivated by heating. Tragacanth consists of Na-Ca-salts of galacturonic acid. The final viscosity is reached only after a few days' rest. Carrageenan, a hydrocolloid obtained by purification of red seaweed, is an anionic thickening agent. It needs calcium ions to get an established gel [5]. It is used in Ora-Plus ®, a commercial available base for oral liquids (see Sect. 5.4.6) Sodium alginate consists of sodium salts of polymannuglucuronic acid. Gelatin is a polymerisate of amino acids. The gel formation occurs after heating, optimally at a pH just outside the iso-electric zone.

23.7.3.2 Cellulose Derivatives

A chemical definition of cellulose can be found in Sect. 23.4.1. Carmellose sodium is the sodium salt of the polycarboxylmethylether of cellulose which is, as an anionic compound, usually incompatible with cationic compounds (lidocain, benzalkonium, chlorhexidine). There is a risk of the formation of ion pairs, resulting in precipitation or inactivation.

The Ph.Eur. uses different measurement methods for their viscosity, sometimes even at different temperatures. Usually a concentration of 2 % is used, although for one substance this is a concentration level where deviations are easily noticed whereas for another substance viscosity hardly depends on concentration at this level [41].

Cellulose derivatives, especially methylcellulose and hypromellose, usually cause a strong foam at preparation because they also possess surfactant activity. For the formulation of settling suspensions they are often unsuitable as they create a sediment that is difficult to disperse. They are used in suspensions and emulsions for oral use (see Sects. 5.4.6 and 5.4.7) at concentrations of 0.25–2.5 %. In suspensions they are often combined with aluminium magnesium silicate. In cutaneous hydrogels the concentration is usually 2–6 %. However, they cause a tightening sensation by xerogel forming.

> Xerogel: from some gels the hydrogel former remains if the solvent evaporates, as a membrane. In such cases it is described as a xerogel. For example, gelatin is available as a powder as well as in sheets, thus: a xerogel. The cellulose derivatives also form a xerogel on drying. On the skin, preparations based on a cellulose derivative therefore cause a sensation of tightening. For cutaneous preparations therefore the mineral hydrogel colloidal aluminium magnesium silicate is usually preferred, which does not form a xerogel. For the same reason the carbomer gels are often used on the skin.

To enhance the viscosity of eye and nose drops hypromellose 4000 mPa.s at a concentration of 0.5 % is used.

Cellulose derivatives degrade in aqueous solutions by opening of the glycosidic bonds. Increasing the temperature and decreasing the pH speed up this process. In acidic solutions (pH < 3) the viscosity will decline during storage. Hydroxyethylcellulose is known to get wetted faster than to form a gel, thus lumps are slowly generated which makes it easier to handle, cold and warm, than the other cellulose derivatives.

Further accelerated wetting and reduction of lump generation can be accomplished by dry mixing in advance with other substances, in particular poorly soluble substances, by using a higher temperature and by using a neutral or higher pH. Table 23.19 gives an overview of the main properties of the cellulose derivatives.

23.7.3.3 Xanthan Gum

Xanthan gum (derived from corn sugar) is a polysaccharide consisting primarily of the hexose units d-glucose and d-mannose and glucuronic acid. It is usually a sodium, potassium or calcium salt and soluble in cold water, in both acid as alkaline environment. Xanthan gum is compatible with high salt concentrations, but not with polyvalent metal ions such as magnesium and aluminium ions in alkaline environment by the negative charge. Solutions retain their viscosity in a wide pH-range of 3–11, are little sensitive to temperature differences and are miscible with up to an equal weight of ethanol. Xanthan gum is processed in suspensions in a concentration of 1–3 % [5].

23.7.3.4 Povidone

Povidone (polyvinyl pyrrolidone, see Fig. 23.13) only creates an increased viscosity at concentrations higher than

Table 23.19 Cellulose derivatives' properties

	Incompatible with	Swelling	Tolerance towards ethanol	Details
Carmellose sodium and mixed esters with carboxy methyl groups	Polyvalent positive ions: precipitation; also with cationic substances	Not in strong acid environment; precipitates at pH < 2	Bad	Hardly decreasing the surface tension
Methylcellulose hydroxypropylcellulose	Salts: flaking; hydroxybenzoates; strongly oxidising substances	In cold water methylcellulose swells and disperse slowly to form a viscous dispersion; hydroxypropylcellulose forms a clear liquid in cold water [5]	Well	Strong surfactant (foam forming)
Hydroxyethylcellulose	Sulfates: flaking	Little tendency to generate lumps	Moderate	Hardly decreasing the surface tension; is hydrophilic and by that no reversible coagulation by heat. It is specifically compatible with aluminium chloride and surfactants
Hypromellose (mixed ether)	Salts: flaking; oxidising substances	High concentrations of silver ions (.30 mg per litre) enhance the viscosity	Moderate [5]	Quite strong surfactant; generates a clear solution or gel

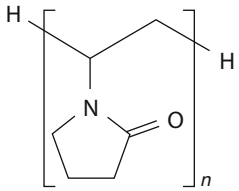


Fig. 23.13 The formula of povidone

approximately 10 %. At lower concentrations it may be used though because of the favourable impact on resuspendability of suspensions.

23.7.3.5 Carbomers

Carbomers are acrylic acid polymers with cross-linking by allylethers of sucrose or penta-erythritol. They have a pK_a of 6 ± 0,5. In dry form the molecule has a compact folded conformation. By interaction with the environment in which carbomers are dispersed a conformational change can occur. By wetting with water the molecules are slightly stretched; the dispersion in water is thus already a little viscous. In water and strong hydrophilic environments the interaction is strengthened as is the conformational change, when the acid groups of polyacrylic acid are ionised by a basic substance. If the molecule is stretched even further, it will lead to a higher viscosity. The resulting pH of a carbomer gel is usually about 6.5. The addition of sodium edetate ensures that bivalent ions such as calcium and magnesium are bound. Cross linking these ions hamper the conformation change that is needed for gel formation. Also the formation of hydrogen bridges between the hydroxyl and carboxyl groups of the carbomer leads to conformational change and thus increased viscosity. Examples of such hydroxyl group donors are propylene glycol, macrogol and non-ionic surfactants.

When the acid groups are neutralised the viscosity increases rapidly. The viscosity enhancement effect by the hydroxyl group donors occurs slowly and is only completed after a few hours.

Next to enhancing the viscosity a small amount of carbomer added to the water phase can stabilise creams; the emulsion becomes much more stable but the cream is still spreadable [42].

The type of viscosity of a (partially) neutralised carbomer hydrogel is plastic: a (large) yield value and a decreasing viscosity with increasing shear stress; a carbomer gel is not thixotropic (see Sect. 18.2). Carbomer hydrogel is not compatible with a number of active substances because of the pH (about 6.5) that is needed for the gel formation. For instance salicylic acid is ionised at this pH and hence not effective as a keratolytic. Weak base salts (e.g. alkaloid, chlorhexidine, aluminium and zinc salts) will precipitate at this pH.

Carbomer is available in several types. Carbomer 974 (Carbopol 974®) is produced using ethyl acetate. In the production of Carbopol 980® ethyl acetate and cyclohexane are used. These types are preferred over the types of Carbopol 940 and 934P®. Carbopol 940 is produced using benzene; it has been demonstrated that 0.2 % benzene may be present in the raw material. In Carbopol 934P, allowed for oral use, traces of benzene, about 60 ppm may be found as well.

Suitable neutralising, alkaline reacting substances for gel formation are sodium hydroxide, ammonia and the amines trometamol or possibly tetrahydroxypropylethylenediamine (Neutrol TE®). Triethanolamine (a tertiary amine) and secondary amines can generate

(continued)

nitrosamines and for that reason should not be used. Sodium hydroxide creates gels in which no more than 30–35 % ethanol can be processed. Carbomer gel that is neutralised with ammonia can include 45 % ethanol without the gel structure being lost. A gel with trometamol is also resistant to approximately 45 % ethanol and a gel with Neutrol TE can include 75 % ethanol.

23.7.3.6 Mineral Viscosity Enhancers

Bentonite and colloidal aluminium magnesium silicate are of mineral origin and do not exhibit all colloidal characteristics. They exhibit rheological properties such as becoming more fluid under stress but they are not always transparent. The colloidal systems of silicates have thus characteristics transitional to the coarser disperse systems. They hardly dissociate and are generally not split into ions. Therefore they are categorised (Table 23.14) under non-ionic viscosity enhancers, despite the fact that some dissociation occurs.

Colloidal aluminium magnesium silicate (Veegum ®) and bentonite are both aluminum silicates, but in Veegum a much higher percentage aluminium is substituted by magnesium. Because of the constant quality aluminium magnesium silicate is preferred to bentonite.

The solid aluminium magnesium silicate has the shape of flakes; these flakes are constructed of a number of layers. The flat sides have a negative charge while the corners are weak positive. The resulting load of the layers is negative and is offset by Na^+-ions and smaller quantities of other cations.

When dispersed in water the flakes become hydrated, the positively charged corners focus on the negatively charged flat sides of other particles and a hydrogel is formed. Because of this structure the liquid is viscous and thixotropic. Aluminium magnesium silicate therefore is often used to stabilise emulsions and suspensions.

The speed of hydration of the aluminium magnesium silicate depends on the amount of energy (mechanical energy and heat) that is supplied during dispersing. A better hydration results in a higher viscosity. After dispersing the hydration increases in the course of time until this is complete. If well dispersed, the maximal hydration is largely achieved after about a day at room temperature.

Adding substances that mix with water or dissolve in water before aluminium magnesium silicate is dispersed, inhibits hydration, sometimes so strongly that no more hydration occurs. When substances such as acids, alkalis, electrolytes and solvents are added after hydration, the viscosity reaches its final value faster.

Table 23.20 Zinc Oxide Cutaneous Paste [43]

Zinc oxide (90)	60 g
Arachis oil, refined	39.3 g
Oleic acid	0.7 g
Total	100 g

Adding a small amount of cations enhances viscosity. However, a large amount of cations causes flaking and sedimentation of aluminium magnesium silicate, this is flocculation of the hydrogel by cations that influence the zeta-potential. The viscosity strongly decreases. This tendency is even stronger as the added cations have a higher valence.

Colloidal anhydrous silica is used to enhance the viscosity of oily and fatty systems such as suppositories (see Sect. 11.4.6). The result is an oleogel.

Another oleogel is created when zinc oxide is mixed with oil. The result is basically a cutaneous oleogel of zinc oleate in arachis oil in which the excess zinc oxide is suspended (Zinc oxide Cutaneous paste, see Table 23.20), see also Sect. 12.7.13 for its use.

Zinc stearate and other zinc salts find application as thickening agents in oily injections.

According to Ph. Eur. definitions (Semisolid preparations for cutaneous application) gels consist of liquids gelled by means of suitable gelling agents.

Lipophilic gels (oleogels) are preparations whose bases usually consist of liquid paraffin with polyethylene or fatty oils gelled with colloidal silica or aluminium or zinc soaps.

Hydrophilic gels (hydrogels) are preparations whose bases usually consist of water, glycerol or propylene glycol gelled with suitable gelling agents such as poloxamers, starch, cellulose derivatives, carbomers and magnesium-aluminium silicates.

Collodion can be considered as a oleogel of cellulose nitrate in a mixture of ether and alcohol to which castor oil is added. Collodion dries in on the skin to a kind of lipo-xerogel that sticks like a capping membrane. Collodion is therefore used to apply salicylic acid on warts.

23.8 Preservatives

Preservatives are substances that, usually in low concentrations, are added to preparations because of their antimicrobial action. Adding preservatives is one of the methods to keep the microbiological contamination of

preparations within limits, especially during storage and use. Sterile preparations in multidose containers need preservatives to control the microbiological contamination occurring during use. Preservatives are also sometimes used to reduce microbiological count at a sterilisation or thermal process (see Sect. 30.7).

Preservatives must never serve to compensate for inadequate preparation procedures, such as poor hygiene or the use of raw materials of insufficient microbiological quality. Moreover, adding preservatives to contaminated raw materials creates the risk of the development of resistance, especially if the concentration of the preservative is low. Resistance against preservatives is found especially with gram-negative bacteria. It has also been reported that customised strains of *Brevundimonas (Pseudomonas)* species and *Enterobacter* species used methyl parahydroxybenzoate as a food source and convert the parahydroxybenzoate to phenol [44, 45]. *Brevundimonas* species are also capable of using quaternary ammonium compounds as a carbon source, which not only has led to the failure of the preservation of preparations but also to dangerous hospital infections when these substances were used as disinfectants.

23.8.1 Hypersensitivity and Toxicity

Preservatives also have disadvantages: they can cause hypersensitivity reactions, irritation and toxicity. Hypersensitivity to preservatives is a particular issue when they are used in cutaneous preparations and eye drops. Toxicity of preservatives is especially important in oral preparations.

23.8.1.1 Hypersensitivity

Hypersensitivity in cutaneous preparations is often caused by methyl parahydroxybenzoate. Sorbic acid or propylene glycol are to be preferred. Chlorhexidine digluconate, though giving few hypersensitivity, is not used very often because it has quite a few incompatibilities [46]. Propylene glycol is proven safe up to a concentration of 15 % (150 mg/g) but occasionally causes some irritation. Therefore, do not use it in cutaneous preparations that are applied to non-intact skin.

Hypersensitivity by eye drops is caused sometimes by thiomersal and benzalkonium chloride, although the adverse reaction to benzalkonium chloride usually regards irritation. Phenylmercuric borate gives fewer hypersensitivity reactions but has been abandoned. Chlorhexidine, as said, is only suitable for a few preparations.

Hypersensitivity to preservatives is often the reason for dispensing non-preserved eye drops, in single use containers.

Because of the possible occurrence of hypersensitivity reactions the name of the preservative should be listed on the label and on the instruction for the patient, see Sect. 37.3.

23.8.1.2 Toxicity

Toxicity of preservatives is especially important in oral preparations if a large amount is taken at one time (oral rehydration fluids, tube feeding, osmotic laxatives). Propylene glycol is toxic with oral use in children and in patients with poor renal function [22].

For chronic oral use of preparations which are used in small quantities the dose must be checked on the basis of the Acceptable Daily Intake (ADI) as for foodstuffs. Problems, however, are unlikely to be met in these cases because of the relatively small quantities that are used. The ADI-value indicates the amount of substance added to foods in mg/kg body weight that one may take daily over a lifetime.

The chronic toxicity of preservatives that are administered in the eye is a constant source of concern and is often reported; benzalkonium chloride and thiomersal would eventually cause epithelial damage and phenylmercuric compounds cause mercury deposition in the lens. However, so far these preservatives have not been banned for that reason. Recent investigations even show that benzalkonium is not toxic for the cornea [47].

23.8.2 Activity, Concentration and Applicability

Table 23.21 displays preservatives in pharmacy preparations with some characteristics, many of them having been taken from [48].

Good preservatives have, by definition, a wide activity spectrum. If one preservative covers the spectrum insufficiently, combination with another, synergistic, preservative or with a potentiating substance (for instance benzalkonium chloride with sodium edetate) improves the activity.

Micro-organisms replicate only in the presence of water. The activity of preservatives depends therefore on the concentration of the free and active form in the aqueous phase of the preparation. ‘Free’ refers to the binding that some preservatives can have with active substances, excipients or packaging materials. Examples of the binding of preservatives are: the adsorption of phenylmercuric compounds to rubber stoppers, the adsorption of benzalkonium chloride to silicon rubber tubes and to cellulose nitrate-membrane filters, the solubilisation of methyl parahydroxybenzoate by polysorbate 80 [49] and by sodium lauryl sulfate [50] and the migration (distribution) towards the lipid phase of methyl parahydroxybenzoate in emulsions.

For most of the preservatives the undissociated form is the active form because only this passes through the

Table 23.21 Survey of preservatives

Group	Substance	Bacteriostatic/bactericidal concentration[a]	Applicable at pH range	Hypersensitivity and toxicity
Quaternary ammonium compounds	Benzalkonium	0.04–0.1 mg/mL	4.5–8.0	Hypersensitivity and irritation in eye drops
	Cetrimide	1 mg/mL	Most effective at neutral or slightly alkaline pH [5]	Hypersensitivity after repeated application [5]
Mercury compounds	Phenylmercuric borate	0.01–0.04 mg/mL (slow)	Independent from pH; at pH 8 slightly better than at pH 6	Ciliotoxic
	Thiomersal	0.05–0.1 mg/mL	Bactericide at acid pH, bacteriostatic or fungistatic at alkaline or neutral pH [6]	Ciliotoxic, sometimes hypersensitivity
Hydroxybenzoic acid esters	Methyl parahydroxybenzoate	1–1.5 mg/mL or mg/g, in combination with propyl hydroxybenzoate 0.5–0.6 mg/mL or mg/g	Stability optimum pH 3–5; better activity in acid environment (pH < 8)	Allergic reactions
	Propyl parahydroxybenzoate	0.3 mg/mL	Antimicrobial activity at pH 4–8, decreasing with increasing pH [5]	Allergic reactions
Sorbic acid and benzoic acid	Sorbic acid	1–2.5 mg/mL or mg/g (as K-salt)	Optimum pH = 5	Irritating
	Benzoic acid	1–2.6 mg/mL (as Na-salt)		Hypersensitivity
Chlorhexidine	Chlorhexidin	0.1 mg/mL	pH 5–8; above pH 8 precipitation occurs	Hardly
Phenols	Chlorocresol	0.75–2 mg/g	Bactericidal activity within broad range (pH < 8); optimum pH 2–4	Hypersensitivity
	Cresol (o-, m- and p-)	2.5–3 mg/mL, in combination with phenol 1.5–1.8 mg/mL	pH < 8, optimum pH 2–4	Less irritating than phenol [5]
	Phenol	2.5–3 mg/mL, in combination with cresol 0.6–0.65 mg/mL	Largest antimicrobial activity in acidic solutions [5]	Irritating
Alcohols, di- and trioles	Benzyl alcohol	9–15 mg/mL, incidentally up to 40 mg/mL	pH 4.5–8.0	Hypersensitivity, limitations with prematures, neonates and children up to 3 years because of toxicity
	Ethanol	15–20 %	No restriction	Not relevant
	Phenoxyethanol	5–10 mg/mL	No restriction	Not relevant
	Glycerol 85 %	>30 %	No restriction	Not relevant
	Propylene glycol	10–15 %	No restriction	Irritation
Silver	Silver ions	Ag+: 0.5 mg/l	No restriction	No data

[a]Whether a preservative is bacteriostatic or bactericidal is not predictable on forehand. It depends on the concentration of the preservative and the kind of germs present in the product

bacterial membrane. This explains their pH dependency; many preservatives are acids and phenols that will only be active in their undissociated form, thus below their pK_a. Thus the availability of preservatives for the higher pH region is very limited, especially for oral preparations. Those preservatives that are active at neutral to slightly alkaline pH, have a bad taste: propylene glycol, chlorhexidine, quaternary ammonium compounds, phenylpropanol [51]. In fact only the parahydroxybenzoic acid esters remain, but they are susceptible to hydrolysis at increased pH. These characteristics also bring about that preservatives as a rule have limited water-solubility and are therefore likely to stay in the lipid phase, of which preservation is not really necessary.

The relationship between concentration and activity differs greatly for the different preservatives and is rarely linear. The doubling of concentration does not necessarily lead to the doubling of activity. Increasing the concentration of phenylmercuric borate in eye drops from 0.002 % to 0.004 % for instance causes no better functioning [51]. In contrast, halving the concentration parahydroxybenzoic acid esters causes a roughly tenfold reduction of the activity.

The activity of preservatives is optimal against micro-organisms in a growth phase. This raises the question whether multidose preparations like eye drops should be kept in the fridge after they have been opened up or not. Micro-organisms introduced by the patient will be killed faster from the preservative action at room temperature,

but will replicate slower in the fridge. Some experts consider the first effect more important than the second one and so they advise that eye drops should preferably be kept at room temperature.

The Chaps. 4–14 on the various pharmaceutical dosage forms cover the use of preservatives in each of those groups of preparations. Further background of preservation and preservatives can be found in Sect. 22.3 and in reference [52].

23.8.3 Quaternary Ammonium Compounds

Benzalkonium chloride and cetrimide (cetrimonium bromide), are good water soluble preservatives that are resistant to steam sterilisation. The applied concentration lies between 0.004 % and 0.01 % for benzalkonium chloride and approximately 0.1 % for cetrimide. They are slightly more effective at higher pH due to the cationic interaction with the negatively charged cell wall of the micro-organism at higher pH [53]. The addition of disodium edetate potentiates their antibacterial effect [54]. For the outer membrane of the micro-organisms is stabilised by cations like calcium and magnesium, by cross-linking the polysaccharides in the cell membrane. Sodium edetate binds these cations and thus renders the outer membrane of the bacteria unstable. As a consequence benzalkonium chloride can penetrate deeper into the bacterial cell.

Benzalkonium chloride is a first-choice preservative in eye drops. For this application it is usually combined with disodium edetate, because benzalkonium chloride alone works poorly against non-fermentative gram-negative bacteria. As a basis solution for eye drops the FNA uses the combination of benzalkonium chloride 100 mg/L and disodium edetate 1 g/L. Benzalkonium chloride in eye drops can irritate and can cause sensitisation. Chronic toxicity is doubted (see Sect. 23.8.1.1).

The safety of the use of benzalkonium chloride for the preservation of nose drops and nebulisation fluids is not easy to be interpreted, see Sects. 8.5.1 and 6.6.3 respectively.

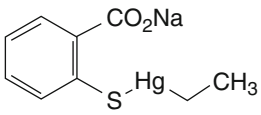
Cetrimide is mainly used in cutaneous preparations, especially in creams in which it is used as active substance (disinfectant) and emulsifier.

Quaternary ammonium compounds are incompatible with many anionic substances. Because quaternary ammonium compounds are also surfactants, they also are used as emulsifier (see Sect. 23.6.2).

23.8.4 Mercury Compounds

Phenylmercuric borate as a raw material is however not available anymore because of toxicological problems to the environment. Thiomersal however is still in use as a preservative in eye drops, contact lens fluids, injection fluids and vaccines [55]. The characteristics of the organic mercury compounds phenylmercuric borate and thiomersal (see Fig. 23.14) will be described. Because of their ciliotoxity they are not used in nose drops and nebulisation fluids. The activity does not depend on the pH. The solutions are stable when subjected to steam sterilisation. Organic mercury compounds can be adsorbed to different plastics and to some types of rubber (see also Sects. 24.2.4 and 24.4.2); this has implications for the choice of the packaging material.

Fig. 23.14 The formula of thiomersal



Phenylmercuric borate is 0.08 % soluble in water. Mercury is in this compound covalently bound to the phenyl group. It is incompatible with many anions, including halides. However a 0.004 % solution is compatible with up to 0.7 % sodium chloride. The active concentration is 0.002 %, but a concentration up to 0.004 % may be used to compensate losses by adsorption on the membrane filter, etc. Eye drop bottles with chlorine and bromine butyl rubber droppers cannot be used with phenylmercuric salts, because a precipitate will be formed. An alternative is packaging the eye drops in a bottle with a polypropylene dropper (see Sect. 24.4.2). Phenylmercuric borate causes few hypersensitivity reactions, but with prolonged use, there might be a risk of mercury deposition in the lens.

Thiomersal is approximately 0.02 % soluble in water. The active concentration is 0.01 %. It is mainly used in eye drops, contact lens fluids and injection fluids. In solution the active molecule is ethylmercuric that is somewhat more toxic than phenylmercuric but less than ionogenic mercury. Also the risk of hypersensitivity reactions is greater than with phenylmercuric borate. With prolonged use in eye drops or contact lens fluids damage of the cornea epithelium may occur.

23.8.5 Hydroxybenzoic Acid Esters

The hydroxybenzoic acid esters are among the most widely used preservatives in pharmacy preparation. They are used in oral liquids, enemas and cutaneous preparations. They are not very active against gram-negative bacteria. The combination with disodium edetate is not commonly used although it may overcome this drawback.

Their solubility in water is 0.1–0.2 %, which is just above the applied concentration of 0.1–0.15 %. During preparation the dissolution speed can be increased by heating. Fast

Table 23.22 Potassium Chloride Oral Solution 75 mg/mL [56]

Potassium chloride	7.5 g
Methyl parahydroxybenzoate	0.1 g
Peppermint oil	0.012 g
Water, purified	96.7 g
Total	104.3 g (=100 mL)

Table 23.23 Prednisolone Oral Solution 1 mg/mL (as disodium phosphate) [57]

Prednisolone sodium phosphate	0.146 g
Bananas essence (local standard)	0.1 g
Disodium edetate	0.1 g
Disodium phosphate dodecahydrate	1.9 g
Methyl parahydroxybenzoate	0.15 g
Sodium dihydrogen phosphate dihydrate	0.21 g
Sorbitol, liquid (crystallising)	25.8 g
Water, purified	77.5 g
Total	106.8 g (= 100 mL)

dissolution can also be obtained by using concentrated solutions in organic solvents such as propylene glycol, for example: methyl parahydroxybenzoate 15 g with propylene glycol 91 g for 106 g (=100 mL). Solubility may be decreased by salts and storage temperature. This effect should be carefully considered when designing a formulation, see the examples in the box.

Crystallisation risk of parahydroxybenzoates.

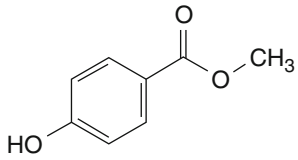
Salts: Because of the high phosphate content in oral phosphate solutions, methyl parahydroxybenzoate has to be used in a concentration of 0.1 %, otherwise it will crystallise. Another example is a potassium chloride oral solution 75 mg/mL (Table 23.22). It consciously contains a minimal amount of methyl parahydroxybenzoate because its solubility is decreased by the relatively high concentration of potassium chloride.

Storage temperature: Prednisolone Oral Solution 1 mg/mL (Table 23.23) cannot be kept below 15 °C because of crystallisation of the methyl parahydroxybenzoate.

Hydroxybenzoic acid esters show pH-dependent degradation by hydrolysis. The stability optimum lies at pH 3–5; beyond this range the hydrolysis rate increases to maxima at pH 1 and from pH 9. At high pH the phenolic OH-group also becomes dissociated.

Due to the high fat-water partition coefficient, hydroxybenzoic acid esters are not always suitable for micellar solutions and hydrophilic creams, it depends on the composition of the aqueous phase [58]. A microbiological challenge test is strongly recommended if this use is considered.

Fig. 23.15 The formula of methyl parahydroxybenzoate



Hydroxybenzoic acid esters can cause allergic reactions [3].

Methyl parahydroxybenzoate (Fig. 23.15) or methylparaben is the most common representative of the hydroxybenzoic acid esters.

At a slightly acidic pH and room temperature methyl parahydroxybenzoate solutions are fairly stable, but at pH 8 approximately 10 % hydrolyses in 6 months. An example of short shelf life due to decomposition of methyl parahydroxybenzoate is the Prednisolone Oral Solution (Table 23.23): the pH is rather high to prevent the hydrolysis of prednisolone disodium phosphate, but as a result the shelf life is determined by the preservative: only 12 months.

Although the taste is better than those of many other preservatives, methyl parahydroxybenzoate causes unpleasant sensations on the tongue in some patients, when used in mouth washes. Solutions with a mildly acidic to neutral pH, under favourable conditions and on validated lines, are stable to heating over boiling water for 30 min (see Sect. 30.7) and sometimes even against steam sterilisation 15 min at 121 °C.

Propyl parahydroxybenzoate is more lipophilic than methyl parahydroxybenzoate and therefore less soluble in water (0.035–0.05 %), but the active concentration is also lower: around 0.03 %. It is currently used with methyl parahydroxybenzoate, mostly because of the synergistic effect. Combinations methyl parahydroxybenzoate : propyl parahydroxybenzoate 7:1, 7:3 or 3:1 give a better preservation than propyl parahydroxybenzoate alone. However, due to the poorer water solubility of propyl parahydroxybenzoate, those combinations will cause solubility problems rather than methyl parahydroxybenzoate alone. No data are known about its resistance to sterilisation.

23.8.6 Sorbic Acid and Benzoic Acid

The ionisable preservatives sorbic acid (see Fig. 23.16) and benzoic acid (see Fig. 23.17) are only active as the undissociated form, because this passes the bacterial membrane.

This explains their dependency on the pH for their efficacy. Sorbic acid and benzoic acid are mainly present in

Fig. 23.16 The formula of sorbic acid

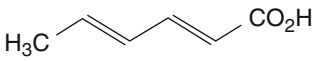
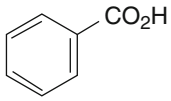


Fig. 23.17 The formula of benzoic acid



undissociated form below their pK_a (4.76 respectively and 4.19) so they can only be used at pH values less than about 5. Reduction of the pH increases degradation thus pH 5 is the optimum value from the viewpoints of both stability and effectiveness.

Sorbic acid is mainly used in cutaneous preparations and in oral liquid preparations. Because of the favourable oil-water partition coefficient it is suitable for formulating hydrophilic creams, emulsions and micellar solutions for oral use. For this reason it is preferred to methyl parahydroxybenzoate in these preparations.

Sorbic acid is 0.15–0.2 % soluble in water, which is slightly above the active concentration of 0.1 %. By adding it to boiling water dissolution is accelerated. Sorbic acid is volatile with water vapour; covering the vessel prevents loss of sorbic acid during heating. By using potassium sorbate the method of preparation can be made easier: potassium sorbate is dissolved in water and the optimum pH is obtained by the addition of acid.

Solutions of sorbic acid or benzoic acid are not resistant to autoclaving.

Sorbic acid is also oxidisable and sensitive to light. Containers should sufficiently protect the content from light. If semisolid preparations are packaged in a jar, they can be protected from oxygen by covering the preparation with foil.

Benzoic acid is soluble in water up to 0.3 %, while the active concentration is 0.1–0.2 %. Benzoic acid also sublimates at higher temperatures and is volatile with water vapour. It is only active in the undissociated form at pH less than 5. Benzoic acid is second-choice preservative in solutions. It works less well than sorbic acid against fungi and yeasts. Benzoic acid in oral preparations and dosage forms is also undesirable for neonates and infants [3].

23.8.7 Chlorhexidine

Chlorhexidine is used as a preservative in the form of the very water-soluble chlorhexidine digluconate. The active concentration is 0.01 %. It is usually obtained as 20 % solution.

The optimal antibacterial activity lies in the pH range 5–8; above pH 8 chlorhexidine precipitates as its base. Solutions of chlorhexidine in usual strengths are not completely resistant to autoclaving. Due to the toxic degradation product 4-chloroaniline a limit test on this impurity after autoclaving should be performed [5]. Chlorhexidine only rarely elicits hypersensitivity reactions but has the disadvantage that it is incompatible with many anions, some of which will cause a precipitate only after many days of storage. The combination with disodium edetate is not common. Chlorhexidine digluconate is mainly used in cutaneous preparations and eyedrops.

23.8.8 Phenols

Phenols also only act as a preservative in their undissociated form (see also Sect. 23.8.6). That means that they can be used at pH less than 8 with an optimum at pH 2–4 [59].

Of chlorocresol (see Fig. 23.18), p-chloro-m-cresol and metacresol (m-cresol, see Fig. 23.19) only the last one is mentioned as a preservative in parenteral preparations (see Sect. 13.5.9). Chlorocresol is used as a disinfectant of clean rooms (see Table 31.5). The solubility of chlorocresol in water is 0.4 %; the active concentration is 0.1 %. The solubility of metacresol is approximately 2 %. Solutions of chlorcresol or metacresol resist autoclaving.

Phenol is up to 7 % soluble in water. The active concentration is 0.5 %. It is used as a preservative in parenteral preparations and exceptionally in cutaneous preparations, because of the unpleasant smell.

The parahydroxybenzoic acid esters can also be classified as phenols, but they are separately discussed in Sect. 23.8.6.

Fig. 23.18 The formula of chlorocresol

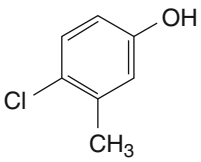


Fig. 23.19 The formula of metacresol

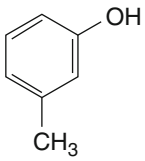


Table 23.24 Some data of preservatives with an alcoholic structure

Preservative	Active concentration (% g/g)	Solubility in water (% g/g)	Pharmaceutical dosage forms in which it is used
Benzyl alcohol	1	4	Intramuscular and subcutaneous dosage forms
Ethanol	15–20	Unlimited	Oral liquids, enemas
Glycerol 85 %	>30	Unlimited	Oral liquids
Phenoxyethanol	1	2.5	Cutaneous preparations, vaginal irrigations
Propylene glycol	10–15	Unlimited	Cutaneous preparations

Fig. 23.20 The formula of benzyl alcohol

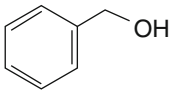
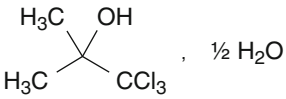


Fig. 23.21 The formula of chlorobutanol hemihydrate



23.8.9 Alcohols, Di- and Trioles

Various alcohols, di-and trioles are used as a preservative. An overview can be found in Table 23.24.

Alcohols are active in the whole pH range.

Benzyl alcohol (see Fig. 23.20) has weak local anaesthetic properties in addition to its preservative activity and is sometimes used for that effect in preparations for intramuscular injection. However it should not be used in injections intended for children < 6 months (see Sect. 13.5.9) nor in injections intended for prematures or neonates. It also causes haemolysis in higher concentrations and dosages [3].

Chlorobutanol (Chlorobutanol anhydrous and chlorobutanol hemihydrate Ph.Eur. see Fig. 23.21) is now little used because of its poor solubility and strong permeation through rubber and plastic. When heated in water it melts before it dissolves which decreases the dissolution rate further. Furthermore, it decomposes at moderate temperature and during storage it is not sufficiently stable.

23.8.10 Silver

Oligodynamic preservation is a different subject. It is based on the principle of preservation by low concentrations of silver ions that are presumed to attack the SH-groups in protein and DNA structures of micro-organisms. Their applicability might be advantageous to circumvent risks of hypersensitivity by preservatives in eye and nose drops. A silver ion concentration of 0.5 mg/L is supposed to be sufficiently active as a preservative. Note that solutions with silver ions should be protected against light because of discolouration by reduction [60].

23.9 Antioxidants

Antioxidants protect products with active substances that are sensitive to oxidation by atmospheric oxygen. For a description of the mechanism of action of antioxidants, see Sect. 22.2.2.2.

The most used antioxidants are ascorbic acid (0.2–0.7 %) and the sulfites: sodium metabisulfite (0.1 %) and sodium sulfite (0.2 %). A particular example of an antioxidant is sodium thiosulfate, used exclusively for the protection of iodide against oxidation.

The percentage of antioxidant to be added, is related to the whole preparation and not to the active substance.

Usually the antioxidant is dissolved prior to the dissolution of the active ingredient. In this way it reduces in advance the amount of dissolved oxygen in the solvent. This is especially relevant if a small amount of a highly active substance needs to be protected.

Sodium metabisulfite (= sodium pyrosulfite) reacts with oxygen by formation of sulfate, causing the pH to decrease. It can also bind to some active substances such as prednisolone disodium phosphate and epinephrine tartrate. Sodium metabisulfite can cause an anaphylactic reaction at parenteral administration; because of this risk take care with the use of this substance. Ascorbic acid generates a yellow oxidation product. This may discolour the preparation although no degradation of the active substance has occurred.

A special group is formed by the radical scavengers butylhydroxyanisole (see Fig. 23.22) and butylhydroxytoluene (see Fig. 23.23). They are used in non-aqueous environments. Concentrations usually start at 0.01–0.1 % of the complete formulation, if necessary increased to 1 %. Butyl hydroxytoluene is used in the lipid phase of a tretinoin cream 0.05 % (Table 23.25).

In addition, these substances are sometimes present in oils and fats (e.g. Wool fat). Its presence should always be mentioned on the label.

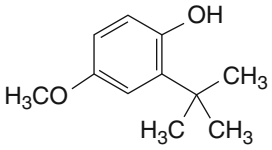


Fig. 23.22 The formula of butylhydroxyanisole

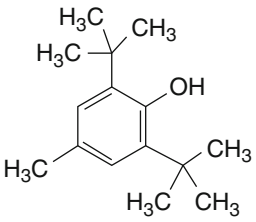


Fig. 23.23 The formula of butyl hydroxytoluene

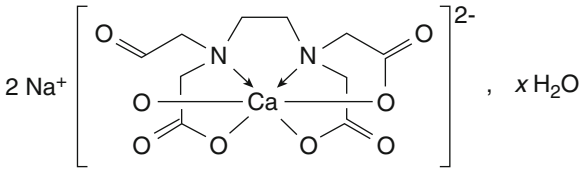


Fig. 23.24 The formula of sodium calcium edetate

Table 23.25 Tretinoin Cream 0.05 % [61]

Tretinoin	0.05 g
Alcohol denaturated 95 % V/V (local standard)	12 g
Butylhydroxytoluene	0.04 g
Cetomacrogol cream FNA[a]	88 g
Total	100 g

[a]Cetomacrogol emulsifying wax (BP) 15 g, sorbic acid 200 mg, decyl oleate 20 g, sorbitol, liquid (crystallising) 4 g, water, purified 60,8 g. total 100 g

23.10 Complexing Agents

Complexing agents most used in pharmacy preparations are disodium edetate and sodium citrate.

Disodium edetate reacts with metal ions resulting in the formation of soluble 6-surrounding complexes as with calcium ions (see Fig. 23.24).

In addition to quaternary ammonium compounds it potentiates the preservative action of these substances by the binding of calcium from the cell membrane of the micro-organisms, see Sect. 23.8.3. The complexation by edetate of heavy metals is applied to prevent degradation that is catalysed by free heavy-metal ions. For this reason, the addition of disodium edetate is necessary in most solutions of sympathicomimetics. Another example is the addition to a sodium hydrogen carbonate infusion solution packaged in glass. By forming calcium complexes, edetate prevents calcium carbonate precipitation when there is a risk of calcium leaching from glass.

Citrate ions may act as flocculating agent in liquid suspensions, see Sect. 18.4.2.2 and examples in Tables 5.6, 5.8 and 5.15. Citrate ions form soluble complexes with zinc ions. The addition of the alkaline reacting citrate to zinc sulfate eye-washes (see Sect. 10.6.1) causes the pH to increase, which will compensate for the acid reacting zinc sulfate. Raising the pH of solutions containing zinc ions generally generates a precipitate of zinc oxide (hydrate), but this is prevented by the formation of citrate-zinc complexes.

23.11 Colouring Agents

Colouring agents are, together with taste and aromatic agents, used to make the medicine more acceptable for the patient. Sometimes colouring agents used to prevent mix-ups. This use, however, is contrary to the principle that the label always should be read well. Colouring agents are also used to protect light-sensitive medicines or to prevent patients' concerns about irrelevant decompositions. It should, of course, not be used to mask a relevant decomposition. Insoluble colourants are used for protecting the active substance of tablets and capsules against the influence of light. Colourants are mainly divided by water soluble colourants (dyes) and water-insoluble (pigments). An extensive overview of all pharmaceutical colouring agents is found in [5]. Table 23.26 is an overview of colourants most used in pharmaceutical preparations.

For use in cutaneous preparations blends of iron oxides are suitable. Table 23.27 gives an an example for blending to get the desired colour.

Legislation on colouring agents for medicines follows Food legislation [63] Azo dyes – especially tartrazine – are suspected of adverse reactions. The latest evaluation by the European Food Safety Agency (EFSA) resulted in 2009 in a continuation of the allowance [64]. Nevertheless the UK Foods Standards Agency advices that avoiding of colourants in the diet of hyperactive children may have a beneficial effect.

It is hard to find quality specifications for colourants. Some of them (riboflavin, activated charcoal, titanium dioxide) have a Ph. Eur. monograph. The specifications of all colourants with a E-number are mentioned in the EU-directive 95/45/EC [65], these are specifications for use in food, but they are well usable for pharmaceutical purposes. Some colourants are specified in the monograph Colouring Agents in [5].

Table 23.26 Overview of colourants

Colouring agent and E number	Synonym	Type	Colour	Water solubility	End concentration in the preparation	Application
Allura red (E129)		azo	Red	Soluble		
Azorubine (E122)	Carmoisine	azo	Red	Soluble	0.01–0.03 %	Solid and oral dosage forms, liquids
Caramel (E150)			Brown	Soluble	0.05 %	Solid and oral dosage forms, liquids
Erythrosine (E127)		Xanthen	Red	Soluble		Solid and oral dosage forms
Indigo carmine (E132)	Indigotine	Indigoid	Blue	Soluble		Solid and oral dosage forms
Iron oxides (E172)			Yellow, red, umber/black	Insoluble	see Table 23.27	Solid and oral dosage forms
Lacquers[a]			Various colours	Insoluble		Solid and oral dosage forms
Patent blue V(E131)		Triarylmethane	Blue	Soluble	0.005 %	Solid and oral dosage forms, liquids
Patent blue V (E131) + quinoline yellow (104)			Green	Soluble	0.005 + 0.01 %	Liquids
Ponceau 4R (E124)	Cochineal red	azo	Red	Soluble		
Quinoline yellow (E104)		Chinophtalon	Yellow	Soluble	0.01 %	Liquids
Riboflavin (E101)	Vitamin B2	Flavoprotein	Yellow	Soluble		Solid and oral dosage forms
Sunset yellow (E110)		azo	Yellow	Soluble		
Tartrazine (E102)		azo	Yellow	Soluble		Solid and oral dosage forms
Titanium dioxide (E171)		Inorganic	White	Insoluble		Solid and oral dosage forms
Vegetable carbon (E153)			Black	Insoluble		Solid and oral dosage forms

[a]Lacquers (or 'lakes') are soluble colouring agents that are made insoluble by precipitation onto aluminium dioxide

Table 23.27 Iron Oxide Concentrated Blend [62]

	Yellowish	Orange-like	Reddish
Iron oxide red	15 g	20 g	25 g
Iron oxide yellow	75 g	70 g	65 g
Iron oxide black	10 g	10 g	10 g
Total	100 g	100 g	100 g

23.12 Herbal Raw Materials

Herbal drugs or herbal substances serve as raw material for herbal medicinal products [66].[a] Definitions for herbal medicinal products as well as for herbal drugs (herbal substances) and herbal (drug) preparations are provided by the European Community [66] and in the Ph. Eur. (see box).

The Ph. Eur. includes general monographs on herbal products: herbal drugs, herbal drug preparations, extracts, herbal teas, essential oils. The Ph. Eur. contains (May 2013) 263 monographs on individual herbal drugs and herbal drug preparations. The science-based or evidence-based use of herbal medicinal products for the treatment and prevention of disease is called (rational) phytotherapy.

Definitions

For the European medicines legislation, herbal medicinal products, herbal substances and herbal preparations are defined the European Directive 2004/24/EC [61].

Herbal medicinal product: Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

(continued)

[a] Contributed by Herman Woerdenbag, Groningen, The Netherlands.

Herbal medicinal products are also referred to in the international literature as herbal medicines, herbal remedies, herbal products, phytomedicines, phytotherapeutic agents or phytopharmaceuticals [67].

Herbal substances: All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

The term 'herbal substance' in the European Community legislation is synonymous with the term 'herbal drug' in the Ph. Eur.

Herbal preparations: Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

The term 'herbal preparation' in the European Community legislation is synonymous with the term 'herbal drug preparation' in the Ph. Eur.

Herbal drugs (and hence herbal medicinal products) are complex in composition, as medicinal plants contain many different constituents (secondary metabolites). The complexity is also implicit to the fact that the quality of raw plant material can be variable and is dependent of various factors. These include the identity and quality of the seed or plant material, inter- and intra-species variations, environmental conditions during growth and development of the plant (temperature, rainfall, sunshine, soil composition, altitude), application of fertilisers, pesticides and herbicides, air and soil pollution, time of harvesting, harvesting conditions, plant part used and post-harvesting treatment (drying, fragmentation, storage, transport). The application of GACP (Good Agricultural and Collection Practices) for medicinal plants assures the quality of the raw material (the herbal drug), prior to any manufacturing process (industrial as well as pharmacy preparations) yielding an herbal drug preparation or an herbal medicinal product. The quality of herbal drugs and herbal drug preparations should comply with the requirements set in the Ph. Eur. or, in the absence of suitable monographs in the Ph. Eur., with another recognised source [67, 68]. For further details, see Sect. 32.14.

23.13 Medical Gases

Medical gases that are administered to patients are medicines and are defined in the Ph. Eur. The gas is in cylinders or liquid tanks and is administered using a distribution system. This can be small-scale, for example a 10 L oxygen cylinder to a wheelchair. Wider, more expansive distribution systems are found in hospitals, see Sect. 27.5.3.

The medical gas in hospitals is usually supplied from a tanker as bulk, or smaller amounts in cylinders. Transport from the bulk storage, or from the cylinder takes place through the pipe network towards the gas terminal units. In a midsize hospital there may be several thousands of them. In many hospitals, the preparation of Medicinal Air is performed locally, from outdoor air that is compressed, dehumidified and purified. For more information about the responsibilities around quality assurance we refer to the literature [69].

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Containers

24

Jan Dillingh and Julian Smith

Contents

Abstract

Packaging is an integral part of any medicinal product. Not only from a regulatory point of view, but also the patients'. It is only the packaged medicinal product which is stable and suitable for use. The stability of the product follows from the successful combination of formulation, packaging materials and method of production. The correct choice of container and closure system will impact every aspect of product life and usage. This is true for industrial as well as pharmacy (re-) packaged products.

Packaging technology encompasses knowledge from fields as material science, chemistry, engineering and ergonomy. With appropriate development, the packaging system and the many different functions it serves will go almost unnoticed. However, an unsuitable packaging system will result in the product's failure to meet the patient's needs.

This chapter aims to introduce the reader to the many different aspects of pharmaceutical packaging technology. It provides basic and applied knowledge, enabling the right choice of container system for almost every medicinal product found in the pharmacy.

Keywords

Package • Container • Closure • Design • Glass • Tube • Dosage delivery devices • Quality control

Based upon the chapter Verpakkingen by Adrie de Jong and Yvonne Bouwman-Boer in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_24,

24.1 Orientation, Scope

24.1.1 Purpose of Packaging, Requirements

Medicinal products are packed in containers to protect them from the adverse effects of external physical, chemical and microbiological influences. The container holds the medicinal product, making it possible to transport and use the product. It also bears the information to identify the medicine and the instructions on how to use it.

There are two kinds of containers:

- Primary containers, which are in direct contact with the medicinal product
- Secondary containers, which enclose the primary container

The closure system seals the container, completing the barrier between the container content and the outside world. Labels belong to a special group of secondary packaging materials. A product's packaging system is tailored to meet the required level of protection and is comprised of the complete set of packaging materials: primary container, closure system, secondary containers when necessary, and labelling.

This chapter will cover the general requirements of containers and closures for medicinal products, the raw materials from which containers and closures are being made and the different shapes of containers that are being used. And finally the quality control of containers will be addressed.

The requirements for containers originate from the functions: protection of the product, facilitate product use and provider of information. In the design phase of the medicinal product the material, form and functions of the primary container are determined. Compatibility of the selected container with the medicinal product is demonstrated by stability studies.

24.1.2 Protection of the Product

The characteristics of the medicinal product define the properties needed to protect the product. For example, the glass quality requirements for injections or eye drops are different from those for an oral medicine.

The requirements could be different for a similar route of administration.

Some products for example have to be protected from light. Protection from external moisture, oxygen, light, micro-organisms, particles, fracture and deformation may be necessary. The medicinal product should not lose moisture or interact with the container in a way that would adversely affect the quality of the product.

24.1.2.1 Protection against Moisture

In case of dry preparations (powders, tablets, capsules) it is important that moisture cannot permeate the container. A hygroscopic product can absorb moisture from the atmosphere and become damp. Moisture can enhance degradation, both chemically and physically. For example capsules can get sticky and disintegrate.

24.1.2.2 Protection against Oxygen

Substances that are sensitive to oxidation should be protected from the ingress of oxygen into the container. Plastic containers are more permeable to oxygen, when compared to glass and aluminium ones. Different types of plastics are more or less permeable to oxygen.

24.1.2.3 Protection against Light

Many container materials, for example coloured glass, effectively shield radiation with a wavelength < 500 nm (ultraviolet range) [1]. This light range will pass through non-coloured glass and transparent plastics. Exposure to light may increase the degradation rate of the preparation. White plastic that is not visually transparent, for example polypropylene, can allow light to pass through. This may cause a faster degradation of product, for example sorbic acid in creams in polypropylene containers. Preparations that are susceptible to light should be stored in amber glass or brown plastic containers. In some cases these containers do not offer sufficient protection and the preparation must be stored in the dark or wrapped with a material that does not transmit light (for example aluminium foil).

24.1.2.4 Protection against Micro-organisms and Particulates

The container has to minimize the chance of (microbiological) contamination during the use of the medicinal product. The preferred container for creams is a tube instead of a jar.

24.1.2.5 Protection against Deformation/ Fracture

Protection against deformation and fracture is a requirement for solid pharmaceutical preparations such as tablets and suppositories. A container for tablets for example protects its contents from external mechanical forces.

24.1.2.6 No Interaction with the Container

Medicinal products can interact with the container or with plastics from an administration system. Possible interactions are absorption, adsorption or the release of additives from the container. Migration of (active) substances from the preparation into the container and migration from additives in the container (softeners, stabilizers) into the medicinal product should not occur.

24.1.2.7 No Transmittance of Liquid, Vapour or Gas

Gas, such as oxygen, or moisture should not permeate across container walls. This permeation should not occur from either the environment to the product or *vice versa*. Permeation of gas and moisture can affect the concentration of the product.

For example the content of nitroglycerin in nitroglycerin tablets can decrease because of evaporation. To prevent this from taking place, the container is lined with an additional layer of aluminium foil.

24.1.3 Transport, Handling and Information

The following characteristics and requirements of containers are important for the transport and handling of the medicine and the possibility of presenting information about the product:

- Sizes and weight; a glass bottle is heavier than a plastic one; square bottles take less space in storage than round ones; a container should be big enough for a label.
- Resistance to fracture; the container should not break during transport or use.
- Resistance to temperature; the container of preparations that are kept in the fridge or freezer should resist these low temperatures (it should not get too rigid or brittle); the container of preparations which are sterilised by hot air or steam should resist high temperatures and moisture.
- Child safety; some preparations should be dispensed with a child-resistant closure (see also Sect. 24.4.20).
- User friendliness for the patient; a container should be easy to handle by the patient.
- Delivery of a reproducible dosage of the medicine (see also Sect. 24.4.19).
- Product identification. Usually the label on the container communicates the necessary information. Regulations concerning the labeling of drug products are extensive and detailed. EU-guidelines [2–6] are accompanied by national legislation on the labeling of pharmacy preparations.

It is not always possible to develop a container that satisfies all the necessary requirements. Certain requirements can counteract each other such as child-resistant closure versus user friendliness and impermeability versus weight. Specific requirements for different types of containers will be described in separate paragraphs (see Sect. 24.4).

24.2 Container Materials

The following substances are the most important starting materials for pharmaceutical containers:

- Glass
- Metal (aluminium)
- Plastic
- Rubber
- Cardboard and paper

These materials will be discussed in Sects. 24.2.1–24.2.5.

The chapter 'Materials used for the manufacture of containers' in the Ph. Eur. describes the quality requirements and the assay methods for some starting materials often used for pharmaceutical containers [7].

24.2.1 Glass

24.2.1.1 Contents and Characteristics

Glass is mostly formed out of silicon dioxide. The addition of other oxides (for example sodium, calcium, potassium, boron and aluminium oxide) decreases the very high melting point of silicon dioxide (>1,700 °C) [8]. The mixture (glass) can thus be formed at lower temperatures. The mixture solidifies without crystallising. The most outstanding characteristic of glass is its transparency. As a result of having only a partly ordered structure, glass does not scatter light.

The addition of boron- and aluminium oxides serves primarily to improve the chemical resistance. To colour glass, small amounts of sulfur and metal oxides (iron, chrome, cobalt) can be added.

Glass consists of an irregular network of Si-O-bonds. The cations of the mentioned oxides are bound to these bonds. Glass is a (weak) ion exchanger and therefore not completely inert.

There are two basic types of glass: soda-lime-silica glass and neutral glass (also known as borosilicate glass). In neutral glass a percentage of sodium oxide is replaced by boron oxide and aluminium oxide. Neutral glass is more resistant to hydrolysis and temperature shock, but is more expensive than soda-lime-silica glass. To increase its resistance to hydrolysis soda-lime-silica glass is surface-treated with ammonium sulfate (wet granules are poured into hot bottles) or sulfur oxide. Hereby sodium ions are exchanged for hydrogen ions. Another method is using a fluorine-containing gas such as 1,1-difluoroethane to increase the surface resistance [8].

Blown glass and tube glass can be distinguished from the way they are manufactured.

Blown glass is manufactured by pouring melted glass into a mould and blowing the cavity from the inside. Tube glass is made by pouring melted glass around a tube [8].

Tube glass is lighter than blown glass and has a very even wall thickness. Tube glass is less sensitive to erosion than blown glass. With blown glass more sophisticated structures can be created.

Advantages of glass as a container material are:
- Few chemical and physical interactions such as absorption, adsorption and migration
- Excellent protection against air, oxygen and moisture
- Transparent material (inspecting the contents is possible)
- Protection against light is more or less possible (by colouring the glass)
- Resistant to high and low temperatures (suitable for steam and dry heat sterilisation and for deep freezing)
- Retaining its shape
- Odourless and tasteless
- Easy to clean
- Environment-friendly (in case of reuse)

Disadvantages of glass are:
- Risk of breaking
- Rather heavy, although tube glass is relatively light

24.2.1.2 Glass: Erosion

Glass is hardly interacting with chemicals but it is not inert. It reacts with water, aqueous solutions and other solvents. Even moisture in the air is able to erode the surface ('weathering'). In aqueous solutions cations of the glass are being exchanged by hydrogen ions. Because of this a surplus of OH^--ions is generated in the solution and the pH may rise. 'Base release' is a rather misleading term for this process. The release of cations by the glass may be harmful: calcium may lead to precipitations and aluminium is toxic in parenteral solutions.

It is hypothesized that the opposing process may also occur: exchange of Na^+-ions from the solution against H^+-ions in the glass [9]. Until now this is only seen in sodium chloride- and lithium chloride solutions.

In weak acid and acid solutions the exchange of cations from the glass against H^+-ions in the solution is restricted to the outermost surface. This release only slightly increases pH.

> The small increase of pH in a weak acid environment by ion exchange with the glass can be relevant to the stability of certain weakly buffered preparations. Atropine sulfate eye drops for example are hydrolysed remarkably faster at pH 6 than at pH 4. If a small increase of OH^--ions is to be expected, which is significant for the preparation, then the preparation should be buffered. When buffering is not possible for other reasons (irritation), a better quality of glass should be used.

Besides an increase of pH in neutral and alkaline solutions because of a surplus of OH^--ions, also hydrolysis of the silicate bridges will occur. Water molecules penetrate into the glass. The network becomes looser, the glass swells (gel forming) and the silicate ions and glass particles are released into the solution. These glass particles often have the shape of very thin shiny flakes or splinters which fall apart in a fine precipitation when being shaken.

The speed of erosion of glass is increased by many anions [10–13]. At pH 7 this concerns phosphate, citrate and fluoride, but not lactate, benzoate and acetate.

Neutral glass, which in principle is suitable for reuse, is being eroded/impaired by borax containing solutions (pH around 9) [14]. This demonstrates that even neutral glass will be impaired by solutions with pH >7. Therefore neutral glass bottles should be used only once for autoclaving solutions with pH >7. Plastic containers are probably more suitable for these solutions.

Calcium ions from glass can be incompatible with certain substances from the solution such as phosphate ($CaHPO_4$ will be formed) and carbonate. To prevent this interaction with glass, for example sodium edetate is added to sodium hydrogen carbonate injection solutions.

> With accelerated stability research (heating for 3 h at 120 °C and storage at 40 °C) a solution for intraocular irrigation with anions chloride, acetate and citrate even affected neutral glass: the pH changed from 7.4 to almost 8. This effect also happened when the irrigation was kept during a longer period at room temperature [13]. If citrate was left out of the solution there were no changes in the neutral glass during the storage time of 2 years at 25 °C. In plastic there was no pH change, not even in the solution containing citrate.
>
> The pH changes ran more or less parallel to the generation of particles in the solution.
>
> In glass bottles of treated soda-lime-silica glass the pH of the citrate containing irrigation rose from 7.5 to 9.3 within 12 weeks of storage at room temperature. An extensive generation of particles occurred simultaneously.

The release of aluminium from glass raises concern from the toxicological point of view. This is mainly relevant related to parenteral solutions and not so much as to orally administered preparations. Aluminium is hardly absorbed in the gastrointestinal tract. Elimination of aluminium after parenteral administration occurs mainly via the kidneys.

Patients having a high risk of aluminium intoxication are:
- Neonates and prematures (high sensitivity for toxic effects and low renal function)
- Patients with impaired renal function

– Patients to whom large amounts of parenteral solutions are administered, such as patients at intensive care units and patients who receive total parenteral nutrition [15]

The aluminium concentration of injection and infusion solutions in glass containers should be checked at the end of the shelf life. Neutral glass generally contains more aluminium than sodium calcium glass. Solutions with calcium gluconate, potassium phosphate, sodium acetate and those with trace elements can contain a high concentration of aluminium [10, 11, 16]. Solutions containing phosphate extract aluminium from glass in such high amounts that plastic containers are preferred [12].

24.2.1.3 Glass: Hydrolytic Resistance and Quality Control

The Ph. Eur. classifies glass by hydrolytic resistance: the resistance against attack by hydrolysis [17]. Hydrolytic resistance is determined by steam sterilisation of the glass with water, followed by titration of the released OH^--ions with acid. Based on the amount of OH^--ions the Ph. Eur. classifies glass into three different classes:

I. Neutral glass or borosilicate glass with high hydrolytic resistance due to the chemical composition of the glass itself
II. Soda-lime-silica glass with a high hydrolytic resistance resulting from suitable treatment of the surface
III. Soda-lime-silica glass with only moderate hydrolytic resistance

Glass is manufactured in a continuous process. The term batch therefore has a different meaning than with the production of medicines. Glass does not have a composition that can be fixed in a way that is comparable to specifications for pharmaceutical starting materials. This disadvantage should be met as much as possible through agreements with the supplier and the design of a certifying system (see also Sect. 24.5).

An extra difficulty is posed by differences in the composition of the same glass type from different suppliers. Type I glass from one supplier is therefore not identical to type I glass from another supplier. This has to be taken into account when determining shelf life.

The differences between bottles within one batch can be observed by the course of the erosion of treated soda-lime-silica glass. The erosion in each bottle does not start at the same moment [13, 18, 19]. A typical course is that once the process has started, the pH rises to a maximum (around 9.5) in a relatively short time (at the utmost several weeks) and stays constant thereafter. The moment of the start of the pH-increase seems to depend on the irregularities in the treatment of soda-lime-silica glass. The final pH seems to depend on the quality of the glass itself. The formation (and sometimes disappearance) of particles, visible by the naked eye, follows a course which is also dependent on the pH and on the composition of the solution (in some solutions silicate dissolves for example).

24.2.2 Aluminium

Aluminium is being used as container material for tubes, canisters with an inhalation solution and as part of blister packages. In blister packages the aluminium lidding foil has a heat seal layer that brings about the attachment to the plastic form foil or to the aluminium form foil. Furthermore, aluminium is still used as a primary container for suppositories and as a secondary container to give extra protection to medicines against light.

Aluminium is also a part of closures:

- A layer of pure aluminium is wrapped around a cork inlay to obtain a damp tight container (for example a tablet container for nitroglycerine tablets).
- Infusion solution bottle closure (screw- and dust cap).
- Crimp cap for bottle for infusion and injection solutions.

Advantages of aluminium are:

- Impermeable to liquid, moisture, gas and air.
- Protection against light.
- Resistant to high and low temperatures.
- Odourless and tasteless.
- Good impact resistance.
- Light-weight.

Disadvantages of aluminium are:

- Sensitive to corrosion.
- Incompatibilities; the chemical resistance of aluminium is only moderate with for instance acids, bases and halogenides; aluminium tubes are therefore often protected by an inside and outside lacquer.

24.2.3 Plastics

Plastics are mixtures of synthetic and natural polymers and additives. These polymers can be divided into two groups:

- Thermoplastics: plastics that soften on heating and set again upon cooling
- Thermosets: plastics that only soften during the production process and irreversibly hardens by the action of heat

When a container made of a thermoset plastic is being heated, the container will not soften, but will decompose.

An example of a thermoset is phenol formaldehyde (Bakelite). Thermosets are mostly applied as material for lids and closures.

Most plastics that are used for containers of medicines belong to the type thermoplastics.

All plastics have advantages and disadvantages. Plastics can be assessed by the following characteristics:

- Mechanical characteristics (e.g. impact resistance, flexibility)
- Optical characteristics
- Chemical resistance
- Temperature resistance
- Permeability/barrier characteristics

Tables 24.1, 24.2 and 24.3 give these characteristics of some plastics. The data are based on literature and are meant as an indication. The abbreviations will be explained in the subsections.

During the production process of a plastic, additives can be added to:

- Affect the production process, for example catalysts
- Improve polymer stability, for example antioxidants
- Alter the mechanical characteristics, for example plasticisers
- Improve the visual appearance, for example colorants

Ph. Eur. specifies a number of additives allowed for plastics for containers for pharmaceutical products [7]. Because of the addition of additives, plastics from different suppliers do not have the same composition. Always request the composition of the plastic container being purchased, from the supplier, and only change the containers of one supplier for those from another after considering the differences in the plastic. A raw material or a preparation cannot just be repacked from a certain plastic container to a container from another plastic without reassessing the shelf life. For authorisation of medicines an extensive declaration of the composition of the primary plastic container is demanded and declarations of technical characteristics, suitability and toxicity have to be submitted.

The characteristics and use of the plastics will be discussed one by one.

Table 24.1 Temperature resistance of some plastics

	Minimal temperature °C	Maximal temperature °C	
	Long time	Short time	Long time
HDPE	−50	90/120	70/80
LDPE	−50	80/90	60/75
PET	−20	80	65
PP	0/−30	140	100
COC	−30	140	100
PS	−10	60/80	50/70
SAN[a]	−20	95	85
SB[a]	−20	60/80	50/70
PVC (hard)	−5	75/100	65/85
PVC + softener	0/−20	55/65	50/55

[a]See under polystyrene

24.2.3.1 Polyamide (PA)

Polyamide is a polymer formed from condensation of dicarbonic acids and diamines or from condensation of amino acids and lactames. In publications, in English, polyamids are called nylon. To distinguish them from one another a number is added that represents the number of C-atoms of the monomer or monomers. Nylon type 6.6 (polyamide 6.6) is the most common commercial grade of nylon. It consists of hexamethylene diamine and adipinic acid.

The characteristics of polyamides depend very much on the composition. They are generally wear-resistant and all forms are hygroscopic. This absorption of water (plastifying effect) significantly changes the properties of polyamides. The thermal resistance of most polyamides is high. They can be sterilised by steam or gamma radiation; polyamide 6.6 can even be sterilised by hot air.

24.2.3.2 Polycarbonate (PC)

The most common polycarbonate is a polymer generated from condensation of bis-phenol-A (= 2,2-diphenylolpropane). Polycarbonate has good thermal and mechanical characteristics. It is a stiff material which is fraction- and impact-resistant and also resistant to strongly diverse temperatures.

Polycarbonate is not resistant to alkali, strong acids and organic solvents (for example chloroform and acetone). The gas permeability of polycarbonate is relatively high compared to for example polyethylene, and comparable to polystyrene.

24.2.3.3 Polyethylene (PE)

Polyethylene (= polyethene = polythene) is a polymer that consists of ethylene units. The different forms are determined by the method of production:

- Low density - polyethylene (LDPE)
- High density – polyethylene (HDPE)

LDPE is produced under high pressure (1,500 bar) and temperature (150–240 °C), in the presence of catalysts. HDPE is produced under low pressure (0–2 bar) and temperature (70 °C), in the presence of catalysts. HDPE is a stiff type of polyethylene whilst LDPE is more flexible. An increase of the density gives a reduction of the flexibility and a not fully transparent product. However, other characteristics are improved by increasing the density.

Table 24.2 Chemical resistance of some plastics

	HDPE	LDPE	PET	PP	COC	PS	SAN	SB	PVC	Soft-PVC
Water cold	+	+	+	+	+	+	+	+	+	+
Water warm	+	?	±	+	+	±	+	±	±	±
Acids weak	+	+	+	+	+	+	+	+	+	+
Acids strong	+	±	±	±	+	±	±	±	+	–
Acids oxidising	–	–	±	–	+	–	–	–	±	–
Base weak	+	+	±	+	+	+	+	+	+	+
Base strong	+	+	–	+	+	+	+	+	+	–
Sol.anorg.salt	+	+	+	+	+	+	+	+	+	+
Halogens	–	–	–	±	–	–	±	–	±	–
Aliphatic hc[a]	+	+	–	+	–	–	+	±	+	–
Choride hc[a]	±	–	±	–	–	–	–	–	–	–
Unsat.chlor.hc[a]	–	–	±	–	–	–	–	–	–	–
Aromatic hc[a]	±	–	–	±	–	–	±	–	–	–
Alcohols	+	±	–	+	+	+	+	–	+	–
Esters	+	±	±	±	±	–	–	–	–	–
Ketones	+	±	–	±	±	–	–	–	–	–
Aldehydes	±	?	?	+	±	–	–	–	–	+
Ether	±	–	±	+	–	–	–	–	–	–
Amines	+	?	?	+	?	+	+	+	±	+
Organic acids	+	+	+	±	±	±	±	±	±	±
Mineral oils	+	±	+	+	–	+	+	±	+	±
Lipids, oils	+	±	+	+	–	–	–	–	+	±

± moderately resistant
? no data
+ resistant
– not resistant
[a]hc is hydrocarbon

Table 24.3 Other characteristics of some plastics and glass

	HDPE	LDPE	PET	PP	COC	PS	SAN	SB	PVC Hard	PVC Soft	Glass
Impact resistance	±	+	+	±	–	–	–	±	±	+	–
Flexible	–	+	–	–	–	–	–	–	–	+	–
Transparent	–	+	+	±	+	+	+	±	+	±	+
Colouring	+	+	+	+	+	+	+	+	+	+	+
Permeable to gas	–	±	±	±	–	+	+	+	±	±	–
Biocompatible	+	±	+	±	+	–	±	–	±	–	+
Permeable to liquid	–	±	±	±	–	+	+	+	±	±	–
Leaching of additives	±	–	–	±	–	–	–	±	±	+	–
Resistant to 15 min at 121 °C	+	–	–	+	+	–	–	–	–	*	+
Streaming water vapour	+	–	–	+	+	–	+?	–	*	*	+

+ yes/good
± possible/moderate
* dependent on the composition (additives)
– no/poor

For HDPE compared to LDPE:

- The permeability to water vapour is lower
- The permeability to gas is lower
- The chemical resistance is higher
- The light transmission is lower
- The temperature resistance is higher

Both HDPE and LDPE are plastics that are widely used because of their low permeability to water vapour and their high chemical resistance. PE is very resistant to gamma radiation.

24.2.3.4 Cyclic Olefin Copolymer (COC)

Cyclic olefin copolymers are a new class of polymeric materials based on cyclic olefin monomers (as 8,9,10-trinorborn-2-ene) and ethene. These materials are also known as cyclic olefin polymers (COP) when only one single type of cyclic olefin monomer is applied. COC is very transparent, the optical properties are in many ways similar to glass. COC is one of the few transparent polymeric materials able to withstand steam sterilisation. Permeability

to water vapour and gas is low. COC shows good chemical resistance to alcohols, acids and bases, but it is attacked by non-polar solvents.

COC vials or syringes can be an alternative to glass containers. Strong points are good barrier properties, good chemical resistance, high purity and low leachables of the material, its clarity, and compatibility with sterilisation by gamma radiation, steam, or ethylene oxide. Being a stiff polymer material, impact resistance can be low compared to more flexible materials.

24.2.3.5 Polyethylene Terephthalate (PET)

Polyethylene terephthalate is a polyester. It is a linear ester composed of ethylene glycol and terephthalic acid. PET has excellent mechanical characteristics; it is for example pressure- resistant. The chemical resistance is good compared to other plastics. PET is not resistant to strong alkali and limited resistant to strong acids and chlorinated hydrocarbons (see Table 24.2).

24.2.3.6 Polypropylene (PP)

Polypropylene (= polypropene) generates from polymerisation of propene. With stereo specific catalysts three types of polypropylene can be produced:

- Syndiotactic polypropylene; the methyl groups are alternately positioned with respect to the polymer chain.
- Isotactic polypropylene; all methyl groups are placed on the same side of the polymer chain.
- Atactic polypropylene; the methyl groups are randomly placed with respect to the polymer chain.

The position of the methyl groups defines the extent of crystallinity and therefore the mechanical and chemical behaviour. Isotactic polypropylene for example is stiffer, harder and stronger than atactic polypropylene. The polypropylene that is used for containers usually consists of a high percentage of isotactic polypropylene. Atactic polypropylene is not used pharmaceutically.

Both chemical and physical characteristics of polypropylene resemble high density polyethylene, but polypropylene is clearer, harder, has a lower density and a better thermal resistance (polypropylene can be steam sterilised). Polypropylene is less resistant to low temperatures than high density polyethylene. The chemical resistance of polypropylene is good (see Table 24.2). To protect polypropylene from oxidation, antioxidants are always added. Resistance to gamma sterilisation is relatively poor, but can be enhanced by additives.

24.2.3.7 Polystyrene (PS)

Polystyrene is generated from the monomer styrene by polymerisation in the presence of a catalyst. It is a crystal-clear plastic, easy to colour and completely free of odour and taste. Polystyrene is quite hard and brittle (little impact-resistance). It is resistant to acids, alkali, alcohol and inorganics. It is not resistant to boiling water and many organic solvents, such as chloroform and ether, or to fatty oils. Therefore polystyrenes are not suitable for packaging dermatological products containing fats.

The characteristics of polystyrene can be modified by:

- Copolymerisation of styrene with butadiene (SB). This generates an impact-resistant polystyrene. This modification however results in a loss of transparency and necessitates the addition of stabilizers such as antioxidants.
- Copolymerisation of styrene with acrylonitrile (SAN). This generates a transparent polystyrene that has a better resistance to chemicals and higher temperatures.

The permeability to oxygen and water vapour of polystyrene and modified polystyrene is relatively high.

24.2.3.8 Polyurethane (PUR)

Polyurethane is a collective term for a group of polymers that contain an urethane group (-NH-COO-). They are generated from a reaction between polyesters and polyethers with di- or poly-isocyanates.

Dependent on the starting materials, polymers with strongly diverse characteristics can be produced, varying from thermoplasts to thermosets.

Polyurethane has a range of packaging functions and is often used as filling material in tablet containers. Polyurethanes do not have a good resistance to acids and alkali.

24.2.3.9 Polyvinylchloride (PVC)

Polyvinylchloride is used as basic material for the production of infusion bags. It can also be found in blister packages. Polyvinylchloride is generated from the monomer vinylchloride with the help of a catalyst. Pure PVC is a hard, transparent plastic.

Additives in PVC for infusion bags are: stabilisers and plasticisers. By adding a plasticiser a flexible, soft plastic is formed. The amount of plasticiser in PVC can rise to 60 % of the total weight. Plasticisers that are often used are di (2-ethylhexyl)phthalate (DEHP) and dioctylphthalate (DOP). DEHP is the only softener that the Ph. Eur. allows to be used in PVC as material in containers for blood, blood products and aqueous solutions that are used for intravenous infusion. In this case the amount of DEHP in PVC should not be more than 40 % [7].

DEHP is a lipophilic compound and can therefore migrate from the PVC into medicines that contain lipophilic or adsorbing substances. Exposure of the patient to softeners should be minimized. Zinc or calcium salts are used as stabilizers. The use of stabilizers is also limited by the Ph. Eur. [7].

The interaction between PVC and liquid medicines has been studied extensively [20].

Critical topics include the release of softener from the PVC as well as the sorption of medicines. Sorption of medicines occurs more to PVC than to glass and polyethylene [21].

PVC can be sterilised in a steam steriliser with pressure compensation.

Hard PVC is used for blister packages. It is preheated in a blistering machine and then round or capsule-like cavities are being formed in a moulding station. PVC is relatively permeable to water vapour and therefore not suitable to contain hygroscopic tablets or capsules. However, water permeability is greatly reduced when the PVC-film is combined with a thin layer of PVDC (polyvinylidene chloride).

24.2.4 Rubber

Rubber is the starting material of elastic packaging materials that are used in closures of containers. Natural rubber, bromobutyl rubber, chlorobutyl rubber and silicone rubber can be distinguished [22–24].

Rubbers are generated by vulcanisation (crosslinking) of elastomers. Elastomers are macromolecular organic compounds that are formed from natural or synthetic substances. In the production process additives are being used as vulcanisers, catalysts, stabilizers, colourings, fillers and lubricants, see Table 24.4.

The different rubbers distinguish themselves by three factors:

- The basic elastomer
- The method of vulcanisation
- The amount and type of additives

Table 24.4 Composition of rubber

Component	Weight percentages
Polymer (elastomer)	40–95
Vulcanisers	1–4
Catalyst	2–8
Filler	0–60
Colouring	0–10
Lubricant	0–4
Stabilizer	0–3

The choice of the rubber depends on the preparation and on the functionality of the container:

- Adsorption from components of the preparation to the surface of the rubber as well as migration into or through the rubber should not happen.
- The rubber should not release substances into the preparation.
- The material should be suitable for its use; rubber closures that are being used for multiple piercing by needles have different requirements than the dropper of an eye drop bottle.

Which rubber is selected for use in a particular pharmaceutical container not only depends on the compatibilities or the most suitable physical characteristics, but also on the availability. In actual practice only industrial producers of medicines are able to choose the most optimal container.

Table 24.5 gives an overview of the characteristics of some rubbers.

24.2.4.1 Vulcanisation Methods

There are three vulcanisation methods: with sulfur, with bifunctional reagents and with peroxides. Most importantly, the vulcanisation method determines which contaminations will be present in the product. The vulcanisation density is the number of bonds between different chains per volume-unit.

Vulcanisation with sulfur

Elementary sulfur or compounds that can be used as a source of sulfur form together with suitable additives at higher temperatures thio-ether-, disulfide- or polysulfide-bridges in and between chains. This vulcanisation method is primarily suitable for those elastomers that have unsaturated bonds. The rubber produced by this method has good mechanical characteristics. However, a disadvantageous chemical characteristic of rubber vulcanised with sulfur is that additives can leach into the product. An example is the release of thiol compounds, which are incompatible with some mercury compounds.

(continued)

Table 24.5 Characteristics of some rubbers

Characteristic	Natural rubber	(Halogen-) Butylrubber	Silicone rubber	Ethylene-Propylene rubber
Elasticity	Very good	Moderate	Good	Good
Deformation rest	Very little	Moderate/large	Very little	Little
Permeability (gas and water vapour)	Very high	Very little	Very high	Moderate/high
Reactivity (ageing)	High	Very little	Very little	Very little
Temperature resistance	Very poor	Very good	Very good	Very good
Release of substances	Possible	(Less) possible	Less possible	Possible

Vulcanisation with bifunctional reagents

The reagent, for example a diamine, forms covalent bonds with the polymer chains. Usually the use of catalysts is not necessary. This vulcanisation method is mainly used for the production of halogen butyl rubbers and results in materials with good chemical characteristics (few incompatibilities).

Vulcanisation with peroxides

The peroxide serves as a producer of radicals and is not being built into the polymer. The result of this vulcanisation is a chemically inert product. The use of a catalyst is not necessary and with a right choice of the peroxide, combined with an after-treatment of the material (extraction of the peroxide) a rubber that releases only very small amounts of substances is produced. This method is being used for the production of silicon-elastomer and of ethylene-propylene rubber.

24.2.4.2 Additives

Silicates, silicic acid, calcium carbonate or barium sulfate are used as fillers. Silicates and silicic acid make rubber more sustainable. Colourings for rubber are for example titanium dioxide and iron oxides. It is better to avoid organic colourings due to the chance of migration of the colouring to the rubber surface, followed by migration into the preparation.

24.2.4.3 Natural Rubber

The oldest form of rubber is natural rubber. The basic elastomer of natural rubber is taken from the latex of the rubber tree (Hevea brasiliensis, Euphorbiacea family). Latex consists of carbohydrates, water, fatty acids, proteins and stearines. The complex composition of latex varies significantly with origin, season, etc. This variation in composition is the main disadvantage when using this material in pharmaceutical products.

Natural rubber consists of polyterpenes. The gross formula of this basic elastomer in natural rubber is $(C_5H_8)n$. The module is isoprene (the base of all terpenoides). It is a polyunsaturated polymer with a structure as shown in Fig. 24.1. The value of n is very high; the molecular weight lies between 200.000 and 300.000.

The chemical structure of the natural latex product determines the characteristics of the rubber produced from that latex:

- Natural rubber can, dependent on composition and origin, release foreign substances (for example UV-absorbing) to a preparation.
- Due to high unsaturation of the basic elastomer, a high crosslink or vulcanisation density can be generated. This results in good mechanical characteristics, as a highly elastic product is generated.
- Due to the high number of unsaturated bonds that are still present in the end product after vulcanisation, the natural rubber is a chemically reactive compound. This reactivity significantly reduces the chemical compatibility and useful shelf life of natural rubber.
- Due to its structure, natural rubber has a high permeability to gas and water vapour.
- Natural rubber is susceptible to the absorption of many substances (for example preservatives such as chlorobutanol and phenylmercuric borate).

24.2.4.4 Butyl Rubber, Bromobutyl Rubber and Chlorobutyl Rubber

The basic elastomer of butyl rubber is the synthetized polymer poly-isobutylene with approximately 3 mol% isoprene. In case of the halogen butyl rubbers the isoprene is replaced by halogen isoprene. The structure of the basic elastomer is shown in Fig. 24.1. The basic elastomer of butyl rubber contains relatively few unsaturated bonds compared to the basic elastomer of natural rubber. The reactivity of butyl rubber is therefore less than that of natural rubber. To advance the vulcanization process, a higher concentration of reagents and/or a longer reaction time and a higher reaction temperature are therefore necessary. This relatively high amount of additives in butyl rubber can cause problems when it comes into contact with the pharmaceutical preparations. 'Leaching' may occur, where dispersed (not chemically bound) additives migrate to the surface of the rubber, followed by extraction into the preparation.

When producing the bromo- and chlorobutyl rubbers, the halogen basic elastomer is used. Like the non-halogen basic elastomer, this contains relatively few unsaturated bonds.

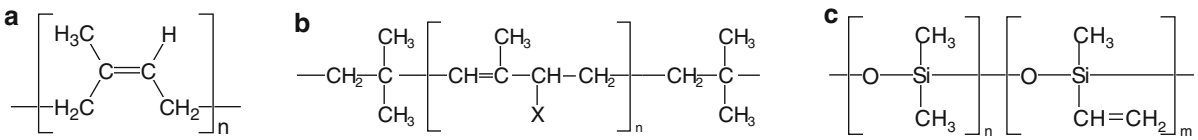

Fig. 24.1 Structural formulas of (**a**): basic elastomer in latex; (**b**): basic elastomer of butyl rubber, in which x = H for butyl rubber; x = Cl for chlorobutyl rubber; x = Br for bromobutyl rubber; (**c**): basic elastomer of silicone rubber

The halogen atom activates the double bond and increases the reactivity of the basic elastomer. Therefore no extra measures to accelerate the vulcanization process have to be taken, unlike the production of butylrubber. The halogen butylrubbers therefore have largely replaced butylrubber.

The chemical structure of the halogen basic elastomer determines the characteristics of the halogen rubber which is synthesised from this basic elastomer:

- Due to the fact that the basic elastomer is mainly unsaturated, only a small amount of crosslinking- or vulcanisation density is generated. This leads to a product with relatively modest mechanical properties, when compared to natural rubber.
- Due to low levels of unsaturated bonds in the final product after vulcanisation, the halogen butyl rubber is chemically unreactive; hence the product is inert and has a long shelf life.
- During the production process of halogen butyl rubbers relatively few additives are necessary and the chance that additives are leached from the rubber into the pharmaceutical preparation is less when compared to natural rubber or butyl rubber.
- Permeability to gasses and water vapour is much less for halogen butyl rubbers than for natural rubber.

Summarising: the mechanical characteristics of halogen butyl rubbers are not optimal (stronger deformation, less elastic than natural rubber), but the saturated structure leads to excellent chemical characteristics (see Table 24.5).

Rubber stoppers to close injection- or infusion bottles and –bags can be coated with a thin layer of a polymer that resembles Teflon (Teflon = polytetrafluorethene, PTFE). The result is a chemically inert stopper with significantly less "leaching" of substances from the rubber.

24.2.4.5 Silicone Rubber

The basic elastomer for silicone rubber is a linear polysiloxane, built from dimethyl siloxane units with a small amount methylvinyl siloxane groups. The ends of the chains are formed from trimethyl siloxane- or dimethylvinyl siloxane groups. The structure of the basic elastomer is shown in Fig. 24.1. Peroxides are usually used for the crosslinking of silicone rubbers (for example dicumyl peroxide or 2,4-dichlorobenzoyl peroxide).

To improve tear resistance, the additive silicic acid can be added. Other additives are usually not necessary, so migration of substances from the final product into the pharmaceutical preparation will usually be limited to residues of the peroxide. By the right choice of the peroxide and adequate after treatment of the final product this problem can be reduced. The Ph. Eur. contains a test for the presence of peroxide residues in the elastomer.

Silicone rubber, like other rubbers that are produced following the peroxide method, can give an aldehyde odour shortly after production. This is caused by traces of peroxide breakdown products. The odour disappears with time or after steam sterilisation.

Silicone rubber is very resistant to ageing and oxidation. It shows a very high permeability to gas and water vapour, which significantly reduces the pharmaceutical usefulness. Silicone rubber is very resistant to a wide range of chemicals. It is resistant to weak acids and alkali, salt solutions and mono- or multivalent alcohols and phenols. However, it is not resistant to strong acids and bases. In low molecular solvents (ketones, esters, aliphatic, aromatic and chlorinated hydrocarbons) a reversible swelling of the elastomer occurs. Many preservatives and active substances are strongly adsorbed into silicone rubber.

The mechanical characteristics of silicone rubber are very highly independent of temperature. The elastomer keeps its original hardness and elasticity with temperatures lower than -50 °C. Resistance to high temperatures is also very good (to 250 °C). Addition of metal oxides to silicone rubber can improve the temperature resistance even further.

24.2.4.6 Ethylene Propylene Rubber

The basic elastomer ethylene propylene monomer (EPM) is generated by copolymerisation of ethylene and propylene. As the polymer chain does not have double bonds, vulcanisation takes place with the use of organic peroxides. The ethylene propylene rubber that is thus generated contains no double bonds. Therefore, the product is inert and has a long shelf life.

Ethylene propylene diene polymers (EPDM) are basic elastomers with double bonds in the side chain. They are generated by adding small amounts of diene monomers in the copolymerisation of ethylene and propylene. Due to the presence of this unsaturated bond in the basic elastomer both vulcanisation with peroxides and vulcanisation with sulfur are possible. Vulcanisation with peroxides is usually chosen. This generates a product that is relatively inert and well resistant to ageing.

When synthesising ethylene propylene rubber usually a filler (for example aluminium silicate or calcium carbonate) and a plasticiser (for example an aromatic hydrocarbon) are added and a colouring if necessary.

As with silicone rubber, ethylene propylene rubber can give an aldehyde odour. Ethylene propylene rubber is highly resistant to water, alkali and dilute acids, and moderately to poorly resistant to hydrocarbons, lipids and concentrated acids. It is resistant to the high temperatures of steam sterilisation.

24.2.5 Paper and Cardboard

Paper is a single-layer material (7–250 g/m^2); cardboard is a multiple-layer material (250–600 g/m^2). Both are made from cellulose fibres that are compressed.

Paper is the primary packaging layer for the packaging of single dose oral powders in powder paper (Sect. 24.4.12). However, it is more common for paper and cardboard to be used as secondary or tertiary packaging layer. Paper is also the basic material of a special packaging material: the label (Sect. 24.2.6).

Powder paper should not be contaminated, should not shed fibres and within one batch there should not be much difference in weight per surface area (= constant powder paper weight).

For weighing of fatty or semisolid starting materials so called greaseproof paper can be used. This type of paper is smoother and stronger compared to 'normal' powder paper. Lipid penetrates slower into the paper, but interactions (migration) are not excluded.

Cardboard is a popular material for the secondary container. It is relatively cheap, easy to design in suitable shapes and easily printed with information. Cardboard is often used as tertiary container to protect the packaged products during transport. The objectives determine the requirements that are set for the material. For example, to send a package to the tropics, a cardboard box with an aluminium inside layer is appropriate to protect the contents against moisture.

24.2.6 Labels

The label is an important part of the pharmaceutical product. The most common label used within the European pharmacy is the self-adhesive label. This consists of a laminate of two special types of paper: the carrier material and the label paper. The carrier material consists of paper on which a silicon layer is fixed. The label paper can be printed on the printing side and on the carrier side it has an adhesive layer. The adhesive is usually of the permanent type, rendering the label non-removable once applied [25]. Label adhesives on plastic containers such as infusion bags require additional attention, see Sect. 24.4.13.

Uniform labels of good constant quality are very important for pharmacy preparation. Quality control of incoming labels, both printed or unprinted, should equal the requirements for containers described in Sect. 24.5.

The way in which information should be put on labels (labelling) is dealt with in Sect. 37.3.

24.3 Closures

24.3.1 Closure Systems and Functions

The container closure system seals the primary container after filling, protecting the contents from interactions with the external environment. In the majority of cases, the closure also allows access and use of the product. Where tamper evidence is required the closure system must be able to show that the container has been opened.

In order to provide these functions, the forms and methods used to provide an effective seal vary widely. The closure systems used in pharmacy usually depend on a system were a relatively soft material is pressed onto a hard material. The softer, more resilient material will compensate for small imperfections on the hard surface, leading to an effective seal. The materials forming the closure are pressed together by means of:

- Threaded screw cap. An example is the bottle screw cap with a relatively soft liner material on the inside of the cap. A screw cap made of (softer) thermoplastic materials often doesn't need an additional liner material. The closing torque force must be sufficient to provide a good seal.
- Material deformation. An example is the vial closure for injectable drugs. The glass container is sealed by an elastomeric stopper, firmly locked in place by means of an aluminium overcap that is mechanically crimped over the stopper and neck of the vial.
- A snap-on closure where a raised ring is forced over a bead or lip. An example is the Sterillab snap cap eye drop bottle (Sect. 24.4.2).
- A push-in closure where a tight-fitting stopper is pushed in place and stays closed by friction forces.

The other preferred form of closure system in pharmacy is heat-sealing. This usually achieves an effective and permanent seal, which can only be opened by destruction of part of the packaging material. An example is the glass ampoule, fused by heat. The fused glass forms a totally hermetic seal. Another example is the blister packaging of tablets. A multilayered film of polymer material is preformed and filled with tablets, and sealed by heat and pressure to a thin aluminium strip foil.

A heat seal which can be peeled open is formed by materials which are not completely fused together. This can be achieved by the use of materials that are more or less incompatible [22, 24].

24.3.2 Container Closure Testing

The design and manufacture of quality packaging materials is a science in itself. Container closure quality is essential and needs to be demonstrated as an integral part of the design of the medicinal product. This task can be most challenging when thousands of containers need to be reliably filled and closed on pharmaceutical packaging lines.

Many different procedures have been developed to test container closure quality:

1. Dye ingress test: the closed container is submerged in a dye solution. Leaks are more easily detected by the

application of external (air) pressure and the addition of a wetting agent to the dye.
2. Air leak detection: the closed container is submerged under water and a vacuum is applied. The addition of a wetting agent helps in the detection of air leaks.
3. Liquid loss: the filled and closed container is inverted and checked for liquid leaks. Application of a vacuum helps to identify a poor seal.
4. Water vapour permeability: a container is filled with water, closed and stored in a warm and dry environment. Weight loss by water evaporation is followed. Alternatively, a desiccant is placed inside the container and the closed container is stored in a high relative humidity environment. Weight gain through moisture is followed. This last test is suitable to test tablet blister packaging and is the preferred method in USP <671 > Containers - Performance Testing.
5. Oxygen permeability: a solution of easily oxidisable drug (ascorbic acid, or acetylcysteine) is filled in the container and the container is closed using nitrogen gas flushing to exclude any oxygen in the head space. At suitable time points, containers are sampled and the ingress of oxygen can be followed by quantification of drug loss.

The above list is not comprehensive and usually performance testing using selected tests will be sufficient. Many variations or combinations of these test methods can be made to tailor a particular packaging system. Testing is performed as part of the product development phase and can be a part of container and closure quality testing on incoming materials, or even production process monitoring. In small-scale production, it is recommended to request from the vendor any known data on container closure performance testing as a container system quality attribute. For any pharmaceutical application, it is wise to perform in-house testing of the container closure to validate the outcome of the packaging process. All that is needed is a balance and if possible some desiccant.

24.4 Packaging Forms

In this section the different types of containers for pharmaceutical preparations will be discussed. Definitions, terminology, functional requirements and materials used for the containers for pharmacy preparations will be dealt with.

Definitions and terminology are taken from the list of standard definitions of the European Directorate for the Quality of Medicines (EDQM) [26].

Besides discussing packaging forms such as bottles, tubes, strips and bags some generally used dosage delivery devices (Sect. 24.4.19), child-resistant containers (Sect. 24.4.20), containers for arthritic patients (Sect. 24.4.21) and stock containers (Sect. 24.4.18) are also discussed. Delivery devices that are specific for a special administration route will be discussed in the chapters on dosage routes and forms.

24.4.1 Bottles

A bottle is a "container with a more or less pronounced neck and usually a flat bottom" [26].

Bottles may be used to package liquid preparations for a variety of administration routes:

- Oral liquid preparations: oral solutions, suspensions and emulsions, drops for oral use
- Rectal preparations: enemas
- Dermal preparations: solutions, suspensions and emulsions for cutaneous use, shampoos
- Parenteral preparations: injection solutions, infusion solutions
- Preparations for the eye: eye drops, eye lotions
- Solutions for irrigation of the bladder, the vagina, for wounds
- Preparations for throat, nose and ear: mouth washes, gargles, ear drops, nose drops, nasal sprays
- Various: stock containers for base solutions for example

Different administration routes lead to different requirements and different designs of bottles. These bottles will also require different closures and different delivery devices. This section describes the general characteristics of these bottles and the materials used to manufacture them. In Sects. 24.4.2, 24.4.3, 24.4.4, 24.4.5 and 24.4.6 some specific bottles are discussed. In Sect. 24.4.19 closures and delivery devices are discussed.

24.4.1.1 Requirements

In addition to the general requirements for product protection (Sect. 24.1.1), handling and carrying information (Sect. 24.1.2) there are several supplementary requirements for bottles:

- A similar filling opening for all volumes
- Standardized dimensions for the neck of the bottle to enable the use of standard closures and dosage delivery devices (see Sect. 24.4.19)
- A grade mark on the bottle to indicate the fill volume

For glass bottles the Ph. Eur. describes general specifications. The suitability of the container for the preparation should always be assessed. Type I glass (see Sect. 24.2.1) is considered to be suitable by the Ph. Eur. for all preparations. Type II glass is not suitable for aqueous parenteral products with pH >7. Type III glass is unsuitable for aqueous parenteral products. These specifications are based on the potential generation of particles in the solution (see Sect. 24.2.1). These guidelines will also apply to other

Table 24.6 Materials of bottles, jars and bags for different pharmacy preparations

Preparation	Glass			Plastic			
	I	II	III	PE	PP	PVC	PET
Oral							
Liquid			+	+	+	+	+
Solid			+	+			
Rectal				+			
Dermal[a]			+		+		+
Parenteral							
Liquid, aqueous	+	+[b]		+	+	+	
Powder; non aqueous			+				
Ocular							
Eye drops	+		+	+	+		
Eye lotions					+		
Irrigations							
For the bladder				+	+	+	
For the vagina			+	+	+		+
Ear, nose, throat							
Mouth wash, gargle		+	+	+	+	+	
Nose drops, ear drops		+	+	+			
Sterile base solution	+	+[b]					

+ usual/possible
[a]Shampoo preferably in plastic
[b]Not for solutions with pH > 7

pharmaceutical products which are meant to be free from particles (for example eye lotions).

24.4.1.2 Materials

Materials generally used for bottles are:

- Glass, transparent or amber; required hydrolytic resistance depends on usage
- Plastic; mainly PET (polyethylene terephthalate), PP (polypropylene) and sometimes PE (polyethylene)

The most significant advantages of plastic over glass are low weight and high fracture resistance. A major disadvantage is the possible deformation when heated.

Glass and plastic differ in permeability and interactions between the packaging material and contents. Glass is the least permeable to air (oxygen) and liquid. The permeability increases in the sequence: glass < HDPE < PP < PET. Glass, PP and PET generally present few interaction problems; HDPE can show adsorption. More material characteristics are described in Sect. 24.2.

Table 24.6 provides an overview of the materials that are being used for packaging different preparations in bottles.

The closure on glass bottles is usually made of polypropylene.

24.4.1.3 Pouring Ring

Glass bottles may require a pouring ring (of polyethylene). To avoid contamination of the bottle, the pouring ring is fitted while wearing gloves. Plastic bottles do not need a pouring ring.

24.4.2 Containers for Eye Drops

In this section the general requirements for eye drop containers is discussed. Various multidose containers and some single use containers are described.

24.4.2.1 Requirements

The ideal eye drop container should:

- Be easy to handle by the patient
- Deliver only one drop at the time
- Deliver a reproducible drop size
- Have a dropping tip that does not damage the eye
- Be easy to fill
- Have dimensions that are suitable for labelling
- Make visual inspection of the contents possible
- Allow steam sterilisation when closed (empty as well as filled)
- Be resistant to high (steam sterilisation) and low temperatures (fridge, freezer)
- Not release substances into the preparation, not during steam sterilisation and not during storage
- Not adsorb substances from the preparation
- Not be permeable to gas or water vapour, not during steam sterilisation and not during storage

- Protect the contents against light
- Protect the preparation against microbial contamination during storage
- Have a tamper-evident closure design
- Be constructed so that microbial contamination during usage is prevented
- Be reliably reclosable in case of multidose containers, or in case of single-dose packaging, the closure cannot be reclosed

There is currently no eye drop container available for pharmaceutical preparations that meets all these requirements. Table 24.7 shows which requirements are met by some containers.

Most eye drop containers deliver drops that are too large for the absorbing capacity of the eye [27]. The drop size varies from 25 to 75 microlitres. The drop size not only depends on the type of dropper used, but also on the formulation of the preparation. A smaller eye drop volume, from 5 to 15 microlitres, provides a sufficient effect. Devices to administer eye drops are discussed in Sect. 24.4.19. Physical factors that determine the drop size are also described in that section.

24.4.2.2 Eye Drop Bottles for Multiple Use

Eye drops are mostly dispensed in a multidose container. The Ph. Eur. describes that this container should contain a maximum of 10 mL [28].

Eye drop bottles for multiple use that are suitable for pharmacy preparations are often composed of a glass bottle with a rubber or plastic dropper. There are differences in construction and the quality of these parts. In this section three types of Gemo bottles, the Eye drop bottle with a polypropylene dropper and the Eye drop bottle with a Zentrop® dropper will be discussed.

The glass of eye drop bottles has hydrolytic resistance I or III (see Sect. 24.2.1). Type I glass is preferable and is most universally applicable.

Most eye drops that are available as a licensed product are packaged in a plastic bottle. These bottles have the advantages of low weight and high fracture resistance. However, plastic bottles are not resistant to steam sterilisation and therefore have to be filled under aseptic conditions. This is a problem for pharmacy preparation because of extra facilities that are necessary for aseptic filling. In addition, these bottles should be delivered sterile and free from dust.

Many pharmacies use a sterile plastic eye drop bottle that is described in the German NRF (see Fig. 24.2) [29]. This bottle consists of LDPE (low density polyethylene) to which no additives are added. The bottle is delivered clean and sterile, ready for use. The NRF recommends the use of this bottle for povidone iodine eye drops.

24.4.2.3 Gemo Bottle

The Gemo bottle® is named after Georg Moldow, the designer of the bottle. The bottle consists of several parts: a glass bottle (hydrolytic resistance type I), a polypropylene part with screw thread in which a rubber dropper is attached and a polypropylene cap (Fig. 24.3). The dropper originally consisted of silicone rubber. As silicone rubber is relatively easy permeable to water vapour and as it shows strong sorption of preservatives, it is replaced in the Gemo bottle "model Gemo" by halogen butyl rubber. In the 'model Sterillab' the cap is also sealed with a strip on to the part with the screw thread.

The cap of the model Sterillab has to be turned onto the shoulder of the bottle with the use of a tool. After closure it is no longer possible to unscrew the cap by hand. The model Sterillab snap cap has a bottle with a specially formed neck for the snap cap push fit closure. The closure is pressed with force onto the bottle using the lever of the closing device. The container closure integrity of the snap cap bottle is superior to eye drop bottles with screw thread. The snap cap bottle also stays hermetically closed during steam sterilisation [30].

The Gemo bottle presents some drawbacks: condensation under the screw cap and possible collapse of the rubber part as a consequence of steam sterilisation, generation of a precipitate and sorption from preparations that contain phenylmercuric borate.

The condensation as seen with the model Sterillab snap cap disappears within several days and does not influence the quality of the product [30].

Eye drop bottles with PP screw thread dropper caps lose their closure torque during steam sterilisation. This affects closure integrity, possibly to such an extent that the steam

When closing threaded PP caps a closing torque force is applied. The torque force leads to some deformation of the PP thread and the resulting material stress maintains the closure force. However, being a thermoplastic material the PP becomes soft and deformable during steam sterilisation. The internal material stress is relieved and after cooling the initial torque force is lost. To maintain proper closure quality the torque force has to be re-applied using the appropriate tool after cooling to room temperature. Relating to the risk of microbiological contamination, any necessary sealing action after heat sterilisation would only be acceptable for eye drops containing preservatives and with a relatively short shelf life.

Table 24.7 Data about several eye drop containers commercially available

	Gemo bottle						
	Model Gemo	Model Sterillab	Model Sterillab snap cap	Bottle with PP dropper	Bottle with Zentrop dropper (Remy)	Redipac	PE dropper bottle
Material bottle	Glass (I)	Glass (I)	Glass (I)	Glass (I)	Glass (III)	PP	PE
Material dropper part	Chlorine butyl rubber	Chlorine butyl rubber	Chlorine butyl rubber	PP	Chlorine butyl rubber	N.a.	PE
Material cap	PP	PP	PP	PP	PP	PP	PP
Volume bottle (mL)	10	10	10	10	10	1 and 2	10
Neck bottle	Screw thread	Screw thread	Snap fit	Screw thread	Screw thread	N.a.	Push-in
Steam sterilisation (closed)	−	+	+	+	−	+	−
No release substances							
Bottle	+	+	+	+	−	+	+
Dropper	+	+	+	+	+	N.a.	+
No sorption substances							
Bottle	+	+	+	+	+	+	+
Dropper	±	±	±	+	±	+	+
Suitable for phenylmercuric borate	−	−	−	+	−	+	+
Protection against light	+	+	+	+	+	−	−
Protection against contamination (storage)	+	+	+	+	±	+	+
Suitable to freeze	+	+	+	±	?	+	+
Contents can be well assessed	+	+	+	+	+	±	±
Presence of tamper-evident closure	−	+	+	+	−	+	+
Patient can not remove dropper	−	+	+	+	−	+	−
Dropper does not damage the eye	+	+	+	±	+	±	±
Easy to drop	+	+	+	±	+	+	+

+ good, ± moderate, − not, or inferior, ? unknown, N.a. not applicable

Fig. 24.2 10 mL PE dropper bottle. On the *left*: before filling and closing. *Middle*: after closing. On the *right*: after opening, note the tamper-evident ring

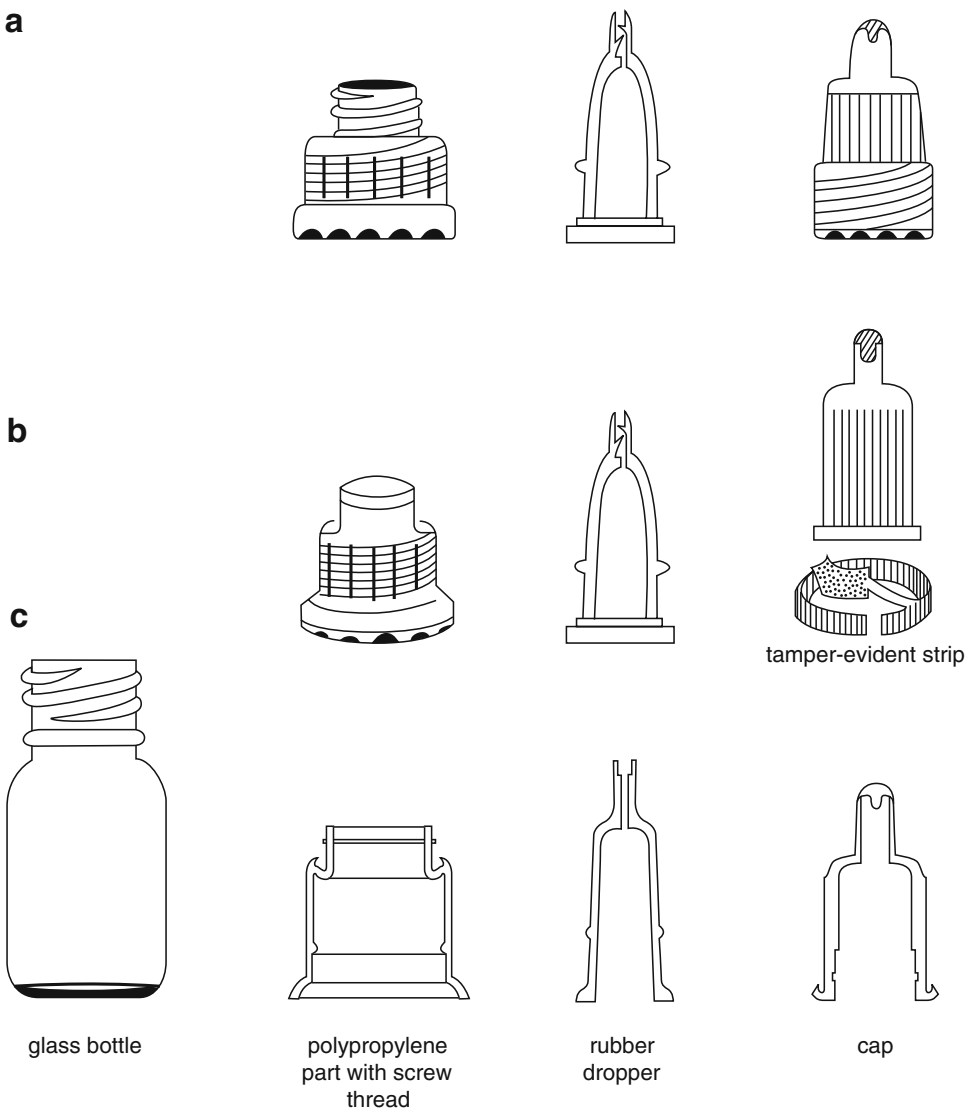

Fig. 24.3 Gemo bottles: model 'Gemo' (**a**), model 'Sterillab' (**b**) and model Sterillab snap cap (**c**)

Fig. 24.4 Bottle with PP upper part (left) and Gemo bottle model Sterillab snap cap (right), both with the cap taken off

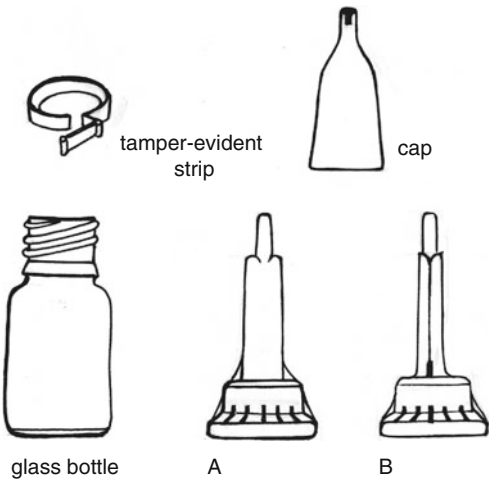

Fig. 24.5 Eye drop bottle with polypropylene upper part, front view (**a**) and side-view (**b**)

sterilisation process becomes an "open" sterilisation process. A bottle that can be sterilised hermetically closed is preferable [31]. With open sterilisation it is not possible to predict what the net effect will be of evaporation of water from the bottle and condensation of water in the bottle. Open steam sterilisation usually leads to a reduction of weight of the contents of the eye drop bottle. When open sterilisation cannot be avoided, it is recommended to weigh the individual bottles before and after sterilisation as a check.

24.4.2.4 Eye Drop Bottle with Polypropylene Dropper

This eye drop bottle consists of a glass bottle (hydrolytic resistance type I) and an upper part that consists completely of polypropylene. Due to the stiffness of polypropylene the dropper does not have a round but a flattened shape so that the patient needs less strength to create a drop. The polypropylene cap is sealed with a tamper-evident strip to the upper part (Figs. 24.4 and 24.5). After applying the upper part onto the bottle using a special tool, it cannot be unscrewed without this tool, for example by the patient. For larger batches an electrical closing device has been developed.

Advantages of this bottle are:

- Most generally applicable from the point of view of incompatibilities.
- No visible condensation under the screw cap.
- Upper part does not collapse as a consequence of steam sterilisation.
- No precipitation in solutions containing phenylmercuric borate.
- No sorption of phenylmercuric borate.

Disadvantages of this eye drop bottle are:

- For closing the bottles a special tool is needed.
- The hardness of the material of the upper part, combined with its shape may damage the eye.
- The hardness of the material makes this eye drop bottle less suitable for patients having impaired muscle power in their hands such as arthritic patients.
- The polypropylene becomes weaker during steam sterilisation. This loosens the screw closure and the steam sterilisation tends to become an 'open-sterilisation process'.
- Removing the tamper-evident seal of the cap is rather tough, and sometimes the seal strip breaks during removal.

24.4.2.5 Eye Drop Bottle with Zentrop® Upper Part

The Zentrop upper part (Fig. 24.6) consists of a dropper fixed in a screw cap and equipped with a small cap on the tip of the dropper. There is no overall cap and no tamper-evident element. The dropper is made from rubber (usually chlorobutyl rubber) or polyethylene. The threaded closure and the cap are made from polypropylene.

The glass quality of the bottle can be type I, II or III. For example the Remy® bottles have a type III bottle and are therefore not generally suitable for eye drops.

Steam sterilisation should be done with unscrewed cap for Zentrop upper parts and precipitation and sorption can occur in preparations that contain phenylmercuric borate.

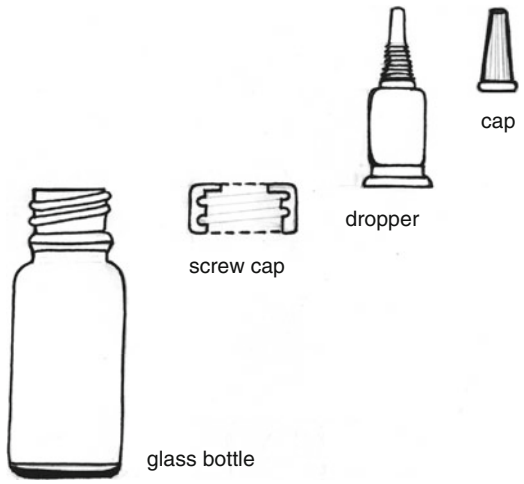

Fig. 24.6 Eye drop bottle with Zentrop upper part

24.4.2.6 Single Use Eye Drop Containers

Containers for single use are necessary for eye drops without preservative and desirable for eye drops that are only used in small quantities (local anaesthetics, diagnostics).

A suitable container for pharmacy prepared single use eye drops is the Redipac® (Fig. 24.7).

A Redipac is a drop container of polypropylene, available in the volumes of 1 and 2 mL. Redipacs can be steam sterilised. A Redipac looks like a small tube, flattened on one side after closure. After removing the cap the container cannot be closed properly anymore so that Redipacs are only suitable for single day use. The polypropylene material of Redipacs is somewhat permeable to water vapour. It is important to check the amount of water loss by evaporation through shelf life research. Licensed single-dose eye drops are often packaged in small polypropylene containers called Minims® (Fig. 24.8).

The Minims have a more conical design. Another popular packaging material for single dose registered eye drops are small blow-fill-seal containers from low density polyethylene.

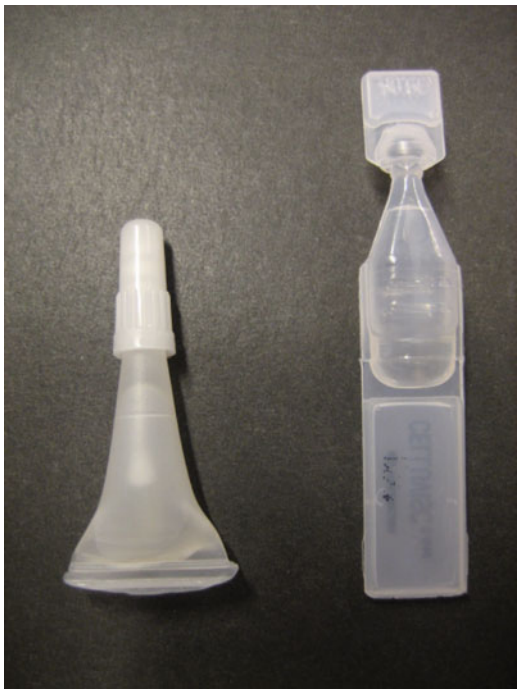

Fig. 24.8 Minims

Redipacs are produced under GMP conditions. They are practically free from dust particles and have a good microbiological quality after production. Redipacs are not supplied sterile. When the preparation cannot be sterilised in the Redipacs, the Redipacs should be sterilised empty before use. When the Redipacs have become contaminated with dust particles, for example during pre-process handling, they should be flushed several times with purified water and dried if they are not immediately filled.

Redipacs are filled via the open side, which is closed by heat sealing after filling. The closing device consists of a metal block with 10 or 8 holes and a closing mechanism. The filling and closing device for Redipacs is available in a hand operated and a semi automatic type.

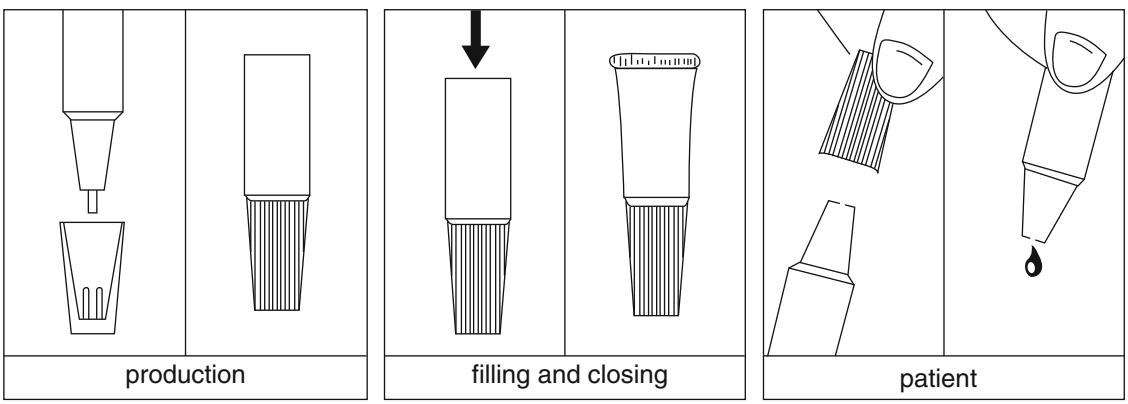

Fig. 24.7 Redipac

24.4.3 Eye Lotion Bottles

The same requirements apply to eye lotion containers as for eye drop containers (see Sect. 24.4.2), with the exception of the requirements to dropping. Eye lotions are usually dispensed in special bottles that are: dust free, of good microbiological quality, a volume of 250 mL, equipped with a hinged lid, made of transparent polypropylene and resistant to steam sterilisation. Steam sterilisation is only possible when the bottle is 'open' (the closure is turned back once). Therefore, the irrigation solution is exposed to an essentially 'open' sterilisation process. A disadvantage of the bottle for eye lotion is that it hardly protects from the influence of light. When protection against light is required, the bottle should be equipped with a secondary packaging.

24.4.4 Enema Containers

Containers for liquid rectal preparations range in volume from several millilitres to approximately 100 mL. The container must be equipped with a rectal cannula to administer the enema. Enemas can be packaged in enema bags (see Sect. 24.4.13.2). These have a longer cannula with which the enema can be administered deeper into the rectum. Another possibility is to package an enema in a syringe on which a rectal cannula is placed (see Sect. 24.4.16).

As well as the general requirements to containers (Sects. 24.1.1 and 24.1.2) the following requirements should be met:

- No migration of product components into the container
- No migration of components of the container (for example softeners, stabilizers) into the product
- No sorption of components of the product onto the container material
- No permeability to gas or liquid
- Flexibility
- Volume remaining after administration should be reproducible and preferably small
- No respiration (no material from the rectum should go into the bottle)
- Protection against light

24.4.4.1 Microenema Bottle

The microenema bottle (see Fig. 24.9) is meant for single-dose enemas with a volume of 3–10 mL. The bottle has a bellows design and is made from low-density polyethylene.

When compared to a syringe with a rectal cannula, a single-dose enema bottle has the advantage that the dosage to be administered is fixed so that the patient cannot make a mistake. A disadvantage is that a small amount of the product remains in the container, requiring an excess fill. Table 24.8 gives an example of the volumes to be filled for chloral hydrate enemas for different dosages of chloral hydrate.

Small enema bottles are challenging to label. When they have a long cap the label can be fixed onto the cap like a flag. Sticking the label onto the cannula itself has the disadvantage that glue and paper fragments can be left behind. The bellows design of the small enema bottle has the advantage that a round label can be fixed onto the flat bottom.

When emptying the micro enema bottle some liquid remains in the bottle. Independent of the fill volume this loss is approximately 1.5 mL of aqueous solutions. When filling the bottle an excess volume is therefore required. When using a more viscous solution the loss in the single dose enema bottle will be greater.

During storage of aqueous enemas evaporation takes place. Due to this the concentration increases, but the

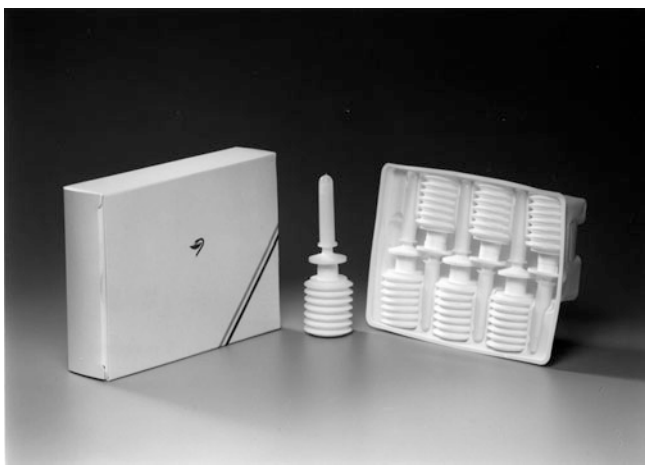

Fig. 24.9 Microenema bottle 10 mL

Table 24.8 Filling volume, delivered volume and dose in enema bottle 10 mL, for Chloral hydrate enema 50 mg/mL and 150 mg/mL FNA (see Table 11.15)

Chloral Hydrate Enema 150 mg/mL			Chloral Hydrate Enema 50 mg/mL		
Filling volume	Delivered volume	Dosage	Filling volume	Delivered volume	Dosage
4,5 mL	3,3 mL	500 mg			
6,5 mL	5 mL	750 mg	6,5 mL	5 mL	250 mg
8,5 mL	7 mL	1,050 mg	8,5 mL	7 mL	350 mg
11,5 mL	10 mL	1,500 mg	11,5 mL	10 mL	500 mg

Fig. 24.10 Enema bottle 100 mL

administered dose does not change much. The water evaporation can measure 5 % of the filled volume after 1 year and 10 % after 2 years at room temperature and should be properly addressed during stability studies.

24.4.4.2 Enema Bottle 100 mL

The 100 mL enema bottle (Fig. 24.10) consists of a bottle and a cannula of low density polyethylene (LDPE).

The nominal content is 100 mL, the maximal fill volume 130 mL. Graduation indicates 50 mL, 75 mL and 100 mL. The closure consists of 4 parts: a strong screw cap, a flexible cannula, a rubber one-way check valve in the screw cap and a cap. The cannula is usually lubricated with vaseline. The length of the cannula is 52 mm and the top is rounded. Due to the bellows design of the shoulder the bottle can bend which makes administration easier. Water loss by evaporation is relatively small in relation to the fill volume. After administration a small volume (<2 mL with a 100 mL enema) remains in the bottle. The enema bottle provides little protection against the influence of light, so the bottle should be wrapped in aluminium foil or packaged in a secondary container if necessary.

24.4.5 Infusion Bottle and Injection Vials with Closure

Intravenous infusion solutions are filled in single-use containers. The Ph. Eur. requires that products for parenteral administration are dispensed in glass containers or in other containers such as plastic containers and prefilled syringes [32]. The material should be sufficiently transparent to make a visual assessment of the contents possible, except for implants and in other justified and authorised cases. The tightness of the container is ensured by suitable means. Closures ensure a good seal, prevent the access of micro-organisms and other contaminants and usually permit the withdrawal of a part or the whole of the contents without removal of the closure. The plastic materials or elastomers used to manufacture the closures are sufficiently firm and elastic to allow the passage of a needle with the least possible shedding of particles.

Standard dimensions of infusion bottles and injection vials are described in ISO-norm 8536.

Glass as well as polypropylene infusion bottles are being used. For the production of large batches, bottles are filled and closed on automated 'filling lanes'. Infusion bags of polypropylene or polyvinylchloride are also being used (see Sect. 24.4.13). For glass bottles the quality of the glass is important, see also Sects. 24.2.1 and 24.4.1.

Infusion solutions are administered gradually. Therefore infusion bottles should have a closure which makes this kind of administration possible but prohibits the ingress of micro-organisms and other contaminations at the same time. Rubber is the most suitable material for this purpose. Infusion bottles are closed with a rubber stopper, fixed in place by means of an aluminium crimp cap. This provides a more secure closure than a rubber disk with a screw cap on top.

The quality of rubber stoppers is important in relation to the release of substances or particles into the liquid, the ease with which the rubber can be punctured and the flexibility around the puncture opening. The most often used material is bromine butyl rubber. For oily injections, closures made from an oil resistant elastomer (silicone rubber) must be used. The Ph. Eur. describes requirements for rubber closures [33]. Rubber closures for containers for aqueous parenteral preparations are classified in two classes: type-I-closures and type-II-closures. Type-II-closures have additional mechanical characteristics, for example being suitable for multiple piercing.

The shelf life of rubber closures for infusion bottles is limited. Freezing of vials or infusion bottles with rubber stopper can result in damage to the stoppers and reduced closure quality. A comprehensive shelf life assessment must include the integrity of the rubber closure.

Glass and rubber can be the source of visible and subvisible particles in infusion liquids. Particle numbers are larger in glass bottles with rubber stoppers when compared to infusion bags of polypropylene or polyvinylchloride. Most particles appear in the production phase during the steam sterilisation process. The rubber stopper can have the highest contribution to the particle contamination of the preparation. The silicone oil that is used in the production process of the rubber stoppers can be the most significant source of the particle contamination. To reduce this risk, the quality of the silicone oil should be carefully controlled. The stopper washing and rinsing process is very important and the

number and quality of the rinses should also be carefully controlled [34, 35]. A good rinsing process is necessary to reduce particle contamination of the glass bottles as well as the rubber stoppers. The availability of high quality, validated rinsing machines is of vital importance.

Injection vials are mostly glass bottles closed with a rubber stopper and aluminium crimp cap. The information about the infusion bottle in general also applies to the vials. Injection vials are usually produced from tube glass in contrast to the larger infusion bottles from blown glass.

24.4.6 Containers for Bladder Irrigations

Bladder irrigation solutions are preferably packed in flexible plastic bags, such as urotainers (See Sect. 24.4.13.1). These containers enable the product to be administered directly from the pack. Bladder irrigation solutions packed in glass bottles often have to be transferred into another container for administration. This process increases the risks of microbiological contamination during the transfer process. Bladder irrigation containers should be tamper evident. To enable this glass bottles are produced with single use "tear-off" crimp seals. Polypropylene bottles are produced with closures that break away on opening demonstrating that the bottle has been opened.

24.4.7 Jar

A jar is defined as "a container, without a pronounced neck, with a wide opening at the top and a more-or-less flat bottom". Jars are frequently reclosable and generally suitable for semisolid and solid pharmaceutical forms [26]. An important difference between a bottle (Sect. 24.4.1) and a jar, is that the jar does not have a neck. The jar for tablets is named separately as a tablet container. A jar with a sifter top is used for powders for cutaneous application.

The jar is the primary container for:

- Solid preparations: tablets and capsules
- Semisolid (dermal) preparations that are too viscous or too physically unstable to be dispensed in a tube
- Suppositories and pessaries that are not filled directly in strips (their primary container); if necessary suppositories can first be packaged separately in aluminium foil
- Powders for cutaneous application

> Zinc Oxide Calcium Hydroxide Weak Paste (see Table 12.39) is a relatively unstable water-in-oil emulsion that may disintegrate faster in a tube than in a jar, because of the pressure in a tube. Therefore this ointment is preferably packaged in a jar.

A jar can be used as secondary container for single dose oral powders in powder paper or sachets, and for suppositories and pessaries in strips.

In addition to the use as primary or secondary container for the patient, the jar can also be used as a pharmacy stock container for semisolid and solid intermediate or base preparations.

The general requirements for containers apply to jars (see Sect. 24.1). Usual materials are

- Glass, brown, hydrolytic resistance type III
- Plastic, polypropylene, amber coloured to provide light protection

The lid is usually a screw cap of polypropylene, with a closing rim to provide for a good seal. A snap-on lid can be a problem for people with a limited function of the hand.

Glass jars sometimes have Bakelite lids. Bakelite lids have the advantage that they are resistant to high temperatures although it may crack during heat sterilisation. The disadvantage of Bakelite is that a liner is needed for a good closure. The liner can provide a growth place for micro-organisms when the preparation contains water. A glass jar with a Bakelite lid is a suitable container for sterilisation of eye ointments in dry heat, 2 h at 170–180 °C.

It is quite common for medicines to be sensitive to light. Therefore it is not recommended to dispense solid dosage forms such as tablets and capsules in a jar that transmits light (tablet container), despite the possible advantage that the contents can be inspected for dispensing without taking off the lid.

In the stability assessment of products packed in plastic jars attention has to be paid to the permeability to water vapour. Water vapour can migrate to the inside as well as to the outside. In plastic jars this can occur via permeation through the container wall, but it can also occur via the closure. Permeation is dependent on for example the type of packaging material and the storage conditions (temperature, relative humidity). In case of aqueous preparations this can lead to a concentration change of the active substance. In case of solid dosage forms this can lead to an array of negative quality changes.

24.4.7.1 Special Jars

The 'Tupo' and the 'Dospo' are polypropylene jars, with a moveable piston base and in the lid a small diameter opening with cap. On the screw cap of the Tupo a cannula can be placed. These jars have the advantages of a tube (small squeeze-out opening) as well as a jar (no deformation during usage). The disadvantages compared to a tube are that they transmit some light and that they are more difficult to handle. Furthermore the patient can unscrew the lid. These jars are being used in combination with mixing devices Unguator® and Topitec® (see Sects. 28.6.8.4 and 28.6.8.3 respectively). They are used as a receiver for the preparation of the product and also serve as final container.

The jar with dose pump, tube with dose pump, pump tube or dose dispenser is a slim plastic jar (usually polypropylene with polyethylene piston), that releases the contents through a pumping mechanism. No propellant is being used. The jar with dose pump is easy to fill via the base and suitable for creams, ointments (not too viscous), gels, solutions for cutaneous use and shampoos. The jar with dose pump is available in volumes varying from 50 to 200 mL. This container is not a tube because it is not made of a compressible material.

A sifter-top container (or a powder castor) is a jar that has a sifter top (this is a closure with small diameter openings to apply a powder onto the skin) and a lid. The sifter-top container is made of plastic, usually polypropylene. The sifter-top container can be filled via the top, after taking the sifter-top applicator off or via a snap-on base. Sifter-top containers are available in the volumes of 50 and 100 mL.

24.4.8 Tube

A tube is a container for multiple doses of semisolid preparations. It consists of compressible material that is squeezed to release the contents via an orifice [26]. A preparation is better protected against micro-organisms in a tube than in a jar. This is because when removing the product from a tube a smaller surface can get contaminated by the user. If microbiological contamination has occurred the circumstances in which further microbiological growth can occur are less favourable in a tube than in a jar [36]. This is mainly because there is less oxygen available in a tube than in a jar.

Next to the normal tube, there are some special designs: the membrane tube, the pump tube (see Sect. 24.4.7.1) and the eye ointment tube (Sect. 24.4.9).

24.4.8.1 Material

Tubes for packaging pharmacy preparations are made from aluminium or from plastic. Aluminium tubes are made from very pure aluminium. The shape is generated by a process called impact extrusion. The formed aluminium is quite hard and brittle and needs an additional heat treatment called annealing to make the aluminium capable of being shaped and folded. Because aluminium has poor chemical resistance (see Sect. 24.2.2), aluminium tubes are coated with an internal as well as an external coating. The internal coating is usually made of a mixture of two resins: an epoxy resin and a phenol-formaldehyde resin. The resin is sprayed into the tubes and the resulting inside lacquer is dried quickly at high temperature. This inside lacquer is resistant to most preparations. Some exceptions are sodium fluoride in an acid gel and also dimethyl sulfoxide in a high concentration (50 %) in cetomacrogol ointment (Table 12.8) damages the inside lacquer.

Aluminium tubes are furnished with an outside lacquer with print if necessary. This outside lacquer should resist the preparation as well as in small scale production and during usage it is difficult to prevent any contact.

Aluminium tubes are filled through the open end that is then folded and closed with tube pliers or filled and closed with automatic machinery.

Plastic tubes have to be heat-sealed, but the reliability of closing can be problematic with small scale production. Plastic tubes also have the disadvantage that the material is flexible and slightly permeable to light and air. During use, the plastic tube tends to regain its original shape after squeezing and draws in air at the same time. Therefore substances that are sensitive to oxidation, such as sorbic acid, will degrade faster in plastic tubes than in aluminium ones. Drawing in air during use is also disadvantageous from the microbiological point of view. Plastic tubes are more environmentally friendly than aluminium ones, also because no secondary container is necessary.

24.4.8.2 Tube Cap

The screw cap of the tube is made from plastic, usually polypropylene and occasionally polyethylene. In addition to the general requirements for containers (see Sect. 24.1) the cap should provide a reliable closure of the tube (no leakage of the contents). When necessary, the cap should be able to withstand (heat-) sterilisation treatment.

For application of ointments and creams in the anus, a rectal cannula (see Sect. 24.4.19.12) can be screwed onto the top of the tube, instead of the cap.

24.4.8.3 Inside and Outside Lacquer Control

Pores in the inside lacquer of aluminium tubes allow the preparation to react with the aluminium. The inside lacquer therefore has to be tested for the presence of pores and adherence onto the aluminium. Application of a copper sulfate solution demonstrates the presence of pores in the inside lacquer. The pores become visible due to a rust-coloured discoloration of the aluminium.

The resistance of the outside lacquer can be tested using an aggressive preparation, for example a cream containing methyl nicotinate appeared to be quite aggressive towards the external lacquer.

Important criteria for tube quality control are detailed in Table 24.9. Quality control of packaging is dealt with in Sect. 24.5.

24.4.8.4 Tubes as Stock Container

Besides the function as container for creams, gels and ointments for direct patient use, tubes can be used as a pharmacy stock container for intermediate products. A

Table 24.9 Tube quality control criteria

Attribute	Example
Delivery of the tubes	Transport container is dry, clean and undamaged
Tube material	Dimensions
	Strength
Tube neck	Shape, dimensions
	Undamaged
Tube shoulder	Shape, undamaged
Screw thread	Deformations
	Plastic remnants
	Metal remnants
Inside lacquer	Regular lacquer coating
	Absence of pores
Outside lacquer	Regular lacquer coating
	Heat sterilisation is possible
	Resistance to chemicals
Print	Colour quality
	Resistance to chemicals
	Missing text elements
	Shifted text
	'Double' printing
Global visual control	Contamination (inside, outside)
	Deformations
Tube cap	Presence
	Contamination
	Heat sterilisation is possible

special use is as a stock container for eye ointment base for extemporaneous preparations. To use a tube in this way, it should be resistant to hot air sterilisation 140 °C during 3 h (see Sect. 24.4.2). In this sterilisation process the tubes are filled to about 90 % of their capacity and placed on their cap to minimise leakage through the folded closure as much as possible. The tubes should not touch each other otherwise the outside lacquer will stick. The 15, 30, 50, 60 and 100 g tubes should only be filled with 12, 25, 45, 50 and 90 g base. Although the standard Ph. Eur. sterilisation process using hot air is 2 h at 160 °C, other combinations of time and temperature are allowed if validated.

24.4.8.5 Membrane Tube

A membrane tube is a tube of which the tube orifice is closed by a membrane. This membrane has to be perforated by the user before using the tube. Therefore the membrane is still intact when a tube has not been used, providing a tamper-evident design.

In aluminium tubes the membrane is formed by a thin layer of aluminium. In order to perforate the membrane:

- The aluminium membrane should not be too thick (ease of perforation)
- Metal particles should not be released during perforation

Because of the risk of metal particle release membrane tubes are not suitable to package eye ointments and eye ointment base.

24.4.9 Eye Ointment Tube

Eye ointments and eye gels are packaged in small, sterile tubes with a rounded cannula. A tube should contain no more than 5 g of eye ointment. The tube screw cap should provide a reliable closure to prevent microbiological contamination [28]. Eye ointment tubes are also regularly used to dispense nose ointments and nose gels.

24.4.9.1 Material

Eye ointment tubes are manufactured from aluminium or plastic, similar to the tubes used for dermatological products. To retain sterility the drawing in of air should be prevented, therefore aluminium is preferred above plastic. The cannula can be made of aluminium or polyethylene. A plastic cannula reduces the risk of eye damage when compared to an aluminium cannula. The cap is usually made of plastic, for example polypropylene.

24.4.9.2 Sterilisation

Eye ointment tubes should be purchased sterile or should be sterilised. An aluminium tube is generally not resistant to sterilisation by dry heat and limited resistant to steam sterilisation, because the outside lacquer may get sticky. A polypropylene cap and/or cannula of low density-polyethylene are not resistant to sterilisation by dry heat; deformation takes place. The resistance to steam sterilisation is very limited. Tubes with plastic parts however can usually be sterilised by gamma radiation.

24.4.9.3 Metal Particles

In addition to the requirements for 'normal' dermatological tubes (see also Table 24.9) there are supplementary requirements for eye ointment tubes. The tube cannula should be undamaged and metal or plastic particle contaminants should be absent. Eye ointments should be checked for the presence of metal particles. These often originate from the location where the cannula is fixed in the tube shoulder. In case of an aluminium tube this is not an issue because tube and cannula are made of one part of aluminium. In case of tubes with a plastic cannula the inside coating is only applied after mounting the cannula, as a result of which these tubes rarely release metal particles in the eye ointment. Finally metal particles can appear in the eye ointment through the opening and closing the cap of tubes with an aluminium cannula. If necessary the methods

described in USP can be used to assess the presence (amount and size) of metal particles [37].

24.4.10 Suppository Strip

A strip is defined as a "multidose container consisting of two layers, usually provided with perforations, suited for containing single doses of solid or semisolid preparations" [26].

Suppositories can be poured directly into the suppository strips or into metal molds after which they are packaged separately. Pessaries (vaginal suppositories) are also packaged in suppository strips.

Important requirements for suppository strips are:

- The suppository forms should be easy to open
- Low permeability to water vapour
- Low permeability to oxygen
- Protection against light
- No migration of (active) substances from the suppositories into the primary packaging layer and no migration of components from the primary packaging layer (for example plasticisers) into the suppository
- Possibility to assess the contents
- Ability to print on the surface

Many users find it difficult to open suppository strips. Especially for patients with a limited hand function suppository strips are a very difficult container to use (see Sect. 24.4.21). The pharmacy can help those patients by taking the suppositories out of the forms and package them in a jar.

Suppositories in strips are dispensed in a cardboard folding box or in glass or plastic jar (see Sect. 24.4.7).

24.4.10.1 Material

Some of the requirements contradict each other, so it is difficult to meet all the requirements. To protect against light non-transparent plastic is necessary. A printed text can be read better on a non-transparent plastic. Non-transparent plastic however hinders the possibility to assess the contents of the suppository forms. Pharmacy-filled suppository strips therefore often have a layer of transparent plastic on one side and a layer of non-transparent plastic on the other side. The secondary container should thus protect against light if necessary.

Suppository strips for pharmacy preparations often consist of a PVC-polyethylene laminate: PVC has the advantage that it shows relatively little permeability to water vapour and oxygen. It has the disadvantage that it always contains softeners that could migrate into the suppository. In the case of polyethylene the permeability to water vapour is comparable to that of PVC, but the permeability to oxygen is greater. The used polyethylene does not release additives. The PVC-polyethylene laminate combines the advantages of both materials: the polyethylene layer is situated on the suppository side of the laminate en thus prevents the release of leachables. The laminate has a low permeability to water vapour and oxygen.

24.4.10.2 Identification

To identify suppositories in strips the following options can be considered:

- Printed suppository forms; the non-transparent side of the suppository form is suitable for printing.
- Taping up the suppository strip on the upper side with pre-printed tape; a disadvantage of the use of tape is that the patient has to cut the suppository forms with scissors to prevent the tape being removed from the whole strip.
- Taping up the suppository strip on the upper side using paper labels with printed text; the advantage compared to the method described before is that paper is more easy to tear as a result of which identification per suppository is still possible.
- Application of easy to tear, small printed labels at the bottom of the strip.

24.4.10.3 Taping Up

Taping up a suppository strip at the upper side provides, as well as the possibility of identification, the advantage that the suppository form is completely closed. This is advantageous for hygiene and when hygroscopic substances are being processed. Furthermore it minimises the chance of crumbling of the suppositories on the upper side and it prevents the loss of contents when they are inadvertently exposed to high temperatures (for example in the doctor's bag).

24.4.10.4 Pharmacy Suppository Strips

Suppository strips used for pharmacy preparations usually contain 12 suppository forms per strip. They are available in the volumes of 1.15 mL (for small children), 2.3 mL and 2.8 mL. Although other plastics are possible, many suppository strips are made of PVC-polyethylene laminate: the PVC-layer is situated on the outside of the forms and has a thickness of 95 μm, the polyethylene layer is situated on the suppository side of the forms and has a thickness of 75 μm.

The suppository forms are opened with the peel-off method: at one side of the suppository form there are two 'flaps' that can be hold between thumb and forefinger. By tearing the flaps apart the form is opened on the sealed seam. Quality control on incoming suppository strips should include checks on fill volume, ease of opening and contamination.

As a secondary packaging for the suppository strips carton folding boxes are available. The format 115 × 19 × 55 mm is made for 1–2 strips of 6 suppositories; the format

115 × 37 × 55 mm is made for 3–4 strips of 6 suppositories. On the reverse side of the specialised folding boxes there are instructions on how to open the suppository forms.

24.4.11 Blister Pack

A blister pack or strip is a container with a foil that is shaped so that it can contain separate dosages [26]. An aluminium lidding foil closes the form foil. Blisters are mostly used to package tablets or capsules. For blister packs a form foil of PVC or laminate of PVC/PVDC (polyvinylidene chloride) is used. The form foil is warmed in a blister machine and a mold station makes round or capsule-like pockets with compressed air. PVC is permeable to water vapour and therefore not suitable for tablets or capsules that are moisture sensitive. To package such products the PVC form foil should include an outside layer of PVDC. PVDC permeates less water vapour. Dependent on product sensitivity to moisture, different PVDC-thicknesses can be chosen. When complete resistance to water vapour is necessary a form foil that consists of a formable aluminium laminate (consisting of polyamide, soft aluminium and PVC) has to be used.

Some patients have objections against blister packs because they are difficult to open, they can be rather large and form a load on the environment [38].

24.4.12 Powder Paper

Single dose oral powders are dispensed in powder paper or sachets. For the packaging of single dose powders, paper qualities of 40–120 g/m^2 should be used. Powder paper must not be contaminated, should not shed fibers and there should be minimal variance in weight per area (= constant powder paper weight) within each batch.

The constant paper weight distribution is important when the weight distribution of single dose oral powders is determined on the powders/paper combination. When the paper weight is not constant the batch can be unjustly rejected based on an out of specification weight distribution.

The primary container powder paper is always enclosed by a secondary container. This can be:

- A cardboard folding box
- A jar (see Sect. 24.4.7)
- A plastic bag, for example a Minigrip®-bag (polyethylene)

The choice of the secondary container is dependent on the extent of protection that the second package layer should offer. When extra protection against influence of moisture is needed, a glass jar can be used.

24.4.13 Bag

A bag is defined as: “container consisting of surfaces, whether or not with a flat bottom, made of flexible material, generally closed at the bottom and at the sides by sealing; at the top possibly to be closed by fusion of the material, depending on the intended use. Equipped with special attachments” [26].

Plastic bags can be used to package medicines. They are primary containers for sterile irrigations, intravenous infusion solutions, blood transfusion and enemas. For these uses special attachments are necessary such as luer-lock catheter connector sites or rubber puncture sites.

When labelling plastic bags the quality of the label glue should be assessed. Some types of glue can react with the bag plastic. Glue components may migrate into the bag and plastic components may migrate into the label and affect the appearance of the label.

Plastic bags should be flexible and for most applications sterilisable. PVC can be sterilised at 121 °C. A disadvantage is that PVC is relatively permeable to water vapour. To resist product water loss the bags have to be enclosed in an overwrap that is less permeable to water vapour, for example a laminate material of nylon with polyethylene.

Plastic bags provide little protection against light. The bag has to be overwrapped in aluminium foil or enclosed in an opaque container in order to prevent light transmission. Tubes connected to the bag, such as giving sets, may be transparent to light, which may lead to degradation of the medicines flowing through them. In order to prevent this from occurring black coloured plastic tubes have been developed. Yellow and orange tubes will also provide limited protection against light.

24.4.13.1 Irrigation Bag

Plastic irrigation bags are used to contain irrigation solutions for the bladder or solutions for continuous ambulant peritoneal dialysis (CAPD). The Ph. Eur. requirements for containers for sterile irrigations [39] are the same as those for parenteral solutions (see under Infusion bag), with the addition that intravenous administration systems should not fit onto the connection site. Small bags for bladder irrigations usually have a volume of 100 mL. They have a tube with a catheter connection site. By carefully squeezing the bag, the irrigation for the bladder is administered. After an appropriate time span the irrigation solution is allowed to flow back in the bag and be disposed of. Bags for CAPD are larger than those for irrigations for the bladder. CAPD-bags also have a tube with a catheter connection site.

24.4.13.2 Enema Bag

In addition to being packaged in bottles, enemas can also be packaged in enema bags. Enema bags can contain a volume

of 50–125 mL. Small scale filling can be achieved by the use of a syringe. The bag can be rolled up during administration so that a one-way valve needed for enema bottles is not necessary. When the disorder is located more distal in the rectum an enema bag is preferable to an enema bottle because the long administration tube of the bag makes it possible to administer the enema solution to that part of the rectum.

24.4.13.3 Infusion Bag

For infusion bags PVC and PP are used. PVC- as well as PP-bags can be steam sterilised. Infusion bags have to meet the requirements of the Ph. Eur. for containers for parenteral preparations [32]. The Ph. Eur. also describes a test for the release of phthalates (plasticisers) from the PVC. This test has limitations and does not seem to predict every practical situation; in practice the release may be much higher than is predicted by this test [40].

24.4.13.4 Bag as Container for Oral Dry Dosage Forms

Automated dispensing systems (ADS) package tablets and capsules into a mini bag printed with all necessary patient information. The medicines inside these minibags are to be taken by the patient at a certain point in time. The minibag should be easy to open, for example by an elderly person with impaired hand function.

Single-dose oral powders in powder paper can be packaged in a plastic bag with a clip. Single-dose oral powders can also be packaged in small sealed pouches from a laminate foil material including an aluminium layer. These primary containers are called sachets. Next to the use as primary container, bags are also used as secondary container.

24.4.14 Single-Dose Containers (Miscellaneous)

Many containers described in this chapter are meant for packaging a single dose, for example an infusion bottle or a bag containing a bladder irrigation. There are some packaging types that are specially designed for packaging single doses: ampoules, Minims, Redipacs and the 'unit-dose cup'. Minims and Redipacs have been discussed already in the eye drop containers Sect. (22.4.2.6). Ampoule and unit-dose cups will be discussed in this section.

24.4.14.1 Ampoule

An ampoule is a container that is closed by melting or fusing and can only be opened by breaking [26]. Ampoules are used as containers for small volume injection preparations; the volume of an ampoule can vary from 1 mL to 20 mL. An ampoule can be made of glass or plastic. Glass ampoules are usually colorless, except for preparations that contain extremely light sensitive substances. For those preparations there are ampoules of (amber) coloured glass. For parenteral preparations the glass has to be of hydrolytic resistance type I (see Sect. 24.2.1).

Glass ampoules have the disadvantage that upon opening glass particles can fall into the solution. To minimize the creation of glass splinters on breaking, ampoules with different break augmenting systems have been developed:

- Ampoules with a ceramic break band: the break ring in the neck of the ampoules are made with a ceramic paint, which shrinks faster than glass during the cooling process. The tension that arises thus eases breaking.
- Ampoules with a score-ring: these ampoules have a notch that is applied around the ampoule. To further ease breaking plastic 'ampoule breaker' caps are available.
- OPC (one point cut): ampoules are cut at one point of the break ring. On the place of the notch a coloured dot is applied on the upper part of the neck of the ampoule. OPC-ampoules give the least chance of glass splinters if the correct breaking technique is used.

Most plastic ampoules are from the blow-fill-seal types of containers. These containers are formed, filled and closed in one production lane and are therefore not available as an empty container for small scale filling. Some of these plastic containers are known as bottle-pack. These plastic containers are designed for sterile liquid pharmaceutical preparations, which can be opened by tearing, screwing or perforating. The bottle-pack-assortment contains a wide range of containers from ampoules to bottles (1–1,000 mL).

24.4.14.2 Unit-Dose Cup

This container (see Fig. 24.11) is meant to package single doses of oral liquid preparations, for example methadone mixture. The unit-dose cup consists of a polypropylene

Fig. 24.11 Unit-dose cup

container of 15 mL volume, with a pointed top that is broken off to open the cup. The cup is filled through the open bottom; the bottom lid is pressed on after filling and cannot be opened thereafter.

24.4.15 Syringes

Syringes consist of a piston and a barrel with a measuring scale. They are usually made from plastic, the piston can contain a rubber part. Plastic syringes with a one-piece plastic piston, without a piston rubber, are called two part syringes. Three part syringes are equipped with a piston rubber part. A syringe can be used as such, for example to administer oral preparations. An administration device can be necessary: a needle for the administration of parenteral preparations or a rectal cannula for the administration of rectal preparations. To connect the needle the syringe is usually provided with a so-called luer nozzle (see Sect. 13.10.2). For other administration routes (oral, rectal) it is preferable not to have a luer nozzle ('non-luer') to prevent accidental parenteral administration of non-parenteral preparations [41]. For the measurement uncertainty of syringes see Sect. 29.1.7.

24.4.16 Oral and Rectal Dosing Syringe

A syringe can be used to accurately dose a few millilitres of a liquid preparation. Specially designed bottle caps can be employed as a dispensing aid, with the syringe nozzle fitting the orifice in the bottle cap (see Fig. 24.12). The filled syringe can be closed using a cap.

Sometimes, the pharmacy or an institution dispenses the required dose in a pre-filled syringe closed with a cap.

For rectal administration of enemas the syringe is equipped with a rectal cannula. In this way a single strength solution can be administered in varying volumes.

Several systems for dosage syringes are commercially available (Oral-dose, Rectal dose, Baxa® and Dose-pac®: Fig. 24.12).

These systems consist of:

- A polypropylene screw cap with hinge lid and syringe connecting orifice, fitting onto a bottle with a 28 mm opening
- A polypropylene syringe with calibration; larger volume syringes can be used
- A cap

Using 1 mL dosage syringes it is possible to dose parts of millilitres. The dosage accuracy increases with increased degree of filling (see Sect. 29.1.7). The Baxa-system also offers a rectal cannula. An important difference between the systems is the type of syringe connecting orifice. This is non-luer with the Baxa-system and luer with the Dose-pac. Non-luer is preferable as non-luer syringes do not connect to needles or infusion tubing, reducing the risk of accidental parenteral administration.

Alternatively an adaptor can be used. This is a small plug which is pushed into the neck of the bottle when the screw cap is placed.

Before dispensing a prefilled syringe from the pharmacy it should be provided with a secondary container. A suitable container is a plastic box or a special plastic case of which the length can be adapted to the length of the (pulled out) dosage syringe.

24.4.17 Syringe for Parenteral Administration

Syringes for parenteral administration are delivered sterile and separately packaged. The maximum contents can vary from 0,25 mL to 140 mL. The barrel and the piston rod usually consist of polypropylene, although other plastics and also glass can be used. The rubber piston consists of a synthetic rubber material. The nozzle of the syringe is luer or

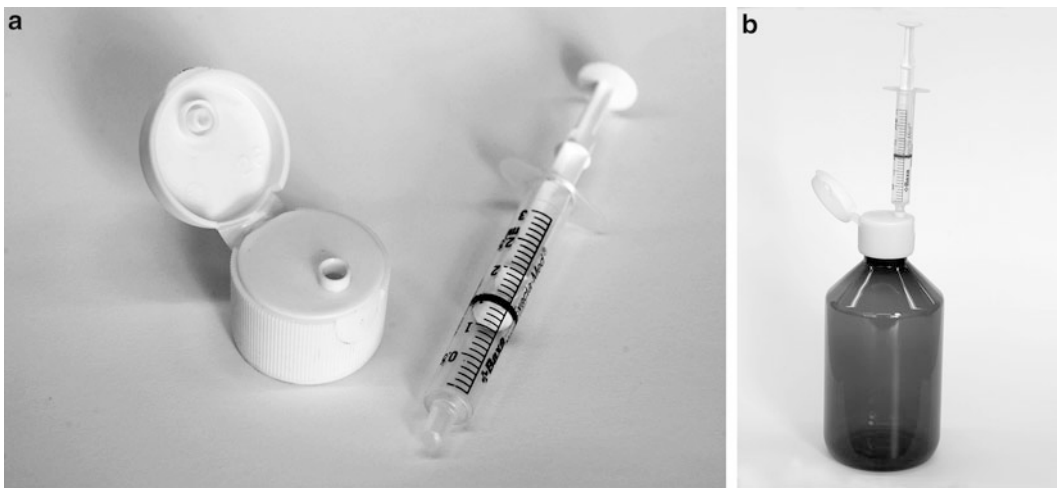

Fig. 24.12 Dosage syringe with screw cap (**a**) and mounted on a bottle (**b**)

luer-lock. Dependent on the additives to the polymer materials syringes can be sterilised with ethylene oxide gas, gamma radiation or steam.

All plastic syringes contain silicone oil to ensure easy and smooth piston movement. The amount of silicone oil is limited in the Ph. Eur. and production standards such as ISO 7886.

For parenteral use sterile syringes have to be filled aseptically (see Sect. 13.8.3) usually just before use. By filling the syringe in the pharmacy under controlled circumstances of aseptic handling (see Sect. 31.3) the (microbiological) shelf life can be extended. The filled syringe is closed with a sterile cap. Various semi-automatic pump systems are available that can support the aseptic filling of sterile syringes.

The administration of infusion solutions employing a syringe pump is a common technique in hospitals. Because of the controllable infusion speed accurate, but flexible dosing is possible. In most cases a 50 mL syringe is used on syringe pumps.

24.4.18 Stock Container

For stock containers in pharmacies the same requirements apply as for primary containers for patients (see Sect. 24.1).

From the quality and logistic point of view it is preferable to fill a product directly in a patient container. Storage in a stock container has the following disadvantages:

- After opening a maximum period of use should be taken into account; this shelf life is restricted by the microbiological, chemical and physical vulnerability of the product.
- More time and material is used than if the preparation is filled directly into a patient container.

In some cases it is necessary to fill the preparation in a stock container, that is:

- With intermediate or base preparations, for example a base solution, a base cream or an (eye) ointment base
- When the preparation will be dispensed in widely varying amounts
- To save storage space

When a preparation is kept in a stock container the size of the batch and the volume of the container should be related to the usage period and to the number of uses. In general it is recommended to choose the volume of the 'stock container' in such a way that it only has to be opened about ten times before it is empty.

24.4.19 Dosage Delivery Devices

For the administration of preparations the use of a delivery device might be necessary. These can be part of the package system or provided separately. There are devices that are mounted on a bottle, a tube or a syringe. To enable flexibility of use – important with pharmacy preparations –both parts of the assembly should preferably be standardised. Many delivery devices are available for bottles, but there are fewer for tubes and syringes. The delivery devices are discussed per route of administration. Devices for parenteral administration are discussed in the chapter on parenteral preparations (Sect. 13.10).

24.4.19.1 Delivery Devices for Dermal Preparations

To apply a preparation onto the skin the closure of a bottle or a jar can be provided with a:

- Dabbing applicator
- Roll-on applicator
- Brush
- Spatula
- Liquid dispensing cap (for example flip top caps with spray orifice)
- Sifter-top applicator

A dabbing or roll-on applicator is in contact with the preparation and may release particles or leach substances.

A jar can be provided with a sifter-top; usually the jar and the sifter top form one unit ('sifter-top container' [43]), which is filled from the bottom (see also Sect. 24.4.7.1).

24.4.19.2 Delivery Devices for Oral Preparations

A glass bottle needs a pouring ring when a liquid is to be poured out of it. For oral preparations the delivery device is dependent on the amount that has to be taken per dose. For amounts of 5 mL and more a measuring spoon or cup is used. For dosages less than 5 mL a measuring syringe is suitable (see Sect. 24.4.16). Although dosing in parts of millilitres is preferable to dosing in drops there is a series of droppers and pipettes available. If necessary the cap can be replaced by a child-resistant cap (see Sect. 24.4.20).

24.4.19.3 Measuring Spoons and Cups

A relatively large volume of an oral liquid can be administered with a measuring spoon or cup (polypropylene). Dosing in kitchen spoons (teaspoon, spoon, tablespoon and dessertspoon) is relatively inaccurate and is preferably replaced by dosing in millilitres.

24.4.19.4 Dropper and Pipette

If a preparation is dosed in drops rather than millilitres, the bottle has to be equipped with a pipette, or a dropper cap, or a dropper insert, or a spout cap. The Ph. Eur. describes requirements with regards to the dose and the reproducibility of the dose [42]:

- The dropping speed does not exceed two drops per second.

- The average of 10 doses of drops does not deviate more than 15 % of the nominal dose.
- Out of 10 weighed doses no single dose deviates more than 10 % of the average dose.

Drop Size

The size of a drop is defined by:

- The type of drop bottle (the diameter of the outflow opening)
- The method of dropping (passive outflow or squeezing in (a part of) the bottle)
- The type of preparation (aqueous or oily) and the formulation of the preparation (the surface tension of the liquid)
- The temperature of the liquid
- The angle at which the bottle is being held
- The fill level of the bottle (this regards certain droppers)

The drop size is represented by the following formula:

$$m = 2\pi r\tau/g = \pi d\tau/g \qquad (24.1)$$

in which m = mass of the ideal liquid drop (kg), r = the radius of the outflow opening (in m), d = the diameter of the outflow opening (in m), τ = the surface tension (N/m) and g = the gravitational constant (9,807 m/s^2). This simplified formula should be expanded with a factor that corrects for the shape of the drop. The effect of the temperature on the size of the drop is caused by the temperature dependence of the surface tension: the surface tension drops when the temperature rises. From this formula can be seen that for different droppers, for caps with pipettes (with different outflow openings) and for different liquid pharmaceutical preparations (different surface tension) the drop weight of the pharmaceutical preparation in the drop bottle to be dispensed has to be determined, so that with the help of this weight the dose in drops can be calculated.

24.4.19.5 Screw Caps with Dropping or Measuring Pipette

The bottle cap with a pipette consists of a glass or plastic pipette mounted in a polypropylene screw cap. With the dropper bulb air is squeezed out and liquid drawn in. The liquid is administered drop by drop. The dropper bulb is made from chlorobutyl-, bromobutyl rubber or from natural rubber. The use of chlorobutyl- or bromobutyl rubber is preferable to the use of natural rubber (see Sect. 24.2.4).

The cap and the dropping pipette are available in different dimensions to suit the bottle. In addition to the dropping pipette, graduated pipettes for measuring millilitres are available: for example a pipette with a graduation of 0.2–1.5 mL with a subdivision in 0,1 mL.

Plastic pipettes are preferred to glass pipettes, because a plastic pipette is unbreakable and weighs less.

The dropping pipette gives a more reproducible drop size than the dropper insert.

24.4.19.6 Dropper Insert

A dropper insert is a dropping mechanism in the neck of the bottle (see Fig. 24.13). Many dropper inserts turn out not to meet the requirements of the Ph. Eur.: the dropping speed is too high or they don't provide drops at all. The reproducibility of the drop weight is often poor. The drop size appears to depend for example on the angle at which the bottle is held and on the amount of fluid in the bottle.

24.4.19.7 Spout Cap

A spout cap is a dropping mechanism on top of the neck of the bottle. The most frequently used spout cap is the Zentrop dropper. This consists of a chlorobutyl rubber dropper mounted in a polypropylene screw cap and closed with a small polypropylene cap. In case of incompatibility of the liquid with the chlorobutyl rubber a Zentrop cap with a polypropylene dropper can be used.

The reproducibility of the drop size of the Zentrop dropper is poor. Both the amount of fluid in the bottle and the angle under which the bottle is held seem to influence the drop size. However, to preserve the microbiological quality of the product a closure with a Zentrop upper part is preferable to a closure with a pipette. For the use of the Zentrop dropper as an eye drop device see Sect. 24.4.2.

Fig. 24.13 Dropper insert on a 25 mL bottle

24.4.19.8 Supporting Devices for the Administration of Eye Drops and Eye Lotions

Due to the vulnerability of the eye some specific requirements apply to the dropper system used for the administration of eye drops. The combination bottle/dropper is discussed in the paragraph on eye drop containers (Sect. 24.4.2). The handling of an eye drop bottle can present problems, for example for people with trembling hands. A supporting device can help to drop successfully. The choice of device depends on the type of dropping bottle the patient uses.

For eye drop supporting devices the following requirements apply:

- User friendliness
- Applicable to as many different bottle designs as possible
- Designed to direct the drop to fall into the conjunctival sac and not in the middle of the eye

Some examples of eye drop supporting devices:

- Autodrop® and Eyot®: these suit most plastic eye drop bottles and are advised to people who have trembling or weak hands and who have difficulties in keeping the eye open while dropping. These devices also help to position the bottle.
- Autosqueeze®: this device also suits most plastic eye drop bottles and is meant for patients who have problems holding and squeezing the bottle. The patient can use it in combination with the Autodrop.
- Dripaid®: this device is meant for glass eye drop bottles with polypropylene dropper.
- Some other devices exist which are specifically developed for a special type of eye drop bottle [44].

For the administration of eye lotions an eye irrigation cup is used. This has to be cleaned after every use and stored in a dry place.

24.4.19.9 Devices for the Administration of Nose Drops and Nasal Sprays

Nose drops are dispensed in a bottle with a dropper cap or dropping pipette. A dropping pipette is more practical because the correct dose can be measured in advance. The pipette is preferably made of plastic instead of glass due to the risk of breakage. The pipette should have a rounded tip to minimize the risk of damage to the nasal mucosa. The use of a pipette is disadvantageous from a microbiological point of view. Without proper washing or wiping, mucus with microorganisms from the nose can be transferred into the nasal drops. Providing good instructions to the patient can reduce this risk. The use of a spout cap to administer nose drops reduces the chance of contamination of the dropping fluid. The probability of microbiological contamination of the dropping fluid limits the in-use stability of (preserved) nose drops to a maximum of 3 months (see Sect. 22.7).

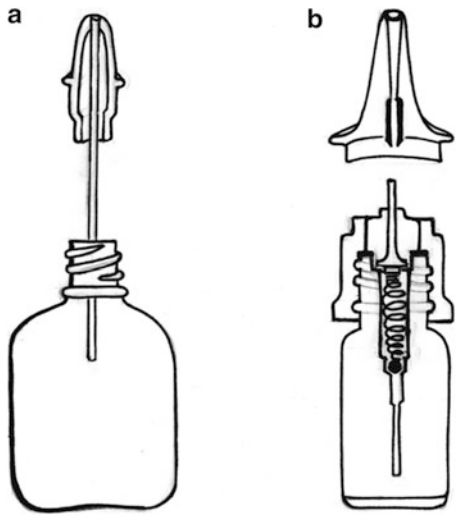

Fig. 24.14 Squeeze spray bottle (**a**) and nasal spray pump (**b**) for spraying liquid into the nose

Unpreserved nose drops should be packaged in single-use containers. The Redipac is suitable for this (see Sect. 24.4.2.6).

Non-viscous liquids can be sprayed into the nose as an alternative to drops. To aid this type of administration two types of containers are available: squeeze spray bottles and nasal spray pumps (see Fig. 24.14).

In case of the squeeze spray bottle (LDPE) the nasal spray fluid is sprayed by squeezing the bottle. The administered dose depends on the squeezing force and the level of the liquid in the bottle. Because of inaccurate dosing, these bottles are not suitable for the administration of highly active medicinal products. When using the simple squeeze bottle there is a chance the spray fluid gets contaminated with nasal mucus. The patient has to keep the bottle squeezed in until it is removed from the nose.

The nasal spray pump consists of a pump mechanism with a spray nozzle mounted on a bottle. A dose is sprayed by pressing the pump mechanism. During the first few pump actions only air is delivered from the nozzle as the pump mechanism fills with liquid. The amount of liquid that is sprayed per pump action is independent on the pump force or the liquid level. This results in accurate, reproducible dosing. The bottle needs to be in the upright position when the pump mechanism is released for a new dose to be drawn from the bottle. The nasal spray pump is best used with the patient in the sitting position.

The nasal spray pump is less vulnerable to microbiological contamination of the spray fluid.

24.4.19.10 Devices for the Administration of Ear Drops

Non-sterile ear drops are dispensed in a bottle with a pipette or dropper cap. Sterile ear drops are packaged like eye drops (see Sect. 24.4.2).

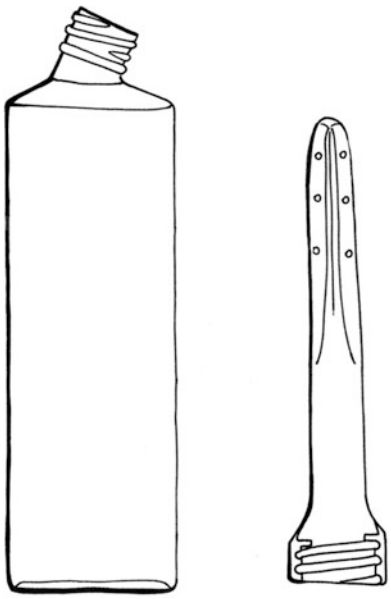

Fig. 24.15 Vaginal irrigator

24.4.19.11 Devices for the Administration of Vaginal Preparations

To administer vaginal creams a separate device, the vaginal applicator, is available. This syringe-like device has a nozzle that fits onto tubes with a screw thread. The material of the applicator cylinder is transparent polyethylene. The applicator is intended for single use, but can be cleaned with hot water. The applicator nozzle is mounted onto the opened tube, the applicator piston pushed onto the tube. The applicator is filled by squeezing the tube. When the applicator is filled completely (a volume of about 7,5–8 mL) it contains approximately 5 g cream.

Irrigations for the vagina can be administered with an irrigator. This consists of a plastic bottle with a long cannula mounted on the top. This cannula has holes in the sides and with some designs the cannula is bent at an angle of 45°. The solution irrigates the vagina through the holes in the cannula when the bottle is squeezed (Fig. 24.15).

24.4.19.12 Devices to Administer Rectal Preparations

Administration of liquid rectal preparations requires a squeezable bottle (see Sect. 24.4.4.1), a bag (Sect. 24.4.13.2) or a syringe (see Sect. 24.4.16), with a rectal cannula (see Fig. 24.10). This cannula is preferably of flexible material to prevent damage to the rectal mucosa. This is less important with short cannulas than with long ones. An enema bag has a long flexible tube cannula. This cannula should be lubricated or should be made of slippery material to ease insertion. The cannula should have a rubber one-way check valve when respiration is possible (with enema bottles, not with enema bags).

24.4.20 Child-Resistant Closure

The requirements for the ideal child-resistant container are:

- The container cannot be opened by children.
- The container is not too difficult to open by adults (especially elderly and handicapped people).
- The container is easy to close effectively.
- The closure continues to function appropriately, even after frequent use.

There are international standards for child-resistant containers, detailing the characteristics and tests they have to withstand. In the European Union two standards are applicable:

- ISO 8317 (2004) for reclosable child-resistant containers for pharmaceutical products.
- EN 14375 (2003) for non-reclosable child-resistant containers for pharmaceutical products.

The two standards describe the quality requirements for child-resistant containers as well as their validation.

For a reclosable child-resistant container the screw-press-principle is the most widely used. A combination of actions (pressing and unscrewing a cap at the same time) is very difficult for a child.

Examples of non-reclosable child-resistant containers are sachets and blister packages. These require a pincer-like movement with thumb and forefinger to open the package. This movement is difficult for a child to perform. However, it cannot be concluded that all sachets and blister packages are child-resistant. As it would necessitate a great deal of work to validate all strips to the ISO-standard some general (mechanical) properties are required to which the strip, sachet or blister package has to comply in order to be child-resistant. Examples are the non-transparency of the material and a sufficient tensile strength of the foil. ISO 13127 (2012) describes mechanical tests which can be used to demonstrate the child resistance of some packaging following minor modifications to existing child resistant containers.

24.4.21 Containers for Arthritic Patients

For patients with impaired hand function, opening of containers can be a problem. The needs of this patient group are not always suitably addressed [39, 45]. Pharmacy preparations or repackaged products for arthritic patients should be dispensed in suitable containers. The container should be:

- Easy to hold (not too small)
- Easy to open (no ‘precision handlings’ should be necessary)
- Unbreakable

The most significant containers that arthritic patients have difficulties with are those for tablets, capsules and suppositories.

24.4.21.1 Tablets and Capsules

A blister package containing tablets or capsules is difficult to open, or cannot be opened by an arthritic patient. The blister packages that consist completely of aluminium give most problems. Blisters with lidding foil that can be peeled off are easier to open, except when the patient mistakes them for a push-through lidding foil [39].

There are tablet presser devices available where a patient with limited hand strength can press the tablets out of a blister package. Alternatively, the lidding foil can be cut open using a so-called Blisterpack Pen/Pill-pen. The pharmacist can also press the tablets or capsules out of the strip for the patient and, provided that the storage conditions allow it, pack them in a jar with a screw cap.

Some easy to open screw caps for patients with reduced hand function have been designed (see Fig. 24.16). The bottle and cap are usually made from unbreakable polypropylene. Special cap features are usually a larger size and ribs to provide a better grip. Some caps have projections that made it possible to open the bottle with, for example, a pencil.

24.4.21.2 Tubes

Tube caps should be large enough and should not have a smooth or sharp surface. Filled or semi-filled aluminium tubes are more difficult to squeeze by arthritic patients than plastic tubes.

24.4.21.3 Suppositories

Suppositories in strips pose an impossible barrier to patients with limited hand function. The container is too small to provide sufficient grip and the action needed to open the strip is too precise. An alternative the pharmacy can offer is to remove the suppositories from the strip and repackage them in a jar. When necessary the separate suppositories can be wrapped with some aluminium foil.

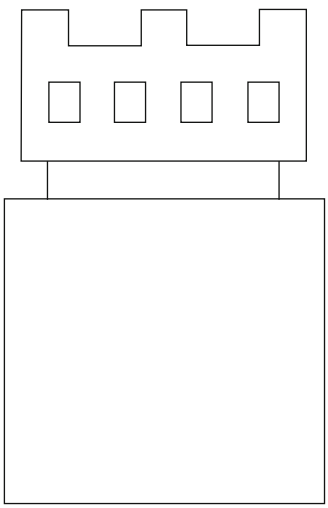

Fig. 24.16 Easy to open design of a tablet bottle

24.5 Quality Control of Packaging Materials

24.5.1 Quality Assessment

The quality control of containers is different to the quality control of raw materials. Raw materials as powders or solutions are homogeneous, so a small sample is representative of the entire population. When the analysis of a raw materials sample reveals a quality issue this problem generally applies to the entire batch. Containers however are discrete units and a sample container may not be representative of the entire batch. For example a crack in a bottle sample does not mean that all the remaining bottles in the batch will be cracked.

A sampling plan for attributes is a method to overcome this problem. An example of such a plan is the Accepted Quality Level system (AQL) (See Sect. 24.5.4. for a more complete description of AQL and Sect. 20.4.5 for a statistic background). In order for the AQL system to be successful an extensive and statistically planned random sample has to be selected. The defects that are found are classified into levels, for example: critical, major, minor. Within each level the system defines an ‘acceptable quality level’. When a quality level is exceeded, then a batch should be rejected. This method of testing requires time and expertise. Sampling has to be performed from a large number of containers from the same batch. Within the pharmaceutical industry it is often necessary for such tests to be carried out by the container manufacturer. For smaller enterprises such as pharmacies quality control can be undertaken by the wholesaler or an independent laboratory. Within a (hospital) pharmacy the quality control is often limited to a visual comparison to reference samples and a check of the presence of the supplier’s statement that the containers comply with the agreed specifications [46].

24.5.2 Defining Quality Requirements

In order to perform quality control the quality requirements or parameters should be known. cGMP regulation demands that the characteristics of containers important for product quality are defined in specifications [5]. The Ph. Eur. describes general requirements for some packaging types and materials (glass, rubber and various plastics). Specifications for containers are more specific for individual

containers and include the shape, dimensions, printing and the relation between different parts of the container (for example the closure of a rubber stopper on a bottle). Container specifications can be requested from the supplier. When specifications are not properly defined, they can be an ongoing source of misunderstanding between supplier and the purchasing pharmacy. It is essential that the quality control department creates an archive of reference samples. Reference samples can be seen as a physical part of the container specification. In addition to specifications the quality control of containers demands an assessment protocol. This assessment protocol describes which tests have to be done and how they have to be performed.

24.5.3 Incoming Container Material Control

The quality control of incoming containers includes a receipt check and an attribute assessment. The receipt check consists of:

- Checking the delivery note against the order information. This confirms whether the delivered materials correspond to those ordered.
- Checking the condition of the transport container. This confirms that the correct transport container was used, that the outer transport container is dry, free from dirt, undamaged and the label information is correct.

The attribute assessment determines whether the container materials meet the specifications. A risk assessment should be performed to determine what level of quality assessment needs to be undertaken. This risk assessment should take into consideration the level of quality assessment performed by the manufacturer or supplier. For example, if the manufacturer has a limited quality assessment system, then the purchaser may be required to carry out an extensive number of checks. An audit of the manufacturer is the best way to determine what level of assessment needs to be undertaken by the purchaser. An audit may be part of certification or accreditation of the manufacturer or the supplier. Audit findings can provide a list of so-called 'reliable suppliers' (see also Sect. 21.5.1). The level of quality control undertaken by a container manufacturer can be obtained from one of these audit reports. When using an established approved supplier, a purchaser could reduce the amount of testing that needs to be undertaken. For example the level of testing could be reduced to an identity test and assessment of the supplier's certificate of conformity. A limited identity test could include; dimensions, colour and text. Additional tests for parenteral product containers could include:

- Type of hydrolytic resistance in case of glass
- Presence of microbiological contaminations

Containers will require more extensive testing when purchased from suppliers who provide insufficient information about their quality system. For complete testing an AQL-system can be used.

24.5.4 AQL-system

The AQL-system is a sampling and assessment system frequently used to check containers. It is a type of attribute assessment, see Sect. 20.4.5 for statistical background. AQL means Acceptable Quality Level. The AQL-value is the percentage of rejected units accepted by a supplier or buyer to approve the concerned batch. Tables are available which describe, for a certain batch size N and an agreed AQL-value, how large the test sample n should be and how many units of that sample are allowed to show a specific defect

The AQL-system classifies defects in classes:

- Class 1 defects (critical defects): These are defects that have a negative effect on the contents of the container and result in a possible danger to the user. For example, glass splinters in a bottle. A defect in this class makes the container unsuitable for use. Class 1 defects can be subdivided into:
  - Class 1a defects: very dangerous defects
  - Class 1b defects: dangerous defects
- Class 2 defects (major defects): These defects can impair the use of the container material and can lead to complaints by the user. For example: holes in the outside lacquer of the tube.
- Class 3 defects (minor defects): These defects reduce the quality of the product. For example: a small shift of the print on the product. A defect in this class either has no effect or hardly influences the usefulness of the product.

All types of container defects should be defined and allocated into one of these classes. For every defect class an AQL-value is agreed between the purchaser and the supplier. Every parameter within each defect class should be described and the maximum number of non-complying units for this parameter defined; this is called the single error (SE). Also, the limit for the total amount of defects of all parameters in one defect class can be defined; this is called the accumulated error (AE). The AE is the sum of SE in that defect class.

24.6 Overview Primary Containers

To conclude this chapter, Table 24.10 provides an overview of pharmaceutical dosage forms and primary containers. As for pharmaceutical dosage forms the classification of the EDQM [26] is provided for containers wherever possible.

Table 24.10 Overview of dosage forms and primary containers

Dosage form	Bottle	Jar	Tube	Strip	Bag	Other details
Application liquid	+					Brush, spatula
Irrigation for the bladder	+				+	
Capsule		+		+		
Cream		+	+			Possibly rectal cannula, vaginal applicator
Oral liquid	+					Cup, measuring spoon, dosage syringe
Drops for oral use	+					Dropper or pipette cap, dropper insert
Emulsion for cutaneous use	+	+				Possibly brush or spatula
Gel		+	+			
Gargle	+					Cup
Injection fluid	+					Vial, ampoule
Intravenous infusion fluid	+				+	
Enema	+				+	
Irrigation for the mouth	+					Cup
Nose drops	+					Dropper or pipette cap
Nose ointment			+			
Eye drops	+					Dropper cap, Redipac®
Eye gel			+			
Eye lotion	+					Eye irrigation cup
Eye ointment			+			
Ear drops						
Nonsterile	+					Dropper or pipette cap, dropper bottle
Sterile	+					
Solution for cutaneous use		+				Possibly brush or spatula
Pessaries		+		+		
Paste		+				Spatula
Powders						
Single dose		+				Sachet, laminate or paper
Non divided		+				
Shampoo	+					
Powders for cutaneous application		+				Sifter-top container
Tablets	+	+		+		
Irrigation for the vagina		+				Irrigator
Solution for inhalation vapour	+					
Ointment		+	+			Possibly spatula
Suppositories		+		+		

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Human Resources

25

Jan de Smidt and Hans van Rooij

Contents

Abstract

This chapter deals with functions, competences, education, awareness of and management by pharmaceutical professionals and their professional decisions. Pharmacists and QP's in industry carry the responsibility for the production of medicinal products considering their education and ethical attitude. Clear and formal relations between the responsible pharmacist or QP, the management of the organisation and relevant employees have to be laid down in functional descriptions and in an organisation chart giving full regard to the respective law and regulations of the individual countries, which are to be harmonised with European Directives and Regulations. Certification such as ISO 9001/EN 15224 may require continuing education of professionals.

Professional organisations of pharmacists and national authorities require on-going training (Continuous Personnel Development) for all personnel involved in any aspect of the profession and in the topics covered in this book.

Keywords

Pharmacist • Technician • Qualified person • Competences • Awareness • Responsibilities • Training • Decisions

25.1 Human Resources in Pharmaceutical Healthcare

The basis of human resources in medicines production, product and patient care may be, following ISO-9001/EN 15224 [1], defined as:

- Professional, trained individuals are necessary to prepare medicines, to purchase and keep them and to advice patients about their practical use.
- Those individuals perform work affecting conformity to product/health service requirements, so they shall be
  - Competent on the basis of appropriate education, training, skills and experience

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_25,

– Aware of how their activities contribute to the achievement of the quality characteristics and quality objectives

Competences of the pharmacists will be described, focussing on their functions in production and product care. The pharmacist is, in most of European countries, the professional who is responsible for the production, availability, storage and procurement of medicines. Part of the role lies in advising and pharmaceutical patient care. The pharmacist must be aware that he is responsible for solving unexpected situations that might have severe consequences despite existing and functioning quality systems. In order to prevent such situations generally, the pharmacist needs a broad view.

Trained support personnel (technicians, assistants) are used to support and supplement the activities of the pharmacist. They can be specialised in the production of medicines.

The pharmacist must be aware that other persons play a major role in the administration of medicines to patients. The pharmacist may be asked, or feel morally or legally, obliged to give care and training to the reconstitution of medicines (see Fig. 1.2) on a ward by nurses, at nursing homes or home for the elderly or to home care workers or family of the patient.

When the Qualified Person (QP) is mentioned, a legally required professional unique for the pharmaceutical industry in Europe will be meant. The person is not only involved in manufacturing by releasing batches, but, if the QP is a pharmacist, he may in practice in some countries act as a health care professional as well in providing information for other health care professionals (HCP's) on product availability and pharmacovigilance issues. Finally the QP handles quality related complaints from HCP's and patients (product care) including recall of products. When the Qualified Person for Pharmacovigilance (QPPV) is mentioned, a person is meant who deals with reporting adverse events, lack of efficacy and safety of products.

When the Responsible Person (RP) is mentioned, European Guidelines on GDP (see Sect. 36.2.4) are referred to. Those guidelines focus on procurement, storage, distribution and shipment.

This chapter starts by presenting responsibilities for the pharmaceutical processes embedded in an organisation starting at receiving a prescription and ordering, and ending at dispensing and instructing the patient, sometimes ending with a (medical) complaint. These processes are in essence similar for industry and hospital pharmacies, and processes in community pharmacy will fit in this template as well. The section on Competences discerns varying pharmaceutical functions in the production of medicines and product care. The section Education zooms in from the general pharmacy education onto production and product care. The section on Awareness includes how to increase awareness of employees, also of persons trained outside the pharmaceutical field. Finally professional decisions and responding to demands from the patient population are discussed.

25.2 Processes

25.2.1 Development

Traditionally, the pharmacist combined preparation, control and dispensing. He was held responsible as a person when a patient was harmed. In addition, when a pharmacist suspected an error in a prescription of a physician he initiated a relevant action. Also when a patient reported an adverse event, the pharmacist informed authorities and industrial parties, the Marketing Authorisation Holder.

The fields of manufacture, control and distribution have been loaded with GMP and GDP related regulations and recommendations in order to minimise errors. These regulations require a Qualified Person (QP), or Responsible Person or Authorised Person to be involved before the product is admitted to the market. Adverse event monitoring and reporting have been subject to pharmacovigilance regulations, supervised by a Qualified Person for Pharmacovigilance (QPPV). These developments in industry have in their turn increased attention and requirements to similar functions in preparation in community and hospital pharmacies.

25.2.2 Product Care, Production and Quality Management

When considering dispensing at small scale such as in a community pharmacy and small hospitals, the pharmacist will, personally, not produce every medicinal product. He has to rely on industry and other (hospital) pharmacies but will need product knowledge to fulfil his position in the supply chain.

Small scale preparation will already bring about different functions, delegation of tasks and the creation of a pharmaceutical quality system.

Large scale production operations in the hospital environment require more personnel involved in production, dispensing and quality control of medicinal products. For the preparation process the pharmacist has to delegate parts or almost all activities to other trained professionals. Assistants, technicians of various educational levels, cleaning personnel and operators may be involved.

Logistics and clinical pharmacy are day to day practice in community and in hospital pharmacies. Logistics in industry is a discipline that has been emphasised, due to current GDP Guidelines [2] and Quality Management.

Quality Management, common both to industry and pharmacies is dealt with in Chap. 35.

25.2.3 Pharmacovigilance

Pharmacovigilance is about the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (see Sect. 35.4.2). The Marketing Authorisation Holder of a product has to have at his disposal a qualified person who is responsible for the pharmacovigilance of that product, the Qualified Person for Pharmacovigilance (QPPV) [3].

Annex 16 of Volume 4 of the Good Manufacturing Practice Guidelines proposes that the ultimate responsibility for the performance of an authorised medicinal product over its lifetime; its safety, quality and efficacy lies with the Marketing Authorisation Holder (MAH) [4].

In (hospital) pharmacies the responsible pharmacist is in charge of pharmacovigilance of the products prepared in the pharmacy.

25.2.4 Scheme of Responsibilities, Product Flow and Communication Lines

The chart (Fig. 25.1) is a generalisation and presents an overview of processes involving the main actors, Marketing Authorisation Holder/Responsible Pharmacist, QP/Responsible Pharmacist, Patient and QPPV. Verifying correct prescription and ordering processes have been kept out of the chart.

25.3 Competences

25.3.1 Functions of Pharmacists

Professionals dealing with medicines are engaged in the following processes: logistics, dispensing, production and control of medicines.

- Logistics is about good distribution practice which includes procurement, receipt and correct storage at all

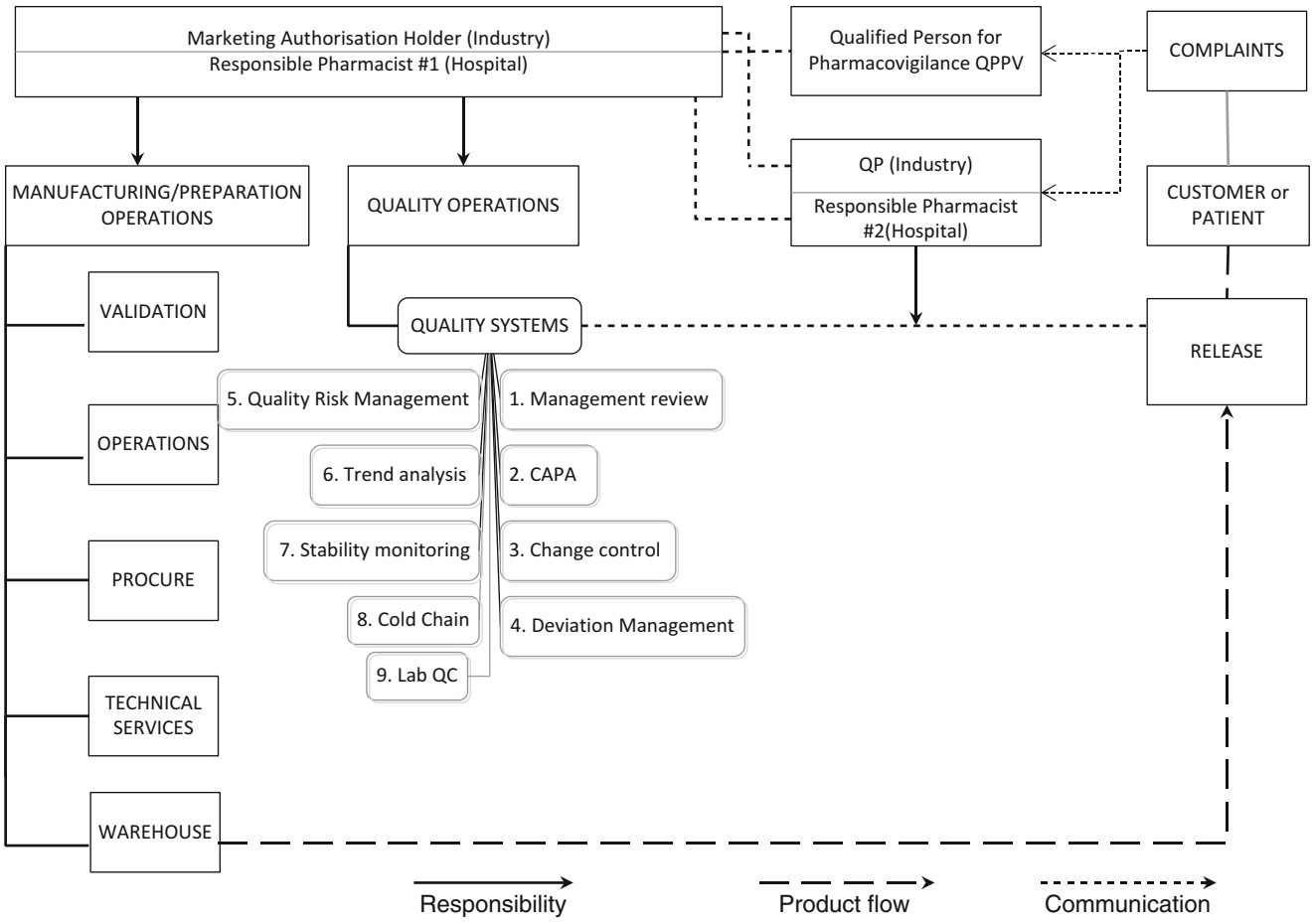

Fig. 25.1 General chart for process responsibility, product flow and communication

stages within the chain and final delivery to pharmacies and the end user (patients) (see Chap. 36).
- The dispensing of medicines is based on prescription checking (see Sect. 2.2), picking the right medicine, appropriately preparing it for patient use and instructing patients about their practical use.
- The production of medicines is the prime focus of this chapter.
- Control of the quality of medicines is focused on the chemical and (bio)-pharmaceutical properties and some are directly related to clinical effects of medicines in patients.
- If medicines are produced on a larger scale, i.e. for more than one individual patient, more professionals will be involved.

Production will be separated from quality control, in a hospital pharmacy just as it is in pharmaceutical industry. In all areas pharmacists can be employed as well as other professionals, assistants, technicians and workers. In specific departments of the hospital pharmacy such as the production department, the sterile production department, the analytical lab, and the microbiological lab employees of other disciplines may also be employed.

25.3.2 Pharmacist in Patient Care and Product Care

Product care and patient care are the essential functions of the pharmacist at the end of the supply chain where the pharmacist meets the patient. Product care is associated with procuring (availability), storage and dispensing, including instruction of the patient of medicinal products as well as with preparation if necessary. Patient care may include counselling on the choice of medication regimens, a key part of basic academic pharmaceutical education. It may also be associated with properties of medicinal products such as efficacy and safety; or lack of safety and lack of efficacy. Healthcare professionals and patients are then the first to complain about the services delivered by the pharmacy.

The basic education of the pharmacist is directed to these responsibilities and to changes and developments in the pharmaceutical field. The education of the pharmacist has to be on an academic level to equip him with independent thinking and to guarantee a good discussion with e.g. physicians, other healthcare professionals (HCP's) and commercially orientated managers. In addition it may be expected that scholarship from a scientific discipline is a reasonable guarantee to cope with progress in current scientific and technical knowledge of the pharmaceutical professional. Further, basic training has to be at an adequate level for further specialisation, e.g. training courses on a wide variety of subjects.

During the last decades new insights in the competences of health care professionals have evolved, centring on the communication with patients. Basic education may be pivotal in pharmacy, however insight and oversight of Healthcare institutions and the way pharmaceutical companies organise their processes are necessary as well.

The Canadian CanMEDS system [5] has inspired many basic and specialised medical and pharmaceutical courses throughout the world. This system is based on the roles and competences that a health care professional has to play in practice and by consequence provides information for an educational program. The diagram of Can MEDS has been adapted for pharmacists and is given in Fig. 25.2.

The different sections of Fig. 25.2 symbolise the different core competence areas of the pharmacist: *pharmaceutical expertise* as a pharmaceutical professional, *communication* with patients, *cooperation* with other health professionals, *management* as an executive, *commitment to society* (health advocacy) in advising patients, *scholarship* in an attitude towards medicines related problems.

Many academic schools use the CanMEDS framework. It is also very useful as a basis for specialised training and for continuing education. A typical example for the training of pharmacists, based on the CanMEDS-system can be found in the training of industrial pharmacists in Belgium (see Sect. 25.4.4).

Certification of health institutions such as hospitals and pharmacies for instance via ISO 9001/EN 15224 may include observations on education of HCP's, stipulating additional programs.

25.3.3 Technicians and Assistants in Healthcare

The competences of assistants and technicians are derived from the corresponding competences of the pharmacist. In this view they perform parts of the roles of the pharmacist. If properly organised, they can be responsible for carrying out the part of the work that has been delegated to them according to the local procedures. The responsibility remains with the pharmacist. The CanMEDS diagram can be used to develop a suitable educational program for these professionals as well.

An international study about the role of pharmacy assistants and their education [6] reveals many differences and many similarities throughout Europe. About the actual preparation of medicines a variety of functions was found. It happens to be mainly a function of the assistant (e.g. in the Netherlands) or the assistant is not involved in preparation at all (in e.g. Slovenia). In some countries (e.g. in Germany)

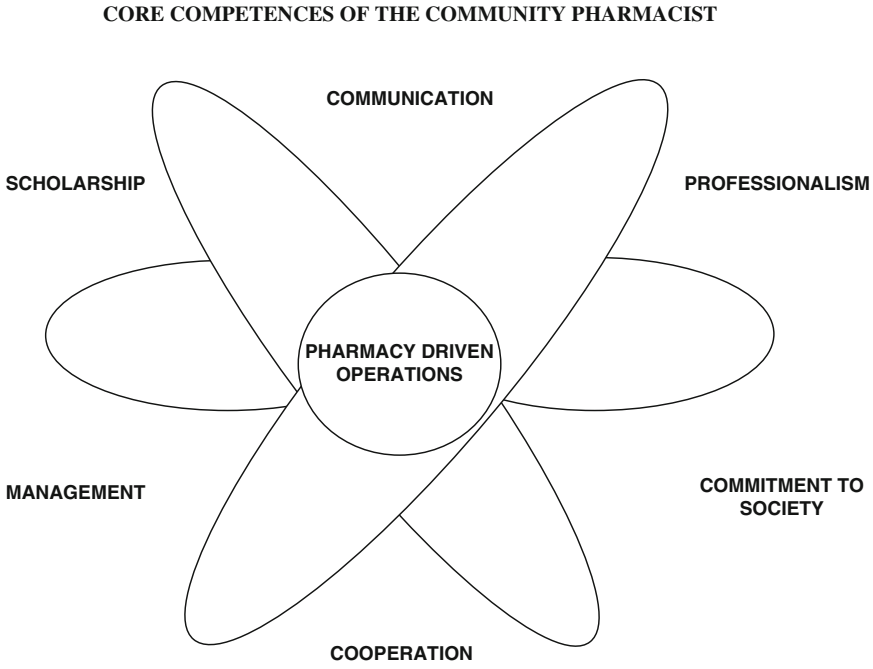

Fig. 25.2 CanMEDS diagram adapted for pharmacy (Copyright © 2005 The Royal College of Physicians and Surgeons of Canada. http://rcpsc.medical.org/canmeds. Reproduced and adapted with permission)

the assistants are trained to carry out chemical analysis on raw materials and pharmacy made preparations.

Technicians and assistants are working in hospital pharmacies as well. In general the same educational program can lead to competences in both community and hospital pharmacy.

25.3.4 Qualified Person

25.3.4.1 Functions

A Qualified Person (QP) has a key position in the pharmaceutical industry and it is that person who releases the batches for the market. The QP deals with quality related complaints and is leading in recall operations.

European Directive 2001/83/EC [7], as amended, states that the QP in the pharmaceutical industry has the responsibility for ensuring that a particular batch has been manufactured in accordance with its marketing authorisation, EU Good Manufacturing Practice (GMP) and equivalent regulations. Other tasks are:

- Starting materials compliance and supply chain security
- Manufacturing and testing performance
- Manufacturing and testing process validation
- Changes and investigations completion

Duties of the QP are described in more detail in Volume 4 Good manufacturing practice (GMP) Guidelines, respectively Annex 16 to GMP (see Table 25.1).

The formal function of a QP exists in Europe and is legal for manufacturers of licensed medicines and investigational medicinal products.

PIC/S GPP ([8], see also Sect. 25.5.5) acknowledges a similar function for preparation in pharmacies: Responsible Person or Releasing Officer:

> 6.5 Release
>
> 1. The Responsible Person is ultimately responsible for the quality of the medicinal products prepared and released. The actual release can be delegated to another appropriately competent person (i.e. Releasing Officer).
>
> 2. Product release should include verification that the medicinal products comply with the valid specifications and that they have been prepared in accordance with valid procedures and with the principles of Good Practices for preparation described in this Guide.

The title, Responsible Person, is also used in the guidelines on Good Distribution Practices of the European Commission [2]

An extensive regulation of the Qualified Person has evolved in recent years because of the important implications resulting from his duty. The role may be considered within the pharmaceutical company formally as that of a watchdog (as it is legally), by assuring that released products meet the specifications from the Marketing Authorisation.

History and Position of the QP

Until about 1900 pharmacists prepared all medicinal products in their own pharmacy,. mostly with help of self-trained assistants. With the upcoming pharmaceutical industry more complex organisations came to life and more pharmacists were needed apart from the pharmacist/owner. The introduction of managers and

(continued)

Table 25.1 Duties of the Qualified Person

Duties	Reference to GMP
Release	Chapter 1.4 (xv) and 1.9 (vii)
Producing a quality review	
Specific place in hierarchy; relation to heads of production, quality control, quality assurance, quality unit	Chapter 1.4 (iv,v) Chapter 1.5
Description of duties:	Chapter 2.6
Ensure compliance with Marketing Authorisation (MA)	
Permanently at disposal of the Manufacturing Authorisation holder	
Handling unplanned deviations	Annex 16 (draft) 5
Contract manufacture	Annex 16 (draft) 2.3.3.
Chain quality	Annex 16 (draft) 3.5.5
Handling complaints	Chapter 8.1
Product recalls	Chapter 8.9

administrative as well as specific technical personnel led to management structures as shown in Fig. 25.1. Most of the scientific positions within the pharmaceutical industry are typically suited for pharmacists. In case of lack of interest of pharmacists to work in a pharmaceutical company a shortage of scientific personnel may have been filled up with chemists, biologists and doctors. Their specific knowledge and scientific abilities cannot be missed in the pharmaceutical industry any more. The QP needs typical pharmaceutical knowledge and abilities. If he is not a pharmacist, additional courses, based on the pharmaceutical education, are available to meet the regulations of the EC. If the QP is a pharmacist by education, he can additionally represent the company towards colleague-pharmacists, doctors and patients as a healthcare professional.

Some countries in Europe, such as the Netherlands have installed a system of administrative penalties for the company in relation to non-compliances as well as the possibility of bringing the company into court when a criminal offence is suspected. A QP could be involved as well. Jail as a penalty is common in other countries, such as Ireland.

25.3.4.2 QP and Quality Systems

The principle of Quality Management has evolved, which has assisted the work of the QP. The European approach in nominating an individual to be an independent arbiter of quality is also applied to Good Distribution Practices in which a Responsible Person (RP) is introduced in legislation for Pharmaceutical Wholesalers [2].

As explained in Sects. 34.9 and 35.1 the release of pharmaceutical preparations cannot only be based on the assay of the content or on studying the preparation documentation, but has to be based above all on knowledge of and trust of Pharmaceutical Quality Systems. The reporting of incidents, deviations, problems with personnel hygiene and problems with equipment is valuable for a QP, but sometimes there has to be reliance, for those issues, on the head of production. In France the daily physical presence of a QP within a manufacturing plant for radiopharmaceuticals is required before manufacture starts.

The functions of an industrial QP resemble very much the functionality of a quality manager as described in ICH Q10 PQS guidance (see Sect. 35.5.9) or ISO-9001 (see Sect. 35.7.2). It is not surprising that a person fulfilling the QP function is increasingly seen as the quality manager, despite comments that his independent individual opinion may be at stake. The 7 Pillars model (see Sect. 35.7.5) sees the QP as the owner of the "Release System" as indicated by law [4] and as an expert to be consulted about all other elements of the Quality Management System.

All these considerations being true, the very first priorities of a QP position is his autonomy in decision making and in having direct access to senior management.

25.3.4.3 Qualified Person for Pharmacovigilance (QPPV)

The Marketing Authorisation Holder of a product has to have at his disposal a qualified person who is responsible for pharmacovigilance of that product [7]. The MAH is supported by expertise from Regulatory Affairs officers who are responsible for taking care of dossier documentation, including Quality, Toxicology and Clinical Sciences, and updates.

The QPPV should have documented qualifications and experience within pharmacovigilance. If the individual is not medically trained, e.g. a biologist, then the QPPV must have easy access to a medically qualified person. The tasks of the QPPV are extensively described in pharmacovigilance guidelines [3].

Dealing with medical information and complaints of HCP's and patients is another duty that relates to a potential non-compliance with the marketing authorisation: off label use, medical related complaints.

Each adverse reaction must be investigated and an explanation must be provided whether product quality may be the root cause. Furthermore, it is a GMP requirement that the QP (and delegated QPs) is informed of adverse effects independent of whether these are related to product quality issues.

25.3.4.4 QP/QPPV- Like Functions in Pharmacy

A legal QP and QPPV is required if investigational medicinal products are being prepared for use in clinical trials (see Sect. 35.5.10). Apart from those legally defined functions for the QP/QPPV are not frequently encountered in hospital pharmacies in routine processes but decision making and being held responsible have been assigned to other individuals of which the pharmacist is an example. For example the presence of a QPPV-like function in the hospital pharmacy organisation is required when medicines are imported from outside the EU and are supplied to other pharmacies.

Digifab® Case

After intoxication with digoxin a physician may need digoxin antibodies (Digifab®). Digoxin antibodies bind to digoxin reducing the digoxin level in heart tissue and in blood. This may be a live saving treatment. No licensed product is available in the Netherlands and currently not elsewhere in Europe. However, there is a product on the US market, Digifab®.

In the Netherlands only a few cases per year occur, which does not warrant a stock position in every Dutch hospital. Therefore the Central Hospital Pharmacy in The Hague imports the Digifab® from the USA and serves as a central stock keeper for all Dutch hospitals. An imported medicine is legally considered a non-licensed medicine in the importer country. The Inspectorate agrees with the above construction on conditions:

- The request has to be justified and authorised by the treating physician and handed over to the competent authority.
- The Inspectorate requires the hospital pharmacy to declare that it performs pharmacovigilance. Therefore the Central Hospital Pharmacy supplies Digifab® together with a request to the physician to report whether or not side effects were observed. Every year a review of all cases is submitted to Inspectorate.
- All tasks and responsibilities have to be described in a SOP and Technical Agreement authorised by the relevant involved pharmacists from the distributing pharmacy and the client pharmacies.

25.4 Education

25.4.1 Basic Academic Education

Every pharmacist must be acquainted to the production of medicinal products and product care. So the basic education of pharmacists must include chemical, physical, microbiological and biopharmaceutical disciplines. Knowledge of herbal products and their production must also be a part of the basic pharmaceutical education, as well as pharmacology and toxicology. Directive 2005/36/EC as amended, provides criteria that are applied when a pharmacist from outside the EU can be recognised [9]. This list allows pharmacists to travel and work in the EU countries. It is a minimum list and only applicable for the training of a basic pharmacist. For specialised pharmacists more training is available and in many countries is a requirement. The list has not been based on CanMEDS systematics and is without focus or hints as to the intensity or duration of the training of the subjects of study.

Different types of workers will be employed in pharmaceutical industry with differing levels of education. Many courses are offered to employees both as in-company and courses by outside companies in the educational market. Pharmaceutical manufacturing is a widely used term for these occupations. Pharmaceutical productions operator is more specific for employees with certain well-defined and established jobs in industry. The duration of these courses differ from 20 h to 2 years, depending on the position of the worker and the responsibilities.

As it is assumed that within 5 years knowledge and skills are lost if not applied in practice, initial training at universities should not contain many subjects that are not useful in expected occupations. If a substantial proportion of pharmacists are not involved in production of medicines only the principles of production should be in the training programs. However, this level should allow students to follow specialised pharmaceutical training without delay. This equilibrium has to be maintained by the educational institutes.

Article 44, 3 from the recognition of qualifications for the pharmacist [9]:

Training for pharmacists shall provide an assurance that the person concerned has acquired the following knowledge and skills:

(a) Adequate knowledge of medicines and the substances used in the manufacture of medicines
(b) Adequate knowledge of pharmaceutical technology and the physical, chemical, biological and microbiological testing of medicinal products
(c) Adequate knowledge of the metabolism and the effects of medicinal products and of the action of toxic substances, and of the use of medicinal products

(d) Adequate knowledge to evaluate scientific data concerning medicines in order to be able to supply appropriate information on the basis of this knowledge
(e) Adequate knowledge of the legal and other requirements associated with the pursuit of pharmacy

The work which a pharmacist is allowed to perform on the basis of this education is formulated by the European Commission as follows:

Article 45, 2:

The Member States shall ensure that the holders of evidence of formal qualifications in pharmacy at university level or a level deemed to be equivalent, which satisfies the provisions of Articles 44, are able to gain access to and pursue at least the following activities, subject to the requirement, where appropriate, of supplementary professional experience:

(a) Preparation of the pharmaceutical form of medicinal products
(b) Manufacture and testing of medicinal products
(c) Testing of medicinal products in a laboratory
(d) Storage, preservation and distribution of medicinal products at the wholesale stage
(e) Preparation, testing, storage and supply of medicinal products in pharmacies open to the public
(f) Preparation, testing, storage and dispensing of medicinal products in hospitals
(g) Provision of information and advice on medicinal products

As a result of the Declaration of Bologna, the academic education of pharmacists in Europe has to be unified. In order to stimulate this trajectory a so-called Pharmine project has been started [10]. It offers help to the different European countries to be active in renewal of the pharmaceutical education. Apart from adaptation to European standards, new subject areas are to be developed based on the evolving pharmaceutical practice in both community and hospital pharmacies. In many countries pharmacists seek new roles in patient counselling, doctor counselling, medication reviews, development and maintenance of pharmacotherapeutic formularies, advising of special groups of patients. Next to these new occupational goals for practical pharmacists, new diseases and new groups of patients will allow the pharmaceutical industry to develop new types of medicines and new production scales. All types of pharmacists will have to be prepared to handle these challenges. Continuous renewal of the educational programs is therefore a must for all educational institutions.

As a useful initiative for education and discussion the SABER community has to be mentioned here [11]. The Faculty of Pharmacy and Pharmaceutical Sciences of the Monash University support this Sharing and Building Educational Resources platform. It can be used to develop and share educational programs and educational materials. Especially for large rural areas such as Australia it offers a good opportunity for developing and keeping up of professional competences. Even materials for (virtual) practical training can be found in the SABER-community.

25.4.2 Preparation in Pharmacies

If a product is prepared for a single patient in a community pharmacy by the pharmacist himself, the quality risks are considered to be low. The academic education, the ethical requirements, his legal position and the supervision by Pharmaceutical Inspection, are all intended to guarantee an adequate product for the individual patient. Eventually the patient himself can complain to the pharmacists who made the product about the quality thereof insofar the patient has enough insight in that. Section 25.6 as well as Sect. 35.6.13 deal with processing patient complaints.

The proper education of the pharmacist in the community setting has to include theory and principles of quality control in order to allow the pharmacist to work in a responsible way. In some countries specialised courses for community pharmacists are available or even required. In these courses there should be time for the specific problems of the production of medicines in the setting of a community pharmacy.

Nevertheless, proper documentation of all actions during the preparation should be available, as explained in detail in Sects. 33.5 and 34.5. If assistants or other personnel are involved in the preparation of products for more patients, there is urgency for extensive documentation. The responsible pharmacist has to release the products. It is the responsible pharmacist who is held to account if the product does not have the desired quality.

The pharmacist is responsible for ensuring that the professionals or workers to whom practical work is delegated are indeed capable of performing those tasks. In some countries specialised educational programs are available on a national specified level. So, vocational education allows pharmaceutical assistants or technicians to work as trusted professionals in any pharmacy. They can have a high level of independence and of responsibility for carrying out the tasks that are given to them. The pharmacist always retains the overall responsibility.

The basic academic training as a pharmacist must allow the students to follow the specialised courses without delay. In most of the European countries a specialised course is available for the hospital pharmacist.

If preparation of medicines for many patients or even semi-industrial production is done in the hospital pharmacy, a prolonged study of the relevant disciplines is a necessity.

Especially for the preparation of sterile products, antineoplastics, and radiopharmaceuticals additional expertise has to be required.

To become an all-round hospital pharmacist a specialised educational period of 4 years is not uncommon. Part of this education period is used for educating the "student" pharmacist for preparation skills.

A course example for hospital pharmacists, which is intended for the preparation of medicines, is derived from a project in the Netherlands [12]. The first part (A, B, C etc.) of this list gives the competences that the hospital pharmacist needs for proper functioning. The second part (K1, K2 etc) consists of knowledge goals, the third part contains skills (C1, C2 etc.) and the fourth part (A1, A2 etc.) gives the attitudes of the well trained hospital pharmacist:

V. Preparation

Preparation includes contributing to pharmacotherapy, drawing up protocols, preparing drugs (including radiopharmaceuticals), assessing the quality of preparations and supporting the administration of medicines.

After training the hospital pharmacist is *competent* to:

(A) Assess the pharmacotherapeutic relevance of individual preparations or stock

(B) Draw up batch preparation protocols for individual preparations and stock production and draw up and maintain product files for stock production

(C) Prepare non-sterile, aseptic and sterile medicines for individual patients as well as for stock

(D) Design and validate preparation processes for non-sterile, aseptic and sterile preparations and implement them

(E) Assess the quality of individual preparations and stock production on the basis of set specifications and determine whether preparations may be released for use

(F) Determine which specifications products, necessary for production (raw materials, additives, packaging materials, equipment and premises), must meet and if they actually meet these specifications

(G) Support and give instructions on preparation and administration of medicines

In order to have the above mentioned competences, the hospital pharmacist must:

K1 Be familiar with the requirements that batch preparation protocols and product files must meet

K2 Be familiar with technical and biopharmaceutical requirements that dosage forms must meet

K3 Be familiar with unusual hospital pharmacy preparation techniques and their necessary equipment, including the requirements these must meet

K4 Be familiar with work hygiene and radiation hygiene (level 4b) and apply them when preparing medicines

K5 Be familiar with the administration of drugs and the standards administration must meet and the devices used (parenteral and feeding tube administration)

C1 Be able to assess preparation requests on pharmacotherapeutic ratio and efficiency

C2 Be able to identify and assess relevant chemical and physical qualities of raw materials, additives, packaging materials and containers

C3 Be able to draw up drug-preparation protocols and product files that meet the technical, biopharmaceutical and other relevant quality standards

C4 Be able to design, set up and validate (including shelf-life tests) non-sterile, aseptic and sterile preparation processes and implement them

C5 Be able to prepare medicines for individual patients and stock production at such a level that the relevant quality standards and legislation are met

C6 Be able to assess whether specifications set for preparations have been met, and consequently release medicines

C7 Be able to instruct physicians and nursing staff as to preparing prior to administration and to administration itself

C8 Be able to formulate and communicate clearly

The hospital pharmacists should

A1 Be prepared to work accurately and carefully

A2 Be able to handle insecurity, make considerations and take decisions

25.4.3 Pharmaceutical Industry

A graduate with a degree in pharmacy will be suitably qualified to apply for jobs in pharmaceutical industry such as marketing and sales, pharmacoeconomics, IT, research and development (R&D), production, quality control, quality management, regulatory affairs, pharmacovigilance and in clinical research. In general, the basic academic education given by the Faculties of Pharmacy equips an individual for the above-mentioned area of interests and for specialised jobs in industry at least as a junior manager.

All pharmaceutical companies have in-house training and educational programs on top of the already acquired knowledge. Specialised courses additional to the basic academic education are available Europe wide and are attended by personnel from pharmaceutical companies in order to cope with current scientific insights and progress.

Such training of key personnel may be checked by Inspectorates and find its legal basis in European Legislation as well, by referring to progress in scientific and technical knowledge (Directive 2001/83 EC e.g. article 23) [7]. A period of on the job training of 2 years is sometimes required in individual countries. The training program of Master's Degree Industrial Pharmacy in Belgium [13] may be used as guidance for education of industrial pharmacists:

The industrial pharmacist has the following competences:

1. *Knowledge of the production of medicines*:
   - Ma IP 1.1 Understands the processes of the production of medicines on industrial scale and is able to work accordingly
   - Ma IP 1.2 Has an integrated vision on the different disciplines that are involved in the development of a medicinal product
   - Ma IP 1.3 Is able to design an adequate delivery form for a drug substance
   - Ma IP 1.4 Has knowledge about the production and uses of biotechnological medicinal products

   Knowledge of the analysis and quality control of medicinal products
   - Ma IP 1.5 Is able to apply relevant techniques for the analysis of medicinal products
   - Ma IP 1.6 Is able to implement and supervise the processes of quality control of medicines
   - Ma IP 1.7 Has insight in the principles and practice of analytical validation processes

   Knowledge of quality management and knowledge of the juridical and economical aspects of the pharmaceutical industry.
   - Ma IP 1.8 Is able to manage quality systems (QA, GMP, ISO)
   - Ma IP 1.9 Understands systems of quality management and quality care
   - Ma IP 1.10 Knows the laws and regulations concerning pharmaceutical industry
   - Ma IP 1.11 Is able to give help to marketing and sales
   - Ma IP 1.12 Is able to apply the principles of company economics
   - Ma IP 1.13 Is able to manage the principles and the practice of the registration of medicines

   Knowledge about clinical research and experimental clinical-pharmacological research.
   - Ma IP 1.14 Is able to give help for clinical research
   - Ma IF 1.15 Is able to participate in experimental clinical-pharmacological research.
2. *Scientific competences*
   - Ma IP 2.1. Is able to educate himself in the pharmaceutical areas with help of ICT, printed material and educational meetings
   - Ma IP 2.2 Is able to design procedures for laboratory based research and implement and control them
   - Ma IP 2.3 Is able to perform fundamental and applied scientific research
   - Ma IP 2.4 Is able to integrate specialised knowledge of different disciplines in a creative way
3. *Intellectual competences*
   - Ma IP 3.1 Is able to think analytically and synthetically as well as problem solving orientated
   - Ma IP 3.2 Is able to analyse complex problems
   - Ma IP 3.3 Is able to think and operate research directed
   - Ma IP 3.4 Possesses an attitude of scientific curiosity and of lifelong learning
   - Ma IP 3.5 Is able to reflect on his functioning in a complex context: "if you are not part of the solution you are part of the problem".
4. *Competences in communication and working together*
   - Ma IF P.1 Is able to report about own research
   - Ma IP 4.2 Is able to communicate and work together in a multidisciplinary professional environment
5. *Societal competences and societal commitment*
   - Ma IP 5.1 Is able to function professionally in an ethical and deontological way

25.4.4 Qualified Person

The education for a qualification as QP is given in article 49 of Directive 2001/83/EC, [7] as amended. As a basis for the education of the QP a course of at least 4 years in one of the following scientific disciplines is mentioned: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology or biology. The course shall include theoretical and practical study bearing upon at least the following basic subjects:

1. Applied physics
2. General and inorganic chemistry
3. Organic chemistry
4. Analytical chemistry
5. Pharmaceutical chemistry, including analysis of medicinal products
6. General and applied biochemistry (medical)
7. Physiology
8. Microbiology
9. Pharmacology
10. Pharmaceutical technology
11. Toxicology
12. Pharmacognosy

A pharmacist with QP experience is the most preferred for the QP function. Because of limited availability of specialised industrial pharmacists, national authorities

allow graduates from other scientific disciplines, as mentioned above in the Directive.

Several courses at graduate level are available lasting 3–4 years and 2 years of practical training, indicated by the European Commission. Apart from the above mentioned subjects the knowledge of pharmaceutical law, the role and professional duties of the QP, and knowledge of quality management systems are objects of study.

The Responsible Person as defined by GDP Guidelines has to have a similar level of knowledge and/or experience in Quality Management systems.

A difference between *authorise*d and *delegate*d qualified persons is described by GMP. Each company has to have one authorised Qualified Person, but they can delegate their work to one or more delegated Qualified Persons. Only the authorised Qualified Person has the overall responsibility for the release of a product. The Danish authorities for instance explain clearly the difference:

> When an authorised QP delegates the release to a delegated QP, the authorised QP must countersign for all releases that the delegated QPs have made on behalf of the authorised QP. The authorised QP must randomly review the releases carried out by the delegated QPs.

The EU Directive requirements for QP's is more or less equivalent to a degree in pharmacy. A document of the Danish authorities presents a possible exception to that. It says: "However, the requirement that a QP must have received training in all of the above-mentioned basic subjects can be waived." A similar waiver exists in Germany.

25.4.5 Academic Professionals from Other Disciplines

Different types of workers will be employed in pharmaceutical industry with differing levels of education. Many courses are offered to employees both as in-company and courses by outside companies in the educational market. Pharmaceutical manufacturing is a widely spread term for these occupations. Pharmaceutical productions operator is more specified for employees with certain well defined and established jobs in industry. The duration of these courses differ from 20 h to 2 years, dependent on the position of the worker and his responsibility.

25.4.6 Assistants and Technicians

As explained in Sect. 25.3.3, the level of competences and responsibility of assistants and technicians differ greatly in European countries. A vocational training of 2–4 years combined with elaborate work placement can lead to a nationally accepted diploma. Additional training is mostly available as well as forms of continuing education and assessment, as explained in Sects. 25.5.2 and 25.5.3.

25.5 Awareness

Each person in an organisation should be made aware of the organisation structure that governs pharmaceutical operations. In addition, individual awareness or anticipation on quality related topics is essential during day to day operations, in industry, hospital and community pharmacy. Each professional should have a leaning towards risk analysis and risk minimisation in order not be annoyed when problems pop-up. This section identifies some well-known issues from daily practice. The QP above all has to have full awareness of hazards, risks and harm.

25.5.1 Structure and Responsibilities Within the Organisation

Each organisation whether it is hospital or industry needs its own chart that shows preferred communication lines and the framework of the company. The chart provides transparency who is in business development, purchasing materials, commercial activities or who is in quality. Such a chart clarifies responsibilities when the company is part of a corporate organisation with headquarters elsewhere or part of a country-wide non-profit healthcare organisation with delegated responsibilities. European subsidiaries of global corporate organisations are considered to be the entities for bringing the products to the market in Europe from a legal perspective.

Line functions and staff functions within the organisation have to be clearly identified. Line is associated with process flow. Line functions have direct responsibility and have the authority and power for realising the mission of the company. Knowledge of reporting lines is useful. 'Staff' supplies information, materials and advices to the 'line'. Staff functions are e.g. counselling on human resources, on procedures, on analytical methods and on systems, on managing a science based service department handling medical information, complaints and recall. A QP or hospital pharmacist may have both line and staffs function(s).

The responsible pharmacist has to be sure that the professionals who perform (parts of the) pharmaceutical functions are suitably educated and have the required knowledge and skills.

Organisational charts, a proper and meaningful job description, a system of allowed delegation of tasks, a system for personal development and a system for continuous

education are all meaningful tools of the pharmacist and the employer for delegation of pharmaceutical tasks.

In a well organised production unit on a daily basis, the pharmacist will be involved only when this is necessary and will timely be asked for help but must be in a position to intervene. This supposes a high level of motivation of all professionals who work at the preparation of the specific product. Communication is essential and in process controls cannot be missed, especially when large batches are being produced. Some countries, such as France and Belgium require that the pharmacist is present on the day and time of operations, to be documented in a daily listing

Senior management, the boss in smaller organisations, has the ultimate responsibility to ensure effective Pharmaceutical Quality Systems (Chap. 35) are in place, adequately resourced and to assure that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation.

Each boss likes however empowered individuals, as they are better suited for solving problems. Staff meetings and review of management are therefore often and frequently required.

25.5.2 Training and Continuous Education

Once employed, the professional has to maintain his own level of professionalism. Management in pharmaceutical industry will see that the professional has the adequate level and maintains that level. The senior management or directors of the hospital will be charged with maintaining the quality level of the professionals and employees. In community pharmacy no authority is available to observe the quality of the professional, unless the organisation of pharmacists or government sets rules for continuous occupation and continuous education and monitors it, which is the practice in some Member States e.g. UK.

The value of continuous education on the skills of a professional is not guaranteed. A controlling system of skills and attitude can better ensure the quality of the work of the professionals. Different types of tests can give insight in the performing level of the workers.

25.5.3 Assessment of Employees

As a part of quality systems, standard procedures can be implemented for functional assessment of employees. Job description of employees and their training records are efficient documents for that purpose. Procedures for the training of a new professional, the continuous education and the yearly examination of qualification can all be part of the quality system of the preparation unit. Such qualification is common practice in industry and in hospital pharmacies with aseptic operations (see Sect. 31.6.3). The human factor is considered to be the most hazardous part in the production process.

Assessment and where necessary additional training has to be followed by an additional qualification test before the employee is considered fit for production. Feedback improves awareness of employee and his departmental manager as well.

25.5.4 Supervising Preparation of Medicines by Others

Doctors and veterinarians are generally not allowed to prepare medicines from raw materials (see Fig. 1.2). If it cannot be avoided, professional education and supervision by a pharmacist is a must. A better solution may be referral to or asking for support in a nearby or centrally located specialised pharmacy.

If medicinal products have to be reconstituted in the setting of a nursing or LTC home or in a hospital ward doctors, nurses and other caretakers can be involved in handling of medicines. The pharmacist should take care to educate and if possible to supervise the doctors and nurses.

In some cases medicines have to be reconstituted at the bed of the patient at home. Family members or nurses will perform the reconstitution of the product. The responsible pharmacist, either from a community pharmacy or hospital should instruct personnel that are involved on the spot or supervise them in order to avoid any harm for the patient. If the quality cannot be guaranteed, a different solution for the patient has to be found.

25.5.5 Patient Complaints

Quality complaints and medical comments by patients have to be dealt with by the organisation in a conscientious way as it is in the interest of the company or hospital. A quality system for evaluation, archiving and reporting of complaints should be in place (see Sect. 35.6.13). It can give unexpected information about the quality of a pharmaceutical product, including how difficult it is to understand package inserts.

QP and Patient Complaints

Quality defects are reported often by the patient to a physician, to the pharmacist and to industry. Such complaints come to the attention of the QP and the Qualified Person responsible for Pharmacovigilance

(continued)

(QPPV). The latter is involved when it comes to adverse events possibly related to insufficient pharmaceutical quality.

For example wrong delivery of product or filthy boxes of product by the logistic department is a major QP concern as it requires corrective actions and taking the lead in that process or the defect may even result in a recall.

Due to limitations in sampling, quality defects may pass final quality control. Not every tablet in a batch can be checked by QC for full compliance. For example when a batch of tablets is being packed into blisters, it could well be possible that line clearance of the packing line has missed the presence of remnants of another product.

The patient is therefore, surprisingly, much more competent for an optimal control of quality, as one can be sure that each unit of the batch is inspected for apparent quality defects by the intended patient population before taking their medication. The patient has an analogous position to the QC laboratory and has better control on the quality of the batch in relation to important user (patient) related aspects.

The position of the QP/QPPV may therefore be considered as the closest contact with the patient such as the community or hospital pharmacist nowadays is supposed to be. Responsibility consists of proper and pro-active handling of complaints, including medical complaints and timely reporting of complaints to management.

Some professional magazines, such as the Pharmaceutisch Weekblad of the Netherlands, publish reports about quality problems that were detected by patients. This can be useful information for the individual pharmacist and for the manufacturer as well.

25.6 Decisions

As said (Sect. 25.1) the pharmacist has to be competent to take professional decisions and respond to demands from the patient population. Decision making requires experience but also knowledge and awareness about tasks, responsibility and legislation. The demands may take the shape of dilemmas.

Reliable production of medicines takes time. So an urgent request to a production department to prepare or provide a necessary medicinal product not yet licensed causes dilemmas for the responsible pharmacist or the QP. The time needed for all of the quality controls does not allow the product to be prepared and released very quickly for the acute use. Different options are open for the responsible pharmacist such as in situ preparation for only one patient, which is costly and disturbs the planned processing. Regulations for industrial supply of such products are referred to as “patient named basis” or “compassionate use” (see Sect. 3.5) and delivery of these products requires a broad oversight of efficacy and safety risks.

The responsible pharmacist or QP may decide not to deliver the product because of lack of timely available quality control, although that may cause delay in the treatment of the patient. This scenario is not pleasant for the patient or for the medical institution or the hospital because it causes irritation and even a bad reputation. It is however not advisable to deliver insufficiently controlled medication to patients, which would be against the philosophy of quality systems. In case of individual preparations it is not against the law to deliver without analysis. The responsible pharmacist has to make a risk assessment on the basis of his clinical insight and product knowledge.

Another challenge appears, when a professional pharmaceutical decision has to be made when a patient or physician insists on the preparation of a medicinal product that should not be made available e.g. because of lack of scientific evidence on efficacy or lack of safety. This scenario is not uncommon in a community pharmacy. The responsible pharmacist has to decide whether or not the prescription will be prepared and dispensed to the patient.

If not, this patient will probably not visit him again because of his decision. If yes, the pharmacist prepares and sells a product that does not meet the medication and therapy standards of local Health Care Professional Communities. Those standards are in general considered as absolute truth worthy and claimed to be valid for the entire patient population. However, an individual patient may belong to a specific sub-population not categorised yet and may benefit from such a product. Again, risk assessment including clinical need (see Sect. 2.2) is expected from the pharmaceutical professional but keeping in mind that the physician has the final decision to prescribe medicines to patients.

The discussion between HCP’s, patients and authorities on availability of products will probably continue to challenge the pharmaceutical and regulatory field. Current non-availability of products is a major concern in the Health Care population. Authorities therefore have implemented an orphan medicinal product regulation for products with a small market potential and potential efficacy within a small patient population (see Sect. 3.6.1). Older products will reappear as registered product in the European market such as para-aminosalicylic acid in 2013 in the treatment of multidrug resistance of tuberculosis, If however the market for those orphan medicinal products continues to be small or alternatively huge investments are found necessary in less frequently used production lines, the non-availability will

reappear or continue to exist. Profitability will not disappear from industry, products will.

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Occupational Safety and Health

26

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Contents

Abstract

Hazardous substances according to the European legislation are those substances with at least one 'H(azard)-statement'. While preparing medicines or manipulating them, exposure to hazardous substances as such or as medicinal products can occur, which may cause a health risk. The types of toxicity (acute, chronic, carcinogenicity, teratogenicity, sensitisation, etcetera) together with the extent and route of exposure, determine the health risk. This chapter focuses on exposure via inhalation and skin contact.

Categorisation of toxicity according to a REACH compatible approach as well according to NIOSH is dealt with. For categorisation of exposure the Advanced REACH Tool as well as a specific model for pharmacy preparation is discussed. Exposure via surface contamination is well researched for antineoplastic medicines with wipe tests.

Employers have the primary legal responsibility for the occupational safety and health of their workers and

Based upon the chapter 'Arbeidsomstandigheden' by Mirjam Crul and Yvonne Bouwman-Boer in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_26,

should assess and diminish health risk to a level that is accepted by society.

Workers have a legal duty to protect their own safety and health and that of their co-workers within the pharmacy or organisation. The European regulations on occupational safety and health are discussed. The strategies for preventing or minimising risks are discussed, including the use of collective (containment, ventilation) and personal protective equipment such as gloves and respirators. Occupational Exposure Levels (OELs), risk acceptance and communication about best practice are part of such strategies.

Fire, explosion, calamities and sharp injuries are dealt with separately.

Keywords

Hazard • Toxicity • Exposure level • Health risk • REACH • NIOSH • Legislation • Hazardous substances • CMR • Wipe test • OEL • Calamity • Sharps • Fire

26.1 Orientation

Although the intent of preparation of medicines is to benefit patients, the substances used may present occupational hazards to the operators preparing these medicines. Pharmacists, nurses, doctors and others who prepare, handle and administer these medicines may be exposed to significant health risks during their work. The greatest risk is for the operators, but people in adjacent work areas (e.g. clerical workers, support staff, maintenance personnel, and visitors) may also be at risk from exposure by inhalation of aerosols or by contact with contaminated surfaces and floors. Pharmacists may be expected to be the professionals who should know most about this topic, but consultation of an occupational health specialist is necessary as well.

Employers should determine if their workers are at risk of exposure to hazards associated with preparation, reconstitution, repackaging, etcetera. Specific measures should be implemented to reduce direct skin contact, reduce exposure via inhalation and minimise the possibility of chemicals being brought home on workers' clothing. As with all potentially hazardous exposures, protective measures should include: engineering controls (e.g. barriers and containments, laboratory hoods, glove boxes, and worker isolation), administrative controls, personal protective equipment (e.g. respirators, gloves and lab coats) and training.

For contact with hazardous substances in the pharmacy categorisation models are developed for both hazard (Sect. 26.3.5) as well as exposure (Sect. 26.5.3) because there is little quantitative data known. This means that the resulting risk does not take the form of a concrete level or value. Still the pharmacist wants to know if the health risk is acceptable or not.

This chapter describes proper handling of hazardous substances in the workplace and exposure to these hazardous substances. It provides some risk assessment methods for different types of preparation and handling of hazardous substances and medicines. However, other risks that are not covered by this chapter should be considered as well, in particular work stress and ergonomics which may give rise to musculoskeletal disorders.

In addition, this chapter focuses on, calamities, needlestick and sharps injuries, fire and explosion

There are many examples of medicines that can be hazardous when prepared. Common situations that may present significant risks to the operator include:

- Some antibiotics, such as penicillins, that with inhalation or skin contact may cause serious allergic reactions. Proper precautions should be taken by individuals allergic to the penicillin class of substances to minimise or eliminate exposure when in a facility where penicillin class of products are handled.
- Aseptic handling of antineoplastic medicines, such as injections prepared with cyclophosphamide.
- Preparation of capsules, creams, suppositories or eye drops with steroids such as progesterone, testosterone, estradiol, and estriol.

26.2 Definitions and Principles

This section defines and describes the main concepts of occupational safety and health that are used in this chapter: (health) risk, hazard, exposure, (health) risk assessment, categorisation and containment.

Risk is defined as: the likelihood that the potential for harm will be attained under the conditions of use and/or exposure, and the possible extent of the harm [1]. In other words, risk is the probability that exposure to a hazard will lead to a negative consequence.

Hazard is the intrinsic property or ability of something (e.g. work materials, work methods and equipment) with the potential to cause harm [1].

Exposure is the state of being in contact with something, either directly or indirectly. For example through contaminated surfaces or clothes. A hazardous substance may cause harm if the worker is exposed to it. Exposure to a substance means that the substance is in close contact with the body that may lead to interaction or even harm. Exposure

has two qualities: its route and its level. Only a significant level of exposure, which can be extremely low such as with sensitisation, via a relevant route may lead to harm.

Health risk – or potential harm – depends on hazard severity and level of exposure, and thus depends on the substance's characteristics and the nature of the work. The relationship between risk, hazard and exposure is expressed in:

$$\text{Risk} = \text{hazard} \times \text{exposure}$$

If there will be no exposure to a substance, no matter how hazardous it may be, there is no risk of harm. Substances which pose only a small hazard but to which there is frequent or excessive exposure may pose as much risk as substances which have a high degree of hazard but to which only limited exposure occurs.

The terms hazard and risk are often used interchangeably, however these are two very distinct terms. Basically, a hazard is anything that can cause harm or adverse effects. A hazard poses no risk if there is no exposure to that hazard.

Health risk assessment is the process of examining and evaluating the risk to the health and safety of workers while at work arising from the circumstances of the occurrence of a hazard at the workplace [1]. A risk assessment is a careful examination of what, at the workplace, could cause harm to people, so that the employer can decide whether he has taken enough precautions or should do more to prevent harm. Workers and others have a right to be protected from harm caused by a failure to take reasonable control measures. Accidents and ill health can ruin lives and affect the business too if for example output is lost, machinery is damaged, insurance costs increase or the employer even have to go to court.

As a rule risk levels are treated for setting priorities: to decide about the risks that have to be mitigated in the first place.

If a manufacturer will be reproached or even sued by any competent body, it will be based on a societal decision about the level of risks that is not (any more) accepted by a group or nation: 'society'.

26.2.1 Categorisation

The risk of each work situation with exposure to substances is unique: it depends on the hazards of the substances, on the exposure of the worker to these substances and on the physical condition and constitution of the worker. However, it is practically impossible to investigate the risk for any individual in any situation. Therefore categorisation is applied to exposure as well as to hazards of substances and even individuals. With categorised hazards and exposures, also the risks (= hazard × exposure) are categorised. Because several uncertainties will affect the 'accounting' of the risk, the risk is not an exact characteristic, level or value, although qualifications as: 'high', 'medium' and 'low' can be given.

26.2.2 Containment

Containment is an engineering control measure, the second risk mitigation principle (see Sect. 26.7.1). It may be defined as a process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone [2] or, to put it differently, the prevention of the escape of a substance.

26.3 Hazard of Pharmaceutical Substances

26.3.1 Definition

This section discusses the hazard that may be created by substances used to produce medicines, with emphasis on workers in health care. These workers are mainly pharmacists, operators, nurses and doctors.

Every substance can present a hazard in general. In principle, being 'hazardous' is a consequence of one or more intrinsic hazard properties of a substance. In accordance with the Classification, Labelling and Packaging (CLP) Regulation [3], see also Sect. 26.6.3, hazardous substance are those substances that fulfil the criteria of at least one hazard class. The hazard classes comprise physical hazards, health hazards or environmental hazards (see Sect. 26.3.2).

However, the use of the term 'hazardous substances' with regard to pharmacy preparation and reconstitution, is often restricted to carcinogenic, mutagenic and reprotoxic substances. Radiopharmaceuticals and gene therapeutics may be counted under this term as well. The National Institute of Occupational Safety and Health of the US (NIOSH) however also counts substances with a high chronic toxic potential to 'hazardous substances', see further Sect. 26.3.3.

So the term hazardous substances may have different notions. In this chapter the CLP definition is followed meaning that all substances are considered potentially hazardous. Carcinogenic, reprotoxic and mutagenic substances are either noted as such or as a group as CMR. Occupational safety and health care investigates all processes and all substances, to prevent health damage of workers.

26.3.2 Hazard Types

Hazards of substances can be acute, for example if a strong acid is spilled on the skin, or chronic, if long term exposure results in health damage, such as sensitisation or cancer.

The Globally Harmonised classification and labelling System (GHS, see Sect. 26.6.3), discerns three major hazard groups:

- Physical hazards: hazards that are directly safety-threatening, for example, substances and mixtures that are (in)flammable or explosive (such as ether and ethanol).
- Health hazards: Firstly direct hazards (acute toxicity), such as from substances that are irritating (trichloroacetic acid, sodium hydroxide), intoxicating (ether) or suffocating. Secondly hazards that arise in the longer term (chronic toxicity), such as damage to the respiratory system, the nervous system or reproductive organs in the long term. Also skin and airway allergies and cancer belong to this type of hazards.
  Within chronic health hazards a further distinction is made into:
  - Carcinogenic: may induce cancer or increase its incidence
  - Mutagenic: may induce heritable genetic defects or increase their incidence
  - Reprotoxic: may produce or increase the incidence of non-heritable adverse effects in the offspring and/or causes either a decrease in fertility or problems with foetal development
  - Respiratory sensitising/inhalant allergenic: causes allergy via inhalation
- Environmental hazards: for example substances and mixtures that are directly or in the long term a hazard to aquatic life or that are poorly degradable. This group also include hazards to the ozone layer. Environmental hazards are further dealt with in Chap. 38.

26.3.2.1 Hazard and Precautionary Statements in GHS

The GHS defines Hazard and Precautionary statements (in brief H- and P-statements), which represent standard phrases used to respectively describe the hazards of hazardous substances and mixtures and the recommended measures to be taken when using/disposing of hazardous substances and mixtures. The GHS couples any H-statement to a P-statement. These statements will assist in ensuring that all users of the products, worldwide, will know and understand proper precautionary measures when interacting with the chemicals.

H- and P-statements are one of the key elements for the labelling of containers under the GHS. Some H-statements are depicted as EUH-statements (these are a classification from previous legislation). These apply, legally, only to European countries and are based on CLP regulations, see further Sect. 26.6.3.

According to the Regulation (EC) No 1272/2008 [3], the substance morphine hydrochloride is for example provided with the following hazard en precautionary statements [6]:

H302	Harmful if swallowed
H336	May cause drowsiness or dizziness
P261	Avoid breathing dust/fume/gas/mist/vapours/spray
P264	Wash hands and other exposed areas thoroughly after handling
P301 + P312	IF SWALLOWED: call a POISON CENTER or doctor/physician if you feel unwell
P304 + P340	IF INHALED: remove victim to fresh air and keep at rest in a position comfortable for breathing
P312	Call a POISON CENTER/doctor/physician if you feel unwell
P330	Rinse mouth
P403 + P233	Store in a well-ventilated place. Keep container tightly closed
P501	Dispose of contents/container to: Hazardous waste. Comply with applicable regulations

In addition, the signal word ‘Warning’ and a pictogram with a white background, a red frame and an exclamation mark identify morphine hydrochloride.

Each packaging must be labelled with the relevant hazard pictograms, signal word and H- and P-statements. More detailed hazard and precautionary information can be found in the material safety data sheets (MSDS) of the substance.

26.3.3 Carcinogenic, Mutagenic and Reprotoxic (CMR) and Sensitisation Hazards

The carcinogenic, mutagenic and reprotoxic hazards are together called CMR hazards. Substances that are carcinogenic, mutagenic or reprotoxic (CMR substances) are of very high concern due to the long term and serious effects that they may exert on human health. Within the regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals, Regulation (REACH) (see Sect. 26.6.2) CMR substances are classified and listed in Annex VI of the EU GHS Regulation [4]). Substances appear on this list if they are registered under REACH or notified under the CLP

regulation (see Sect. 26.6.3) or both. The classification in Annex VI is legally binding for Europe. National authorities may have extended this list with substances they consider being relevant [7].

The National Institute for Occupational Safety and Health (NIOSH) of the United States describes in the section 'Determining whether a drug is hazardous' how human and animal data on carcinogenicity, reprotoxicity and genotoxicity are interpreted for their list of hazardous substances [8].

26.3.3.1 Classification of Carcinogens

According to CLP, CMR substances are classified into three categories based on the strength of evidence showing that they present one of the CMR types of hazards to human health. Apart from the European CMR classification, there are other classifications, in particular the classification system established by the International Agency for Research on Cancer (IARC). This classification includes agents, groups of agents, mixtures and carcinogenic exposure circumstances. It includes four groups of classifications, based on different levels of scientific evidence of carcinogenicity for humans.

European CMR classification [5]:
- Category 1A: Classification is largely based on human evidence.
- Category 1B: Classification is largely based on animal evidence.
- Category 2: Classification is based on the evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B.

Carcinogenic classification from IARC [9]:
- Group 1: "Carcinogenic to humans" There is enough evidence to conclude that it can cause cancer in humans.
- Group 2A: "Probably carcinogenic to humans" There is strong evidence that it can cause cancer in humans, but at present it is not conclusive.
- Group 2B: "Possibly carcinogenic to humans" There is some evidence that it can cause cancer in humans but at present it is far from conclusive.
- Group 3: "Unclassifiable as to carcinogenicity in humans" There is no evidence at present that it causes cancer in humans.
- Group 4: "Probably not carcinogenic to humans" There is strong evidence that it does not cause cancer in humans.

The corresponding H-statements (see Sect. 26.3.2) for CMR substances, according to the European CMR classification, are depicted in Table 26.1.

Table 26.1 Correspondence between H-statements and European CMR classification

	Category 1A or 1B	Category 2	Effects on or via lactation
Carcinogens	H350: May cause cancer	H351: Suspected of causing cancer	
Mutagens	H340: May cause genetic defects	H341: Suspected of causing genetic defects	
Reprotoxics	H360: May damage fertility or the unborn child	H361: Suspected of damaging fertility or unborn child	H362: May cause harm or to the breast-fed children

26.3.3.2 Carcinogenicity and (Non-)Genotoxicity

Apart from differentiation on the basis of the level of evidence, as done by categories 1A, 1B and 2, another distinction within the category carcinogenic substances can be made: whether they are genotoxic or non-genotoxic.

Genotoxic carcinogens interact directly with DNA, causing damage to DNA which may lead or contribute to cancer development. Non-genotoxic carcinogenic substances have no direct interaction with DNA but are capable of influencing by one of many secondary mechanisms the proliferation process of the tumour, thereby leading or contribute to cancer. The action of non-genotoxic substances is subjected to a threshold; below a certain concentration there will be no effect (No Observed Effect Level, NOEL). By definition for genotoxic carcinogens no safe threshold without a theoretical cancer risk can be derived.

This difference between genotoxic and non-genotoxic carcinogens brings about a principally different approach to protection. If exposure to non-genotoxic substances does not exceed the threshold value, humans are considered to be safe from getting cancer from those substances, just as is the approach regarding other toxic substances having a threshold value. Exposure to even one molecule of a genotoxic substance however may lead to cancer, although the chance that it occurs is limited. A decision about that limited level of risk is made by society. This leads to an acceptable level of exposure, rather than a threshold, to keep a distinction between both approaches. With a genotoxic carcinogen, linear extrapolation is used for estimating the risks associated with a given level of exposure [10].

For pharmacy practice this distinction between genotoxic and non-genotoxic carcinogenic substances is at the moment of little practical value, because only very few carcinogenic active substances have been defined as non-genotoxic.

Among the most widespread non-genotoxic carcinogens are a group of compounds collectively referred to as peroxisome proliferators. Peroxisome proliferators are a diverse class of chemicals, including the lipid and cholesterol lowering fibrate drugs (clofibrate, fenofibrate, and gemfibrozil), plasticisers (phthalate esters), solvents (e.g., trichloroethylene), and naturally occurring chemicals (e.g., phenyl acetate) or hormones (e.g., dehydroepiandrosterone sulfate) [11].

Chloroform is another example of a non-genotoxic carcinogen. In most European countries chloroform has a 8 h limit value (see Sect. 26.7.2) of 10 mg/m^3 [12].

As a summary Table 26.2 lists the characteristics of genotoxic and non-genotoxic carcinogenic substances.

It is to be noted that the decision on a threshold and a non-threshold mode of action may not always be easy to make, especially when, although a biological threshold may be postulated, the data do not allow identification of it. If not clear, the assumption of a non-threshold mode of action would be the prudent choice.

Establishing exposure limits with genotoxic and non-genotoxic substances, is dealt with in Sect. 26.7.2.

26.3.3.3 Reprotoxicity

Next to the classification based on the evidence, also for reprotoxic substances two types of toxicity can be discerned:

1. Mutagenic: causes damage to genetic material in sperm and ova;
2. Teratogenic: causes damage to the unborn child.

The concepts of genotoxicity and mutagenicity are sometimes used interchangeably, but do not have the same content. All mutagens are genotoxic, however not all genotoxic substances are mutagenic. Genotoxic substances can cause damage to DNA in different ways, but only when there has been damage to DNA in sperm and ova, are they mutagenic. Mutagenicity is thus a form of genotoxicity (Fig. 26.1).

26.3.3.4 Classification of Monoclonal Antibodies (mAbs)

A decade ago all antineoplastic agents (ATC class L01) were considered to be carcinogenic. That is no longer the case, especially if monoclonal antibodies (mAbs) are considered.

NIOSH re-evaluated the inclusion of monoclonal antibodies as hazardous substances because of their specific targeted mechanisms of action and their high molecular weight that prevent skin penetration and accidental inhalation. The 2014 NIOSH list of hazardous substances [8] contains now only mAbs conjugated with antineoplastic active substances.

A German working group evaluated whether mAbs are to be classified as carcinogens, mutagens or reprotoxic at dermal, oral or inhalative exposure. Sensitising properties were evaluated as well. They assigned H-statements to mAbs based on a systematic literature review, European public assessment reports (EPARs) and data provided by national and international occupational safety and health organisations. Expert opinions were also obtained. Recommendations for the protection of workers handling mAbs were agreed with experts in the fields of chemistry, pharmacy and occupational safety as well as representatives of the pharmaceutical industry. They happened to classify some mAbs as reprotoxic however not as carcinogenic [14, 15].

Swiss hospital pharmacists [16] do not consider monoclonal antibodies as hazardous for healthcare practitioners and only gloves are recommended for their manipulating at wards.

26.3.3.5 Respiratory Sensitisation

Exposure to inhalant allergens can lead to respiratory allergies. This generally begins with sensitisation (= to

Table 26.2 Characteristics genotoxic and non-genotoxic substances (From Klaunig et al. [13] with permission)

Genotoxic carcinogens	Non-genotoxic carcinogens
Mutagenic	Non-mutagenic
Direct DNA reactivity	Non-directly DNA reactive
Tumorigenicity is dose response	
Threshold??	Exhibits threshold
Can be complete carcinogens	
Irreversible	Reversible
Usually not strain or species specific	Usually exhibits strain, species and tissue specificity
Functions at initiation and progression stages of cancer process	Functions at the tumour promotion stage of the cancer process
Examples: nitrosamines, polycyclic aromatic hydrocarbons, aromatic amines	Examples: chlorinated substances, organochlorine pesticides, hormones, barbiturates

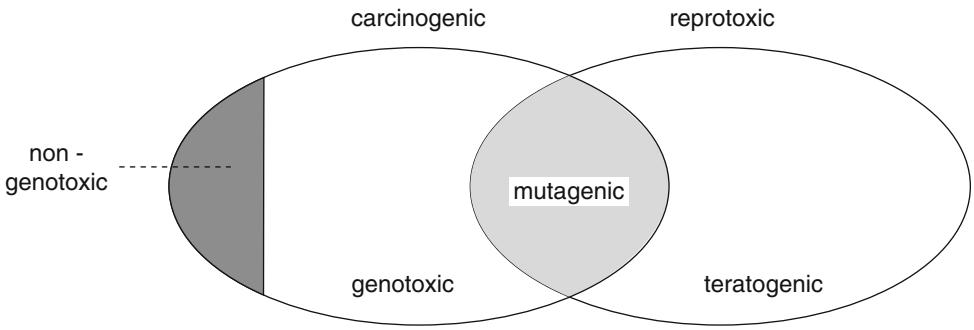

Fig. 26.1 The relation between mutagenicity and genotoxicity

become sensitive to the relevant substance). Eventually, however, an allergy develops that is harmful to health, even when exposure is minimal. The clinical description of this process is to be found in [10]. For the endpoints sensitisation and irritation it is supposed that a substance exerts its effect by a threshold mode of action, but the available data do not allow a reliable identifcation of the threshold [10]. A situation similar to that of genotoxic carcinogens occurs. This will lead to a similar risk-based approach to setting exposure levels (see Sect. 26.7.2).

26.3.4 Information Sources on Hazards

Information on hazards of substances may originate from several sources. The first recommended source is the Safety Data Sheet (SDS) of substances and mixtures, under the REACH regulation. The second source may be human toxicological and pharmacologic data.

26.3.4.1 Safety Data Sheets

The SDS contains information on the identity of the substance or the mixture, potential health effects, toxicological properties, physical hazards, safe use, handling and storage, emergency procedures, and disposal requirements specific to the chemical (see Fig. 26.2). Intermediate products are to be considered as mixtures of substances.

For some products, such as licensed medicines, safety data sheets do not have to be provided [18] but sometimes suppliers provide them anyhow. So if pharmacists or nurses have to manipulate oral dosage forms they usually cannot refer to a SDS but sometimes they can. The Summary of Product Characteristics (SmPCs) usually doesn't provide information for these situations. In the United States so-called manufacturers' safe handling guidance (MSHG) are available for some medicines, including antineoplastics [19] and in section 16 of the Label information leaflet a safe-handling warning may be given.

Reliability of SDSs

The compilation of a good SDS requires extensive knowledge in different fields, as the SDS itself covers a wide range of aspects concerning the substance or mixture properties, occupational health and safety, transport safety and environmental protection. REACH indicates that the SDS should be compiled by a competent person, but no specific definition of competent in this context is given in the Regulation [20].

The SDS is commonly first compiled by the manufacturer but the requirements of REACH in relation to the provision of SDSs apply at each stage of the supply chain. Any supplier of a substance or mixture must provide a SDS for it. Each supplier remains responsible for the accuracy of the information in the SDS they provide even though they may not have prepared the safety data sheet.

Some of the SDSs found on the Internet may be of questionable quality or may not be the most current version. The manufacturer is often the best source of the current and accurate SDS. Employers may rely on the information received from their suppliers. If receiving one that is obviously inadequate, an appropriately completed one should be requested.

A number of studies and investigations have raised concern that some SDSs may be incomplete or contain erroneous or out-of-date information. The U.S. Occupational Safety and Health Administration (OSHA) has confirmed there are inaccurate SDSs in circulation, but a comprehensive study on this topic that provides more than anecdotal evidence about a limited number of SDSs has not been performed [21].

The authors consider the SDSs for the Ph. Eur. reference substances [22] as a reliable source of SDSs for pharmaceutical substances.

PARACETAMOL CRS

Safety Data Sheet

Safety Data Sheet in accordance with Regulation (EC) No. 1907/2006, as amended.

Date of issue: 22/08/2013 Revision date: 07/03/2014 Supersedes: 22/08/2013 Version: 10.0

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1. Product identifier

Product form	:	Substance
Trade name	:	PARACETAMOL CRS
EC no	:	203-157-5
CAS No	:	103-90-2
Product code	:	P0300000
Other means of identification	:	RTECS No : AE4200000 (paracetamol)

1.2. Relevant identified uses of the substance or mixture and uses advised against

1.2.1. Relevant identified uses

Main use category	:	The product is intended for research, analysis and scientific education.
Use of the substance/mixture	:	For professional use only
Function or use category	:	Laboratory chemicals

1.2.2. Uses advised against

No additional information available

1.3. Details of the supplier of the safety data sheet

European Directorate for the Quality of Medicines & Healthcare
EDQM, Council of Europe
67081 Strasbourg - France
T +33(0)388412035 - F +33(0)388412771
www.edqm.eu

1.4. Emergency telephone number

Emergency number	:	+44(0)1235239670

SECTION 2: Hazards identification

2.1. Classification of the substance or mixture

Classification according to Regulation (EC) No. 1272/2008 [CLP]

Acute Tox. 4 (Oral)	H302
STOT RE 2	H373
Aquatic Chronic 3	H412

Full text of H-phrases: see section 16

Classification according to Directive 67/548/EEC or 1999/45/EC

Not classified

Adverse physico-chemical, human health and environmental effects

No additional information available

2.2. Label elements

Labelling according to Regulation (EC) No. 1272/2008 [CLP]

Hazard pictograms (CLP) :

GHS07 GHS08

Signal word (CLP)	:	Warning
Hazard statements (CLP)	:	H302 - Harmful if swallowed H373 - May cause damage to organs through prolonged or repeated exposure H412 - Harmful to aquatic life with long lasting effects
Precautionary statements (CLP)	:	P260 - Do not breathe dust/fume/gas/mist/vapours/spray P264 - Wash hands and other exposed areas thoroughly after handling P270 - Do no eat, drink or smoke when using this product P273 - Avoid release to the environment P301+P312 - IF SWALLOWED: Call a POISON CENTER/doctor/…/if you feel unwell

Fig. 26.2 First page of a EDQM safety data sheet of paracetamol [17]

26.3.4.2 Human Toxicological and Pharmacologic Data

For occupational safety and health information for the preparation of pharmaceutical products a second valuable source about hazards is the information on pharmacologic and toxicological effects on humans of active substances and excipients. This information can be used with some restrictions:

- For occupational safety and health, the inhalation and dermal routes are most interesting; most therapeutic information is however about oral and parenteral administration.
- Any adverse effect is accepted (or not) by a patient in relation to his illness; for workers the same effect usually weighs more heavily because it is related to a long-lasting work situation.

26.3.5 Categorisation of Hazards of Substances

Categorisation of hazards of substances (also called 'control banding') instead of considering every substance separately serves practical work procedures. Two approaches are met:

- Categorisation of all substances based on grouping H-statements and making use of human toxicologic and pharmacologic data
- Categorisation of the most toxic substances by a procedure with public consultation (NIOSH)

26.3.5.1 Categorisation Based on the GHS and Human Toxicology and Pharmacology

Based on the ideas of Naumann [23]: categories of hazards of pharmaceutical substances have been distinguished by 3 (groups of) investigators: Ader et al. [24, 25], Tielemans et al. [26] and Vincent et al. [27]. They all use a comparable approach: 4 or 5 categories of increasing hazards with category 1 representing the lowest grade with the (relatively) lesser hazards and the highest category (which is 4 or 5 depending on the model) containing the most serious hazards. Only Tielemans [26] and Vincent [27] make use of the GHS hazard statements. All of them make use of human toxicological and pharmacologic information.

H-statements (in fact the original R-phrases) have been divided over the different categories guided by the COSHH (Control of Substances Hazardous to Health) essentials scheme [28], mainly led by the height of exposure giving toxic effects, the presence of a threshold value, the severity of the effect and reversibility of the effect.

Table 26.3 reflects the general approach that all three sources follow. About category 1 Tielemans [26] says: If there is no exposure limit value, no H-statements to attach, no dosage details are known and it is plausible that the substance causes no harm; the substance is classified into hazard class 1. Whereas Ader [24] considers category 4 as the 'default category', to be understood as: if there are any doubts about harmlessness, consider it to belong to category 4.

The relation between hazard statements and classes of the system of Tielemans [26] are given in Table 26.4, with the notion that the translation of the R-statements into the H-statements, is the authors' view.

This categorisation system relates to occupational exposure limits (OELs) as well. An OEL being a limit level of exposure (so the product of hazard × exposure, see Sect. 26.2), it needs some explanation as to how it is used in the categorisation of just hazards. Although the reason for categorisation is to determine

(continued)

Table 26.3 Categories of hazards, generalised approach based on [24–27]

	Category 1	Category 2	Category 3	Category 4	Category 5
Harm characterisation	Very low	Low	Intermediate	High	Extremely high
Type of toxicity (example) (for connection with H-phrases see Table 26.4)		Reversible Low acute or chronic toxicity	Reversible Systemic toxicity	Irreversible effects Carcinogenicity, mutagenicity, reprotoxicity	Irreversible effects Genotoxic carcinogenicity, mutagenicity, reprotoxicity
Pharmacological effect, potency	Very low > 100 mg/day	Low (effect at 10–100 mg/day)	Moderate (toxicity at 0.1–10 mg/day)	Significant potency (effect ~ 0.01–1 mg/kg or 0.1–1 mg/day clinical dose)	Highly potent pharmacological effect (~10 micrograms/kg or < 0.1 mg/day)
Example of adverse effect		Irritant to the skin or eyes	Weak (skin or respiratory) sensitisers	Sensitisers	Severe sensitisers
Approximate OEL [24]		>0.5 mg/m^3	10 micrograms/m^3 to 0.5 mg/m^3	30 ng/m^3 to 10 micrograms/m^3	<30 ng/m^3
Approximate OEL [26]	>5 mg/m^3	1–5 mg/m^3	10–1,000 micrograms/m^3	1–10 micrograms/m^3	<1 micrograms/m^3

Table 26.4 Categorisation based on hazard statements, OEL and therapeutic dose [26]

	Category (hazard class)				
Criterium	1	2	3	4	5
Therapeutic dose (mg/day)	>100	10–100	0.1–10	0.1	<0.1
Occupational Exposure Limit value (micrograms/m^3)	>5,000	1,000–5,000	10–1,000	1–10	≤1
Acute toxicity	H304	H302	H301	H300	H370 (R39/26, R39/26/27, R39/26/27/28, R39/26/28, R39/27, R39/27/28, R39/28)
	H336	H312	H311	H310	
		H332	H331	H330	
			H371	H370 (R39/23, R39/23/24, R39/23/24/25, R39/23/25, R39/24, R39/24/25, R39/25)	
Irritation (skin, respiratory tract and/or eyes)	H315		H314		
	H319		H318		
	EUH066		H335		
Sensibilisation (skin and or respiratory tract)			H317		
			H334		
Chronic toxicity			H373	H372	
Mutagenicity					H340
					H341
Carcinogenicity				H351	H350
					H350i
Reproduction toxicity				H360F	
				H360D	
				H361f	
				H361d	
Flammability	H224 (flash point < 23 °C and boiling point ≤ 35 °C)	H224 (boiling point ≤ 35 °C)	H220		
	H225 (flash point < 23 °C and boiling point > 35 °C)	H225 (boiling point > 35 °C)	H221		
	H226 (flash point ≥ 23 °C)	H250	H224		
		EUH018	H242		
		EUH029			
Explosivity		EUH001	H200		
		EUH006	H201		
		EUH019	H202		
		EUH044	H203		
		H204	H205		
		H240			
		H241			
Oxidising properties			H242		
			H270		
			H271		
Reactivity with water			EUH014		

a limit for maximal exposure for each individual substance is not feasible, it is still an ambition. For several substances, mainly those to which many workers and the general public may be exposed, reliable occupational exposure limits (OELs, see Sect. 26.7.2) have been determined. If these OELs are related to other characteristics of those substances, the OELs could virtually be put into the categorising systems. By doing so, the categories of the system could be provided with 'approximate OELs'.

As an example Table 26.5 gives per category about 10 active substances that have been categorised following Table 26.4, with expert interpretation.

26.3.5.2 Categorisation by NIOSH

The National Institute for Occupational Safety and Health (NIOSH) of the United States has developed a categorisation system for 'hazardous substances'. NIOSH defines hazardous pharmaceutically active substances using six criteria:

1. Carcinogenicity
2. Teratogenicity or other developmental toxicity
3. Reproductive toxicity
4. Organ toxicity at low doses in humans (<10 mg/day) or in animals (<1 mg/kg/day)
5. Genotoxicity
6. Structure and toxicity profile of new active substances that mimic existing active substances determined hazardous by the above criteria

NIOSH reviews each active substance on an individual basis and does not group them into classes. The review process is accounted for in [29], from which it can be concluded that:

- Safe handling recommendations from the manufacturer of a medicine is followed without requiring further review.
- Peer reviewers and stakeholders are independently reviewing the status of specific active substances.
- NIOSH experts made the final determination; some scientific principles that are followed in that process are given in [8].
- Draft conclusions are published for public review.

While the majority of the hazardous active substances in the NIOSH list are antineoplastics, active substances from other classes are included, such as phenytoin and tacrolimus [8]. As part of the categorisation some reference is given about which hazard is the main reason for being included in the list. This NIOSH list is updated regularly which is a great advantage, however as said only the most hazardous substances are included.

26.3.6 Categorisation of Hazards of Products

Categorisation of pharmaceutical preparations (within the field of occupational safety and health seen as mixtures) into hazard categories is relevant because exposure to it can occur in practice. This happens for example when dissolving a mixture of freeze-dried substances or by the crushing of tablets for patients who cannot swallow.

Customising H-statements from substances to products though is not simple. The GHS sets a calculating method for fixing the health hazard of mixtures of substances. The hazard of a mixture depends on the type of hazard and how the concentration of the substances affects the hazardous properties in the preparation. The GHS gives per separate H-statement, if relevant, on how to determine whether the H-statement is maintained, changes or expires depending on the concentration in the mixture. For instance for a property such as corrosiveness, a 10 % content in a mixture may lead to a tenfold decrease of hazard. But for a property such as mutagenicity, although the content in a mixture may be only 0.1 %, the hazard may be classified as large as with a 100 % content [30].

26.4 Exposure Routes and Protection

Different routes may lead to exposure to hazardous substances at the workplace:

- Inhalation
- Eye contact
- Skin contact; primarily with the substance or secondarily via contaminated surfaces
- Ingestion
- Injection

Table 26.5 Hazard categorisation of substances according to the model described in this section: some examples per category[a]

Category (hazard class)	Examples of active substances and excipients
1	Aluminium magnesium silicate, borax, ethanol, magnesium oxide, paracetamol, peppermint oil, sodium citrate
2	Acetylsalicylic acid, aspartame, caffine citrate, isoniazide, lidocaine, nitrazepam
3	Butylhydroxytoluene, clioquinol, cocaine hydrochloride, hydrocortisone acetate, phenytoin, omeprazole, salicylic acid, tetracycline hydrochloride
4	Atropine sulphate, boric acid, ethinylestradiol, lithium carbonate, testosterone propionate, thioguanine, tretinoin
5	Coal tar, colchicine, ganciclovir, methotrexate, mitomycin, paclitaxel, vincristine

[a]For more information or an update the second author can be approached

26.4.1 Inhalation

When an individual breathes in polluted air, any substance may enter the respiratory tract causing direct harm to the respiratory system and indirect harm due to uptake via ingestion. Especially sensitising substances may require attention. As airways and the lung cannot be closed off, only ventilation (exhaustion) and filtration of inhaled air remain as protective measures, such as working in safety cabinets and wearing masks with air filters (respirators).

Ventilation, at which the air that is contaminated with the substance is carried away from the operator, reduces the exposure. Filtration may be necessary to prevent the withdrawn air from contaminating people elsewhere. Ventilation or exhaust can be achieved with the following measures of increasing effectiveness; also increasing containment is attained:

- Ventilation of the work space
- Use of powder exhaust unit or a fume cupboard
- Use of safety cabinet
- Use of isolator

Powder and vapour (fume) exhaustion is the first measure to protect the respiratory system of the operator against the hazards of substances. See Sect. 28.3 for a discussion about the equipment and its effectiveness. Section 27.5.1 goes into the air handling (HVAC) of premises when the product should be protected from the operator (with aseptic processes) as well as the operator from the product.

For protection of the airways to inhalation of substances, respirators can be used. Effective respirators however are not pleasant to wear, as the worker never breathes freely and they may be rather heavy as well. Many mouth masks are provided with an in- or exhalation valve or both which eases breathing, see Fig. 26.3.

Respiratory protection products or respirators are classified on the basis of the achieved applied protection factor (APF). This is the factor by which the exposure by inhalation is reduced as the protection equipment is used in the required manner. Dust filters are positioned in three classes: FFP1, FFP2 and FFP3, usually called P1, P2 and P3 respectively. They provide protection against powders or aerosols or both.

Respirators should comply with national or European standards such as EN 143 for Particulate filters and EN 149 for Filtering half masks to protect against particles. Distinction has to be made between suitability for solid or liquid particle filtration.

FFP1-filters have an APF of 4 for solids, FFP2-filters have an APF of 10 and FFP3-filters have an APF of 20. Quarter masks (which cover a quarter of the face), half-face masks and full-face masks can be discerned. The half- and full-face masks can, if provided with a combined filter for both gas and dust, attain an APF of 40. In addition, quarter or half-face masks if provided with filters for both gas and dust have an APF of 10 for liquids. Full-face masks have an APF of 20 for liquids.

In pharmacy practice employers sometimes choose to provide respirators instead of buying safety cabinets or isolators. This is against the general principles of risk mitigation (see Sect. 26.7.1) and may only be accepted if preparation scarcely takes place. Some specific situations however rely on personal respiratory protection by respirators:

- As an additional measure to working in a safety cabinet with solid (powdered) substances of the highest hazard category (which is 4 or 5 depending on the model) for example with the preparation of capsules
- Processing heavily corrosive substances
- In case of calamities

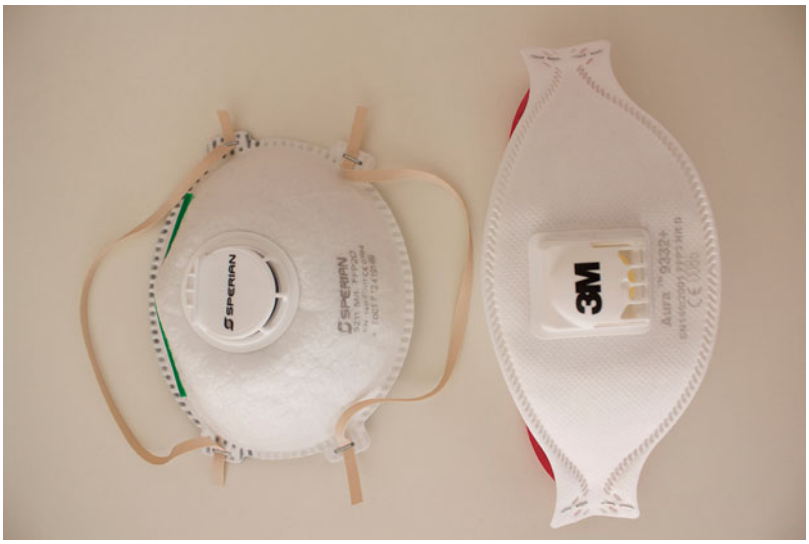

Fig. 26.3 Examples of FFP2 disposable respirators

It is not necessary to wear a respirator when working in an isolator except when the containment is breached for example during the maintenance operations.

26.4.2 Eyes

With regard to eyes corrosive substances are most feared. The wearing of safety glasses can protect eyes rather well. The glasses should fit well and protect the eyes completely. Wearing safety glasses is in any case necessary when:

- Operating the ampoules machine
- Working with glass equipment under pressure
- Filling out corrosive substances
- Cleaning up spilt corrosive substances

Wearing of safety glasses is minimally indicated when the substance bears specific H-statements, see Table 26.4, row 'Acute toxicity': H314, H318 and H319.

26.4.3 Skin

Corrosive substances are most feared because of their direct harmful effect on the skin. Antineoplastics are most feared with regard to absorption via the skin. The skin of operators may be primarily contaminated by the substance, but also secondarily via contaminated surfaces. Contamination of surfaces is very difficult to avoid, so potentially also contamination of skin of operators, cleaners and even staff who are working in adjoining areas (see further Sect. 26.5.4).

The wearing of the appropriate clothing and gloves can protect the skin rather well. Proper cleaning should diminish the surface contamination and thus the secondary exposure of the skin.

26.4.3.1 Protective Clothing

Clothing may protect the body from hazardous substances. The risk for dermal exposure depending on personal clothing was investigated [31], and can be summarised as Table 26.6; a low score is aimed at.

Corporate clothing that covers the clothes should always be worn during preparation processes, and should be changed according to a fixed regime: for example, daily and immediately after spillage. Long hair should be bound together in order to avoid contaminating the product and causing an accident with rotating equipment. Wearing hair and possibly beard caps is part of the clothing regime.

Table 26.6 Hierarchy in dermal exposure risk with clothing

Personal cloth protection	Score
No clothing	1
Woven clothing	0.3
Non-woven clothing-permeable	0.1
Non-woven clothing impermeable	0.03

In aseptic processes in pharmacy specific clothing is required to protect the product against micro-organisms from the operator (see Sect. 31.3.3). This may include the wearing of non-shedding suits or coats (depending on the classification of the environment), hair cover, shoe covers or dedicated clean room shoes, gloves, and a respirator covering the nose and mouth.

If also protection from substances is required it is recommended to wear suits or coats made of polyethylene-coated polypropylene (which is nonlinting and non-absorbent). This material is recognised to offer better protection than polypropylene against many antineoplastic substances. The suits must have closed fronts, long sleeves, and elastic or knit closed cuffs. They must be disposed after each use. Moreover, disposable sleeve covers are recommended to protect the wrist area and be removed after the task is complete.

26.4.3.2 Gloves

Wearing gloves for protection of the skin is increasingly common practice with pharmacy preparation. In the risk assessment model of Sect. 26.7.3 it even replaces any effort of estimation of skin exposure. Gloves are minimally indicated when the substance bears specific H statements, see Table 26.4, rows Irritation (skin, respiratory tract and/or eyes) and Sensibilisation (skin and or respiratory tract).

Gloves are available made from different material and having different thickness. They must comply with European standards (for instance [32]). The choice for a particular type depends on:

- The mechanical properties of the glove (abrasion resistance, flexibility)
- The chemical properties (resistance to the substance from which protection is required)
- The permeability of the material for the substance from which protection is required

Substances potentially penetrate gloves, thereby exposing the skin. Specific studies assessed dermal exposure to antineoplastics with regard to the use of gloves [33–38]. The permeability of the gloves is expressed as breakthrough time, the time that a substance needs to pass through the polymer layer. Permeation is related to a variety of factors, such as glove composition, glove thickness, exposure period, and the physical characteristics of the substance [39–41]. Due to the large number of substances and kinds of gloves, only limited data on permeation of specific substances are available.

In practice, for pharmacy preparations the required gloves are of natural rubber (see Sect. 24.2.4) or thick plastic (polyvinyl chloride or polyethylene, see Sect. 24.2.3) if

working with corrosive substances. Gloves of thinner material (latex, nitrile rubber, polyvinyl chloride) may be suitable for working with other substances. People who are allergic to natural rubber (latex) can try gloves of nitrile butadiene rubber, vinyl or neoprene.

Gloves are expected to be more permeable as they come into contact with alcohols, for example during disinfection of the workplace. However some authors investigated permeation of antineoplastics when using alcohol and did not find increased permeation with the investigated gloves. Permeability of gloves to selected antineoplastics after treatment with ethanol or isopropyl alcohol is given in [42].

A gloving procedure should take into account:

- Glove material and thickness; suppliers of gloves with a CE label supply on suitability for types of substances, protection time (if no other damage has occurred).
- Change time, this is the time that gloves will be changed even if no damage has occurred; 30 min is often taken for this.
- Inspection; the worker has to be aware of and actively search for any damage that may occur; any damage should lead to changing the gloves.
- Single or double gloving; double gloving increases barriers but diminishes precise feeling.

The outcome of these considerations may differ. For handling antineoplastics in many countries in Europe single gloving is the standard in practice, which has to be warranted by frequent change and frequent inspection. The European Society of Oncology Pharmacy [43] seems to prefer double gloving, however without being explicit about the other variables (changing time, thickness, frequency of inspection). NIOSH recommends [44] double gloving when working with NIOSH 'hazardous substances' (see Sect. 26.3.4: this represents a high toxicity class) as well as a changing time of 30 min.

In chapter Aseptic handling (see Sect. 31.5) product protection results in single gloving and change after 30 min or earlier when damaged.

26.4.4 Ingestion

Ingestion may occur unnoticed after inhalation or skin contact. Workers have to be taught not to touch their face during preparation. Direct ingestion of hazardous substances may occur accidentally and can usually be prevented by prohibition of food and drink in all preparation areas of the pharmacy (see Sect. 27.7). Hand to mouth ingestion is particularly well known in smoker population. Hand washing with soap when leaving preparation area is a basic, efficient measure to remove chemical contamination.

26.4.5 Injection

Percutaneous injuries can result from needlestick injury, cuts or abrasions from contaminated items. These exposures are particularly serious because of the potential for immediate entry of the solution into a bloodstream. Hazards are not only related to toxic substances but also to micro-organisms. All sharps items should be handled and disposed of as noted in Directive 2010/32/EU (see Sect. 26.10).

26.5 Exposure Levels

26.5.1 Necessity of Models

Exposure has to be quantitated to be able to quantify the health risk of a specific activity with a specific substance (risk = hazard × exposure).

Exposure by inhalation is of most concern and is the prime topic of this section. Exposure via skin and eyes will be treated at the end.

The inhalation exposure level is the amount of substance per m^3 in the breathing zone of the worker, which is the volume of air within 1 metre in any direction of the worker's head). Measuring the exposure level of each activity would be the ideal approach to assess the associated risks. But this is not realistic, not in general and especially not for small-scale situations [45]. The accurate measurement of health risk through atmospheric monitoring requires many samples in order to take into account within, and between, worker sources of variability [46–48]. The cost and practical difficulties associated with atmospheric monitoring represent an often insurmountable obstacle for companies, especially for small and medium enterprises (SMEs). A model-based approach remains as a possibility.

In the last decades some models have been developed, the most well-known probably being COSHH Essentials [28], INRS [27], Stoffenmanager [49] and especially the Advanced REACH tool [50].

26.5.2 Advanced REACH Tool (ART)

Since 2010 a new, international, model has become available: the Advanced REACH Tool [50], with a thorough and highly recommended explanation of the method and its backgrounds [45].

This interactive tool helps to estimate the exposure level for a huge variability of work situations, in the chemical and food industry, transport but also small-scale situations.

ART takes, apart from the amount to be handled, into account nine 'principle modifying factors' that influence inhalation exposure level [51]:

- Substance emission potential (e.g. fine powder, granules, liquids, etc.)
- Activity emission potential (e.g. mixing, pouring, weighing, etc. but also milling, compressing powders, picking objects, bending metal tubes, hammering)
- Localised controls (e.g. local exhaust, containment, glove box, open, etc.)
- Segregation
- Dispersion (e.g. indoors/outdoors, room size, ventilation rate)
- Personal behaviour
- Surface contamination (cleaning)
- Personal enclosure
- RPE (= respiratory protective equipment).

The tool uses some of these factors as configurable variables. By changing input variables it is easy to assess their

ART REPORT – Preparation of capsules in dust exhaust cabinet – 28-Sep-14

Ethinylestradiol 1 mg, 200 capsules

Chemical details	
Chemical	Ethinylestradiol
CAS No.	57-63-6

Operational Conditions

Substance emission potential	
Substance product type	Powders, granules or pelletised material
Dustiness	Extremely fine and light powder
Moisture content	Dry product (< 5 % moisture content)
Powder weight fraction	Small
Activity emission potential	
Activity class	Movement and agitation of powders, granules or pelletised material
Situation	Movement and agitation of 10 - 100 gram
Agitation level	Handling with low level of agitation
Containment level	Open process
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	30 m

Risk Management Measures

Localised controls	
Primary	Fixed capturing hood (90.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Dispersion	
Ventilation rate	1 air changes per hour (ACH)

Fig. 26.4 Example of a report following an ART exposure scenario

influence on the outcome, the estimated exposure level band. In this way it can be discovered which measures will contribute most to a lower exposure.

ART takes volatility of liquid substances into account, however not yet the volatility of solid substances.

ART cannot be used yet for dermal exposure (but is developing it). Also integration of ART predictions with tools for modelling internal dose is foreseen.

As an example of assessing the exposure level during the preparation of capsules the ART report is given in Fig. 26.4.

26.5.3 Exposure at Pharmacy Preparation

26.5.3.1 Preparation from Raw Materials

Exposure during pharmacy preparation from raw materials can be estimated with the ART, which is not surprising as outcomes of specific exposure measurements during pharmacy preparation, described in this subsection, have been used to develop and calibrate the ART.

Pharmacy preparation from raw materials or through adapting of products, as well as reconstitution of medicines accounts for numerous different preparation methods, batch sizes and operators. Some exposure measurements have been performed with these methods for small-scale preparation in pharmacies [52], which led to a specific exposure model for small-scale preparation in pharmacies for inhalation exposure.

The investigations considered small-scale preparation of capsules, cutaneous preparations, aseptic handling in a safety cabinet with laminar down flow. The inhalation exposure was measured by filtration of the air in the breathing zone, see Fig. 26.5a and b.

The ventilation, exhaust and containment facilities during pharmacy preparation that have been investigated concerned four different types (see Sect. 28.3 for description of equipment). The effectiveness decreases from 1 to 4:

1. Isolator
2. Safety Cabinet
3. Powder exhaust unit (solids and non-volatile liquids) or fume cupboard (fumes)
4. Work bench without any form of local ventilation

The investigations showed the level of inhalation exposure depending on:

- The physical form of the substance(s): solids (powder or crystalline) can blow and are easier to be inhaled than semisolid and liquid substances
- The quantity of the substance(s)
- The duration of the operation
- The ventilation and exhaust measures taken to remove substances from the breathing air

The types of handling (weighing, rubbing, crushing, mixing, shaking, and stirring) turned out to have a minor influence on the exposure level.

The preparation activities that have been investigated covered 2 amounts of the active substance: $<$ 10 g and 10–100 g. So for working with either very small amounts ($<$ say about 100 mg) or higher amounts $>$ 100 g, this specific model may not offer the most suitable solution. Working with very small amounts occurs, for instance, within pharmacies, hospitals or nursing homes where employees crush tablets for patients with dysphagia (see Sect. 37.6.2) or reconstitute antibiotic mixtures or parenterals (see Sect. 26.5.3).

The investigation [52] assessed which ventilation and exhaust measures decreased exposure and to what extent. If, for example, 10–100 g of material is used, working in a

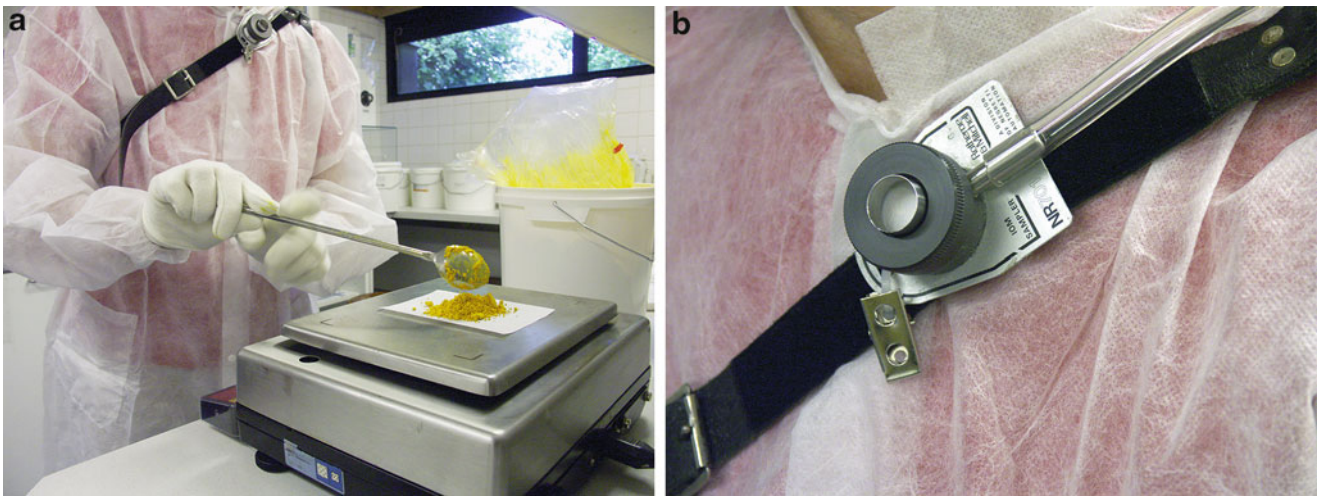

Fig. 26.5 (**a** and **b**) Measuring inhalation exposure level by filtration of the air in the breathing zone (photos Ruud Briedé)

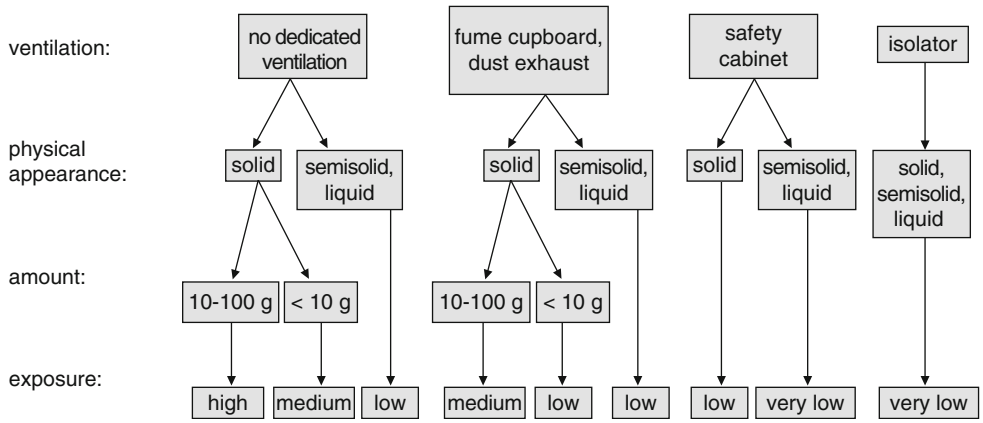

Fig. 26.6 Inhalation exposure model for different ventilation situations at pharmacy preparation from raw materials (Adapted from [52] with permission)
very low = GM (geometric mean): 0.1 microgram/m^3
low = circa 10 – tens of microgram/m^3: GM 13 micrograms/m^3
medium = circa 100 – hundreds of micrograms/m^3: GM 71 micrograms/m^3
high = >1 mg/m^3: GM 329 micrograms/m^3

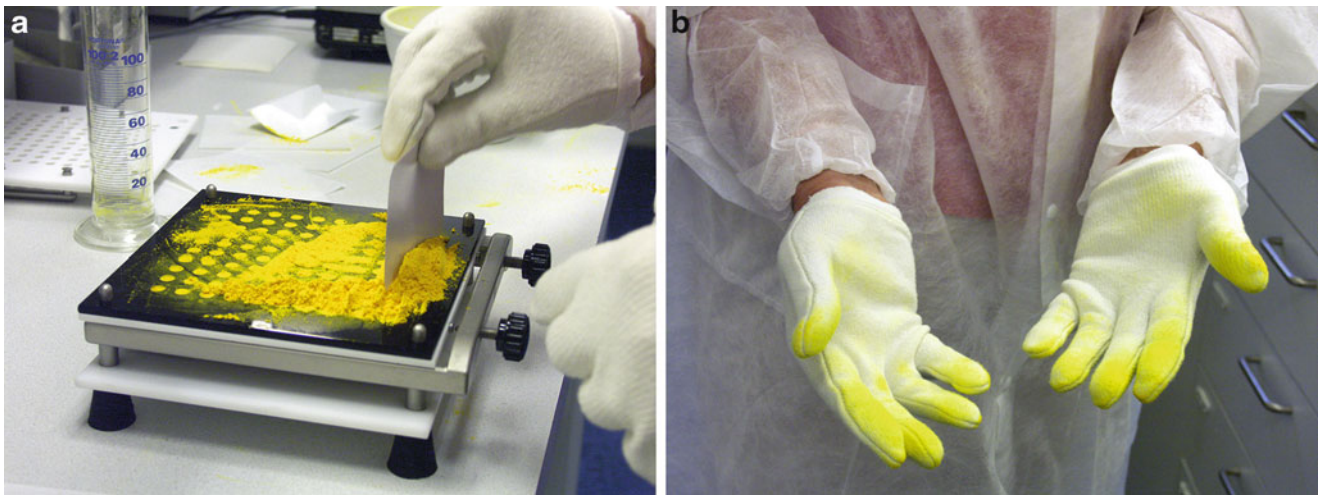

Fig. 26.7 (**a** and **b**) Exposure of investigational gloves during the filling of hard gelatin capsules (test substance riboflavin) (photos Ruud Briedé)

safety cabinet instead of in a powder exhaust unit, changes the exposure class from medium to low (see Fig. 26.6).
Four exposure classes have been discerned:

- Very low
- Low
- Medium
- High

Within assumptions the levels have been quantified. Each exposure class corresponds to an amount of micrograms/m^3 dust. These values represent the so-called geometric mean (GM). The GMs of the low, medium and high levels are thus supported by measurements. The GM of the class 'very low' however is taken from the literature [23]. The isolator turns each type of physical appearance into a very low exposure. See further Sect. 28.3.

Dermal exposure was investigated as well. It appeared that exposure of the hands was extensive (see Fig. 26.7a and b).

The difference with inhalation exposure however is that the skin of the hands can easily be protected by wearing gloves (see Sect. 26.4.3). The wearing of gloves with all pharmacy preparation activities is thus strongly advised by the occupational health professionals.

The RISKOFDERM Dermal Exposure Model [53] is a model for estimating potential dermal exposure, i.e. the total amount of a substance coming into contact with the protective clothing, work clothing and exposed skin. It is based on statistical analysis of data gathered in the RISKOFDERM project, a European project on dermal exposure. The model originally consists of a set of equations as reported in the deliverables of the RISKOFDERM project. These equations have been entered into a user-friendly spread sheet in Excel.

As said ART is developing a tool for dermal exposure as well, taking into account the RISKOFDERM model.

26.5.3.2 Reconstitution

Exposure from antineoplastics in hospital pharmacies and wards during reconstitution of parenteral medicines is monitored and evaluated by assessing contamination levels in air, on surfaces or personnel (blood, urine). Publications originate from all over the world, for example in the Netherlands [33–37, 54], in Sweden [55], Germany [56–58], UK [59], Italy [60, 61], France [62–64], US and Canada [65, 66] and Japan [67].

These studies confirmed the presence of antineoplastics in blood and urine samples of workers. However, there is no direct correlation with personal health risk. Biological monitoring may be used for occasional assessment but not for routine evaluation.

The studies demonstrate the persistent spreading of surface contamination. They also establish notions about acceptable contamination levels although the main aim of measuring surface contamination remains monitoring (benchmarking). It appears that the benchmarking strategy enables improvement of the protection of the workers. For example the biological monitoring by urine sampling (assessing platinum), in pharmacies using isolators, highlighted the importance of handling procedures in the background area of isolators [59, 64].

Additional attention had to be paid to the implementation of personal protective measures and the significance of the investigational results. See further Sect. 26.5.4.

26.5.4 Surface Contamination

Contamination on outer surfaces of medicines containers as well of working places (table tops, safety cabinets) leads to exposure of operators, other healthcare personnel and cleaners. Tests on surface contamination (wipe tests) illustrate spreading of contamination and the difficulty of proper cleaning of surfaces; contamination is often found on objects and premises a fair distance from the primary source. The external surface of vials for antineoplastic parenteral medicines for instance represent a significant source of contamination that spreads into the entire working environment including the outside of safety cabinets and isolators by contact via contaminated materials (gloves, sleeves, etc.) [59, 62, 64]. These results may be expected to be valid for vials of other medicines such as antibiotics for which maximal mitigation of exposure is indicated due to their sensitising potential.

Surface contamination is apparently not influenced by ventilation or filtration of air. Skin contact through surface contamination would therefore probably pose people in adjoining areas to a greater risk than exposure by inhalation.

26.5.4.1 Wipe Tests

At a wipe test a sample is taken with a tissue or a swab from a surface, after it has been cleaned. The tissue must be moistened with a liquid in which the substance to be expected will dissolve. The sample is then analysed for example for radioactivity or traces of substances used. Results of wipe tests may be in the order of 0.1 nanograms/cm^2, very much depending on the method of sampling and method of analysis. A reference value (threshold guidance value) can therefore only be set in relation to a specific method of sampling and analysis. A general consensus isn't available yet.

The USP <797> recommends surface monitoring on a regular basis initially for benchmarking and at least every 6 months, locations to be assessed are the working area of the safety cabinet or isolator (see Sects. 28.3.6 and 28.3.7) and adjacent areas, including floor directly under the working area, the counter top where final preparations are placed, and the ward. Cyclophosphamide, ifosfamide, methotrexate, fluorouracil are recommended as representative antineoplastics. If chemical contamination is found the root cause shall be investigated and corrective measures implemented. These may involve thorough cleaning with an alkaline soap and water, training and supervising. Improvement of the effectiveness of local exhaust equipment has to be considered as well.

USP warns that levels greater than 1 ng/cm^2 of cyclophosphamide were found to cause human uptake.

Table 26.7 Threshold Guidance values for 5-fluorouracil and Platinum in hospital pharmacies (Adapted from Schierl et al. [58])

5-fluorouracil (pg/cm^2)	Platinum (pg/cm^2)
<5	<0.6
5–30	0.6–4
>30	>4

26.5.4.2 Threshold Guidance Values

Assessment of surface contaminations brought some authors to suggest guidance values to improve working practice. Fluorouracil, cyclophosphamide and platinum are currently used as tracers. Threshold Guidance Values (TGVs) for platinum and cyclophosphamide, were proposed based on a large investigation of 102 hospital pharmacies (see Table 26.7) in Germany [58]. TGVs were based on the 50th and 75th percentiles of contamination values.

The MEWIP program, which was a large-scale investigation in Germany [68], investigated several antineoplastics (cyclophosphamide, docetaxel, etoposide, 5-fluorouracil, gemcitabine, ifosfamide, methotrexate, and paclitaxel). The program led to a substance-independent performance-based target value of 0.1 ng/cm^2 based on the 90th percentile of the contamination values.

Sessink [69] purposed guidance values for cyclophosphamide based on wipe and urine samples collected in the Netherlands based on 90 % (<0.1 ng/cm^2) and 99 % (<10 ng/cm^2) wipe sampling results. No positive urine samples were found at contamination levels < 0.1 ng/cm^2, which is an indication that no measurable exposure of the healthcare workers has occurred. Therefore Sessink [69] suggested that the reference value 0.1 ng/cm^2 reflects a safe situation and 10 ng/cm^2 is not acceptable (Table 26.8). For this last situation immediate corrective measures must be implemented and its efficacy should be evaluated. In between-values would need monitoring and searching for root causes in order to reach the target 'green' level.

Swedish investigations [55] led to a suggestion for 'hygienic guidance values' (HGVs).

26.6 Legislation

Occupational safety and health legislation regulates the standards of workplace safety and health with the aim of preventing workplace accidents, injuries and diseases. It details responsibilities of employers and workers. Generally, the legislation requires that the employer protects the safety and health of their workers in the workplace to a reasonable measure and that the workers must enable their employer to comply with these duties.

In the context of this textbook legislation is discussed that affects preparation in pharmacies, mainly concerning exposure to chemical substances. Legislation provides the logic for determination of 'safe levels', for which risk acceptance by Society takes part.

26.6.1 Occupational Safety and Health Directives

The European Framework Directive on Safety and Health at Work (Directive 89/391/EEC [72]) provides the fundamentals of European safety and health legislation. On the basis of the Framework Directive nearly twenty individual directives have been developed, covering a range of risk factors and different categories of workers [73], for example the Carcinogens Directive (see Sect. 26.6.4) and the Pregnant Workers Directive (see Sect. 26.6.5). The OSH Framework Directive continues to apply in full to all the areas covered by the individual directives, but where individual directives contain more stringent and/or specific provisions, these special provisions of individual directives prevail.

The Framework Directive sets out minimum requirements and fundamental principles, such as the principle of prevention and risk assessment, as well as the responsibilities of employers and workers. Member States of the European Union have all transposed a series of directives into their national legislation. Member States are free to adopt stricter rules for the protection of workers when transposing EU directives into national law, and so legislative requirements in the field of safety and health at work may vary across EU Member States.

The Netherlands has transposed EU directives into its national occupational safety and health act [70]. Since 2007 the authorities do not regulate the health safety policy anymore on detailed level. This policy should be established within companies, so customisation is possible. As far as European regulations permit, the Dutch authorities determine the targets to be achieved. How employers and workers achieve the targets, can be regulated per sector. The idea is that trades unions

(continued)

Table 26.8 Guidance values (Adapted from Sessink [69])

Cyclophosphamide monitoring	Target risk level			Prohibitive risk level
Urine (micrograms/24 h)	<0.02	0.02–0.2	0.2–2	>2
Wipe sample (ng/cm^2)	<0.1	0.1–1.0	1.0–10	>10

and employers' organisations compile a so-called Safety and Health Catalogue where it is indicated how and with what means companies can achieve the target requirements. In the Netherlands there is a health and safety catalogue for working in the community pharmacy [71]. For workers in the hospital pharmacy, the Health and safety Catalogue for (Dutch) hospitals applies. It sets out in more detail the situation of exposure to hazardous substances in the hospitals, for example the risks of working with antineoplastics, radiopharmaceuticals and anaesthetic gases.

Employers should map and evaluate all the risks of the work, suggest and implement measures that assure an improvement in the level of protection and evaluate the policy. This is called the RI&E-procedure, RI&E being the abbreviation of Risk Inventory and Evaluation. The employers should inform and instruct the workers about the risks and the measures taken to manage the risks. Workers must follow the safety instructions and use the provided protective equipment.

The labour inspectorate can impose penalties if an institution or company does not comply with the legislative requirements. In the event of incidents they always hold an inquiry.

Further information on European legislation, its implementation and other practical documents on safety and health at work can be found on the website of The European Agency for Safety and Health at Work (EU-OSHA) [72].

Employers' and Workers' Obligations [72]

The employer shall:

- Evaluate all the risks to the safety and health of workers, inter alia in the choice of work equipment, the chemical substances or preparations used, and the fitting-out of work places
- Implement measures which assure an improvement in the level of protection afforded to workers and are integrated into all the activities of the undertaking and/or establishment at all hierarchical levels
- Take into consideration the worker's capabilities as regards health and safety when he entrusts tasks to workers
- Consult workers on introduction of new technologies
- Designate worker(s) to carry out activities related to the protection and prevention of occupational risks
- Take the necessary measures for first aid, fire-fighting, evacuation of workers and action required in the event of serious and imminent danger
- Keep a list of occupational accidents and draw up, for the responsible authorities reports on occupational accidents suffered by his workers
- Inform and consult workers and allow them to take part in discussions on all questions relating to safety and health at work
- Ensure that each worker receives adequate safety and health training

The worker shall:

- Make correct use of machinery, apparatus, tools, dangerous substances, transport equipment, other means of production and personal protective equipment
- Immediately inform the employer of any work situation presenting a serious and immediate danger and of any shortcomings in the protection arrangements
- Cooperate with the employer in fulfilling any requirements imposed for the protection of health and safety and in enabling him to ensure that the working environment and working conditions are safe and pose no risks

Health surveillance should be provided for workers according to national systems.

To the best of our knowledge there are no guidelines or standards elaborating general OSH guidelines specifically for (hospital) pharmacies on a European level.

26.6.2 European Regulation REACH

OSH directives address only health risks at the workplace and are mainly process-oriented. Other regulations address product-oriented health and environment risks on a European level such as the European Regulation REACH and the CLP regulation (see Sect. 26.6.3).

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals [77]), applies to chemicals that are manufactured, imported, placed on the market or used in the EU. REACH has two main aims: to ensure a high level of protection for human health and the environment, including by improving knowledge and information about chemicals; and to enhance the competitiveness of the European chemical industry [78].

REACH came into force in all EU countries on 1 June 2007 and states the obligations for the whole supply chain:

manufacturers, importers, downstream users and distributors of chemicals. All categories are obliged to register their use of chemicals and to have information on its hazards. Preparing pharmacies belong to the category downstream users.

26.6.3 GHS and CLP

Different classification and labelling systems for the hazards of substances are currently used throughout the world. The same substance may thus be classified as 'toxic' in the United States, 'harmful' in the European Union and 'moderately dangerous' in China. To eliminate disparities a Globally Harmonised classification and labelling System (GHS) was developed under the auspices of the United Nations. It was formally adopted in 2002 by the United Nations Economic and Social Committee (UN ECOSOC) and revised in 2005 and 2007 [78, 79].

GHS aims to:

- Define physical, health and environmental hazards of chemicals
- Create classification processes that use available data on chemicals for comparison with the defined hazard criteria
- Improve the communication on hazard information, as well as protective measures, on labels and Safety Data Sheets (SDS).

26.6.3.1 GHS Implementation in Europe: CLP

The GHS is a set of international recommendations. As GHS is non-binding rather than legally binding, it had to be adopted through a suitable national or regional legal mechanism to ensure it becomes legally binding. That's what the CLP Regulation does for Europe. CLP is the regulation on **C**lassification, **L**abelling and **P**ackaging of substances and mixtures (EC No 1272/2008), it came into force in 2009 [80].

GHS is also known as EU-GHS in Europe. As of 2015, when GHS will be fully in force, all substances and mixtures (products are considered as mixtures) must meet the new classification, labelling and packaging requirements CLP.

26.6.4 Carcinogens or Mutagens Directive

One of the individual directives under the Framework Directive is the directive on the protection of workers from the risks related to exposure to carcinogens or mutagens at work: Carcinogens or Mutagens at work Directive (2004/37/EC) [74]. This Directive obliges the employer to assess and manage the risk of exposure to carcinogens or mutagens. This assessment shall be renewed regularly and data shall be supplied to authorities on request. Special attention is made to all possible ways of exposure routes (including the skin), and to persons at particular risk. The employer shall reduce the use of a carcinogen or mutagen by replacing it with substance not or less dangerous. If replacement of substances is not possible (see also Sect. 26.7.1), the employer shall use engineering measures, mainly containment. If a closed system (total containment) is not technically possible, the employer shall reduce exposure to minimum.

The Directive adds a series of detailed guidelines for employers to minimise exposure, inform employees, reporting workers that may be exposed, reporting incidents (also to the authorities).

The Carcinogens Directive is the origin of two notions in pharmaceutical practice: the ALARA (as low as reasonably achievable) principle at the processing of carcinogenic substances and the registration of working with carcinogenic substances.

The Directive requires that an employer of employees exposed to carcinogenic or mutagenic agents registers the following, in addition to the data of the general mandatory registration:

- The reason why the carcinogenic or mutagenic agent is used and cannot be replaced
- The quantity of the substance used per year
- The type of work done involving the substance
- The number of employees who could be exposed to the carcinogenic or mutagenic agent
- The measures to minimise that exposure
- The personal protection equipment in use
- The situations in which carcinogenic and mutagenic agents have been replaced

This registration requirement should be converted in pharmacies into a practical procedure because the vast number of carcinogenic substances, the number of employees and the large variations in processes.

As REACH does not overrule this Directive, the approach of controlling workplace exposure should comply with ALARA [10]. See Sect. 26.8 for further interpretation.

26.6.5 Pregnancy Workers Directive

The Directive on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding, The Pregnant Workers Directive (92/85 EEC) [75], has been attached to the Framework Directive (Sect. 26.6.1). These guidelines treat, apart from risks from

hazardous substances, also risks from physical movements and postures, mental and physical fatigue and other types of physical and mental stress. Employers' duties include "the identification of specific chemical substances and categories of chemical substances and reducing the use of, and exposure to chemical substances that may affect a pregnant or breastfeeding worker". In practice, also workers with a desire to have children (men and women) should be taken into account, since some substances may be harmful to the fertility or harm in the very first stage of a pregnancy. That is why it is important to point out that workers report as soon as possible that they are pregnant. They also need to know that reporting a desire to have children, men and women, may be of interest to their own safety.

Each pharmacy must draw up a maternity policy. The pharmacist needs to identify in the Risk Inventory and Evaluation (RI&E) which substances are present that may cause damage, and which activities otherwise could be dangerous for pregnant women (such as lifting heavy boxes).

26.7 Risk Mitigation

Investigating hazard and exposure means to mitigate the health risk of workers (risk = hazard × exposure).

In an exceptional situation the actual exposure can be determined (see Sect. 26.5.3), the hazards of the substance has been defined sufficiently (see Sect. 26.3.5) and above all, the exposure limit to the substance has been set by the competent authority. This may apply for instance to working with ethanol, see also Sect. 26.7.2. In such an ideal situation it is possible to claim completely safe working conditions or, in case of genotoxic and sensitising substances, safe with a societally accepted minor health risk (see Sect. 26.7.2). In practice for pharmacy preparation and reconstitution medicines hardly any exposure limits exist at the moment.

In most situations risk mitigation means:

- Analyse the working situation
- List potentially harmful situations
- Assess the risk by using categorisation
- Prioritise risks for which mitigation is most necessary
- Convert priorities into actions keeping general risk mitigation principles in mind

This chapter subsequently discusses general mitigation principles, exposure limits and working with a risk categorisation model.

26.7.1 General Principles

In an ideal situation the health risk is known and preventative and protective measures can be taken to control the risk. However if the risk is only guessed or put relative to another risk, it is possible to perform control measures.

Occupational hazards and exposure can be controlled by a variety of methods.

Four general categories of control measures in widely accepted order of effectiveness are (see Fig. 26.8):

- Elimination or substitution: eliminate the exposure before it can occur
- Engineering controls (or: collective protective measures): require a physical change to the workplace
- Administrative controls (collective protective measures); require worker or employer to change work flow or organisation
- Personal protective equipment (PPE, or: individual protective measures); requires worker to wear a device

Control measures mentioned as first option should be considered before the next ones because they are most effective. The reason for a better effectiveness is that measures that protect the whole of the workplace and everyone who works in there (collective protective measures), are more effective than individual protection. The measures will be dealt with in order of decreasing effectiveness.

26.7.1.1 Elimination or Substitution

Elimination is the most effective measure to remove the hazard completely. This measure should be used whenever

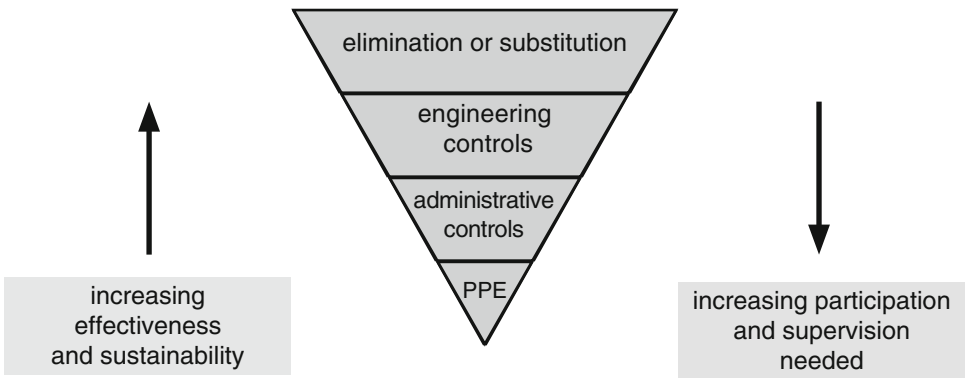

Fig. 26.8 Hierarchy of consecutive control measures to control and minimise the risk associated with the hazard and the exposure, adapted from Quality Systems Toolbox, software and services for quality management www.qualitysystems.com, with permission

possible but will be hard to achieve in pharmacies. If it is possible, this step needs to be taken at the time the pharmacy receives the request for a preparation. It is part of one of the assessment models of a prescription (see Sect. 2.2.3). Replacing a hazardous substance or work process with a safer substance or work process is also an option. Choosing a different dosage form, such as an oral liquid instead of capsules, is also a way of substitution to decrease the hazard. Preparing an oral liquid than capsules generally creates less dust whereby the exposure by inhalation will be decreased. Using semisolid concentrates of active substances in dermatological preparation is not only advantageous for an effective dispersion (Sect. 29.7.2) but also for mitigating exposure.

26.7.1.2 Engineering Control Measures

Engineering controls require implementation of physical change to the workplace which eliminates or reduces the risk on the work process. Examples of engineering controls are:

- The use of ventilation measures (exhausting, see Sect. 28.3; pressure regime, see Sect. 27.4.2)
- Isolation or containment of the work processes
- Change the engineering of work processes to minimise contact
- Proper cleaning procedures, including monitoring

The numerous investigations on spreading of contamination with antineoplastics have increased the insight about measures to counter it. The establishment and observance of good cleaning, clothing and gloves protocols and workers' awareness are important measures, as well as training of operators, other healthcare personnel and cleaners in the proper handling of contamination. For cleaning procedures see Sect. 34.16.

The performance of wipe tests (Sect. 26.5.4) may help to investigate sources of contamination and monitor work and cleaning procedures.

General rules to minimise spreading of contamination are:

- Close containers with (raw) material directly after use.
- Place containers which require specific storage (for example a safe) back in the store immediately after use.
- Do not eat, drink and chew in the preparation areas and also do not keep food and drinks in those areas.
- Move all objects at an even pace and avoid quick movements that cause turbulence in the airflow.
- Clean contaminated exteriors of containers (bottles and jars).
- Make sure all containers, weighed quantities and intermediates are also recognisable from others, e.g. by a label.
- Prevent the spread of the substances as much as possible by working on a clearly delimited place.
- Keep contaminated material (glassware, mortars, vessels etc.) separated from clean equipment.
- Prevent contamination of items that are not immediately necessary for work (such as logbooks, instructions, pens).
- Grip vials with antineoplastic parenteral preparations with the (gloved) hand put in a sandwich bag that is discarded afterwards.

26.7.1.3 Administrative Control Measures

Administrative control measures include for example job scheduling to limit exposure, posting hazard signs, restricting access and training. Job scheduling in pharmacy preparation however is not always desirable from the point of view of routine which is considered advantageous for pharmaceutical quality. A pharmacy example of an administrative control measure is the relocation of reconstitution of medicines with class 4 and 5 substances from the ward to the hospital pharmacy where better protection can be provided.

26.7.1.4 Personal Protective Equipment

Personal protection equipment is the least desirable but may still be effective. Personal protective equipment (PPE) may be indispensible for instance:

- When handling substances at places where no engineering controls reasonably can be provided (for instance on wards)
- In emergency situations, see Sect. 26.9

In Sect. 26.4 personal protective equipment (respirators, goggles, gloves, clothing) are described related to the route of exposure.

26.7.1.5 Combination of Measures

A combination of measures usually provides a safer and healthier workplace than relying on only one method. A strategy of combination of methods is given in Fig. 26.9. It combines quantity, occupational health hazard, task duration and physical form of the substance.

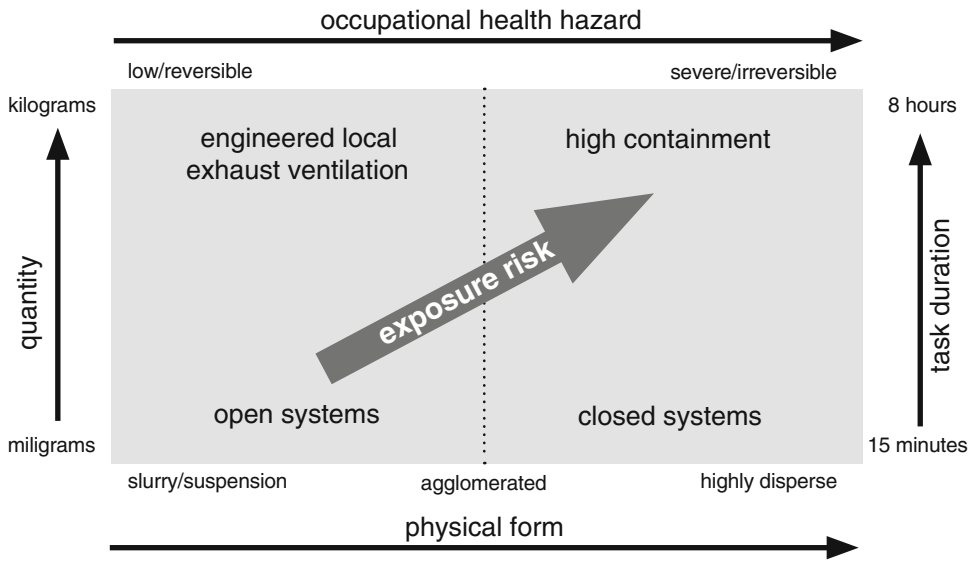

Fig. 26.9 Combination of control measures (After Donna Heidel with permission)

26.7.2 Exposure Limits

If the level of exposure is known, whether by measurements in the air that the worker breathes or by estimation via an exposure level model, would this level be safe enough to prevent health damage? If exposure cannot be prevented, is it necessary to control it not exceeding that acceptable level?

An exposure limit reflects the concentration of a substance at the workplace that is considered safe for the worker. This concentration has to be specified:

- Is this concentration valid for a short period, a working day (how many hours?), a week or even a lifelong employment?
- Does it apply to the inhalation route, dermal route or even another route?
- Is it quantified based on scientific evidence or is it the qualitative approach 'as low as possible achievable (ALARA)'?
- Which body has set the limit?
- Is feasibility in the social context taken into account?

For working situations in Europe the most relevant exposure limits are the OELs. They are elaborated and the relation with DNELs and DMELs is shortly given. For surface contamination currently no standards exist but threshold values are proposed (see Sect. 26.5.4).

26.7.2.1 Occupational Exposure Limit (OEL)

An Occupational Exposure Limit (OEL) is the maximum permissible concentration of a given gas, vapour, fibre or dust in the air in the workplace [76]. It is intended to be the level at or below which a given substance can be present in the air in the workplace without harming the health of workers and their offspring, based on current knowledge. This should be the case even if exposure to the substance at that level occurs repeatedly or over a long period of time, even a worker's entire working life (8 h a day, 40 years). Some authors proposed the use of Dermal Occupational Exposure Limits (DOEL) [81].

OELs are not absolute limits, but time-weighted averages measured over an 8-h period. During this period, exposure may at times exceed the OEL, providing that lower levels balance such higher levels of exposure, so that the average level for the 8-h period does not exceed the OEL. An OEL can also be defined as a 15-min time-weighted average (expressed as TWA-15 min). OELs may also be defined by a ceiling value (expressed as OEL-C). This is an absolute OEL that must not be exceeded at any time.

OELs are considered as levels, thresholds, that guarantee safety: no-effect levels. From a scientific viewpoint it may be considered impossible however to give advice on an absolute safe limit. Some uncertainty has to be taken into account but that is merely about interpretation of scientific studies. Two specific adverse effects however cannot be connected with a no-effect level: genotoxic carcinogenicity and sensitisation on inhalation.

According to the Body who prescribes them, two types of OELs exist:

- Public (i.e. statutory) OELs, set by the competent authorities
- Private OELS, set by companies or other bodies

26.7.2.2 OELs for Genotoxic and Sensitising Substances: Target Risk Levels

For genotoxic carcinogens no no-effect level (a safe threshold) can be determined (see Sect. 26.3.3). The only way to eliminate any risk would be to impose a complete ban.

However, as long as such substances are indispensable (or put differently as long as Society accepts the use of such substances, e.g. many antineoplastics), the risk of exposure, and thus the risk of cancer, cannot be completely avoided. The same applies to limits for sensitising substances (see Sect. 26.3.3). Limiting the risk level is the general approach for these substances. Limits are set based on an accepted risk of 10^{-p} (the value of p being decided upon by Society).

Instead of an OEL, then, a target risk level will be identified by governmental bodies, feasibility will be discussed, and a discussion will be repeated every 4 years where necessary [10]. The target risk level states the extent to which exposure must be minimised in order to ensure that the extra risk of harm is negligible or will be reduced to a natural background risk. The feasibility discussion focuses not only on technical feasibility, but also on operational and economic feasibility.

In the Netherlands (also in Germany and Switzerland) for instance use is made of a system of 'feasible' risk levels: a 'prohibitive risk level' (prohibiting an additional risk of cancer higher than 10^{-4} per substance per year) and a 'target risk level' (10^{-6} per substance per year). For sensitisation the target risk level corresponds to a 10^{-3} extra risk of sensitisation owing to exposure to an inhalant allergen beyond any inherent sensitisation to the substance.

Thresholds for sensitisation are so low that they in most cases, with the current state of scientific knowledge, cannot be determined. The Dutch Health Council [82] prefers to start from 'risk numbers' being air concentrations associated with a predetermined accepted (extra) chance that an employee is sensitised by occupational exposure for that particular allergen. In determining the predetermined chance, political, social and political aspects are taken into account.

Based on this consideration the H-statements 317 and 334 lead for the time being to classification in danger class 3 in Fig. 26.4. Active substances with the H-statements 317 and 334 are found in a wide range of therapeutic classes, such as hydrochlorothiazide, methadone, cefuroxime, chloramphenicol and polymyxin.

As feasibility is an economical or cultural concept rather than a scientific one, differences in OELs for genotoxic substances between countries may be expected.

In the case of non-genotoxic carcinogens (see Sect. 26.3.3), a safe threshold, OEL, can basically be defined. These OELs have the same status as OELs for 'normal' health-damaging substances.

26.7.2.3 Public OELs

The European Commission is advised about OELs by the Scientific Committee on Occupational Exposure Limits (SCOEL) [83]. As a result legally binding as well as indicative OELs (as an indication of what should be achieved) are laid down in European Directives. Each Member State in the European Union establishes their own national OELs, based on the European Directives. The corresponding national lists usually include more substances than the Directive. National OELs can again be legally binding or indicative limits.

Ethanol

Hazard type: EU listed as carcinogenic and reprotoxic. Many public OELs exist, for instance 260 mg/m^3 (TWA-8 h) and 1,900 mg/m^3 (TWA-15 min) in the Netherlands.

Risk mitigating in pharmacies (disinfection at aseptic processes) can be attained by:

1. Substitution/elimination: don't use ethanol for cleaning purposes.
2. Engineering controls: apply ventilation and exhaust.
3. Administrative and work practice controls: provide job rotation, perform disinfection only when necessary.
4. Respiratory protective equipment: wear appropriate gloves.

Expert Advice about meeting the OEL:

- Contact with the raw material at preparation: the wearing of gloves and working in fume cupboards (anyway because of risk of explosion) is sufficient;
- Disinfection of LAF units and safety cabinets:
  - Moisten a cloth, don't spray (except for wrapped utensils with a rough surface, but only if absolutely necessary).
  - Use only just enough.
  - Exhaust and discharge on outside environment.
  - Background ventilation at least 2 h^{-1} but preferably 5 h^{-1}.
  - If in very small rooms: leave the room after disinfection and return after a quarter of an hour.

26.7.2.4 Private OELs

As so few public OELs are established but the employer is responsible for the occupational safety and health of his workers, he has often to decide on OELs. This is of course an extremely difficult and expensive job, not within reach of common companies or institutions. Within REACH (ECHA guidance) however procedures have been developed for

establishing private OELs, more specifically called DNELs and DMELs [10, 84].

A DNEL is a Derived No-Effect Level and a DMEL is a Derived Minimal Effect Level. A DNEL applies to non-genotoxic substances and a DMEL to genotoxic carcinogens and substances sensitising by inhalation. Note the principal difference between the two approaches that is reflected in the terminology: a DNEL is connected with absence of effect; a DMEL is connected with a (low and accepted) effect level.

Some private OELs for pharmaceutical substances may be available in the GESTIS database [12] such as:

- Theophyllin: 0.5 mg/m^3 (private OEL from Latvia)
- Hydroquinone: OELs from 0.5–2 mg/m^3 (several countries)

26.7.2.5 Information Sources of Exposure Limits

For Europe a very promising database has been created for retrieving existing OELs and DNELs: the GESTIS (International limit values for chemical agents Occupational exposure limits (OELs) database) [12].

GESTIS database provides workplace-related DNELs which have been established by manufacturers and importers under their own responsibility and have been published by the European Chemicals Agency (ECHA), in the first instance without review. Key data for each substance are also listed for its identification (synonyms, index numbers, formulae) together with a link to further substance data.

The GESTIS DNEL Database currently contains for about 1,300 substances DNELs for workers (local and/or systemic effects in the event of inhalative long-term exposure) with additional information. Should different DNELs be published for one and the same substance, they are stated side-by-side without evaluation. These data are also available in the form of an Excel file. The DNEL values are gathered from various EU member states and about 10 other countries worldwide.

No DMELs are published in this database. The crucial framework is therefore missing (as feasibility depends very much on societal decisions that will be country specific). Since the corresponding cancer risk is not generally stated for DMEL values in the ECHA registration entries and the procedure for their derivation is not transparent, DMEL values will not be incorporated into the GESTIS DNEL Database.

26.7.2.6 Threshold Values for Surface Contamination

The proposals for threshold values for surface contamination, especially directed at antineoplastics, have been discussed in Sect. 26.5.4. These levels very much depend on the method of sampling and analysis. The establishment of these threshold values are yet on the level of best practices, see also Sect. 26.8.

26.7.3 Risk Matrix Models

A risk categorisation model combines hazard categories with exposure categories for the identification of those situations that require most attention to be improved. The risk matrix model which have been developed with the hazard and exposure categorisation given in Sects. 26.3.5 and 26.5.3 will be given as an example. It applies to inhalation risks of small scale pharmacy preparation. This approach is similar to those by the INRS [27] and COSSH [28].

The first step of a risk assessment is to determine the hazard category of the substances involved, the second step is to determine exposure via inhalation or skin and the third step involves combination of others into a risk category by the equation: risk = hazard × exposure.

Table 26.9 depicts the risk matrix obtained.

The indicative occupational exposure limit values are depicted horizontally as well as their midpoints (derived from Table 26.4). The limit values correspond to the amount of substance, in micrograms per m^3 air to be maximally inhaled as an average on an 8-h working day. Analogously a table can be made with limit values valid for a 2-h working day. The geometric exposure averages are given vertically, associated with the measured exposures at the investigations of pharmacy preparation (see Sect. 26.5.3). Each exposure class corresponds to specific ventilation measures, as given in Fig. 26.6. It follows that if the hazard class of a substance is known, as well as the physical form and quantity, then a workplace advice can be given on the necessary ventilation and exhaust measures in order to achieve an acceptable (low) health risk.

As an example, Table 26.10 gives the workplace advice for 8 h preparing pharmacies for substances with hazard class 3.

Ventilation and personal protection measures should be implemented on the batch preparation instruction to inform the operator.

As explained in Sect. 26.5.3 this model can be used for small-scale preparation with quantities from about 100 mg up to 100 g. For higher quantities reference is made to ART (see Sect. 26.5.2) for estimating the exposure. Having the exposure will enable to use the matrix of Table 26.9 for the risk determination.

Table 26.9 Estimated inhalation risks in three classes: small, moderate and high

	Hazard class	1	2	3	4	5
	Limit value	> 5,000 micrograms/m^3	5,000–1,000 micrograms/m^3	> 10–1,000 micrograms/m^3	> 1–10 micrograms/m^3	≤ 1 microgram/m^3
	Midpoint	5,000 micrograms/m^3	3,000 micrograms/m^3	505 micrograms/m^3	5.5 micrograms/m^3	1 microgram/m^3
Exposure	Very low GM = 0.1 microgram/m^3	Small	Small	Small	Small	Small
	Low GM = 13 micrograms/m^3	Small	Small	Small	High	High
	Medium GM = 71 micrograms/m^3	Small	Small	Moderate	High	High
	High GM = 329 micrograms/m^3	Small	Moderate	Moderate	High	High

Table 26.10 Workplace advice for 8 h preparing pharmacies for processing substances with hazard class 3

Workplace	Physical form	Measures
Type 1 (isolator) and 2 (safety cabinet)	Solid, semisolid or liquid	No additional measures
Type 3 (fume cupboard, dust exhaust)	Solid	<10 g substance: no additional measures
		≥ 10 g substance: use substance in another physical form (semisolid or liquid)
		or:
		Wear respirator with APF ≥ 4
	Liquid and semisolid	No additional measures
Type 4 (no dedicated ventilation)	Solid	Use substance in another physical form (semisolid or liquid)
		or:
		<10 g substance: wear respirator with APF ≥ 4
		≥ 10 g substance: wear respirator with APF ≥ 20
	Liquid and semisolid	No additional measures

26.8 Hazardous Substances in Hospital Pharmacy Practice

The key question is: do all precautions, procedures and monitoring lead to a safe work situation? Safety is a matter of risk acceptance. If there exists a public OEL to refer to, one could speak of a 'safe' situation on behalf of Society. However hardly any OELs for pharmaceutical substances have been set (see Sect. 26.7.2 for the ethanol example), and if so the extent of the exposure has to be measured to be able to find out if the OEL has been met. Even then, it is only possible to know something about safety with reference to inhalation, because most OELs refer only to exposure by inhalation and not to skin exposure. The next option is to use a private OEL or to decide for a private OEL together with other professionals. This approach is more or less equivalent to the formulation of a best practice, not using OELs, by professional organisations. This best practice should be open for review by the Competent Authority.

Best Practice Class 5 Substances (Example)
As an example the following best practice may be formulated for a country such as the Netherlands. The categorisation model given in this chapter (see Sect. 26.3.5) applies the REACH approach to the hazard classification of any substance. Sufficient investigations on the exposure at working with up to 100 g of substance in situations with different ventilation options, led to the use of the risk matrix of Sect. 26.7.3 in practice, as basis for an interactive tool (called RiFaS) resembling ART, see Table 26.10 for an example of a RiFaS working place advice.

(continued)

Due to uncertainty about the validity of measurements of inhalation exposure when working in safety cabinets and isolators and because the awareness about the significant role of skin exposure via surface contamination, processing class 5 substances are to be dealt with in a less straightforward manner.

A best practice for handling class 5 substances (to which most antineoplastics belong) could be proposed as:

- Try to avoid the need of processing solid class 5 substances, by pushing back individual dose corrections or by developing liquid formulations.
- Aseptic handling of solutions with class 5 substances in a safety cabinet or an isolator is safe for inhalation exposure.
- Preparation of capsules (working with solid substances) with class 5 substances requires apart from working in a safety cabinet the wearing of a respirator type P3, or should be performed in an isolator (positive or negative pressure) (see Sect. 28.3.7).
- Monitor surface contamination in order to minimise skin exposure; follow trends in the own hospital and benchmark with other hospitals. Agree upon target and prohibitive levels (see Sects. 26.7.2 and 26.5.4) in relation to type of analysis.

A consequence of agreeing on a best practice is that risks (not being nil) and costs of the approach are apparently accepted by Society.

By agreeing to best practices the legal requirements for carcinogenic and sensitising substances (ALARA As Low As Reasonably Achievable) are generally fulfilled. 'Reasonably' implies a level of risk acceptance. Risk acceptance includes the notion that application of any further precautionary measures may lead to either risk increase on other aspects as well as to financial consequences that society don't want to bear (see also Sect. 21.4.3). Risk acceptance will mean at a hospital level that other situations where antineoplastics are handled have to be taken into account. It may for instance be conceived that implementing safety measures for other healthcare workers in hospitals (such as the advice of no reconstitution of class 4 or 5 substances on the wards) have a higher priority than further improving safety in pharmacies.

A similar idea exists on the manipulation of oral solids in homes for the elderly. Although exposure levels have not been measured, the same advice may be valid: licensed oral solid medicines with class 4 and 5 substances are to be manipulated in the pharmacy, not on the ward or in nursing homes.

Keep in mind: not all antineoplastics belong to hazard categories 4 or 5 (see Sect. 26.3.3), and the other way round: some other active substances (such as ethinylestradiol, lithium carbonate, ciclosporin, coal tar, metronidazole and tacrolimus) belong to class 4 or 5.

26.9 Calamities with Hazardous Substances

A calamity with a hazardous substance may occur during preparation, but also before (transport, unpacking of incoming goods) and afterwards (delivery). It is therefore necessary that all employees of the pharmacy, and if applicable the employees of the institution where the pharmacy belongs, are well aware how they should act during a spill or release of hazardous substances. It also concerns logisticians, delivery personnel, nurses and cleaners.

26.9.1 Procedure

The policy in an emergency must be recorded in one or more procedures and should be trained for, regularly. As for any calamity, a company safety officer must be warned as soon as possible. Every institution must have one or more safety officers who are trained in the measures to be taken in case of calamities. The safety officer judges in case of calamities if the pharmacy must be cleared and coordinates the measures to clean up the spilled substance. The employee that has caused the calamity, or sees it first, ensures that:

- He places himself in safety.
- The safety officer is warned.
- Other colleagues stay out the contaminated area.
- Close the door(s) to adjoining areas to allow dilution by room ventilation to enter into force and thus prevent distribution of particles in the air.

The procedure should prescribe how to clean up the spilled substance and the personal protective equipment (gloves, respirators) that should be worn in such a case. Specific emergency kits are used in hospital pharmacies and wards where antineoplastic medicines are handled and administered. These ready-to-use kits, also called spill boxes, are commercially available A standard content is provided by the ESOP (European Society of Oncology Pharmacy) [85].

26.9.1.1 Background Pressure

In areas where aseptic processes are performed in a safety cabinet, an overpressure in the background area may be kept relative to the adjoining areas to keep micro-organisms out. However in a calamity with hazardous substances in a background area with overpressure, particles in the air can spread to adjoining areas when opening doors. The dilemma is whether the aseptic requirements or the eventual spread of hazardous substances will dominate the pressure regimen. A reasoning could be that if the exposure in the air in a calamity ends up in the adjoining areas, this exposure will be lower than in the preparation and background areas because of the clean-up of the contamination, the behaviour of particles (precipitation), the technical specifications of the areas and the ventilation system, and the occurrence of dilution. Moreover these calamities occur, at most, once a year and the duration of exposure is short, the impact of this temporary higher exposure on the total cumulative exposure is likely to be minor. As a result of this reasoning the overpressure for aseptic process will dominate. This reasoning precludes a good calamity instruction. Another or additional option may be the installation of a switch that can stop ventilation when a calamity occurs.

The outcome of reasoning may however be different if it doesn't concern a safety cabinet but an isolator. Firstly the need of having an overpressure in the background area is less severe. Secondly a calamity may not only concern hazardous medicines but also the sterilisation gases in isolators (hydrogen peroxide and peracetic acid). In some countries therefore a negative pressure in the background area is decided for. Additionally a provision may be created for increasing the ventilation rate during a calamity.

26.10 Needlestick and Sharp Injuries

The EU Directive to prevent needlestick and sharps injuries in the hospital and healthcare sector (Sharps Directive) 2010/32/EU [86] implements the Framework Agreement on prevention from sharps injuries in the hospital and healthcare sector signed by the European social partners HOSPEEM (the European hospital and healthcare employers' association) and EPSU (the European Federation of Public Services Unions).

Needlestick and sharps injuries (NSI) are a common occupational hazard for healthcare workers. Although nurses are most at risk from needlestick and sharps injuries, it may also affect pharmacy staff, for instance at the collection and handling of patients' waste (i.e. insulin syringes) and at aseptic processes.

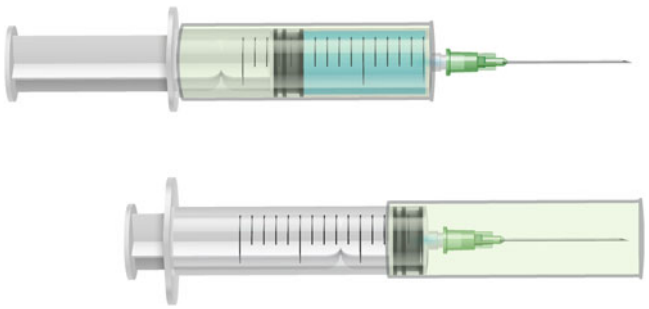

Fig. 26.10 Example of an active safety device: a cap snapping over the needle

The aseptic processing of medicines such as antineoplastics may expose the operator to hazardous substances via NSI. An aseptic non-touch technique involves frequently recapping of needles which is banned under the Sharps Directive. Consequently, procedures will need to be reviewed and alternative products, such as blunt fill needles/filters and recapping blocks, should be considered [87].

As pharmacists are responsible for the purchasing of medical devices, they will be involved with risks for other healthcare workers as well. They may know that the best prevention against NSI is the use of safety-engineered sharp devices (SEDs). There a two kind of SEDs [88]:

- Active devices (manual, semi-automatic): require the user to activate the safety feature. For example: snapping a cap over the needle (see Fig. 26.10). Active devices are only as good as the operator using them. If the operator fails, for whatever reason, to activate a safety feature, then the device is not protected and, therefore, the healthcare worker is at risk from a NSI.
- Passive devices (fully automatic): the safety mechanism is integral to the device design, requiring no any additional actions by the user to activate the safety feature. For example, self-sheathing needle.

The main requirements of a SED are:
During use

- The safety feature can be activated using a one-handed technique.
- The safety feature does not obstruct vision of the tip of the sharp.
- Use of the product requires the use of the safety feature.
- This product does not require more time to use than does a non-safety device.
- The safety feature works well with a wide variety of hand sizes.

(continued)

- The device is easy to handle while wearing gloves.
- The device does not interfere with uses that do not require a needle.
- The device offers a good view of any aspirated fluid
- The device will work with all required syringe and needle sizes.
- The device provides a better alternative to traditional recapping.

After use

- There is a clear and unmistakeable change (audible or visible) that occurs when the safety feature is activated.
- The safety feature operates reliably.
- The exposed sharp is either permanently blunted or covered after use and prior to disposal.
- The device is no more difficult to process after use than are non-safety devices.

Training

- The user does not need extensive training for correct operation.
- The design of the device suggests proper use.
- It is not easy to skip a crucial step in the proper use of the device.

26.11 Fire and Explosion

Some raw materials are inflammable or explosive. It is necessary to know what steps are needed to take in order to control these hazards.

Fire is the reaction between the vapour of a substance and oxygen from the air. So from a liquid or solid substance vapour has to be formed to cause fire. The flash point of a liquid is the lowest temperature at atmospheric pressure (1,013 mbar) at which the liquid gives off so much vapour (on or near the surface of the liquid) that this vapour can become lighted by a flame or a spark.

Fire is initially limited to the immediate surrounding area of the flammable substance. An exception is ether. The vapour of ether mixes very slowly with air because due to its high density it drops to the ground and it spreads quickly over there. At a relatively large distance from the fluid the ether vapour can be lighted.

Liquid can evaporate quite some time before a flame or spark lights the vapour. If this happens in a restricted area and the vapour itself mixes well with air, a lighter source that is far apart from the liquid can cause the fire. Due to the high concentration of inflammable mixture the inflammation will involve an explosion: in a short time a lot of heat is given off.

The flash point of flammable substances (see Table 26.11) gives an indication whether measures should be taken to prevent fire. Especially if the flash point of a substance is lower than about room temperature, it is necessary to ensure that there are no incendiary sources that may come into contact with the vapour near the liquid. Incendiary sources used in preparation processes may be a gas flame, but may also be electric devices that are not automatically explosion-proof, such as some ointment mills, rotor-stator mixers and refrigerators.

Many preparations with flammable and explosive substances can be carried out in a fume cupboard or in a safety cabinet with discharge to the external environment.

Preparation on a larger scale, such as filling out of bulk flammable liquids in containers, is not possible in a fume cupboard and therefore ventilation of the work area itself must sufficiently reduce the concentration of the vapour.

Whether an explosion risk exists at a preparation process can be calculated taking into account the ventilation rate of the room. The following properties must be known:

- The flash point of the substance
- The vapour pressure from which combustion is possible (= lower explosion level, LEL)
- The temperature of the room
- The amount of liquid in relation to the size of the room
- The saturated vapour pressure (= the maximum concentration of the vapour in the air at a specific temperature)
- The vapour density

The concentration C of a given substance, which can be maximally achieved at a given temperature is the saturated vapour concentration (in mg/m^3). This can be derived from the saturated vapour pressure p (a value that often can be found in the substance properties) using the following formula:

$$C = (M/22.4) \times (p/1013) \times (273/T) \times 10^6 \qquad (26.1)$$

Table 26.11 Flash points and the lower explosion levels (LEL) of some common organic solvents

Substance	Flash point	LEL
Ethanol 100 % v/v	12 °C	3,4 % v/v
Ethanol 95 % v/v	14 °C	3,4 % v/v (ethanol)
Ethanol 70 % v/v	21 °C	3,4 % v/v (ethanol)
Acetone	−19 °C	2,3 % v/v
Ether	−45 °C	1,7 % v/v
Isopropanol	12 °C	2,0 % v/v

T = temperature in Kelvin, and M = molecular weight. At 20 °C this equation leads to: 41 × M × p_{20} mg/m^3.

The explosion limit is usually specified in volume% in air. The amount that at least must evaporate in order to reach the LEL in a room filled with air can also be calculated. The vapour pressure in mbar is related to volume% in air as follows:

$$p = \text{volume}\% \times 1013/100$$

From the LEL, the related concentration (at 20 °C) can be calculated with (26.1):

$$C = (M/22.4) \times (LEL/100) \times (273/T) \times 10^6$$
$$= 416 \times M \times LEL \left(\text{unit} : \text{mg/m}^3\right)$$

For the maximum allowable concentration of the flammable vapour a safe margin can be taken such as 10 % of the LEL. This takes into account that the mixing is not optimal, whereby locally the explosion limit can be exceeded. In that case, the maximum allowable concentration will be: 41.6 × M × LEL (in mg/m^3).

The amount of liquid that can evaporate up to this maximum (or should not be exceeded in order to prevent an explosion in the preparation area taking place), can be calculated by multiplying the obtained numbers with the size of the preparation area in m^3.

26.11.1 Work Example

The saturated vapour pressure of ethanol is 58.5 mbar and the lower explosion level is 3.4 vol.%.

At 20 °C and atmospheric pressure, a maximum of 41.1 × 46 × 58.5 = 110,600 mg ethanol vapour in 1 m^3 air can be present.

For an explosion, however, a concentration of 416 × 46 × 3.4 = 65,062 mg/m^3 may be sufficient and the safety approach requires that not more than 6,506 mg/m^3 ethanol vapour should be present in the area, so 6.5 g/m^3.

So, in an area of 3 × 3 × 3 m^3, 1,760 g of ethanol has to evaporate to reach the explosion limit, a safety margin coming to 176 g (10 % of the LEL). This corresponds to about 200 mL of absolute ethanol or alcohol 95 % v/v.

These values would argue for using no more than one small bottle of alcohol 95 % v/v at a time or, alternatively, for a procedure that bottles should be closed immediately after taking out amounts. This would infer that the batch should not require more than 200 mL.

The use of explosion-proof equipment would not be necessary in that case.

A warning for fire danger remains relevant because of the low flash point (14 °C).

When working with larger quantities, a fume cupboard (see Sect. 28.3.2) is needed.

26.11.2 Fire Prevention and Handling Measures

Premises have to enable public, staff and goods moving easily in and out of the pharmacy, this applies even stronger to abnormal conditions of fire (and other) accidents. Areas in which inflammable substances are processed, must have two exits as far apart as possible. At least one of the two must offer a good and accessible escape route. If the area is not on the ground floor, the escape route can be realised with a landing with a caged ladder. Escape routes and fire escapes must be clearly indicated, should never be blocked and should be made antiskid. The emergency exit doors must open outwards and preferably have a panic snap. This is a system with a horizontal and a vertical rod, with which the door can always be pushed open outwards.

If possible equipment and lighting should be explosion-proof; if not, the amount of inflammable substance to be handled has to be minimised (see Sect. 26.11.1). In the laboratory a gas flame or a gas stove may only be used in the fume cupboard.

The risk of fire in the pharmacy is largest where flammable substances such as ethanol, ether and petroleum ether may be present: the laboratory, storage area and, to a lesser extent, the production area. Any area with flammable substances should have at least one extinguisher per exit. The staff should know the positions and should be trained in its use. An emergency shower in such areas may be useful, as well as providing a fire blanket. Fire alarm can be given manually (with or without automatic notification to the fire department) or fire can be automatically detected. The emergency telephone number (112 in the European Union except the UK which uses 999) may be put on phones and fire extinguishers.

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Premises

27

Willem Boeke and Paul Le Brun

Contents

Abstract

This chapter outlines the general aspects of premises designed for pharmaceutical preparation activities and the steps to consider in order to achieve a justified design, construction and qualification of these premises. Also the built-in technical facilities are discussed. Premises and its technical facilities are an essential link in achieving good preparation practice. Their design and qualities should be derived from the kind of products that will be produced in it.

European and WHO GMP define in general terms preconditioned criteria that have to be met by premises, including storage areas, weighing areas etc. However this chapter does not define exactly what is appropriate in any specific facility. The emphasis is on the interrelationship between the demands, the building, the installations and the provisions. The scope is general so that all small-scale production facilities for healthcare establishments and preparation centres are covered in the discussion. Also ready-made premises or modules can be assessed by comparison of their qualities with the ones mentioned in this chapter.

This chapter's arrangement follows the general approach of best practices in qualification. Important subjects covered are:

- Processes that underlie the necessity to build a preparation facility
- Products and the legislative framework
- Routing of goods and personnel and communication
- Specification and classification of premises
- Built-in installations for HVAC, water and gasses

Based upon the chapter Ruimten en Installaties by Willem Boeke, Marco Prins and Jeannine van Asperen in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_27,

- Detail specification and building execution
- Walls, doors, floors, ceilings, heating, fixtures and fittings

Keywords
Premises • Building • HVAC • Construction • Built-in facilities • Water

27.1 Processes as a Starting Point for the Design of Areas and Installations

At the initial design stage for a new preparation facility attention should be paid to a variety of subjects, such as:

- The type and product range of medicines that will be required from the facility
- Developments within the pharmaceutical and medical environments and possible future product and process demands
- The production scale and the batch volumes per product, considering peak loads and annual volume
- The scope of the facility and its requirements, e.g. to supply other pharmacies with pharmacy prepared medicines

Whatever motives there might be for a (re-)building project it should always be kept in mind that the design is specific to the type and volume of products for which it is built. Cutting out one detail might ruin the possibilities to achieve a validated production process.

Small Detail; Big Consequences. . .
Standard doors will always have certain tolerances in their rate of warping. However the entry doors to premises with an air pressure hierarchy, as required by the production process, must be checked for this property in advance. This is to avoid the almost unsolvable problems in the qualification of the air pressure hierarchy due to leakages by not perfectly closing doors. Neither the suppliers of doors nor contractors are usually aware of the importance of assessing these tolerances in advance. After all, if this air pressure hierarchy really was required but could not be qualified as such, a validated production process will not be achieved.

Therefore, at the initial design stage in the construction of premises for pharmaceutical preparations the responsible pharmacist or an advisor who has proven capabilities in this specific area must have a decisive input and a coordinative role. He will have to deal with architects, companies of consulting engineers, (sub-)contractors and installers, all of them having substantial knowledge in their fields. Still the specific knowledge of the design and qualification of a pharmaceutical preparations facility and its installed equipment might be insufficient among those parties, unless a specialist company is chosen for the design and building.

Conversely consulting engineers are important for the incorporation of every aspect of safe building which usually is an unfamiliar topic for the pharmacist. This should prevent failures in construction stability, escape routes, fire and explosion prevention, etc.

It should be decided which categories of products are to be prepared and on what scale. The products involve preparation processes that basically determine what is necessary for a specific facility, taking into account legislation.

Pharmacy preparation processes can arbitrarily be subdivided into the following categories each with their own specific premises:

I. Extemporaneous sterile and non-sterile preparations
   Examples of this kind of preparations are: Aseptic handling, i.e. uncomplicated operations with sterile medicines in closed containers after which they get a very short usage period, reconstitution of sterile and non-sterile authorised medicines and extemporaneous non-sterile preparations from raw materials.
II. Extemporaneous preparations involving specific risks, such as complex aseptic handling and preparation with hazardous substances. Involved in this category is aseptic handling with most antineoplastics, medication cartridges, radiopharmaceuticals, biological or advanced therapy medicinal products (ATMP's).
III. Sterile and non-sterile stock preparations. Involved are:
   - Non-sterile stock preparations
   - Sterile stock preparations (sterilisation in final container)
   - Sterile aseptic stock preparations

The products to be prepared can be organised into a table as in Table 27.1, related to their categories. This may help to estimate the extent of provisions and the level of required standards that are necessary per product type.

27.2 Design

27.2.1 Main Layout Considerations

Starting from the classification of preparation processes a rough preliminary design is drafted indicating the position of production areas, their interrelationship and logistics. The relations between departments and premises, flow of goods and persons are plotted. This start document is preferably formulated by the one who will be responsible in future for the preparation processes.

Table 27.1 Categorisation of products for designing premises

A. Stock preparations	Categories
A1 Sterile	
Aseptic preparations (vials, ampoules, infusion fluids in bags, prefilled syringes)	III
Autoclavable preparations (vials, ampoules, infusion fluids in bags or bottles)	III
Eye drops	III or II
Sterile ointments and creams	III
A2 Non-sterile	
Packaging e.g. in Unit Dose	III
Tabletting	III
Fluids (solutions and suspensions)	III
Ointments and creams	III
Suppositories	III
B. Extemporaneous preparations	
B1 Sterile	
Aseptic handling (complex, see Sect. 31.3.2)	II
Total parenteral nutrition, medication cassettes	
Aseptic handling (hazardous, see Sect. 31.3.5)	
Antineoplastics, radiopharmaceuticals	
Simple aseptic handling; short shelf-life	I
B2 Non-sterile	
Capsules, suppositories, fluids, ointments and creams	I
Reconstitution of licensed pharmaceutical preparations	I

The preliminary design should be drawn up based on the following considerations:

- The extent of the preparation department: Available premises usually are confined. However, sufficient room must be available for apparatus and materials. Apparatus should be stored in a way that minimises contamination. Therefore, a separate accommodation near the preparation premises is preferred over the placement in the preparation room itself.
  Sufficient room should be available for the operators to work efficiently and safely.
- Avoiding crossing routes for personnel and goods: In a pharmacy several products are usually being prepared on the same day. This brings about a higher risk of cross contamination when compared to a large pharmaceutical industry producing only one product on a dedicated production line. Inadvertent mixing up of a sterile and a not yet sterilised product or of products of different batches constitutes a similar threat.
- Entrance: The entrance to premises for preparation should be provided by means of, preferably sex-separated, gowning rooms for staff and a separate air locked entrance exclusively for goods. If necessary the separation of the sexes might be achieved by separating in time. However it should be realised that this may jeopardise the efficiency of the production.

A correct constructional design has to be derived from the process and will prevent any confluence or crossing of routes. However, in practice crossing cannot always be avoided. In that case procedural solutions should warrant that all goods are to be labelled and packed securely (e.g. in closed boxes) before being exposed to crossing lines. Routing questions at the design of a layout of premises will frequently be with regard to processes such as weighing raw materials, sampling, input and output to and from any temporarily deposit store for intermediates or quarantine, cleaning of reusable utensils and label printing.

For example, it is important to consider if the weighing process will or will not be carried out in a centralised weighing room thus requiring subsequent transport of the labelled portions to the preparation room. In a centralised weighing room, thorough precautions should be taken to prevent cross contamination of the raw materials. The same goes when two workers use the same set of weighing apparatus in a pharmacy.

- The location of the preparation department in relation to logistic functions, etc. For example radiopharmaceuticals (see Sect. 15.6.1) should be prepared nearby or at the nuclear medicine department.
- The required apparatus and utensils, the preparation processes they are used for and the required provisions such as air conditioning, clean water, electricity, compressed air and gasses. For extremely hazardous preparations (antineoplastics, radiopharmaceuticals, see Sect. 26.3.5) and for sterile preparations separate premises may be required to protect products and operators adequately, as is also laid down in GMP. Scaling up of the processes may lead to partitioning of the rooms into areas for dedicated functions.

After classifying the preparation processes and the corresponding premises and its outlines the preliminary design will be drafted. Some examples are given below for a few preparation processes.

27.2.2 Sterile Stock Preparations

Separate rooms are necessary for the preparation and for filling into e.g. infusion bags or ampoules prior to final heat sterilisation. In addition, one or more sterilisers with corresponding technical rooms (including the access) are needed.

The premises for the most critical preparation steps (e.g. filling) must be built as a clean room (see Sect. 27.3) and require a controllable air conditioning installation.

Those premises must comply with GMP class C (see Sect. 27.4.2 and Table 27.2) [1].

Sterile stock preparations usually require such high volumes of water that separate technical installation premises are required to accommodate the installation for the production of water for injections.

Finally, premises for examining and for packaging and labelling are necessary.

Appropriate rooms (laboratories) for pharmaceutical microbiological control and for chemical quality control should not be left out. However the possibility of microbiological contamination from this laboratory requires a completely separated air handling.

Alternatively the microbiological control could be outsourced implying yet other, more procedural complications such as the need for Service Level Agreements and meeting the requirements of GMP Chap. 7 (Outsourced activities).

27.2.3 Aseptic Stock Preparations

In premises for aseptic preparation from sterile raw materials the preparation room usually is combined with the filling room because carrying the bulk product into another room will introduce an additional contamination risk. In this situation a separate room for preliminary operations, e.g. disinfection of utensils and surfaces of containers, is required.

At the most critical places, especially at the filling point of the aseptic fluids, the premises must meet GMP class A conditions [1]. A class A condition usually needs a background condition of class B to be able to maintain the class A condition during operation. However exceptions to this rule can be warranted, e.g. using an isolator.

Classified premises are expensive both in procurement and maintenance. Therefore, it is justified to analyse each preparation process for all critical steps and to limit their number as far as possible.

Premises for examining and for packaging and labelling can be combined with those for sterile stock preparations.

27.2.4 Aseptic Extemporaneous Preparations

Also in this situation a separate room is required for preliminary operations, e.g. disinfection of utensils and surfaces of materials. In the preparation room medicines are reconstituted, e.g. filling of syringes, infusion bags, medication cartridges, disposable infusion pumps and irrigations. In addition, parenteral nutrition fluids, antineoplastics, radiopharmaceuticals and eye preparations may be prepared in these premises. Radiopharmaceuticals and other very hazardous products, may require dedicated rooms and containment conditions (see Sect. 26.7).

For aseptic handling in closed systems a cabinet with unidirectional airflow (LAF or safety cabinet) or an isolator can be used (see Sect. 28.3). The requirements for the background room depend on national guidelines and on the types of containment in the cabinets. Adjustments are allowed but must be based on a risk assessment.

> Strictly, air quality class A cannot be claimed if the background qualification is less than class B. However this class A safeguard is strictly only required for aseptic stock preparation and any aseptic handling that is executed with non-closed systems. Under specific conditions a class C condition as background might be acceptable. On the basis of a thorough risk assessment and a monitoring and validation program even a class D background for well-defined aseptic handling may be justified, see Sect. 31.3.4.

27.2.5 Non-sterile Stock Production

This department can be divided into separate premises for solid (dusty), semisolid and fluid preparations. Preparation processes with inflammable substances may require specific provisions such as a fume cupboard or more intensive ventilation. Premises for tableting and similar dust-producing preparation processes should be equipped with a suitable installation for air conditioning and dust exhaustion. Applying a negative pressure will prevent dust from active substances escaping from the preparation room. Even for repackaging activities (e.g. into unit dose package) a separate room is to be preferred. Specific GMP classification A-D is not required for non-sterile preparations. However the GMP principles such as cleanability are applicable. Therefore, in practice, facilities for non-sterile preparation are often classified as grade D.

27.2.6 Non-sterile Extemporaneous Preparations

The underlying principles for premises for non-sterile stock preparations should be used for extemporaneous preparations as well. Preparation activities in a community pharmacy usually are confined to reconstitution, aseptic handling, manipulation of licensed medical products and non-sterile preparation from raw materials. The avoidance of crossing process lines in small-scale situations is a

challenge but it is almost impossible to prevent crossing lines just by the layout of the premises. Routing has to be specified by procedures and organisational measures have to be taken, e.g. working with trays or closed boxes per activity.

The requirements for the premises may turn out to be quite moderate, provided that they are based on a well-documented risk assessment. It will at least imply that premises shall be exclusively dedicated for preparation activities, e.g. shall not give direct access to toilets and will have to be physically separated from any public area. The layout should not compromise a logical sequence of activities. Specific gowning and cleaning procedures must apply.

Attention should be paid to the ventilation of any premise and its upkeep. In newly built premises, the ventilation capacity might have been minimised due to energy saving policy, especially in northern countries. Therefore the risk has to be assessed that the ventilation might fail to meet minimal requirements. Any so-called 'natural ventilation' might clear the way for insects to enter, unless specific measures are taken (e.g. insect screens). Air quality can be improved by using a recirculating dust exhaust cabinet which should be available in every community pharmacy, e.g. for the reconstitution of antibiotic oral liquids.

27.2.7 Storage Rooms

Apparatus to achieve specific, usually low temperature, storage conditions are described in Sect. 28.9. The design of storage rooms should take into account that the temperature should not exceed 25 °C for prolonged periods (see Sect. 36.9.4). This may involve the necessity of air conditioning. Additional provisions should be provided to avoid long lasting humidity levels over 60 % RV or below 20 % RV or penetration of direct sunlight.

Specific conditions, like lockable safety cupboards, may be required for the storage of any specific class of hazardous (e.g. inflammable or poisonous) products.

A properly considered location of storage rooms, separated quarantine storage and laboratory may ease routing very much.

There should be ample space for input and output of goods without the need of rearranging the goods at each occasion (first-in first-out principle). Especially the manoeuvring of pallets should be accounted for.

Empty packing material is usually wrapped in airtight wrappings or transport casings. However after opening the wrap, packing materials are open to the rather unconditioned environment of the storage room and thus open for pollution with dust or even insects. So either only complete units have to be used or the remaining materials should be rewrapped or repacked.

Storage rooms should be kept clean at a normal household level and vermin-free. No specific additional demands are made because the package of the products should protect them sufficiently against any contamination.

27.3 User Requirements Specification

As soon as the draft design, the program of requirements and a thorough (risk) analysis of the anticipated production activities is gathered, this information should be 'translated', usually by professional advisors, into a keynote document or user requirements specification (URS). This document should describe and specify in detail the required situation after the (re-)building. It should clearly underpin the listed demands and points of departure, which for their part should be traceable to relevant legislation. In addition the URS should, after realisation of the building, offer direct control points to all critical aspects of the intended processes. The conformity of the final situation to the original plan must be proven which only can be done by checking systematically all critical control points of the completed premises to the original plan as previously specified in the URS.

The delivery of this evidence is called the performance qualification (PQ), see further Sect. 34.15. It is important to pay attention to the future PQ as, in contrast to other qualifications, the PQ cannot be outsourced. A well-formulated URS takes account of the implementation of the future PQ tests and therefore its tenor extends far beyond a more trivial 'Plan of Demands'.

The URS should account for regulatory demands of GMP, Occupational Safety and Health and Environmental Care. Additionally preparation demands, required apparatus, HVAC (installations for Heating, Ventilation and Air Conditioning) controls, routing of personal and goods as well as gowning and cleaning instructions should be specified. It should be stated explicitly which regulations (e.g. GMP, ISO standards, Occupational Safety and Health legislation) do apply, thus delimiting the legislative framework. By adding the prefix 'c-' (current) to the name of any law (e.g. c-GMP) it is stated that the regulation may be developing during the life of the premises and that always the most recent version has to be consulted.

Clean rooms are usually involved in the design of a pharmaceutical production facility. The term 'cleanroom' is specified in detail in the ISO standards 14644 (parts 1, 2, 4, 5 and 7) and 14698 (parts 1 and 2) [2–5]. Particularly ISO 14644 part 4 deals with the design, the construction and the

initial start-up of a clean room and includes a useful checklist [4].

27.4 Functional Specification

27.4.1 Contents

Next step in the design process is drawing the functional requirements specification (FRS), also called the physical requirements specification. The FRS documents elaborated demands for connections, heat burden, floor load, acoustic demands, specifications of the walls, HVAC etc.

The heat burden is the amount of heat that is generated in a room per unit of time by humans and apparatus. Provisions for air supply have direct impact on product quality. In the FRS for clean rooms the limits are specified for the allowable number of particles at rest and in operation, i.e. the clean room class (see Sect. 27.4.2 below), along with desired turbulence limits, limits for air pressure and microbiological limits. It provides the final specifications for premises, fixtures and fittings and a map with the positions of furniture and apparatus. The FRS contains also technical or procedural measures to prevent cross contamination or crossing lines for personal or goods [5]. Obviously all specifications in the FRS are substantiated at the base of their application. As an example, in premises intended for complex aseptic handling or reconstitution of hazardous sterile medicines, any choice for the classification of the background conditions should be justified.

27.4.2 Classification of Premises

The idea behind GMP is to preclude any factor with an unpredictable or undetermined impact on the production process as this impairs the process validity. Particles, micro-organisms and (gaseous) chemical contaminants arising from the air from outside might constitute such a factor, especially relevant for the process of producing sterile and aseptic preparations. Therefore, GMP requires that premises for this kind of preparations must be classified. Since the absence of invisible micro-organisms and dust is hard to be proved at any moment and place, measures are prescribed that should guarantee this absence with substantial safety margins:

- The inlet air should be filtered, through HEPA (Highly Efficient Particulate Air) filters.
- A specified air replacement factor per hour (ventilation factor; see Sect. 27.5.1 HVAC) should be achieved.
- The premises must be kept clean in relation to lower classified neighbouring premises by the application of pressure differences.

Annex 1 of the GMP applies. This document specifies four grades for low particulate premises: A, B, C and D. See Table 27.2.

GMP Annex 1 states that a certain air quality class can only exist when the access to the room is achieved through an air lock in which the same class prevails. The Annex 1 classification refers to the ISO classification (see Table 27.3) that define intermediate air quality specifications by decimal class designations.

According to ISO 14644–1 the air classification scheme is distinguished by a mathematically coherent approach and based upon a formula:

$$C_n = 10^N (0.1/D)^{2,08} \qquad (29.1)$$

where

C_n = maximum number concentration of particles per m3 with diameter $\geq$ the considered particle diameter, rounded to a maximum of 3 digits;

N = ISO classification number;

D = considered particle diameter;

0.1 = the reference diameter, a constant with the dimension mm.

As the ISO classification is defined by a continuous formula with the particle size as a variable and the GMP grades are defined in discrete counts for specific particle sizes, the comparison between GMP grades and ISO classifications is formally not possible. Additionally ISO classifications can be formulated in decimals where the GMP grades cannot. However as a practical approach the comparison is possible as e.g. grade B at rest will match ISO 5 for most practical purposes.

Table 27.2 Grades of air conditioning according to GMP

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	0.5 μm	5.0 μm	0.5 μm	5.0 μm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	Not defined	Not defined

Table 27.3 ISO 14644–1 classification of air cleanliness

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size (in operation)					
Class	≥0.1 μm	≥0.2 μm	≥0.3 μm	≥0.5 μm	≥1 μm	≥5 μm
1	10	2				
2	100	24	10	4		
3	1,000	237	102	35	8	
4[a]	10,000	2,370	1,020	352	83	
5(GMP B at rest)	100,000	23,700	10,200	3,520	832	29
6	1,000,000	237,000	102,000	35,200	8,320	293
7 (GMP grade B in operation, Grade C at rest)				352,000	83,200	2,930
8 (GMP grade C in operation, Grade D at rest)				3,520,000	832,000	29,300
9				35,200,000	8,320,000	293,000

[a]EU GMP Grade A meets ISO 4.8

How Is the Classification of the Premises Actually to be Derived from the URS?

A basic principle is that raw materials, intermediate products and final products that are not yet in their final, primary package should never be exposed to any unconditioned air. The primary package is the airtight enclosing package of the final product that is in direct contact with the product. Should therefore also non-sterile extemporaneous preparations (Category I; community pharmacy or small hospital pharmacy) be prepared in a classified premise? The principal objective is that during preparation of non-sterile products no contamination from whatever source can occur. To that end adequate procedures should be organised such as a warranted adequate maintenance (cleaning, prevention of impairment) and also warranted procedures should apply to prevent disturbances such as any opening of doors or windows during preparation activities. Under such conditions, a specific classification of premises has limited meaning and usually can be left out. After all Class D only specifies a maximum number of particles at rest which is usually easy achievable except when a current badly functioning ventilation system is in action or during specific (weather) conditions, incurring a high concentration of fine particles or pollen.

Also if products are sterilised in their primary package a low microbial starting contamination is essential. Therefore products to be sterilised must be filled under class C conditions but the preparation of the bulk solution may take place under class D conditions.

Aseptic handling and preparation must be executed under class A conditions, usually a LAF (Laminar Air Flow) cabinet, a LDF (Laminar Down Flow) cabinet, a safety cabinet or an isolator see Sect. 28.3. The background room for stock preparations in a LAF, or LDF cabinet is at least class B. The background room for aseptic reconstitution or handling in a LAF, or safety cabinet may have a lower classification than B, provided that it is based on risk assessment. Conformation to the latest views of inspectorates and professional associations e.g. PIC/S [1] is advised.

For premises designed for non-sterile preparations overpressure is preferable to prevent any penetration of uncontrolled air. For premises designed for sterile or aseptic preparations this is required by GMP.

Generally working with hazardous substances – as almost all active substances are – requires containment. In the specific case of radiopharmaceuticals, Nuclear Energy legislation requires the application of negative pressure (see Sect. 15.6.3). In the situation of aseptic handling, which requires positive pressure, with radiopharmaceuticals, this results essentially in contradictory pressure demands. A solution may be achieved by putting the whole complex of preparation rooms with air locks at negative pressure relative to its environment. The system of walls, floors and ceilings should be completely airtight in that case. Pipe entries, electrical sockets as well as porous stone in the wall parts above the ceiling are frequent sources of (substantial) leakage of contaminated air. Thus all chinks and gaps have to be filled and porous stone has to be coated.

By now putting the air locks at some additional negative pressure a relative overpressure in the preparation premises is created relative to the admission air locks. The deeper negative pressure in the air lock will however lead to a vigorous influx of contaminated air as soon as the outer door is opened, contaminating the lock and compromising its function. To prevent this an additional 'front air lock' should be considered. The front air lock should have a slight

negative pressure relative to the environment and will be supplied with clean HEPA filtered air. Alternatively, a clean air lock or corridor giving access to other (positive pressure) premises can serve as a front air lock to a negative pressure premise. See Fig. 27.1.

In many respects the hazards of many antineoplastics and radiopharmaceuticals for staff are similar. Also the required skills for aseptic handling are similar. This may lead to the consideration of designing a standard layout for all premises for handling with extremely hazardous substances. However, for antineoplastics no formal requirement for pressure applies (see Sect. 26.8). Therefore, the viewpoint that overpressure warrants a better microbiological air quality usually will prevail. In addition the validity of negative pressure premises may be impaired as a result of almost unavoidable air leakages.

The objective can also be achieved with the use of negative pressure cabinets sited in positive pressure rooms.

Weighing of solid substances will release dust. A dust extract cabinet, equipped with a High Efficiency Particulate Air (HEPA) or Ultra Low Particulate Air (ULPA) filter (see Table 27.4) in the rear wall or in the exhaust, or both, will limit the exposure of operators to active substances. Additional options are the wearing of respirators (see Sect. 26.4.1) and a closed weighing vessel.

The air turbulence from a dust extract cabinet may disturb the functioning of electronic balances. A dedicated construction in each of the preparation premises to manage this is

Table 27.4 Survey of HEPA and ULPA filters

Filter class according to EN 1822:2009	Efficiency %	Penetration %
E10	85	15
E11	95	5
E12	99.5	0.5
H13	99.95	0.05
H14	99.995	0.005
U15	99.9995	0.0005
U16	99.99995	0.00005
U17	99.999995	0.000005

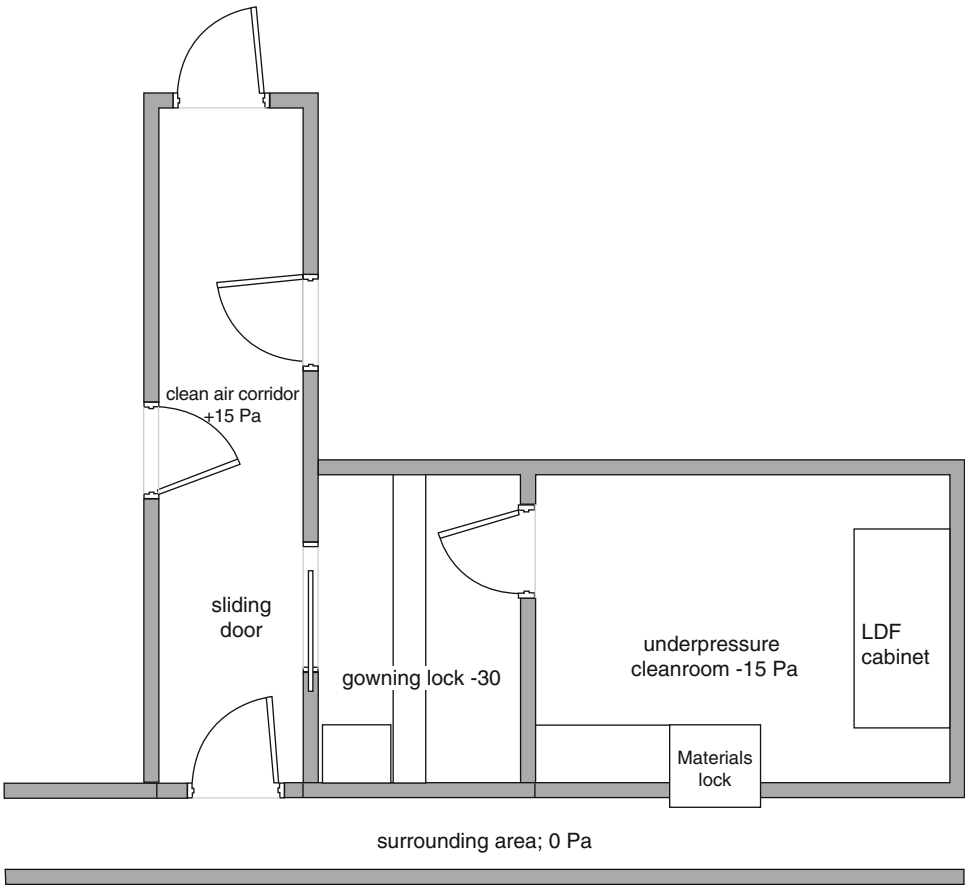


Fig. 27.1 Model plan for pressure hierarchy around negative pressure premises. Adapted from Recepteerkunde 2009, ©KNMP

expensive and therefore cannot always be achieved. If for this reason a separate weighing chamber is designed all measured portions should be transported in well-closed and identified vessels.

27.4.3 Interlock Systems for Air Locks

For the maintenance of an air pressure regime and an air quality class of a preparation premise an air lock is required. It controls access from any lower qualified premise. Personnel locks should be discriminated from materials locks. In personnel locks the required gowning regime has to be determined in advance. In most cases this results in the requirement of sex-separated gowning locks.

For materials locks the prevailing transport direction and the usual volume of materials is important. If possible the transport direction should be assured for instance by means of a catch that transmits a standardised vehicle (e.g. a crate) in only one direction.

All air locks must be equipped with a so-called interlock system. This system ensures that both doors of the air lock will never be opened at the same time.

Different interlock principles exist:
- Both doors are permanently closed by magnets, necessitating a separate hand operated switch to open one of them.
- Both doors are permanently unlocked, in which case the opposite door is locked by opening the other door.

Considerations for the choice are: the hand operated switch is a potential source of cross contamination, magnets consume electricity and emergency escape routes depend on easy access.

27.4.4 Communication and Interior Design

Employees who are working in separate rooms within the premises should be able to communicate with each other. If no well-designed communication resources were in place the personnel would be forced to communicate to each other through windows, locks, opened doors, etc. Routing of personnel and goods will then be seriously jeopardised.

Mobile telephones in preparation premises are notorious sources of cross contamination and thereby not appreciated. The same goes for a hand operated intercom apparatus. A ‘voice actuated system’ - the voice of the speaker actuates the communication line - might be a better solution. Background noise (e.g. from LAF cabinets) however may impart the correct functioning of such a system. A wireless headset or a mobile telephone that stays within the premise and is cleaned / disinfected daily may be an alternative.

27.4.5 Routing and Gowning

The FRS design document should consider the usual tracks of personnel. Routing of personnel and thus required gowning rooms are principally independent of the routing of materials. Therefore, materials locks or transmission cabinets are indispensable in a good design. A correct gowning procedure for personnel can hardly be maintained when employees have to use the changing lock for material transport.

For a gowning lock the following requirements can be put forward:
- A clear division between the ’dirty’ and the ’clean’ part, preferably by means of a step-over bench
- A correct location of a washbasin and a dispenser for hand disinfectant
- Drains (from washbasins) should not be sited on the ’clean’ side of the lock
- A cabinet for clean, unused clothing, and a bin for used clothing is provided
- A locker to stow away personal belongings

Toilets should not be accessible directly from a preparation premise from the clean part of a gowning lock [2].

For the design of the routing and communication it might be useful to have well in advance the future staff ‘virtually’ preparing the products, based on concept drawings and let them document all of their detailed activities. Together they should properly review all process steps in detail to find out which provisions have to be taken.

27.5 Built-in Installations

Built-in installations that will be dealt with in this chapter are:
- Air conditioning installations
- Installations for storage and distribution of pharmaceutical water
- Provisions for pressurised air, vacuum and gasses

- Electrical installations (power supply, emergency power supply, signalling and ICT provisions.

In a community pharmacy (category I preparations; see Table 27.1) usually limited provisions will be sufficient, e.g. if water of suitable pharmaceutical quality is purchased in bottles. See also subsection 27.2.5.

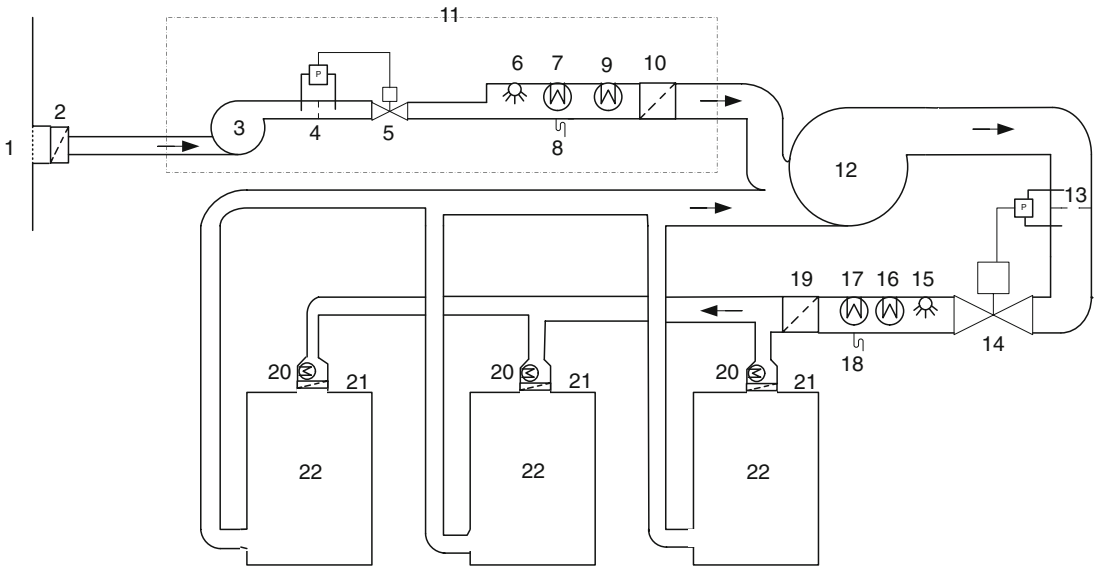
27.5.1 Installations for Heating, Ventilation and Air Conditioning (HVAC)

A HVAC installation is quite space consuming as air ducts usually must be voluminous to warrant the distribution of the required air volumes within acceptable noise nuisance limits. In existing constructional premises the layout of the air ducts often is not possible without any compromise. Ideally, but expensive, each room is to be equipped with its own separate air inlet and outlet. In practise overflow grids are used frequently to transport air from one room with relative high air pressure to an adjacent room or air lock with a lower air pressure. However, in that case no independent control of the air pressure or the ventilation factor is possible. So during the design it is necessary to consider any possible contamination of overflow air from an adjacent room and the limitations to control it.

In principle a HVAC installation consists of three components, i.e. the preliminary treatment installation (make-up casing), the recirculation- and control installation (recirculation casing) and the distribution network with fine tuning per room. See the example in Fig. 27.2.

27.5.1.1 Preliminary Treatment Installation

The make-up casing draws in fresh air through a bird grid and a rough dust filter. Subsequently the air is, according



Legenda Figure 27.2

1. Bird grid (air inlet)
2. Coarse dust filter
3. Inlet ventilator
4. Restriction with pressure difference measurement (Δp)
5. Regulating valve
6. Steam injector (moistening)
7. Heat exchanger for cooling and drying
8. Drain for condensate
9. Heat exchanger for heating
10. Dust filter
11. Pretreatment installation
12. Recirculation ventilator
13. Restriction with pressure difference measurement (Δp)
14. Regulating valve
15. Steam injector (moistening)
16. Heat exchanger for heating
17. Heat exchanger for cooling and drying
18. Drain for condensate
19. Dust filter
20. Heat exchanger for temperature adjustment in the premise
21. HEPA filter and inlet grid
22. Premise

Fig. 27.2 Schematic representation of a HVAC installation for clean rooms

to weather conditions, heated, cooled, moistened or dried. In the (almost) airtight classified clean rooms, with recycled air, atmospheric humidity can easily increase above limits by water vapour or exhaled human air. This will not level with environmental air conditions as quickly as usual in normal, non-airtight buildings. Drying of (inlet or recirculated) air is achieved by condensing over a cold heat exchanger placed in the air stream. Provisions for drying and moistening are critical installation parts because moist air can easily foster growth of accumulating moulds. A well-designed control plan should prevent this.

27.5.1.2 Recirculation- and Control Installation

To save energy, as well as to control air quality a substantial portion (usually 80 %) of air returning from the premises is reused by means of a recirculation ducting. The remaining 20 %, leaving the premises by leakage and by direct exhaust to the outside of the building has to be replenished by the make-up ducting. The recirculation ducting controls air quality by:

- Filtering the supply air through a central HEPA filter
- Adjusting temperature and humidity
- Adjusting airflow rates (volume of air per unit of time) to the distinct rooms

The air drying over cold heat exchangers makes independent control of humidity and temperature difficult. Apart from that the circulation of air through filters generates frictional heat. The prediction of the amount of heat and moisture generated from the production process therefore is both complex and important design information.

The HEPA filter makes the distributed air (almost) free from particles (see Table 27.4). Preferably the pressure fall over the filter is continuously monitored to signal leakages (pressure fall is too low) or blockage by pollution (pressure fall is too high and has usually gradually increased).

The volume of each room and the required ventilation factor determine the airflow rate that has to be achieved in the room. The ventilation factor or replacement factor is the number of times that the volume of a room is completely replaced with fresh air. In the ISO standard 14644-4 [4] advisory ventilation factors are given in relation to the air quality class in a classified premise. Occupational safety and health legislation will also add requirements to the ventilation factor.

Air Velocity, Ventilation Factor and Airflow Rate Control

Starting from ISO class 5 no ventilation factor is given as this class can only be achieved by a unidirectional or laminar airflow, having a velocity of about 0,4 m/s. Higher velocities soon give raise to turbulence of the air; lower velocities displace any particles too slowly. The airflow rate (volume per unit of time; D) can be derived from this air velocity s and the area A of the air inlet grid [5]: $D = s \times A$.

It has to be decided whether the total airflow rate to be distributed over the premises is controlled by a so-called fixed volume controller or by a variable volume controller. A fixed volume controller maintains a constant pressure fall over a fixed constriction in the main air transportation channel. The controller thus serves to maintain a steady air volume per unit of time independent of variations in input air pressure (wind!), pressure fall over filters and leakage through chinks and gaps. A variable volume controller delivers the air at a slightly variable flow rate as this controller directs the airflow at the basis of a specific air pressure in one or more reference rooms.

The consequence of a fixed volume controller is that small variations in the amount of air leaking through chinks and seams soon give raise to substantial differences in the air pressure hierarchy. In this case pressure steps between different rooms need a level of 15 Pa to cope with any unavoidable variations in leakage.

With a variable volume controller there is a direct feedback from the air pressure in each separate room. Small variations in air leakages will result in adjusting the air control valve in such a way that the air pressure differences are maintained. Usually a smaller pressure step between rooms, e.g. 10 Pa, will be sufficient to maintain the pressure difference and airflow. The ISO standard 14644-4 mentions pressure steps of 5 – 20 Pa. However it should be borne in mind that 1 Pa (1/100.000 bar) is a very small pressure difference, which is hard to control. In the design therefore a certain margin should be observed. GMP specifies a guidance value of 10–15 Pa between rooms.

Although at first glance a variable volume controller would be preferred it has a drawback that the recovery time of a clean room after the introduction of contaminating particles at validation will not easily show reproducible results.

An additional problem may be raised by the controller. The opening of a door for instance will create a zero pressure difference. If the controller reacts too fast overcompensation of the feedback loop takes place resulting in fierce auto-reinforcing fluctuations of air pressure [5].

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Apart from the fixed volume controller and the variable volume controller also hybrid controllers are available: a variable volume controller with a limited range of variation or a fixed volume controller with a variable controlled exhaust volume. Which type suits a specific clean room depends on the level of control of the flushing pattern of the air inside the room, the air pressure differences and the recovery time.

27.5.1.3 Distribution Net and Fine Tuning

For the design of preparation premises an air balance per room should be drafted regarding:

- The free volume of the room (room volume minus the volume of fixtures and fittings)
- The required overpressure relative to linked premises
- The required ventilation factor
- Any volume of direct exhaust (e.g. through safety cabinets)
- The heat burden (amount of heat generated by apparatus and humans)

Additionally the required air quality class (GMP, see Table 27.2 or ISO, see Table 27.3) must be documented and it should be documented that the pattern of air flushing through the room is effective at all functionally relevant spots. The actual air sweep will have to be validated after construction and must meet the specifications.

The ventilation factor and the room pressure determine the volume of air that has to be let in and thus the dimensions of the air duct, the number of inlet grids and the position of the metering valve of the involved supply channel or the area of the involved overflow grid. The heat burden and the admitted airflow rate furthermore determine the maximum inlet air temperature or the required capacity of any after-heating radiator.

The air quality class determines the type of HEPA filter (see Table 27.4) mounted in the inlet grid and the thereby raised air friction. All HEPA filters should be entered into a maintenance plan; at least once a year a leakage test and a filter integrity test should be performed [5].

In premises equipped with direct external exhaust it has to be determined in advance if the connection to the exhaust duct will be fixed or achieved by means of a so called draught diverter (Fig 27.3).

Examples of equipment with an external exhaust are e.g. fume cupboards and flue gas exhausts, fitted to an ampoule filling machine or to an atom absorption spectrophotometer. Also a safety cabinet or a non-recirculating dust suction cabinet (e.g. Wibojekt®) and negative pressure isolators have external exhausts. When the equipment has a fixed connection the exhaust ventilator must be switched on continuously and thus the equipment has a direct impact on the designed air balance within the room. The use of a draught diverter facilitates the possibility to switch off the cabinet itself as the extraction ventilator will then bypass it. The functioning of the extraction ventilator should be interlinked with the HVAC installation in such a way that if the latter fails or is switched off, the capacity of the extracting ventilator should be adjusted, or, in case of fire alarm, switched off. In addition any direct or indirect failure of the extracting ventilator must lead to an alarm condition as this impairs directly staff safety.

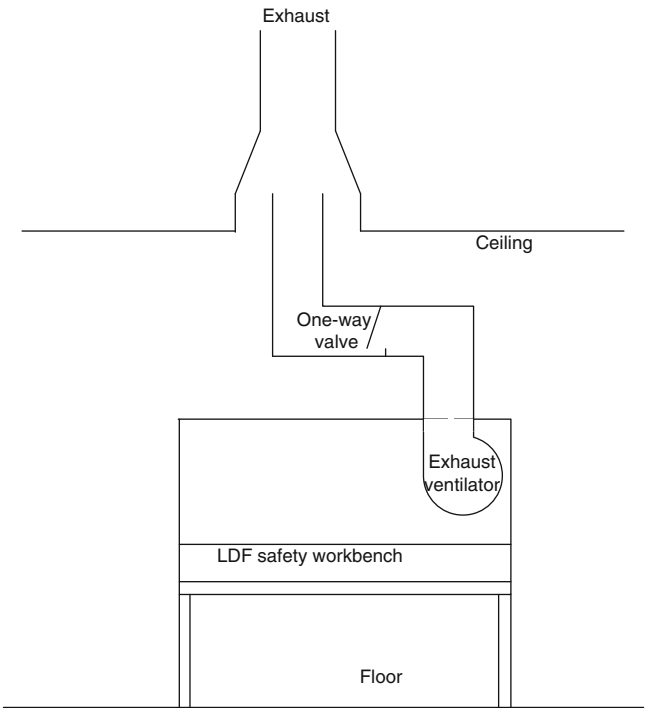

Fig. 27.3 Draught diverter

Principle Draught Diverter

When a so called draught diverter is implemented the exhaust channel is placed over the outlet of the equipment like an inverted funnel. At switched-off status, air will be sucked out from the room, bypassing the equipment. When switched-on the air leaves the room mainly through the equipment. Accounting for the volume of air that passes through the equipment is necessary in the calculation of the air balance. For the air pressure or ventilation factor in the room it doesn't matter whether the equipment is switched on or off.

In any case it should be warranted, whether the equipment is fitted with a draught diverter or with a

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fixed outlet connection, that never, e.g. in the case of breakdown of the external exhaust ventilator, outside air can enter the preparation premise. The opposite should be prevented as well: if a safety cabinet shuts down the exhaust should close at the same time, because otherwise environmental air could exchange with the air from within the premises, thus contaminating the HEPA filter. A well-designed draught inverter with a one-way valve provides all those functions.

27.5.2 Installations for Storage and Distribution of Pharmaceutical Water

In this subsection only built-in installations required for storage and distribution of pharmaceutical water are discussed. Apparatus for the production of pharmaceutical water are discussed in Sect. 28.4.

Water of pharmaceutical quality is used as a raw material, excipient, solvent, and as cleansing agent. In addition the pharmaceutical production facility needs water for (thermal) disinfection or sterilisation and for the preparation of pharmaceutical quality reagents [6].

Engineering of installations for the storage and distribution of pharmaceutical water can only be understood with knowledge of the specifications of pharmaceutical quality water. The most important characteristics and the categorisation of pharmaceutical water, according to the European Pharmacopoeia, is discussed in Sect. 23.3.1.

The leading principle in storage and distribution of pharmaceutical water in bulk is continuous circulation in a loop that includes at least the following:

- Apparatus for the measurement of temperature, conductivity and TOC (Total Organic Carbon; i.e. the total carbon load of organic, carbon containing substances)
- A storage vessel
- Filter(s) in the production part of the installation and for pressure levelling out with air from the outside of the system
- Apparatus for heating
- Apparatus for cooling
- Taps
- Apparatus for disinfection (only for cold water systems). See Fig 27.4

Distinct requirements that apply for different qualities of pharmaceutical water will be discussed below.

27.5.2.1 Purified Water in Bulk

The most commonly used systems for the production of purified water deliver water with temperatures around room temperature. Therefore adequate measures have to be

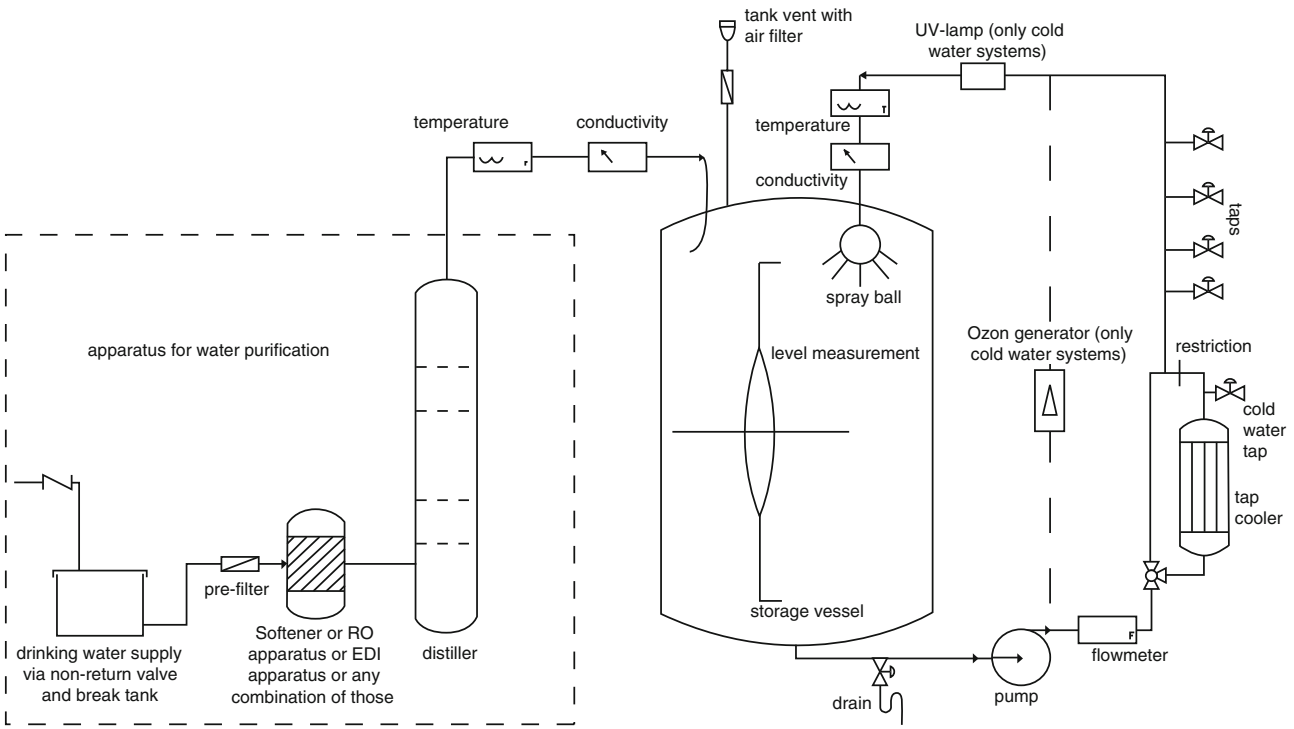

Fig. 27.4 Schematic diagram of water storage and distribution systems. Source Recepteerkunde 2009, ©KNMP

taken to manage and control total viable aerobic counts during preparation and storage (see Sect. 23.3.1).

The design capacity should be balanced with the predicted need per instance, e.g. for the most water consuming activity and the predicted need over time. Involved are considerations of production time per batch, investment costs and the time to re-fill the storage vessel. It should be taken into account that drawing off or flushing out the water will curtail the ongoing growth of micro-organisms.

During transport through the loop the water passes several valves in which biofilm formation may occur (see Sect. 19.3.5). This biofilm can easily extend beyond the valve as the system for purified water usually is not heated. Therefore the most critical place in the loop is the point beyond valves, i.e. where the water runs back into the storage vessel. That is the right spot for placing critical measurement apparatus in the loop, such as for temperature and conductivity.

27.5.2.2 Water for Injections in Bulk

The Ph. Eur. specifies that 'water for injections in bulk is obtained from water that complies with the regulations for water intended for human consumption or from purified water by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets.' So the quality of this water is essentially defined by the very specific way it is produced. The reason for this is that there is no reference water quality to compare.

During production and storage adequate measures should be taken to monitor and control the total viable count (see Sect. 19.6.3). This can be measured in freshly tapped water for injections in bulk (maximum 10 CFU/100 ml). Ph. Eur. actually gives this value as an action limit, but to control microbial contamination it is better used as a maximum value. During production by means of distillation, water for injections reaches a temperature between 94 and 99 °C. By maintaining high temperatures in the storage vessel and the loop any growth of micro-organisms is prevented. In this way the content of endotoxins (see Sects. 19.3.4 and 32.8) can be kept low (standard: less than 0,25 IU/ml), as well as the total viable count.

The water for injections limit for conductivity is lower than that for purified water. At 80 °C water for injections may have a conductivity of maximal 2,7 microSiemens/cm.

Usually only the storage vessel and not the loop is heated. So during the passage of the loop the water will cool down gradually. Additionally any inadvertent leakage of a valve (e.g. the one that provides a washing machine with water for injections) may impair the quality of the water in the system. These facts underline the choice of the most critical spot for all measurements being the place where the water runs back into the storage vessel.

27.5.2.3 Design Criteria for the Quality of Water

For the chemical specifications of pharmaceutical water see Sect. 23.3.1. A sufficient low conductivity, specified in the Ph. Eur., warrants that any metals, ions and inorganic contaminants will be practically absent. During the production, storage and distribution Water for Injections in bulk is tested continuously at conductivity, temperature and at TOC content. TOC can be measured either in-line, involving a metering sensor that is permanently mounted into the loop, or off-line, implying periodical measurement in tapped water samples [7]. Water samples should be tested off-line periodically on nitrates, aluminium (especially in water intended for dialysis applications), heavy metals and bacterial endotoxins. Purified water in bulk should be monitored at the same parameters. The (expensive) TOC assay might be partly replaced by periodical testing on oxidisable substances. Bacterial endotoxins in purified water should be monitored, especially when the water is used in haemodialysis. In purified water additional monitoring might be indicated, e.g. of ozone (during and after disinfection), the hardness of the feeding water and the luminosity of the UV source (decaying ozone).

> Suppliers of equipment usually use American terminology in their documentations, including the term "sanitisation" referring to disinfection methods that are known to be effective to sterilisation processes, however in which (formally defined) sterility as a final result will not be proven.

27.5.2.4 Measuring Conductivity

Measurement of conductivity during production, storage and distribution of (highly) purified water and water for injections is indispensable. One conductivity sensor usually will be mounted into the pipe that carries the hot, freshly distilled water from the distiller into the storage vessel. Usually this sensor is combined with a temperature sensor. Additionally a conductivity and temperature sensor must be mounted into the return flow of the loop. This is necessary to prove that the water that runs back into the vessel still has adequate quality.

> Ph. Eur. extensively describes the procedure for the measurement of conductivity, the calibration of the conductivity sensor and the calibration of the system. The measurement is complicated as there is no reference for low-level conductivity measurements. When the off-line conductivity turns out to be too high a

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second measurement is prescribed after previously stirring atmospheric carbon dioxide into the water. When this second measurement still reads too high a third step is prescribed adding a potassium chloride solution and measuring pH. Only then a conclusion can be drawn about the quality of the conductivity measurement.

27.5.2.5 Total Organic Carbon (TOC)

TOC is an indicator for any existent (decayed) organic material in the water, often originating from living or dead micro-organisms. A low TOC (less than 0.5 mg/ml) may be interpreted as a useful indicator that the water has a proper microbiological quality [7, 8]. This assay can be performed easily and immediately before use.

27.5.2.6 Microbiological Quality of Water

Operations, storage and transport methods all can influence the growth of micro-organisms.

In practice microbiological quality of water is monitored by action and alert levels. Thus the user will be early notified about any deviation of critical parameters. For instance an alert level might be put at a factor 10 below an action level. To determine these levels a good set of total viable aerobic counts, endotoxin assay results and TOC assay results should be available. For the collection of these results, particularly in the start-up phase very frequent measurements must be executed.

The development of a biofilm (see Sect. 19.3.5) in the water production system has to be prevented. The rougher the surface the easier a biofilm will develop. Nevertheless even onto polished metal, synthetic materials, glass and in streaming water it may develop, therefore the microbiological quality of the water has to be controlled frequently. In demineralised water the growth proceeds faster than in distilled water as a consequence of more available nutrients. As soon as a biofilm causes contamination the term biofouling is used. The best way to eliminate a once formed biofilm is mechanical cleaning, which is becoming more and more common in industry. However, when the surface is not accessible for mechanical cleaning, other cleaning methods must be applied, such as flushing with hot alkaline followed by hot acetic acid or flushing with concentrated sodium chloride solution followed by hot acid solution or hot alkaline. The microbiological safety of the installation thus not only depends on the application of heat but on the (im-)possibilities to dispose of any formed biofilm as well. Risky surfaces are demineralisation resin, tubes, transport pipes made of stainless steel or synthetic materials, the inner side of storage vessels, taps and membranes in valves.

27.5.2.7 Systems for the Storage of Pharmaceutical Water

At the design of the pharmaceutical water installation the capacity of the storage vessel should be determined based on the maximum daily consumption, the average consumption and the maximum peak consumption per product batch. The water consumption by sterilisers and washing / disinfection machines should also be taken into account.

The higher the peak water consumption, the larger the storage vessel. If the demand for water has a more steady character then the vessel can be smaller. In case of a large vessel the available floor area and its load capacity must be accounted for. Continuous production implies that one or more tanks are being filled and drained continuously. Quality control should take place in a continuous way, completed with intermittent additional tests. After maintenance and also periodically the system should be disinfected. The frequency of the disinfection depends on the results of the process validation [9, 10]. Further specifications of the system follow the required water quality. The required storage temperature also plays a role:

- Cold storage implies storage conditions between 4 °C and 10 °C at which micro-organisms grow very slowly. Cold storage renders the system effective and reliable. Disinfection occurs only occasionally and can be performed with hot water. Drawbacks are the expense of a cooling installation and its considerable energy consumption. Stainless steel, PVDF, polypropylene and polyethylene cross-linked (PEX) all are suitable as a material for the storage of purified water at low temperatures. The design of the vessel should be aimed at the lowest possible total viable aerobic count. This implies that all surfaces, pipe holes, valves, etc. should be accessible and made of very smooth material.
- Storage and distribution at ambient temperatures (15 °C - 30 °C) is reasonably effective and reliable and the investment and operation is comparatively cheap. However the risk of building up a biofilm is substantial. Therefore, non-cooled storage systems should be disinfected frequently by flushing with hot water or by adding ozone. Materials for loop and storage vessel are similar as for cold storage [9, 10] however the method of disinfecting can limit the choice. More aggressive methods such as treatment with steam are preferable, but require expensive materials such as stainless steel.
- Hot storage and distribution means storage and distribution at a temperature continuously kept over 70 °C [1]. In

practice an ample safety margin is implemented and usually the actual storage and distribution temperature is well above 85 °C. Hot storage is the most effective and reliable way to prevent growth of micro-organisms. With the aid of well mounted isolation material in the heating mantle a storage vessel can be kept at high temperature at low expense. The loop piping should also, preferably, be insulated. Taps should be placed at short distances from the loop. Before use the tap has to be flushed with hot water. Hot storage involves relative high investment costs and moderate running costs. It introduces a specific risk of rouging. Hot storage does not diminish the content of endotoxins. The distribution loop can be combined with taps equipped with sanitary coolers to deliver the pharmaceutical water at ambient temperature.

Rouging

At sustained exposure to very pure hot water or steam a thin red, reddish brown, orange, light blue or black deposit (tarnish) might built up. This is seen particularly at less polished spots, e.g. burrs, scratches, sharp edges, material transition areas or bad welds and is called rouging. In fact rouging is an oxidation process. When metal ions in micro-caves dissolve into the water potential differences might occur at a microscopic scale leading to hydrolysis and oxidation. The coloured material consists of iron oxide, iron carbonate or iron hydroxide or any combination of these. Rouging itself doesn't yield any immediate hazard. However once rouging has been built up it might expand and eventually lead to development of rust in which case the smoothness of the texture is affected and the risk of biofilm formation increases. Therefore, highly polished stainless steel constitutes a barrier both against rouging and biofilm formation. Removal of rouging is a very expensive process involving experts [10, 11].

Tap for Cooled Water

A tap cooler mounted into a hot distribution loop requires a special design. The loop and the storage vessel must be kept at high temperature while no long branches filled with stationary (colder) water can be accepted. Therefore the loop splits near the cold tap into two parallel pipes both continuously being flushed with the hot pharmaceutical water. In one of the two branches a heat exchanger is mounted. Only during tapping the heat exchanger is temporarily flushed with cold water, locally chilling the pharmaceutical water. Only a very limited amount of the chilled pharmaceutical water will return to the loop by means of mounting a so-called restriction disc just before the junction. So chilled product water will hardly mix with the main stream in the loop. When no chilled water is tapped sufficient water will pass the heat exchanger, the tap valve and the restriction disc to maintain this part of the loop at the required temperature.

The water level in the storage vessel has to be controlled continuously, preferably with the aid of a building control system (see Sect. 27.5.5). Thus a low level signals to restart the production, however a very low level should produce an alarm signal shutting down the complete installation to prevent, among other things, the circulation pump running dry. A high level will stop the production and an extra high level should give an alarm signal to alert the risk of overflow through the vent filter.

The storage vessel and the loop for water for injections is preferably made of stainless steel AISI 316 L and polished to a roughness grade of 0.4-0.6 μm mean pore diameter [9, 10]. The water should return from the loop into the vessel through a (rotating) spray ball. By this means the empty upper part of the vessel will be kept hot and germ free. The vessel or at least the lowest point in the loop should be equipped with a sanitary bottom valve ensuring that after complete draining (e.g. for maintenance purpose) no tainting water will stay behind in the system [10].

Tank Vent

A level control system can only be used if the system has been designed according to GMP. Tapping of water from the storage vessel will lower the level in the tank. The sucked-in air entering the vessel has to be filtered through a 0.2 μm hydrophobic membrane filter that can be tested and which should be mounted in a stainless steel casing onto the vessel. A pressure safety provision is mounted to safeguard against any possible overpressure in the vessel. The filter has to be replaced at least once yearly as a preventive measure. During the hot storage of pharmaceutical water the filter also has to be kept at a high temperature to prevent the occurrence of condensate. This condensate would provide an ideal substrate for micro-organisms which might grow through the filter.

27.5.2.8 Maintenance and Disinfecting Water Storage and Distribution Systems

Biofilm will emerge especially fast on ion exchange resins, Reversed Osmosis (RO) -membranes and piping made of stainless steel or plastics. Therefore, systems for pharmaceutical water should not contain stationary water and should be disinfected at start-up and after each maintenance process. Even systems for the preliminary treatment of feed water have to be constructed as a recirculating system [10].

Cold water systems usually cannot be steamed. Instead chemical disinfection or disinfection using ozone is customary. An important benefit of ozone treatment compared to other chemical methods is that it can be executed automatically.

Frequent hot water disinfection is a good alternative as a preventive measure, provided that all materials are sufficient heat-resistant. It is carried out at a temperature of 90–95 °C during at least 2 h of exposure. This process must be validated [10]. The problems to remove a once formed biofilm is discussed above in Sect. 27.5.2.6.

RO membranes may not be exposed to ozone. The producer of the membrane should indicate how to treat and disinfect it in a correct way.

27.5.2.9 Chemical Disinfection

If the equipment is provided with adequate connection systems a chemical disinfection is possible. Commonly a solution of hydrogen peroxide and per-acetic acid is diluted to 8-10 % and then flushed through the equipment. The system must be thoroughly rinsed afterwards.. The method is quite effective, however it involves the additional efforts of purchasing, storage and handling of the disinfecting agent.

27.5.2.10 Ozonisation

Ozonisation is a specific means of chemical disinfection as the active agent (ozone) is generated in the equipment itself. Ozone is used for the periodical disinfection of pharmaceutical water installations when disinfection by steaming or with hot water is not possible. Ozone is a strong oxidising agent and kills micro-organisms in water. To obtain sufficient disinfecting power ozone should be present in the water for a sufficient time and in an adequate concentration, according to the guidance of the producer of the ozonisation apparatus. Concentrations with a maximum of 10-50 ppm (sometimes even less) are most common. The ozone generator that is mounted in the loop produces the ozone gas. However after ozonisation the utilised pharmaceutical water must be freed of ozone again. Therefore, UV lamps are included in the loop at a spot that is transparent to UV light. UV light of 254 nm degrades ozone turning it into oxygen. Thus quality control of the lamp is necessary; it usually consists of continuously monitoring the intensity of the UV light. An alarm signal should indicate when the lamp has to be replaced [9, 10].

27.5.2.11 UV-light for Germ Reduction

UV-light with a wavelength of 200–300 nm not only degrades ozone but also reduces the total viable aerobic count in pharmaceutical water, especially in systems with cold storage and distribution. UV-light disrupts the DNA of micro-organisms and thus obstructs their growth. Irradiation with UV-light is not intended to replace any disinfection method. The effectiveness of the irradiation process depends on water quality, light intensity, flow rate of the water, duration of the irradiation and the identity of the micro-organisms in the water and thus is difficult to validate [9, 11].

27.5.2.12 Clean Steam

Only the USP includes a monograph for pure steam [12], also called clean steam. Clean steam is obtained from purified water heated over 100 °C and brought into the vaporised phase in such a way that no drops of feeding water are carried over. In any situation where steam or steam condensate might stay in immediate contact with critical, product affecting surfaces, clean steam must be utilised. An example is the interior surface of a filling apparatus. Technical steam is steam generated at some central location in the building. The quality is defined with pressure and temperature. Clean steam may be utilised during preparation, in steam sterilisation and during controlled steaming of installation as a sterilisation method after cleaning [13].

Quality control of clean steam is carried out on its condensate. Additional requirements are in force when the steam is utilised for sterilisation (see Sect. 30.5.1).

27.5.2.13 Transport Systems for Pharmaceutical Water

A system for transport or distribution of pharmaceutical water should meet at least four requirements:

- It should deliver water that meets all quality requirements (see Sect. 23.3.1).
- The water should always flow at the required flow rate, especially at the instance of drawing off.
- The water should be delivered at the temperature required for the process at hand.
- The system should function at acceptable investment and running costs.

27.5.2.14 Piping

By means of a sanitary pump and a flow rate meter showing the flow rate, the water circulates in a loop through a sanitary (hygienic, well-disinfectable) piping system. Unused water

runs back into the storage vessel. Micro-organisms, corrosion, (hidden) construction flaws and aging can all affect the loop system. The loop should not contain any branches in which water is stationary. For this purpose specific calculation schemes exist. Generally the length of any branch in the loop never should exceed 6×D (diameter of the loop pipe) but in practice 3×D or even 2×D is to be preferred. Also purified water as feeding water for a distiller installation should recirculate when nothing is drawn off.

The support and mounting of the piping should be constructed in such a way that no sagging occurs, a risk that is more prominent with synthetic materials at higher temperatures than with stainless steel. Preferably the piping is mounted at a slight slope with the bottom valve at its lowest point. The usual angle of the slope of horizontal piping at short distances is advised at 2 % and at 0,5-1 % for greater lengths.

Joints must never be mounted at a residual strain because that could cause leakages, which can lead to considerable damage. The support system for the piping must not cause any galvanic corrosion. The distribution system must be immune to ozone or the heat of steam. It has to resist a specified water pressure and turbulence as well. The interior of the piping should have a surface as smooth as possible to prevent corrosion and formation of a biofilm. Stainless steel piping must be polished at the inside for this reason. Piping of synthetic materials used for the distribution of pharmaceutical water are smooth plastics like PVDF, polypropylene or PEX. The piping may not release any substances or (metal) ions and should be corrosion resistant [9, 10].

Welding, Mordanting and Passivation

Stainless steel contains chrome that generates a tarnish of chrome dioxide, which protects against rust. However over time some form of corrosion will develop; totally non-rusting steel does not exist.

The installer should weld the piping work orbitally. Orbital welding is the partly automated method of welding highly alloyed steel pipes together using a tungsten electrode under inertial gas, also indicated as TIG-welding (tungsten inert gas). By this method a very smooth weld develops. Subsequently the installation must be cleaned, mordanted, passivised and finally be flushed and steamed. Cleaning after welding is done by flushing with caustic detergents and water. Mordanting implies that the corrosion resistant tarnish is removed temporarily using strong acids (chromic acid or strong nitric acid). Immediately thereafter the reactive metal alloy is passivised by oxidising in the air. Passivation is also executed by flushing with oxygen-rich water, diluted nitric acid or oxalic acid. When all residues of acid are flushed away with water for injections the installation can be steamed and put into operation.

The welds in a stainless steel loop never should corrode, leak or become a source of rouging or biofilm. Welding work therefore should be inspected closely and be thoroughly documented. Specialised instruments are being used for this purpose. The welder must be qualified. All handmade welds should be fully controlled; in orbital welded pipework usually 20–30 % of the welds are tested.

Other, also demountable, fittings between pipes and installations are of the type clamp, flange or screw fitting.

For transport of water for haemodialysis and purified water, plastics may be used for the tubing. However for these materials it is also required that connections are meticulously welded, inspected, documented and cleaned. The use of glues (e.g. the glue to join classical grey plastic, PVC, tubes for non-pharmaceutical use) introduces an unacceptable uncertainty because residues of the glue and solvents may contaminate the water. Analysis of this kind of contaminants preceding the formal acceptance of the system is not a realistic option [9, 10].

For pharmaceutical water guidelines of, among others, FDA and DIN 11864 apply for these kind of fittings. Anyhow, the number of fittings should be kept as low as possible.

27.5.2.15 Pump

A circulation pump should have a highly polished finish and should be well cleanable. It must resist any disinfecting process, preferably steaming. Also the pump must allow complete drainage. The latter implies that no water residue must stay behind when the complete loop is drained during maintenance.

The pump should be able to generate a flow rate of 1–2,5 m per second in the loop, still achieving an acceptable water pressure. The pressure depends also on the loop resistance. Usually a restriction disk mounted in the loop serves to prevent a major pressure drop when water is withdrawn by opening a tap. The flow rate causes the flow to be turbulent and thus prevents the risk at (almost) stationary water e.g. near valves and other small bulges in the loop. After all, any stationary water would substantially increase the risk of building up biofilm [9, 10].

27.5.2.16 Tapping Points

Membrane valves must be completely drainable and disinfectable, preferably by steam. The membrane made of plastic should be replaced 1–2 x per year. Sometimes globe valves are used to shut off steam pipes, because they are more wear-resistant.

A sufficient number of sample tapping points should be available. The tapping of water during any dysfunction (e.g. deviation of temperature, deviation of conductivity or low level) of the water installation must be prevented. This can be done by automatically blocking all tapping points at the basis of any alarm signal originating from the installation [9, 10].

27.5.2.17 Responsibility for the Validation and Qualification of Water Systems

The validation of this equipment has to account for its built-in status. Therefore the validation plan already has to be part of the design and realisation phase of the installation.

The person responsible for the water quality to be used in pharmaceutical preparations usually is the pharmacist who is also responsible for the preparation processes. This person is accountable for all procurement, validations, qualifications, maintenance, deviations and changes of the installation(s). He should always be fully informed about all those aspects. This also applies when the water preparation installation is installed outside of the premises of the pharmacy e.g. in the premises of the technical services or any laboratory [11].

27.5.3 Provisions for Pressurised Air, Vacuum and Various Gasses

27.5.3.1 Gasses and Pressurised Air

Medical gasses (including medical air) are gasses that as such are used in the treatment of patients. Medical gasses administered to patients are medicines [13], see also Sect. 23.13.

Gasses used in production processes are called pharmaceutical gasses. They are applied as:

- Gasses that are immediately immersed into the intermediate medicinal product, e.g. nitrogen as a means to dispel oxygen from aqueous solutions or pressurised air to carry over fluids.
- Gasses that are necessary at the preparation or filling process, but are not directly in contact with the product, e.g. natural gas and oxygen for opening and sealing of ampoules.
- Gasses used for pharmaceutical analyses, such as acetylene for atomic absorption spectrophotometry and helium for gas chromatography.
- Gasses (usually pressurised air) for technical purposes such as pneumatic operation of installations.

Requirements depend on the use and therefore may differ from those to medical gasses. Gasses that are in direct contact with the (end-) product should meet the requirements derived from the product itself.

> The requirements for medical gasses may differ from those for pharmaceutical gasses. As an example, requirements to safeguard continuous availability carry more weight with the clinical process of artificial respiration than with a pharmaceutical application. But the chemical purity of e.g. nitrogen used for filling ampoules will be more important in pharmaceutical than in medical applications. Purity has to be backed by traceability of the origin. Certain suppliers therefore provide cylinders with designations such as 'trace pharma'.

The requirements for gasses can be:

- Technical (capacity, pressure, availability)
- Chemical (content assay, contaminants, moist content)
- Physical (absence of particles and oil)
- Microbiological

A low moisture content (dew point) in a gas under pressure is most important because at expansion moist could lead to condensation, which would enable micro-organisms to grow [9, 13].

27.5.3.2 Vacuum

A vacuum installation may have impact at the final product, e.g. when vacuum is used to prevent air being beaten into a viscous mass or to remove air from it. A choice has to be made between a central installation and a local one such as a water jet pump or an electrical vacuum pump. At a centrally placed installation a provision has to prevent the pressure inside the tubes rising above a predefined value. Otherwise contaminated air could enter a negative pressure room if the pump were to break down.

27.5.4 Electrical and ICT Provisions

At the design of preparation premises the availability of electrical and ICT provisions should be well considered in advance. Sufficient data and electrical sockets should be provided in walls and at worktops.

Keyboards and mouses should easily be cleaned and disinfected and therefore must be chemically resistant. The casings of the computers should be installed in such a way that accumulation of dust is diminished, for the protection of the computer as well as the pharmaceutical product. The air in classified rooms will hardly carry any dust, but

nevertheless the casing should be opened at least once a year to remove any dust. The casing should also being placed as far from the critical places as possible, if possible outside of the room. Wireless tablets may circumvent all difficulties with cables and fans. Cleaning and disinfecting of worktops is much easier when cables are tucked in cable ducts or under the worktop.

For each apparatus or installation it should be considered whether it has to be provided with emergency power supply or preferential power supply. Therefore, the risks of any short or longer lasting power cut should be analysed in advance. Especially the consequences of any disturbance of air pressures and the breakdown of exhaust installations must be considered.

27.5.5 Building Control Systems

Apart from the pharmaceutical installations, already mentioned in this chapter, buildings are generally equipped with heating and cooling equipment, fire prevention equipment, burglar security systems, personal access control, sun blinds, elevators, sewage pumps, etc.

So altogether the building incorporates a vast multitude of technical systems, several of them influencing each other. This might raise a need for an overall monitoring and control system.

Usually control and monitoring are integrated in one system providing a central point from which the functioning of all systems can be monitored, registered and adjusted. Furthermore, failure alarm signals are channelled through the building monitoring system.

When pharmaceutically critical systems (refrigerators, HVAC systems, purified water systems, etc.) are to be monitored by a building monitor system it has to be independent from more general systems in the building and its validity has to be assessed in advance. Additionally systems for the registration of measurements must be independent of systems that operate the installations and all installations (i.e. their sensors, adjustment tuners and alarm signals) must be fit to be connected to the building control system.

All possible alarm signals have to be listed and documented regarding alert- and action levels, hysteresis (to prevent them from switching on and off continuously at a non-stable parameter) and timeliness (providing short-termed deviations without unnecessary alarms or providing a reaction time before exciting the alarm). A scheme of procedures has to be defined to be followed after any alarm is triggered. The follow-up instruction after any alarm should include an indication about its urgency, e.g. if immediate action is obligatory when the alarm occurs in the night or in the weekend. No alarm signal should be overruled, covered up or left invisible in case of concurrent triggering of independent alarms. Also rules have to be implemented regarding the procedure for the resetting of any alarm and for the documentation of its actual follow-up.

27.6 Detail Specification and Building

The documenting of the functional specification (FRS) of a preparation facility is followed by the detail specification (DS) or tendering specifications. A subtle difference between DS and tendering specifications is that the latter will be drafted for the purpose of contracting-out. However the DS is primarily aimed at verifiability during the IQ phase. Usually just one document will serve both functions. In this document choices are made (usually a professional advisor does the job) for floor and wall covering, ceiling materials, etc. The HVAC installation will now be specified in full detail, communication means are specified and detailed building and arrangement maps are drafted and updated.

The choices must comply with the FRS, which in turn must comply with the URS. Therefore each choice should be well documented and justified at this basis.

What should be attended to in the assessment of the DS? In premises intended for sterile and aseptic preparations (clean rooms) the most severe requirements apply to the walls, doors, floors, ceilings, heating and furniture, see further subsections. Premises which are only intended for non-sterile preparations can do with less far-reaching demands. Nevertheless in practice it might be wise to apply the requirements for sterile premises also for non-sterile premises if both are at stake. In the first place in a new building the itemisation of methods and materials between premises meant for sterile preparation and for non-sterile preparation usually doesn't yield much cost reduction. Additionally many of the starting points for the requirements for sterile preparations more or less apply to 'non-sterile'.

27.6.1 Inner and Outer Walls

Where premises for preparation are adjacent to any outer wall a specific problem emerges. Constructional walls, also outer walls, never will be completely airtight. In case of wind pressure always air from outside will influx, bringing pollen (in spring), mould spores (in autumn) and fine particulate dust (in winter). This can only be prevented by building a double wall system, i.e. by complete separation of the preparation premises from all outer walls (so-called box-in-box principle) which is usually accomplished by building a gallery corridor. If this is no option, then at least a separate secondary glazing is necessary in the windows of outer walls to level out any wind pressure. Such a secondary glazing

At places where damage could occur the wall should be made of impact-proof and scratch-proof material, e.g. melamine resin sheet material like Trespa®. At other places, e.g. above breast height, cheaper gypsum board walls can be used, provided that they are treated with a specific water-resistant coating that can also resist the chemicals used for cleaning and disinfecting.

Seams, e.g. at places where fixed cupboards are placed against the wall, should be closed with a well-chosen acid-resistant joint sealant. Any seam should have a width between 2 and 4 mm to safeguard that the sealant will stick firmly into the joint. Wall connectors for electricity and ICT provisions must not give entry for contaminated air or vermin. Therefore the interior supply pipes should be made airtight with sealant. In practice usually a hollow wall modular construction is used for clean room building ('Metal Stud', see Figure 27.5) with all pipework and tubes sealed within the wall.

All pipework and tubes (electricity, water, gasses, air ducts, etc.) should be documented by photographs before the wall is finally closed during construction. Those pictures can demonstrate later that the finished construction indeed does correspond with the as-built drawings. As-built drawings are the drawings that exactly represent the finally built constructive reality. At places where the wall should be loaded with objects to be mounted, the constructor should apply back styles. These are fortifications introduced in the wall, usually as a metal corner bracket or metal u-moulding, which must be protected against rust. This again requires early planning of the right layout of any suspended cupboards, worktops, etc.

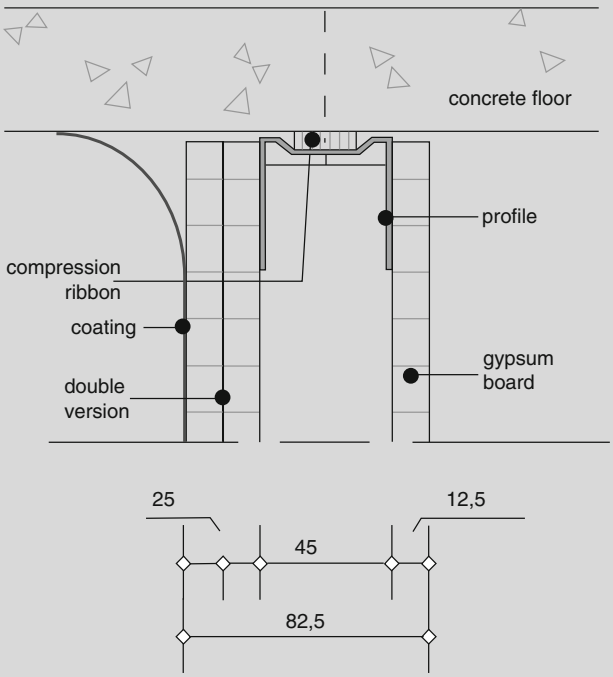

Fig 27.5 Metal Stud wall. Source: Recepteerkunde 2009, ©KNMP

introduces a wasted space between the inner glazing and the outer one, in which at some time vermin will emerge. Cleaning might be facilitated by having the outer glazing accessible from the outside.

27.6.1.1 Inner Walls

A requirement for premises for sterile preparations (clean rooms) is that walls are free from any ledges and seams to enable effective cleaning and disinfection. The provision of ample glazing for supervision and well-being of personnel should be considered. The ledge free and seamless mounting of windows and doors into walls is known as 'flush fitting'.

In order to adequately flush the room with clean air the exhaust should not be positioned near the inlet grids in the ceiling. Special inlet grids (diffusers) should generate turbulent airflow. In air class B exhaust at floor level is mostly preferred. A hollow wall construction offers the possibility of incorporating air ducts (exhaust channels) within the wall. These may make, however, other provisions on that particular part of the wall impossible.

Light switches, as being touched by many persons, can be best placed outside of the room e.g. at the entrance to personnel gowning locks. In that way an important source of cross contamination is ruled out.

If carrying in or out large apparatus must be possible, a demountable, resealable, partition in the wall should be considered.

27.6.2 Doors

Doors in clean rooms must be flush mounted, smooth, cleanable, if necessary disinfectable and as far as possible seamless. This especially goes for doors in GMP classified premises as indicated in Sect. 27.4.2. Points of special interest are:

- Air leakage through chinks between doorframe or threshold and a shut door will render the air pressure within the room out of control and it may raise an annoying wheezing noise. Therefore, doors should close firmly and not warp.

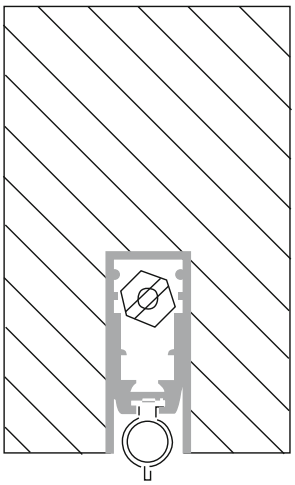

Fig. 27.6 Dropseal. Source Recepteerkunde 2009, ©KNMP

- Air leakage by the bottom of the shut door may be prevented by implementing dropseals mounted within the bottom part of the door (see Fig. 27.6). A pawl at the hinge side actuates a lever mechanism at shutting the door. This mechanism pushes a rubber strip against the floor. At the opening of the door a spring mechanism pulls the strip back up again into its casing.
- Doors should never shut against the air pressure, as the higher air pressure behind the door may raise leakages. If the preferred turning direction is not feasible, e.g. in case of an emergency route from a positive pressure room, the door should seal on all sides, including top and bottom, into a soft rubber groove. In some cases the preferred turning direction of a door based on function is opposite to the preferred turning direction based on air pressure hierarchy. A sliding door may solve that problem, provided that it is equipped with an effective push mechanism when shut and is well cleanable.

27.6.3 Floors

Floors must be easily cleaned and disinfected. Drains should be avoided, as these are important sources of contamination. If a drain is unavoidable because the equipment demands it, it should be equipped with a sanitary valve, preferably a type that closes automatically when the connected equipment is shut down. Such a drain requires a well-documented disinfection procedure.

Floors should be practically seamless because seams can easily become filthy. However each type of floor covering will come with seams and dilatation joints are necessary to allow for any shrinkage or dilatation, also in clean rooms. At least any seams and dilatation joints must be avoided near the most critical places.

Floor Covering Materials

The choice for floor covering materials depends on the kind of activities. As an example, in a preparation room where iodine or organic solvents will be processed, the floor should be chemically resistant in the first place. When processing inflammable products the generation of sparks due to static electricity has to be prevented. For aseptic handling chemical resistance of course is much less important. The primary emphasis for a floor in a premise for handling radiopharmaceuticals or other very hazardous substances, is on suitability for thorough and effective decontamination and disinfection.

A synthetic floor covering, e.g. like marmoleum or a good quality of vinyl, laid in strips or tiles and sealed with synthetic laces is a quite frequently used material. As an alternative a floor made of epoxy resin (a so-called cast floor) can be considered, with its advantages of high load bearing capacity, smooth surface and absence of seams. A drawback is its slipperiness, especially if wet there is a risk of skidding. Additionally it is very critical to have the cast floor applied completely free of dust or dirt.

The floor covering material preferably should butt to the walls by means of a hollow skirting. Fitted furniture that is not mounted hovering over the floor should be placed upon pre-mounted dado's, after which the floor covering can be installed with a hollow skirting against the dado.

27.6.4 Ceilings

Ceilings are preferably completely closed, i.e. manufactured from fixed mounted, smooth and cleanable sheets. Pipework should be tucked away behind the ceiling, because otherwise dust builds up. If possible pipes or tubes transporting water should be avoided at the top of any preparation premise because leakage would have disastrous consequences. This is in regard not only to pipes transporting pharmaceutical water but also to the sewer system, rainwater drains, condensate drains and steam pipes. The possibility of the occurrence of condensate on cold water pipes during warm weather should also be considered. If the pipes cannot be avoided, any leaking water should drain off by a gutter. Regular maintenance of the pipework and timely replacement of gaskets will be necessary as well.

System Ceilings or Closed Ceilings
A lowered, so-called system ceiling can be used, however it has several snags: the joining to the walls usually results in a right angled corner that is difficult to clean. Additionally the system sheets, lying rather loosely within the frame, can easily snap open, especially when air pressure jolts occur at the opening or closure of doors. If that occurs unpredictable amounts of dust and dirt will enter the room. Even special clips to fix the ceiling tiles cannot prevent this completely, as after maintenance work those clips are frequently not replaced. Sealed ceilings are free of those drawbacks and they force the designer of the building to create an alternative entry to the space above the ceiling. This entry will not come from the preparation room, but by means of an admission hatch e.g. from a neighbouring gallery corridor or by means of a trapdoor from an upper storey. The benefit of this is that maintenance or repair work, e.g. at pipework or the replacement of lamps, situated behind the ceiling, can be executed without entering the premise itself. If completely sealed ceilings are not feasible in all rooms entrance to the space above the ceiling from gowning rooms or connection corridors are preferred; the ceiling should never be entered from the preparation room itself.

Light fittings do easily attract dust as a consequence of their static electricity. Therefore they should be incorporated in the ceiling and be shut off by means of a glazed or transparent synthetic sheet. In classified premises no substantial air leakage must occur past the fitting.

27.6.5 Heating

The cleaning of heating radiators is very laborious and not very feasible in practice. Therefore, they are unsuitable for pharmaceutical preparation premises. If they nevertheless cannot be avoided, sheet radiators mounted at sufficient distance from the wall to allow effective cleaning, are to be preferred. However, in GMP classified premises as meant in Sect. 27.4.2 even sheet radiators are absolutely undesirable. Heating and cooling in that case should be achieved by means of the ventilation system (see Sect. 27.5.1).

In using air for heating, attention should be paid to the type of inlet grid. In a well-designed preparation premise a high ventilation factor will prevail. If not a specific whirl grid is mounted draught will occur. This is not only annoying for those working within the premise, it also may lead to inadvertent displacement of weighed portions of active substances. The flow pattern in a safety cabinet can easily be disturbed by an incorrectly placed or ill-chosen air inlet grid in the ceiling [5].

27.6.6 Furniture

The upper side of cupboards should join to the ceiling, or alternatively a slant finishing should connect the upper side to the ceiling. Personnel should not be able to place objects on top of a cupboard. As far as cupboards are made from wood, plywood or chipboard these parts should be laminated on all sides, e.g. also at the backside of shelves. Holes to adjust shelves in height should be filled up. 'Open' wood or chipboard may release spores. Workbenches should preferably hover or be attached to the wall. Floors under worktops must be well accessible for cleaning. Fixed furniture preferably should be placed upon pre-mounted dado's.

Refrigerators and freezers within the preparation premise are unwanted for several reasons such as that the expansion radiator at their backside cannot be cleaned. If a refrigerator or freezer in the preparation premise is indispensable it should be airtight separated from the room, e.g. by means of a flat shaft of sheets up to the ceiling or a throughput through the wall.

Chairs should not possess seats made of wood or covered with textile. The undercarriage should be easily cleanable.

27.7 The Implementation Phase of Building or Rebuilding

During the execution phase of newly built or rebuilt pharmaceutical premises (including clean rooms) the building control department should take a few particularities into account. The ISO 14644-4 standard [4] specifies those particularities for clean rooms.

- Verification of matters that cannot be demonstrated after implementation. Design drawings should be continuously updated such as to be finally correct 'as-built' drawings. Pictures of the inner part of hollow walls can support the verification process. The sealing of any pipe holes or cutaways must be checked systematically.
- Special attention should be paid to prevent the fouling of air channels during their mounting. Air channel components must be supplied clean and closed on both ends. Partly mounted air ducts again must be shut at the open end to keep them clean inside. The building area should be swept clean daily.
- Eating, drinking and smoking in the building area has to be forbidden and this ban should be enforced strictly to prevent that any organic material (like bread or tobacco

crumbs) are left in hollow walls, under or behind cupboards or in air channels.

As a consequence of its high costs the execution phase of a building usually is very tight. Especially in the end phase this can result in working against the clock. A common completion process assumes the premises to be put into operation immediately after completion, accepting the documentation of a few residual points that will be settled later, in practice already during operation. For clean rooms this is not possible. The starting-up procedure involves many steps that must be planned well in advance and are described in a Validation Plan. This plan encompasses general examination, qualification and validation. During examination the as-built premises are checked against the detail specification (DS). In addition some of the specifications will be checked that are described in the FRS and even the URS e.g. the smoothness of the walls. The control of all these specifications is also called as-built verification. If all specifications are met the premises and built-in equipment is qualified. Next all systems such as HVAC are put in use and checked for their proper operation and safety. The air balance is adjusted. Calibration of e.g. pressure difference meters is performed. This phase is also called commissioning and is usually executed by the contractor.

All deficiencies found during commissioning have to be solved. The premises and installations are cleaned and subsequently the validation can start based on procedures approved by the owner, usually the pharmacist. Validation has several standard structures with the main subjects: IQ, OQ and PQ (Sect. 34.10). Validation is a formal GMP requirement.

In case of a (new) building with installations the IQ and OQ phase comprises a verification of the checks done during the as-built verification and the commissioning including the check of all GMP critical aspects. It is not necessary to repeat all tests of the commissioning. Some additional tests are done such as challenging critical limits of documented functional specifications in practice and adjusting them if necessary, provided that they still comply with the FRS. Also the documentation is completed such as manuals, cleaning, disinfecting and maintenance procedures, instructions, a monitoring program. Microbiological (contact) samples (see Sect. 31.6) are taken, recovery time of the rooms after disturbance is checked, viable and non-viable particles are counted, temperature- and humidity are measured, etc.

The IQ and OQ are usually executed by the contractor in cooperation with the customer. When this phase is completed, the work is delivered up to the customer and accepted. Then the performance qualification (PQ) is executed by the customer. In this phase it will be proven that the premises will work as they were meant to be working as defined in the URS. Installations will function and classifications of the rooms are met (see Sect. 34.15).

The validation requires time and manpower. For a small scale preparation facility a time frame of 3 to 6 month is not uncommon. It is quite obvious that the start-up process to operational status of preparation premises will never allow time for any delayed activity for a constructive residual point such as the mounting of another light fitting afterwards. Planning in advance is paramount.

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Equipment

28

Marco Prins and Willem Boeke

Contents

Abstract

This chapter is about the design, quality and application of equipment for the preparation of medicines in a pharmacy or for preparation in small scale pharmaceutical industry. The type of pharmaceutical equipment needed depends on the type of products to be produced, on the required productive capacity and the batch size. A list of essential and critical equipment for production and quality control must be included as attachment in the URS (User Requirements Specification) of any facility. In this chapter only equipment commonly used for preparation in pharmacies and small scale industry is discussed. The equipment, requirements, qualification methods, main applications, maintenance and cleaning procedures are described for:

- Powder exhaust units, Laminar airflow units, Safety cabinets and Isolators
- Pharmaceutical water production
- Heating and Ultrasonic water baths

Based upon the chapter Apparatuur by Willem Boeke, Marco Prins and Jeannine van Asperen in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_28,

- Grinding, mixing and dispersing
- Filling, dosing and closing for liquids, suppositories, capsules and tubes
- Fridges and freezers

Keywords
Equipment • Maintenance • Exhaust equipment • LAF • Water production • Mixers • Filling equipment • Fridges • URS • FRS • FAT • SAT

28.1 Orientation

What type of equipment is needed in the pharmacy or preparation facility depends on the type of products to be prepared or manufactured, the required production capacity and the batch size. The choice of apparatus discussed in this chapter is arbitrary. Larger apparatus and installations such as large stainless steel autoclavable mixing tanks are intentionally not discussed, neither are infusion fluid production lines, filling lines for injection vials, syringes and ampoule machines. Larger machines usually consist of many components assembled on client specifications, resulting in many variations.

In this chapter we discuss the main applications of equipment that is commonly used in pharmacies and small scale industry as well as the maintenance and cleaning procedures or installation. Small equipment and materials such as volumetric glassware and weighing equipment are described in Chap. 29. Sterilisation and sterile filtration equipment is discussed in Chap. 30.

The publications of ISPE (see Sect. 39.5.6) are recommended for more detailed technical information on equipment, for instance Water and Steam systems, Cold chain management.

Some ISO (see Sect. 35.7.2) standards are appropriate as well, such as EN 14175 Fume cupboards. PIC/S (see Sect. 35.5.5) documents may be helpful such as on Isolators used for aseptic processing and sterility testing (PI 014-3).

28.2 General Requirements and Qualification of Equipment

Pharmaceutical equipment should be appropriately qualified and fit for use. That means that the device or equipment is:

- Safe for the user, but also for the environment (check, for example, the required CE marking)
- Easy to use in daily operational practice for its intended use
- Capable of being effectively cleaned, disinfected and sterilised if applicable
- Provided with accurate and complete technical and operational documentation
- Provided with essentials spare parts

It must be proven that a device will be suitable for the intended function in the preparation process by appropriate validation or qualification, see Sect. 34.15. Qualification and validation must be planned, described and documented. Responsibilities must be clear before the validation process starts. Tests, calibrations, inspections and acceptance criteria must be laid down in a pre-approved qualification protocol. Raw and processed data, test results and conclusions must be documented. The result is the qualification or validation report, including test results and conclusions. Qualification effort are highly dependent on the criticality of the equipment and the direct or indirect effect (impact) of the device on the quality of the preparation process and product. When purchasing a new device it is often possible to ask the supplier (by quality agreement) to qualify the equipment. This involves, usually, the Installation Qualification (IQ) and the Operational Qualification (OQ), sometimes also parts of the Performance qualification (PQ), although usually the user of the equipment has to take the responsibility for the execution of the PQ (see Sect. 34.10).

Preferably the essential list of equipment is included as attachment in the so called URS (User Requirement Specification) of the facility, as discussed in Sect. 27.3.

28.2.1 Design

A set of a well-formulated User Requirements Specification (URS), Functional specifications and Detail specifications has key importance proceeding any purchase (see Sect. 34.15). A good URS is used in the performance qualification and relates the actual production capacity and variety to the required machine qualities.

With a couple of potential suppliers a limited list can be drawn up of apparatus that might qualify for selection.

Specifications have to be listed, such as:

- Ease of cleaning and of sterilisation
- Ease of mounting and demounting and of exchange of tools
- Hygienic design for product-contact surfaces, sealing rubbers and membranes
- Product loss at starting and stopping
- Ease of operating, and the extent that operating or hand-operated adjustments have impact on the product
- Safety
- Failures should not pass unnoticed

At the final selection the compliance with the original URS should be warranted and from this a large number of premises issues will ensue, such as:

- Required capacities of utilities (electricity, water, steam, gases, and if applicable, IP-network connections, etc.)
- Floor load and possibilities of setting up; routing possibilities for transporting equipment to its final installation place
- Heat release and other influences on the HVAC during operation
- Product transport in and out and accessibility: logistic aspects of personnel and product to and from the machine

Although the manufacturer will build a chosen machine with standard components, the final result will be more or less unique. The manufacturer will often only accept limited liability for the performance of the machine in a specific situation. Agreement on a so-called Factory Acceptance Test (FAT) is recommended and it should be executed at the site of the manufacturer when the apparatus has reached the ready for testing status. At this stage it is possible to solve any unforeseen problems that would be either impossible to solve, or only against huge costs after installing at the final destination.

Agreement on a so-called Site Acceptance Test (SAT) is recommended as well, as is the execution immediately after setting up. This is especially important when there is a considerable amount of time between the time of delivery and the actual operation in practice as a consequence of elaborate qualification tests. Issues as the starting date for the guarantee period, the setting off of the maintenance plan and the transfer of remaining ownership responsibilities should be well indicated in advance. The SAT offers a good opportunity to reveal issues such as transport damage, any forgotten components or spare parts, etc. and it is also a check of the fulfilment of understandings made during the FAT.

28.3 Local Air Filtration and Exhaust Units

In this section local air filtration and exhaust units are discussed. Filtration being necessary for removing micro-organisms and dust from the air. Exhaust being necessary for carrying away contaminated air. Dedicated HVAC installations for heating, venting and air conditioning of clean rooms are described in Sect. 27.5.1.

28.3.1 Functionalities

This equipment is needed for supplementary and dedicated air filtration or exhaust at the site of preparation. In pharmaceutical preparation or quality control the objectives of air filtration and exhaust may be the protection of the product or the operator and the environment or both.

28.3.1.1 Protection of the Operator and Environment

During the preparation of medicines, steam, vapour, aerosols, dust and fumes can be released, which may pose a health risk for the operator. It is not always possible to change the process releasing these hazardous substances. As a consequence it can be necessary to protect operators in preparation or quality control areas from exposure to the product or the active substance. This can be done by active ventilation and exhaust and by filtration in order to protect the environment (see also Sect. 26.4.1). The appropriate equipment may be fume cupboards, moveable exhaust ducts, powder exhaust units, (bio)safety cabinets and isolators. Fumes, gas mixtures and volatiles might be absorbed by special filters, but in pharmacy practice only the technique of exhausting and screen filtration is usually used.

28.3.1.2 Protection of the Product

The operator might be a microbiological hazard for the pharmaceutical product, because of the operator's micro-organisms coming from the skin, hands, nose etc. Apart from shielding the body to prevent these particles being discharged into the product, working in airflow directed from the product may contribute to the protection of the product. The air in the production area must be of sufficient quality not to be a contamination source.

Annex 1 of the EU GMP defines the quality of the air in the preparation of sterile products. See Sect. 27.4.2 for elaboration of this topic.

28.3.1.3 Types of Equipment

The terminology for local exhaust units is sometimes unclear and non-specific. E.g. the term 'biological safety cabinet', which is historically derived from working with micro-organisms, is rather confusing. Any definitions can be found in [1].

In this section a distinction is made between:

- Fume cupboard
- Moveable exhaust duct
- Powder exhaust unit
- LAF unit or booth
- Safety cabinet
- Isolator

Figure 28.1 shows the general (schematic) construction of the different types of local exhaust and air filtering equipment.

For the protection of the operator and co-workers the most basic engineering control measure to minimise inhalation exposure (see Sect. 26.4.1) is ventilation of the work area. A ventilation rate of 2 h^{-1} or 5 h^{-1} is common for offices but not sufficiently efficient for preparation areas. A better effect will be obtained by containment of the activities that releases hazardous substances. In order to prevent

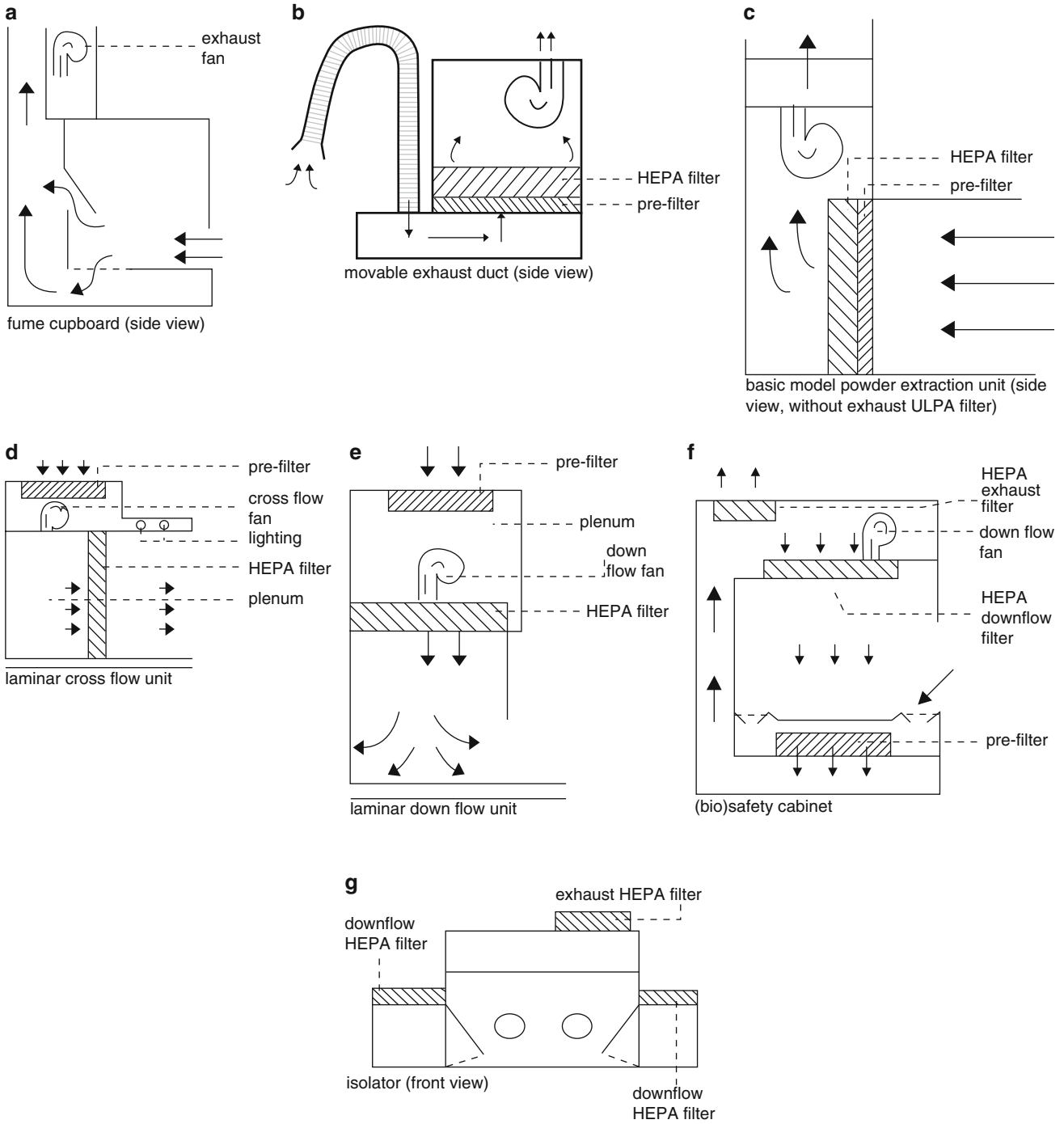

Fig. 28.1 Schematic construction of exhaust and air filtering equipment (= Fig. 28.1**a**–**g**). Source: Recepteerkunde 2009, ©KNMP

contaminated air to enter the room, the exhaust is guided to the outside of the building and discharged in the environment or the exhausted air is filtered before re-entering the room. Filtration of exhaust air will decrease any exposure of the environment outside the building and filtration is generally expected.

For the protection of the product, working in a laminar airflow directed from the critical places or working in a complete gastight box are options used in practice.

Complete protection of operator and product can be achieved by an isolator (see Sect. 28.3.7). Apart from complete product and operator protection other advantages are: controlled disinfection procedures, lower initial investments costs of the background area and exploitation costs. Disadvantages are higher costs compared to a LAF unit and its elaborate cleaning and maintenance. Therefore, in practice the choice of type of local exhaust equipment is determined by a risk assessment of the

process (taking into account the contamination of the product and of health damage of the operator), the available investment and the local experience.

For a systematic approach to the choice of the right local exhaust ventilation, the allowed level of exposure is compared with the actual exposure level and the assumed effectiveness of the exhaust device. Reference is made to [2]. Local exhaust ventilation is generally expected to establish a ten-fold reduction of the exposure level. Containment with 'small-scale breaches' is considered to establish a 100-fold reduction. Total containment as is accomplished by using an isolator.

For a general approach of preparation situations in community and hospital pharmacies (working with maximal 100 g of substances of hazard classes 1–5) reference is made to Sect. 26.5.2. For higher exposure levels the Advanced REACH Tool (see Sect. 26.5.1) offers guidance. The small scale preparation in pharmacies may generally require:

- A powder exhaust unit for most dust releasing operations: weighing, capsule filling, mixing of solids, rotor-stator mixing
- A horizontal or vertical LAF unit for the common aseptic handling with closed containers (see Sect. 31.3.4)
- A safety cabinet or isolator for processing class 4 and 5 substances
- An isolator if capsules have to be prepared with class 5 substances
- A fume cupboard for processing volatile, inflammable or corrosive substances

It cannot be stated that a 'normal' down flow cabinet, with open front and without sleeves to the work top (so not a safety cabinet), or a down flow unit is safe for the operator if working with half-open or open systems. It may very much depend on airflow patterns if any contamination with a substance will be actively blown in the direction of the operator. If so, the exposure would be higher, in which case no ventilation or exhaust is preferred.

Influence of Local Devices on the Performance of Room HVAC

Local safety cabinets of any type will influence the air pattern, temperature and HVAC system in the preparation area. (HVAC means heating, ventilation, air-conditioning; see Sect. 27.5.1). The influence will vary. Sometimes all doors of the room must be closed in order to insure a correct function of a fume cupboard. Air expelled by the local safety flow systems will also influence the ventilation and the pressure in the room. Local devices produce energy in the form of heat and, unless exhausted, will change the room temperature. This can be uncomfortable for the operator.

28.3.2 Fume Cupboard

Fume cupboards are meant to protect the operator from fumes, steam, volatiles and corrosive fluids.

Fume cupboards are not effective enough for the safe handling of aerosols and powders.

28.3.2.1 Description

In pharmacy practice mainly the ducted type of flowhood is used, which is not recirculating the air into the room. The air in the hood, eventually mixed with the volatiles is discharged into the open air outside the building, often by flexible special ducting. The extractor (fan) of a fume cupboard does not come in contact with these volatiles. This is the reason why explosive or highly combustible material can be exhausted safe.

The direction of the flow inside a fume cupboard is upwards at the end, see Fig. 28.1a. Heavy volatiles concentrate on the bottom of the fume cupboard; lighter volatiles can be found somewhat higher in the fume cupboard. In both areas of the fume cupboard sufficient force of the airflow is obligatory: 0.5 m/s for vapours and 1 m/s for dust [3]. However, the speed of the inflow in a fume cupboard is not high enough for the exhaust of small solid particles. The material of the fume cupboard and the exhaust fan and duct must be resistant to corrosion, in order to work with corrosive or caustic agents.

In front of the fume cupboard there is a transparent safety sash, sliding gently up or down with a counterbalance mechanism to reach precisely the defined and properly validated working or loading position. The loading position is not safe, but high enough to place equipment inside. Low airflow alarm control panels are common. The working position creates a safe area under the glass window to work in with (gloved) hands and arm covers for that part of the arm entering the fume cupboard working area.

28.3.2.2 Maintenance and Inspections

Fume hood maintenance involves periodical (daily, quarterly, annual) cleaning, maintenance, calibration, qualification and inspections. In daily inspection the fume hood area is visually inspected by the operator. Hood function indicating devices (LEDs) are a part of the modern fume cupboard. Periodic inspection covers capture or face velocity measured with a velometer or anemometer.

Annual maintenance: Yearly the fume cupboard must be maintained, calibrated and tested by a certified firm and competent person and the results of the official tests reported. Exhaust fan maintenance comprises lubrication, belt tension, fan blade deterioration and speed of the fan. Air velocity at different points, window performance, brightness of the light in the cupboard are tested in the working situation, with all doors of the room closed. Control of the

frequency and method of cleaning the interior is also important.

Validation of the velocity of the incoming air in the area under the sash and validation of the volume of the exhausted air is not sufficient proof of the safety of the fume cupboard. The quality of design of a good fume cupboard is as important as it guarantees a stable vortex of the airstream. A good technical design of the ventilation system is essential too, as is the dimensioning of the interior of the fume cupboard itself. Last but not least: without good operating procedures and trained operators a good technical design is useless.

The main goal of the operation within a fume cupboard is that it will not be possible for contaminated air to enter the area or room outside the fume cupboard.

Never start activities in a brand new fume cupboard with certificate of the manufacturer only, because on site initial qualification and validation of the performance and proper training of the operators is essential.

For initial validation (and periodical revalidation) mostly a combination of tests is carried out:

- Validation of the velocity of the exhausted air in the opening under the glass window and validation of the volume of the exhausted air (extract volume flow rate test).
- Containment testing - sometimes this test shows initially differences between test results in the test environment of the manufacturer (as built) and the results obtained in the pharmacy or in the laboratory of the end user (on site, as installed).
- The test protocol of European Standard EN 14175-4 [4].

28.3.2.3 Operation

It is important not to disturb the performance and airflow pattern of the fume cupboard. Staff standing or walking in front of the fume cupboard will disturb the air exhaust. The operator must have sufficient space in front of the fume cupboard to work easily and comfortable. Room doors that open frequently during operation in a fume cupboard and (strong) inflowing air from the room ventilation system (in the direction of the fume cupboard) may have a negative impact on the performance of the fume cupboard. Airflow visualisation with smoke is illustrative and often necessary.

28.3.3 Moveable Exhaust Equipment

28.3.3.1 Applications

Moveable extraction equipment can be used for the local and small scale exhaust of fumes and vapours at the point where these fumes and vapours are produced in an environment with no classic fume cupboard available. For example the handling of organic solvents in a laboratory, near the analysis equipment.

An extraction duct may not be the best choice for the extraction of powders and dust. However, by placing the hood very close to the point where the dust is produced we can create a situation with high air velocity and an effective exhaust for dust. In that case the exhaust duct is a dust remover, but eventually without a dust collector bag for the dust. A problem is that collected dust in the duct or the hood can fall back on (other) products. This is a serious risk for cross contamination and needs a proper cleaning schedule in place.

A better solution for exhausting dust and powder is combining the exhaust unit with filters, see Fig. 28.1b. Contaminated air enters the pick-up hood and is drawn through the hose and into the dust containment unit. The flexible duct with pick-up hood is easily adjusted to any position by an externally mounted, self supported, adjustable arm. Larger, heavier particles are collected in a removable collection pan for easy maintenance. The first stage of filtration is a pleated pre-filter, designed to capture mid-sized particles before reaching the main filter therefore extending the life of the main filter. The main filter is a high efficiency 95 % filter designed to capture fine particulate before being exhausted. Other main filter options are available including a 99.97 % efficient HEPA Filter. Clean filtered air is returned to the environment.

Professional dust removers are used in tableting, capsule filling and closing machines and powder filling machines. They are used to clean the equipment during processing or to remove adsorbed dust and powder from the pharmaceutical product. Dust removers are not designed to extract fumes, because fumes pass the filter unit and are blown back in the room.

Mobile dust removers (vacuum cleaners) with integrated HEPA filter are used in clean rooms, most of the time to clean the floor and ceilings. Dust removers are not designed to extract fumes, because fumes pass the filter unit and are blown back in the room. The HEPA filter has to be replaced periodically.

28.3.3.2 Description

Extractors for industrial or laboratory environments are available in several duct diameters (Ø 75–200 mm), duct

materials and sizes, with various constructions for ceiling, wall and bench installations. The standard model for fume extraction is used in most laboratory environments. The joints are made from polypropylene and ducts from anodised aluminium, for example. Polypropylene PP is used in environments containing high concentrations of corrosive pollutants; joints and tubes are made from polypropylene. ATEX material is used where hazardous explosive atmospheres may occur (see Sect. 26.11); joints and tubes are made from conductive polypropylene.

28.3.4 Powder Exhaust Units

28.3.4.1 Application

Powder exhaust units are often benches with horizontal backward flow and final vertical HEPA filters (see Fig. 28.1c), suitable to protect the operator largely from fine powder particles in the air or from water-based aerosols that otherwise would be released in the working area. These exhaust units might recirculate the exhausted air and pollutants can (also through basic filtration material) enter the room. In a Wibojekt® powder exhaust units the extracted air with particles is blown towards a special slit. That air is filtered and exhausted outside the room.

The filtration efficiency depends on the type of filter but is as said above generally expected to establish a ten-fold reduction of exposure.

These types of exhaust units usually don't have a duct leading to the outside of the building and therefore are not suitable for the extraction of gasses, fumes and volatile products.

28.3.4.2 Description

Fine dust particles or small aerosol droplets generated in a powder exhaust unit must be extracted from the operators working space horizontally in the backward direction. The airflow is sometimes downwards into a special slit (Wibojekt®).

After passing a coarse pre-filter and a final ULPA filter the exhausted air can be exhausted into the preparation room. It that case the unit is recirculating the air. It is possible to discharge the air via a duct outside the building. As a result the room pressure will become lower.

The efficacy of an exhaust unit depends on the air velocity in the unit. For that reason the area of the filters is not too small. Settled dust cannot be exhausted once it has fallen down onto the horizontal work area in the unit.

The place in the room where the exhaust unit is installed and qualified has to be chosen carefully. A recirculating exhaust unit needs enough space to blow the exhausted air around the unit. An exhaust unit very close to a door will be influenced by the changing air pattern every time the door swings open or is closed.

> The velocity of the incoming air stream in an exhaust unit must be between 0.25 and 0.50 m/s, with no major disturbing air pattern around or in front of the exhaust unit. A higher exhaust velocity causes unwanted turbulence before and in the unit.
>
> Weighing in an exhaust unit is possible. Dependent on the results of the accuracy of the weighing tests it can be necessary to shut down the exhaust unit at the very moment that the weighing result is recorded.

28.3.4.3 Operating Instructions

- Switch on the exhaust unit just before starting the activities. Clean the unit inside before and after activities.
- Check the velocity meter. Check the status of the filtration area, no damage may be seen.
- Check the unit once a year on air velocity; a leak test for HEPA or ULPA filters is easy to perform by an expert.
- Change all pre-filters and the HEPA filter only after leakage or damage.

28.3.4.4 Replacement of the Pre-Filters

The pre-filters have to be changed when after a visual check the pre-filter is dirty or saturated, or after a chosen time interval (once per 1–3 months for example).

During a change of the pre-filter the operator has to wear a protective P2- or P3 mask (see Sect. 26.4.1) for dust and aerosols. The exhaust unit fan is switched on, so dust particles are trapped in the HEPA or ULPA filter cassette. Clean the filter frames and remove the old filters in a closed bag.

28.3.5 Laminar Airflow Units

A Laminar airflow unit, also called laminar flow -cabinet, -closet, -hood or -bench is a general and rather non-specific term for an enclosed workbench, with a HEPA filtered laminar airflow inside.

The laminar airflow is unidirectional, so not turbulent. This is achieved by choosing the right design, technology, air velocity and filter sets. This unidirectional airflow must not be disturbed too much by the environment or movements of the operator. So a specific working technique and behaviour for the operator(s) is necessary. The direction of the filtered and clean laminar airflow can be horizontal (from the left to the right or from the back of the cabinet towards the operator), or downwards: from the HEPA filter in the top

of the cabinet to the bottom (which often is a flat stainless steel work area). See Fig. 28.1d and e. In pharmaceutical terminology: HEPA filtered horizontal or vertical laminar airflow (cross- or downflow) in a laminar flow bench creates an ISO 14644-1 (Class 5) / GMP Annex 1 (Class A) work area and prevents contaminated ambient air entering the work area. With the right working techniques, a trained operator and the right classified background this can result in good product protection.

28.3.5.1 Application

In pharmacies a laminar flow unit is used to protect the product against microbiological contamination from the operator. With a cross flow LAF cabinet the HEPA filtered air is directed over the working area to the operator. This type of LAF bench thus cannot be used for operations with hazardous substances (hazardous being defined as any substance with a H statement, so with a hazard class higher than one, see Sect. 26.3.1). It can be used for aseptic preparation processes with closed systems, such as aseptic handling, see Chap. 31.

For larger equipment a down flow LAF unit is common, e.g. a HEPA plenum in a preparation area for sterile products. A HEPA plenum with plastic curtains mounted in and hanging from the ceiling creates a dedicated area for aseptic processes. A plenum can be used for example to protect washed and opened glass infusion containers, moving in a filling line in the downflow of the plenum to the point of aseptic filling. As said, it depends on airflow patterns if any substance is actively blown in the direction of the operator. If so, the exposure may be higher than when no ventilation or exhaust takes place. This means that a down flow LAF unit cannot be used for open processing substances with a hazard class higher than one.

28.3.5.2 Description

In general, the air from the production area enters the front of the LAF cabinet in a controlled way, passes at first a set of pre-filters in the cabinet that separates coarse dust. Sometimes more HEPA filters placed in series after the pre-filters act as supplementary pre-filters (in certain types of safety cabinets). After pre-filtration the air is forced via a ventilator box through a set of framed HEPA filters and finally enters the aseptic process area as sterile filtered air in a unidirectional flow. The speed of the unidirectional flow is kept between limits. Finally the exhaust air re-enters the room (crossflow LAF units), or can be exhausted to the outside with or without extra HEPA filtration (safety cabinets).

With these principles in mind horizontal crossflow LAF cabinets, downflow LAF cabinets, downflow safety cabinets or downflow LAF units with a large area (HEPA filter plenums) are constructed.

The exact positioning of pre-filters in a LAF cabinet depends on the brand and type of the LAF cabinet and is an important part of the functional and detail specifications of it.

Testing of HEPA Filter Units.
Filter efficiency, dust holding capacity and differential pressure changes are tested frequently.

HEPA filters can be tested with different methods. A wide range of test equipment for on-site measurements include particle counters, pressure gauges, airflow meters, energy data loggers, corrosion monitors and gas analysis equipment. One of the tests is the measurement of penetration of dispersed oil particles (DOP) through the HEPA filters. DOP used to be the abbreviation of DiOctylPhtalate, which however has been replaced by safer products.

By dispersing the oil aerosol towards the HEPA filters in the air channel the testing operator can measure how many particles penetrate the HEPA filter and can be counted at the clean part of the HEPA filter. According to ISO 14644-3 the filter area is scanned in small well-defined sequential parts. This percentage penetrated particles can be dependent on the exact position on the filter where the particle counter measures. Inferior and good parts of the filter area are detected and the position is documented. The condition of the filter is expressed as percentage penetration giving filter efficiency. The penetration is the percentage of the particles that passed; the filter efficiency is the part that was blocked by the filter material. The efficiency for the most penetrating particle in a H14 HEPA filter can be 99,995 % and for the particles with a size larger than 0.3 μm the efficiency can be 99,999 % or more. Small defects in the filter can be repaired by a professional operator.

Other important functional details of LAF cabinets are:

- The light intensity in the cabinet, measured on the work spot must be sufficient to reach a minimum level of 1,000 lux. The lighting unit must be built inside the cabinet and the frame of it must be easily cleaned and disinfected.
- The speed of the ventilator must be adjustable, and automatically controlled in order to reach the required quality of laminar flow and speed.
- Detection of full speed, half speed, on and off or night function.
- The speed of the unidirectional flow must be monitored and shown on a display to detect disturbances in the flow by a clogged filter or a defective ventilator.

To keep the flow as unidirectional as possible a minimal number of extra utilities inside the working area of LAF cabinet are allowed. Extra utilities might be:

- Nitrogen and compressed air valves, for membrane filtration devices.
- Vacuum valve, used only in dedicated LAF units for microbiological quality control: the filtration of fluids for sterility testing or bioburden control.
- Electricity sockets.
- Electronic balances. They can be used inside the LAF cabinet but give disturbance of the laminar airflow and in return the LAF cabinet might disturb the weighing result. Use only following a risk analysis.
- Clamps outside on the front of the LAF unit, to attach temporary documentation.
- A stainless steel rail with hooks in the LAF area to attach infusion bottles and bags for the aseptic processing.
- Computer monitor for instructions.
- (Continuous) monitoring equipment.

It is advised to require silent, modern ventilators. The expected daily noise of a LAF unit in operation must be reasonable low and specified in dB. The best solution is to choose a cabinet ventilator with enough spare capacity. In that case the ventilator will not work at the maximum capacity and the noise level in dB will be reasonable or low.

A laminar flow cabinet will continuously produce heat from the ventilators. If the exhaust airflow from the LAF unit is returned into the room (recirculation), the temperature in the room will rise and more room ventilation and cooling is necessary. Air exhaust to outside the room will give less heating of the room.

28.3.5.3 Operating instructions

Commonly two operators are at work in a LAF cabinet. One is the operator, working with the arms and hands inside the cabinet. The second person is standing aside, supporting and controlling the operator, or supporting two operators working simultaneously in two different cabinets.

These persons must move gently in the room. Opening a door will have some effect on the balance of the airflow in the cabinet. So try to avoid opening clean room doors during aseptic processing.

Spillage of material must be removed as soon as possible for example with a cloth wetted with disinfectant.

The interior of the LAF cabinet (horizontal bench, two sides left and right and the back inside of the bench) is disinfected with alcohol 70–80 % at the end of each working session (shift of about two hours) and at the end of the working day. For LAF benches that keep running 24 h a daily disinfection of the horizontal working bench only between sessions and before start of the activities the next morning might be allowed. This decision is based on a risk analysis, and might be allowed because the rest of the interior was disinfected at the end of the past working day. In addition on disinfection the interior must be cleaned frequently with lukewarm water and a detergent, followed by a disinfection.

LAF cabinets that do not run 24 h a day must be switched on first; after 15 min operating at full speed the cabinet must be disinfected and can be used.

Disinfection efficacy must be proved with contact plates (RODAC plates, see Sect. 31.6); specifications of the results can be found in Annex 1 of the European GMP.

Validation of the aseptic process can be found in Sect. 31.6.2.

28.3.5.4 Qualification of a LAF Unit

Once or twice a year (depending on the criticality of the processes) the LAF cabinet is inspected, calibrated and qualified. Commonly a contract is signed with a specialised external firm for this.

The following aspects are important in qualification:

- Inspection and installation of new pre-filters. Sometimes the filters are grey or coloured, as proof of the need of change.
- Efficacy of the HEPA filters. It is not necessary to change the HEPA filters too often. Change of a HEPA filter is expensive and must be a result of documented defects that cannot be repaired.
- Air velocity.
- Intensity of the light.

28.3.6 Safety Cabinets

28.3.6.1 Application

A safety cabinet is a laminar down flow cabinet, which is constructed specifically for protection of both the sterile product and the operator. It is frequently used in (hospital) pharmacies for aseptic preparation (when products are not fully closed) and for aseptic handling of class 4 or 5 substances (see Sects. 26.5.2 and 26.8). Laminar down flow has the advantage compared to cross flow that the operator does not feel the continuous flow in his direction. Other names for a safety cabinet are: biosafety cabinet, biosafety bench, biohazard bench, biohazard cabinet, biological safety cabinet etc.

In safety cabinets with a “slope” glass window the operator works with both arms under the window into the half-open sterile working area.

28.3.6.2 Description

The air within a safety cabinet comes from the HEPA filter in the top of the cabinet (see Fig. 28.1f). The flow is led into exit grills at the back and the front of the work bench. A second airflow is drawn from the working room into the front grill where the elbows of the operator are. This flow prevents air or aerosols from the working area escaping the cabinet and protects the operator from inhaling aerosols.

After being collected through the slits the air is prefiltered through coarse disposable filter material situated under the work bench in a tray.

In safety cabinets of the type partial or total exhaust, the air eventually is collected in a box on top of the bench, connected via a HEPA-filter with the air in the room (see Fig. 28.1f). The box has underpressure due to the exhaust air velocity. In case the safety cabinet has a breakdown, the box construction prevents the ventilator of the exhaust channel to continue while the down flow ventilator in the cabinet stops. Otherwise contaminated air from the room would be sucked under the sash, contaminating the clean side of the HEPA filter in the work area of the safety cabinet.

28.3.6.3 Specifications and Classification

The specifications of the airflow pattern in a safety cabinet might be confusing. Following EN 12469 (Biotechnology – Performance criteria for microbiological safety cabinets) [5] the velocity of the incoming room air under the glass panel must be between 0.4 and 0.7 m/s; the mean downflow velocity must be between 0.25 and 0.50 m/s, with no individual measurement outside +/− 20 % of the mean. However, in pharmacy the GMP [6] takes precedence. In Annex 1 the down flow air velocity differs somewhat from the EN 12469. The mean velocity for the down flow in Annex 1 (Class A) must be 0.45 m/s +/− 20 %. It is important to stress GMP compliance during installation and initial qualification of a new safety cabinet in a pharmaceutical environment.

The air in a safety cabinet is filtered through pre-filters and HEPA filters so the resulting workspace inside the bench complies to GMP Class A. All safety cabinets of type II are built with a HEPA filter at the point where the used air is finally expelled through the exhaust channel. This is an extra HEPA barrier, preventing aerosols contaminating the HVAC system.

Classification of Safety Cabinets

Safety cabinets must comply to Class II of the European Standard EN-12469. Some types comply moreover to the German DIN 12980. Document your specifications well before purchase and be aware that in pharmacy practice a down flow velocity of the air in a safety cabinet must comply with current GMP. Communication about GMP is very important, because these safety cabinets are used in non-GMP laboratories too.

The Classification IIA and IIB is not found in the EN-12469 but in US-CDC guidelines (see further down). In a Class IIA cabinet the (potentially contaminated) air from the work bench is led without filtration to the last exhaust HEPA filter; in this way the ventilator compartment can be contaminated after sustained use of this type of safety cabinet. In Class IIB cabinets an extra HEPA filtration cassette is placed below the work bench; as a result HEPA filtrated (potentially contaminated) air from the work bench enters the ventilator part before it passes the last HEPA exhaust filter. The ventilator compartment remains cleaner by this extra HEPA filtration step. The environment is better protected, as well as service personnel working inside the safety cabinet.

Safety cabinets placed in a room with underpressure (for the preparation of radiopharmaceuticals for example) must have an extra exhaust ventilator, discharging the exhaust air outside the building. This exhaust ventilator must be tested also in daily practice and at periodical electricity break tests. Safety cabinets have visual and acoustic alarms that warn for deviations in airflow (down flow and in flow alarms).

The classification by the U.S. Centers for Disease Control and Prevention (CDC) is to be found in Appendix C: Types of Biological Safety Cabinets (BSC) of the draft USP monograph Hazardous drugs – handling in healthcare settings [7]. Terminology (biological safety) may be confusing but is historically determined: the first safety cabinets were developed for working with dangerous microbiological materials. The classification of the cabinets is based on their technical construction which is described in this Appendix. The fields of application are suggested for each class.

Class I: A BSC that protects personnel and the environment but does not protect the product/preparation. Personnel protection is provided when a minimum velocity of 75 linear feet/min of unfiltered room air is drawn through the front opening and across the work surface. The air is then passed through a HEPA/ULPA filter either into the room or to the outside in the exhaust plenum, providing environmental protection.

Class II: Class II (Types A1, A2, B1, and B2) BSCs are partial barrier systems that rely on the movement of air to provide personnel, environmental, and product/preparation protection. Personnel and product/preparation protection is provided by the combination

(continued)

of inward and downward airflow captured by the front grid of the cabinet. Side-to-side cross-contamination of products/preparations is minimised by the internal downward flow of HEPA/ULPA filtered air moving toward the work surface and then drawn into the front and rear exhaust grids. Environmental protection is provided when the cabinet exhaust air is passed through a HEPA/ULPA filter.

Type A1 (formerly, Type A): These Class II BSCs maintain a minimum inflow velocity of 75 ft/min, have HEPA-filtered, down-flow air that is a portion of the mixed down-flow and inflow air from a common plenum, may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy, and may have positive-pressure contaminated ducts and plenums that are not surrounded by negative-pressure plenums. They are not suitable for use with volatile toxic chemicals and volatile radionucleotides.

Type A2 (formerly, Type B3): These Class II BSCs maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered, down-flow air that is a portion of the mixed down-flow and inflow air from a common exhaust plenum, may exhaust HEPA filtered air back into the laboratory or to the environment through an exhaust canopy, and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for minute quantities of volatile toxic chemicals and trace amounts of radionucleotides, they must be exhausted through properly functioning exhaust canopies.

Type B1: These Class II BSCs maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered down-flow air composed largely of uncontaminated, recirculated inflow air, exhaust most of the contaminated down-flow air through a dedicated duct exhausted to the atmosphere after passing it through a HEPA filter, and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for work involving minute quantities of volatile toxic chemicals and trace amounts of radionucleotides, the work must be done in the directly exhausted portion of the cabinet.

Type B2 (total exhaust): These Class II BSCs maintain a minimum inflow velocity of 100 ft/min, have HEPA-filtered down-flow air drawn from the laboratory or the outside, exhaust all inflow and down-flow air to the atmosphere after filtration through a HEPA filter without recirculation inside the cabinet or return to the laboratory, and have all contaminated ducts and plenums under negative pressure or surrounded by directly exhausted negative-pressure ducts and plenums. These cabinets may be used with volatile toxic chemicals and radionucleotides.

Class III: The Class III BSC is designed for work with highly infectious microbiological agents and other hazardous operations. It provides maximum protection for the environment and the worker. It is a gas-tight enclosure with a viewing window that is secured with locks and/or requires the use of tools to open. Both supply and exhaust air are HEPA/ULPA filtered. Exhaust air must pass through two HEPA/ULPA filters in series before discharge to the outdoors.

28.3.6.4 Operation Instructions

The operational aspects of maintenance and calibration for safety cabinets are almost the same as for cross flow laminar airflow units (see Sect. 28.3.5). Additionally the inflow as protective barrier has to be measured.

Daily cleaning and disinfection of the interior of a safety cabinet is important. The tray under the work bench as well as the pre-filter contains spilled fluids. This area has to be cleaned and disinfected at least once a week wearing a P3 mask (see Sect. 26.4.1) and protective impermeable clothing. The pre-filters must be changed every 3–6 months; the HEPA filters must be changed only after significant failure at qualification tests, repair being not possible any more.

28.3.6.5 Qualification

The protection performance of a safety cabinet is given by the so called Protection Factor, which is determined by the Potassium Iodide test. Potassium Iodide solution is dropped on a spinning drive. An aerosol inside the work area of the cabinet is formed; some droplets are forced in the direction of the protecting air curtain. The number of aerosol particles inside the bench is counted (A). Outside the cabinet (where the operator normally is sitting) the number of aerosol particles that escaped the air curtain in front of the bench is counted again (B). A/B is the protection factor. The protection factor has to be at least 1.5×10^5.

A second test is a test with spores of bacteria. This is a factory test for obvious reasons, see EN-12469.

The potassium Iodide test is time-consuming. This test is performed in OQ/PQ qualification or when possible harm could have occurred, for instance when the cabinet is moved to another place.

28.3.7 Isolators

An isolator, as is in its name, offers physical isolation of the operator from the product. It offers complete containment (see Sect. 26.7.1). Its presence in pharmacies differs considerably between countries.

In industry an isolator technique is often used for critical aseptic processes. Other techniques with robots and barrier system isolator technology are in use also. Isolators for aseptic manufacturing can be placed in class C or D clean rooms, whereas LAF cabinets should be placed in GMP class B.

28.3.7.1 Description

An isolator is according to the description of EN-12469 a Class III safety cabinet, as said a complete physical barrier, see Fig. 28.1g. The air inside the isolator is HEPA filtered, so inside the isolator a GMP Class A air quality is maintained. The gloves or full or half suits are the physical barrier between the sterile product inside the isolator and the operator standing outside and the integrity of this barrier requires very much attention.

The main compartment of an isolator is often made of stainless steel and has two rubber gloves in the front of a clear viewing panel. The HEPA filtered airflow can be laminar or turbulent.

The pressure inside the main compartment is higher or lower than the background area of the isolator. Containment isolators often employ negative internal air pressure and most isolators use positive pressure for aseptic processing. A sporicidal process, usually delivered by gassing can be used to aid microbiological control. A gas generator delivers the gas (e.g. peracetic acid or hydrogen peroxide) via defined ducts [8].

If the isolator is only used for non-hazardous products the exhaust air can be discharged into the background area. However, commonly the air is discharged outside the building.

Some isolators have a modular construction for many different kind of applications. Sometimes an extra HEPA filter is built in, underneath the working surface. An isolator may have no, one or two hatches, constructed as a lock. The hatches may have their own HEPA filters and have a door to the main compartment and another door to the background area. The isolator has an interlock system for the hatches to prevent loss of air pressure. As an alternative for the hatches special isolator transport and loading boxes can be used with a tight (screw) fitting to the main compartment ('mousehole'). In practice the terms 'open' and 'closed' isolators are used. In 'closed' isolators all materials are inside the isolator during the gaseous disinfection and the aseptic handling is done without opening hatches or mouseholes.

The operator wears disposable gloves and puts the hands and arms in the long rubber isolator gloves, which have inflatable gaskets for tight fitting to the isolator. Half or full suits are also a possibility.

The isolator gives an acoustic alarm when the pressure drops or with other deviations.

Maintenance or repair of an isolator has to be done with gloves, a protective mask and protective clothing. Change of HEPA filters has to be done very carefully and with qualification after replacement. Further descriptions can be found in [8].

28.3.7.2 Using an Isolator

After delivery of a new isolator a qualification protocol is followed (see Sect. 34.15). The interior of the isolator must comply to GMP Class A (particles and microbiological tests). A program to minimize the risk of loss of integrity of gloves, sleeves and suits should be present including operator practice, vigilance and the absence of sharp edges. The glove ports and, if applicable, the suits present particular risk because they are more prone to damage and if not noticed will contaminate the product. Transfer of material in and out should not compromise the critical zone. The transfer is especially critical if no gassing is used. In that case a proper disinfection procedure such as used in normal LAF has to be used.

As the absence of micro-organisms is expected, the question of laminar versus turbulent flow and the strict application of aseptic procedures during operations might be irrelevant.

The isolator and gloves are tested daily for leakage. Airflow velocity if applicable is measured in-line with a calibrated instrument. The pressure inside the isolator is checked continuously. Furthermore, gas detection in case gaseous disinfection is used.

Before working the inside of the isolator has to be cleaned and disinfected. Disinfection can be done with peracetic acid or hydrogen peroxide, using special disinfection devices and procedures. For small scale or incidental use ethanol 70–80 % may be used as an alternative.

28.4 Apparatus for the Production of Pharmaceutical Water

Water is the most important pharmaceutical substance. The requirements to be met are being discussed in Sect. 23.3.1. The equipment for storage and distribution (loop system, pump and storage vessel) is considered as a built-in installation and therefore is discussed in Sect. 27.5.2. The development of biofilms is discussed in Sect. 19.3.5.

Pharmaceutical water (Ph. Eur.) is produced by a multi-staged process using different techniques with different

apparatus in series [9, 10]. In this section those different apparatus producing water with a pharmaceutical quality are discussed, e.g.:

- Water softeners
- Demineralisation apparatus based on ion exchange
- Apparatus for reverse osmosis
- Apparatus for electro-deionisation
- Distillation apparatus

28.4.1 Water Softeners

28.4.1.1 Application

The water softening process removes most calcium and magnesium ions from tap water. By doing so a downstream placed apparatus, such as reverse osmosis, electro-deionisation or distillation apparatus, is protected against the deposit of calcium and magnesium salts ('limescale').

28.4.1.2 Description

The principle of a water softener is based on ion exchange using synthetic resins. The synthetic resin has negatively charged functional groups with sodium as a counter ion. Calcium and magnesium ions from the water are exchanged for the sodium ions of the resin. Therefore, this type of water softeners is called cation exchangers. See Sect. 23.3.1 for the hardness degrees. The resins pearls do not retain any other contamination such as solid particles.

28.4.1.3 Operating Procedure

Water softeners must be regenerated periodically. This regeneration involves the immersion of the resin, being saturated with calcium and magnesium ions, in a concentrated sodium chloride solution (brine). This brine is prepared and kept in a separate vessel. The calcium and magnesium ions bound to the resin will exchange with the sodium ions in the brine. After regeneration the brine containing calcium and magnesium must be flushed thoroughly. Often the softening apparatus is provided with fully automatic regeneration equipment. In that case regeneration will occur periodically or be triggered by an in-line hardness tester.

Larger installations for continuous water purification usually have two automated softening apparatus mounted in a parallel arrangement. As soon as one of them has to be regenerated an automated control system will switch that water softener off. The other one will continue delivering soft water in the meantime.

Water softeners are a good substrate for bacteria. Therefore, apart from being regenerated, the system must be disinfected periodically as well. Some (automated) softeners can generate chlorine gas from the brine solution during regeneration. This chlorine gas dissolves in the water as hypochlorite and acts as a disinfectant. All chlorine must be flushed away thoroughly after the combined regeneration and disinfection process.

The quality of the water will be controlled by means of pressure and flow meters and by a hardness tester. The hardness tester consists of an automated titration apparatus. The reservoir, with combined titre and indicator solution, should be refilled regularly.

28.4.2 Demineralisation Apparatus Based on Ion Exchange

28.4.2.1 Application

Purified water (Ph. Eur.) can be produced from tap water or from pre-softened tap water by demineralisation. As this production method easily leads to microbiological growth the product will not always meet the microbiological requirements. Passing through a bacteria retentive filter may render the demi-water compliant. However this treatment should be monitored because of micro-organisms growing through the filter. Endotoxins will not be removed by filtration.

28.4.2.2 Description

Ion exchangers can be applied both as a water softener (see Sect. 28.4.1) and as a demineralisation apparatus. After softening of tap water, calcium and magnesium ions have been removed; however any other mono and bivalent ions (cations such as potassium and sodium and anions such as nitrate, chloride, sulphate, bicarbonate and carbonate) have still to be removed in order to obtain Purified Water Ph. Eur. This process is called deionisation or demineralisation. It proceeds at room temperature. Demineralisation apparatus based on ion exchange consist of columns filled with several varieties of synthetic resin pearls that remove unwanted ions from the water by exchanging them for hydrogen and hydroxyl ions. The general principle is that all cations are being exchanged for hydrogen ions and all anions for hydroxyl ions. Finally the recombination of hydrogen and hydroxyl ions results in pure water.

An ion exchange resin is a synthetic resin with positively and negatively charged functional groups. The demineralisation process (which might proceed over one combined or over separate columns) exchanges cations from the water for hydrogen ions from the cation exchange resin and anions from the water for hydroxyl ions from the anion exchange resin. Exemplified (s = solid):

(continued)

$$Na^+(aq) + RH^+(s) \rightarrow RNa^+(s) + H^+(aq)$$

Any bivalent anion, e.g. sulfate, exchanges for 2 hydroxyl ions in a anion exchange resin.

Two different types of anion resin are used for demineralisation: weak basic and strong basic exchange resins. Both types exchange anions such as chloride, sulfate, bicarbonate and carbonate for hydroxyl ions. However strong basic exchange resins can additionally exchange silicic acid and silicates for hydroxyl ions.

The quality of demineralised water depends on several factors, such as the quality of the feeding water, the type of exchange resin, the quantity of resin and the number of resin containing tanks.

In a mixed-bed demi-tank or column, cationic resins and anionic resins are thoroughly mixed in just one container. The alternating cationic – anionic resin pearls in one column can provide water of excellent quality. A mixed bed column can achieve a water quality with a conductivity of less than 1 microSiemens/cm.

Dual-bed demineralisation columns consist of two serially arranged containers, one with cationic resin and one with anionic resin pearls. A dual-bed weak basic demi-column delivers water with a conductivity of approximately 20 microSiemens/cm. A dual-bed strong basic demi-column delivers water of approximately 5 microSiemens/cm.

An ion exchange demineraliser has to be regenerated periodically by flushing the resin pearls with a highly concentrated regeneration fluid. The type of regeneration fluid depends on the specific type of ion exchange resin. Commonly a solution of sodium hydroxide or hydrochloric acid is used. Afterwards, the regeneration medium has to be flushed thoroughly and the ion exchanger can be reused again. Regeneration sometimes takes place at the site of the user, sometimes used columns are exchanged for regenerated ones by the supplier.

28.4.2.3 Operating Procedure

The quality of the water is controlled with conductivity meters, pressure meters and flow meters.

If the feed water contains a relatively high concentration of dissolved substances a dual-bed system is usually preferred. If the feed water contains low concentrations a mixed bed ion exchange demineralisation will be preferred. As said above for water softeners, the resins pearls in a demineralisation column do not retain any other contamination such as solid particles. They constitute a rather good substrate for the growth of bacteria; mixed bed systems are even more vulnerable. The investment costs are comparatively low in contrast to the relatively high operational costs including regeneration. If the installation must produce Purified Water Ph. Eur. the microbiological quality has to be monitored or the bacteria filter has to be changed frequently.

28.4.3 Apparatus for Reverse Osmosis

28.4.3.1 Application

An apparatus for reverse osmosis removes more than 95 % of all ions and more than 99 % of all particles, colloids and dissolved organic material including endotoxins. Nevertheless the permeate still contains too much small, univalent ions to comply with the requirements for purified water after one filtration step. Therefore, reverse osmosis is often used as a preliminary treatment, preceding distillation or demineralisation. The available reverse osmosis systems will only be economically feasible if a rather large amount of purified water is required. As an example reverse osmosis installations are being used, in combination with other purification methods, as a preliminary treatment in the production of Water for Injections and in the production of purified water for haemodialysis. Sometimes purified water is prepared using just a series of semi-permeable membranes. Reverse osmosis has the advantage compared to demineralisation that few chemicals are being consumed. However, as the process does not involve any heating, a substantial risk exists of microbiological contamination and biofouling.

28.4.3.2 Description

Reverse osmosis utilises semi-permeable membranes. The name "reverse osmosis" (abbreviated as "RO") uses the fact that the osmotic pressure building up over a semi-permeable membrane has to be overcompensated. In a reverse osmosis process the water is forced by high pressure to flow through a semi-permeable membrane thereby eliminating any particle or larger ion, see Fig. 28.2.

RO membranes are designed to pass water through the intersegmental space between the polymer molecules. This space is wide enough to allow individual water molecules to pass, but too small for any hydrated ions. Because the system has many additional surfaces beyond the membrane, on which undisturbed biofilms could built up, the prevention of microbiological contamination in a reverse osmosis system is a challenge. Biofouling is effectively limited by a smart choice of materials and by avoiding blind angles, however still intensive control is mandatory.

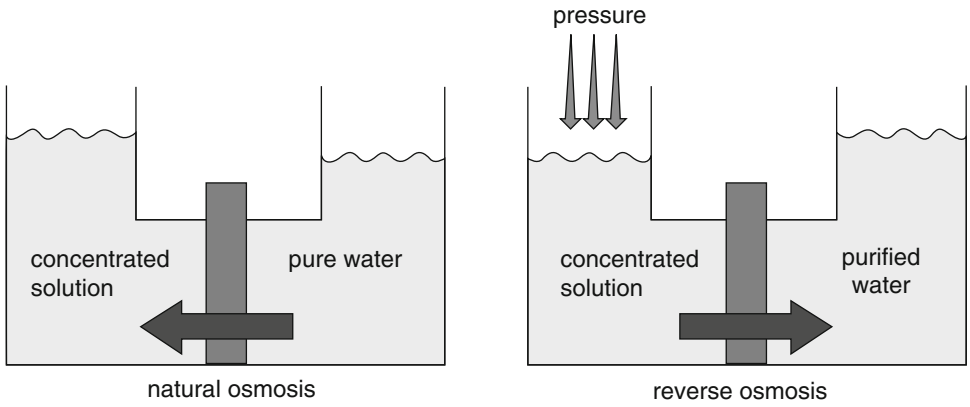

Fig. 28.2 Principle of reverse osmosis. Source: Recepteerkunde 2009, ©KNMP

28.4.3.3 Operating Procedure

Apparatus for reverse osmosis can function for a long time without much maintenance. The semi-permeable membrane should be replaced periodically because of ageing. The average lifetime of a membrane is 2–3 years.

During the first start-up a balance has to be found between the amount of water being produced as permeate and the amount that is flushed away as concentrate. Usually an optimal result in water quality and quantity will be achieved when approximately 10 % of the feed water is drained away as concentrate. By choosing a higher percentage the quality of the permeate might increase. However, this will have a negative impact on the yield of the installation. A lower concentrate percentage will decrease the quality of the permeate.

Most attention should be paid to the microbiological quality of the water. Again a well-monitored bacteria retentive filter can be significant.

28.4.4 Apparatus for Electro-Deionisation

28.4.4.1 Application

Electro-deionisation (EDI) is used in combination with other purification methods. Electro-deionisation is applied to the production of Purified Water Ph. Eur. or Highly Purified Water Ph. Eur. Highly purified water may be used in the haemodialysis department for in-line production of dialysis fluids for continuous dialysis. EDI in combination with other techniques can be used for in-line dialysis, it requires thorough in process controls. A distillation apparatus, suitable for water for injection, would not comply the large peak demand at dialysis unless equipped with a very large storage vessel and an extremely powerful (energetically unrealistic) cooling system.

Sometimes hospital pharmacies use an EDI installation for the preparation of water for pharmaceutical non-sterile stock preparations.

28.4.4.2 Description

Electro-deionisation (EDI), also called *continuous* electro-deionisation (CEDI), is a special type of demineralisation.

The apparatus using this technique is equipped with mixed resin pearls and selectively permeable membranes. It functions by applying an electrical current fed through resin and membranes. The feeding water will be normally deionised by flushing through the resin. However, the "captured" ions subsequently do not stick to the resin, but are being removed under the influence of the applied potential difference and drained through the selectively permeable membranes. The potential difference also splits a part of the pure water into H^+ and OH^- ions that regenerate the resin at their turn, see Fig. 28.3.

The potential difference and the pH-gradient impede the growth of micro-organisms additionally, but the risk of growth of micro-organisms still exists.

28.4.4.3 Operating Procedure

A (C)EDI-installation requires relatively limited maintenance efforts. To maintain the potential gradient a pure sodium chloride solution has to be fed behind the selective permeable membrane. This sodium chloride solution is drained away with a part of the feed water. The stock sodium chloride must be refilled regularly. The product water should be checked for its conductivity.

Tap water must be softened before being used as feed water. This water still contains micro-organisms and particles as well as quite a lot of minerals. Therefore, the water should be filtered as well. To achieve a stable and reliable supply of the required water quality, it is common practice to apply a softening installation, a reverse osmosis installation and a (C)EDI installation in sequence.

The application of a firm potential difference in the water not just causes the migration of H^+ and OH^- ions to the ion exchange resin pearls, but leads to the generation of small amounts of free hydrogen and oxygen gas as well. Therefore, an effective degassing of the storage vessel containing the

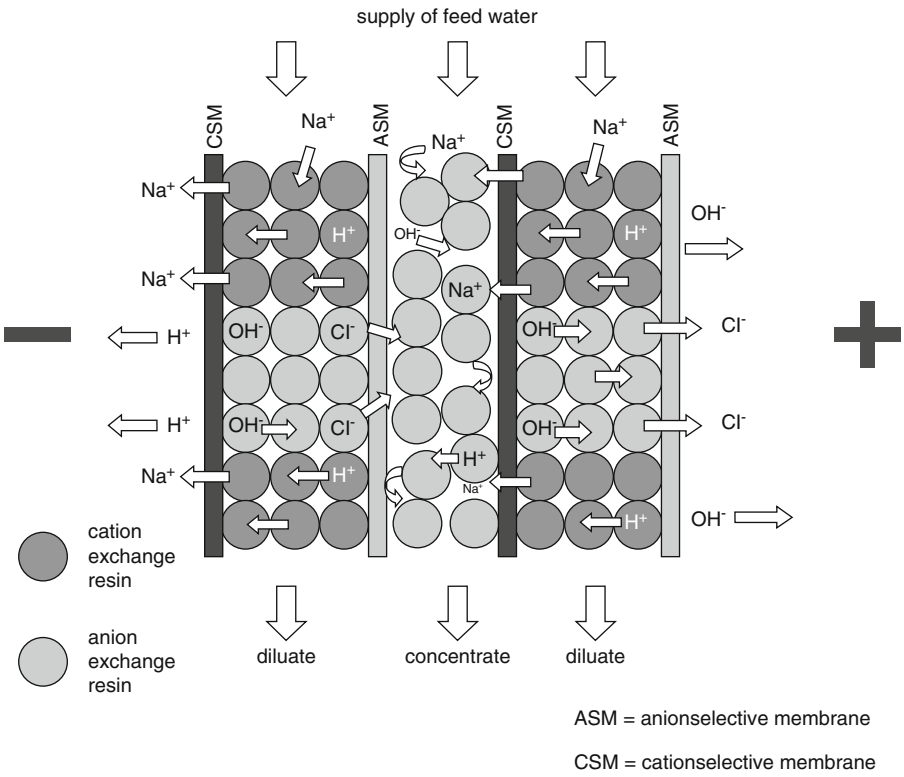

Fig. 28.3 Principles of electro-deionisation. Source: Recepteerkunde 2009, ©KNMP

product water is necessary to prevent the accumulation of these gasses which otherwise might cause an explosive mixture.

28.4.5 Distillation

28.4.5.1 Application

With distillation chemically pure and sterile water can be produced. Provided that any carry-over of water droplets is effectively avoided, it can be relied upon that not just chemical impurities but micro-organisms and endotoxins as well will be removed. Distilled water complies to the requirements of being pyrogen-free according to the Water for Injections Ph. Eur. monograph.

To maintain the sterility and apyrogenity of the distillate it is necessary to collect and store the water in a sterile and pyrogen-free way as well. In larger installations this is achieved by keeping the water in a storage vessel at least at 80 °C and by pumping it around in a loop in a turbulent flow, see Sect. 27.5.2.

The sterility and apyrogenity immediately after the purification process constitute the most important distinction with other purification methods.

28.4.5.2 Description

For distillation the feed water is heated to boiling. On the evaporation of the water any chemical and microbiological impurities are retained in the boiling water. The pure water vapour is then condensed. However, even this method of purification cannot yield absolute purity. Even the highest quality distillation apparatus will not be able to remove 100 % of all ions and endotoxins. It is commonly accepted that a maximum of a log 3–4 reduction in the concentration of impurities can be achieved. For this reason it is important to put requirements on the quality of the feed water for a distillation apparatus.

For small scale distillation a simple (single effect design) water distillation apparatus can be used. For a middle or large scale distillation stainless steel built apparatus are constructed in a different way, using multi stage distillation, steam compression or thermo compression, to yield a much higher capacity and a better efficiency, see Fig. 28.4.

In the past stainless steel was known for its release of metal ions, but that is not the case any more in presently deployed steel qualities. Nevertheless it is important to make inquiries of the supplier about this.

A simple classical water distillation apparatus consists of a boiling vessel from glass, holding a heating element made of metal or quarts and fitted to a glass condenser. To reduce water and energy consumption the feed water is first used as a coolant in the condenser or it is pre-heated with the aid of a heat exchanger, see Fig. 28.5. The velocity of the vapour carry-over is relatively small. Consequently the risk of carry-over of any water droplets is small as well. In larger apparatus specific measures have been taken to prevent this carry-over.

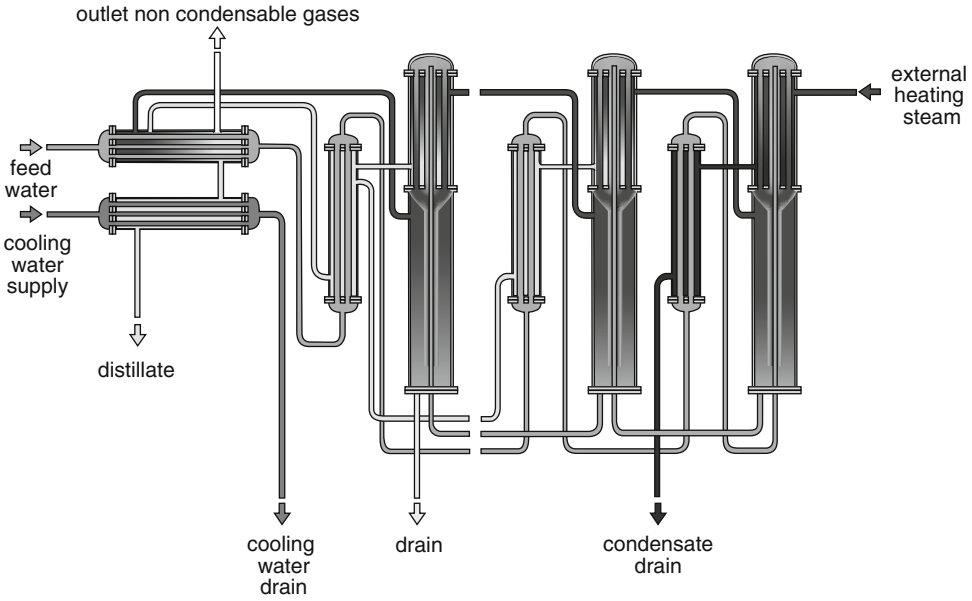

Fig. 28.4 Multi stage distillation. Source: Recepteerkunde 2009, ©KNMP

Provided a correct design and performance, distillation is a very reliable process. However the apparatus does not tolerate being fed with tap water quality because calcium, magnesium and silicates would precipitate in the evaporator. In addition volatile components from the tap water could co-distil and condensate in the product water. Examples of those volatile constituents are trihalomethanes, ammonia and carbon dioxide. Therefore the feed water has to be pre-treated. Purified Water Ph. Eur. is suitable as feed water. The chemical and microbiological properties of this water are defined unequivocally. Other non qualified water should not be accepted as feed water for a pharmaceutical distillation apparatus.

28.4.5.3 Operating Procedure

A distillation apparatus usually requires little operational attention. Obviously regular maintenance is mandatory and all measurement probes for temperature, pressure and conductivity must always be calibrated.

The permanent exposure of the stainless steel to steam and ultrapure hot water might provoke the development of rouging. This phenomenon and its prevention is further discussed in Sect. 27.5.2.7.

28.5 Ultrasonic Baths and Heaters

28.5.1 Orientation

Heaters and ultrasonic baths are mainly used to increase dissolution of substances. The most generally used heaters are: the gas stove and gas burner, electric heating plate, heating lamp, water bath and microwave. Table 28.1 summarises the qualities of various heaters.

Heating is based on three different physical principles: radiation, conduction, and convection. All principles are to a higher or lesser extent present in the various heaters. In an ultrasonic bath, convection is promoted by means of high frequency sound waves instead of heat.

Other important characteristics of the heating equipment are the option of keeping the temperature of the object at a constant level, the option of simultaneous stirring, the heating velocity and the space that the apparatus occupies.

The energy costs are determined by the efficiency and the heat transfer to and into the product. In general, the more conversions, the lower the efficiency. Compared to the energy that is required for heating and lighting of the premises, the energy usage of the heaters in the pharmacy is however quite modest. Differences in efficiency are therefore only described qualitatively.

Differences in thermal conductivity of various materials may play a role in the choice of a heater and the choice of the material of a heating vessel as well. A high thermal conductivity coefficient means a high conductivity, see Table 28.2.

28.5.2 Ultrasonic Baths

28.5.2.1 Application

Ultrasonic baths are used to increase the dissolution rate of slowly dissolving substances, especially when a substance is not very heat resistant.

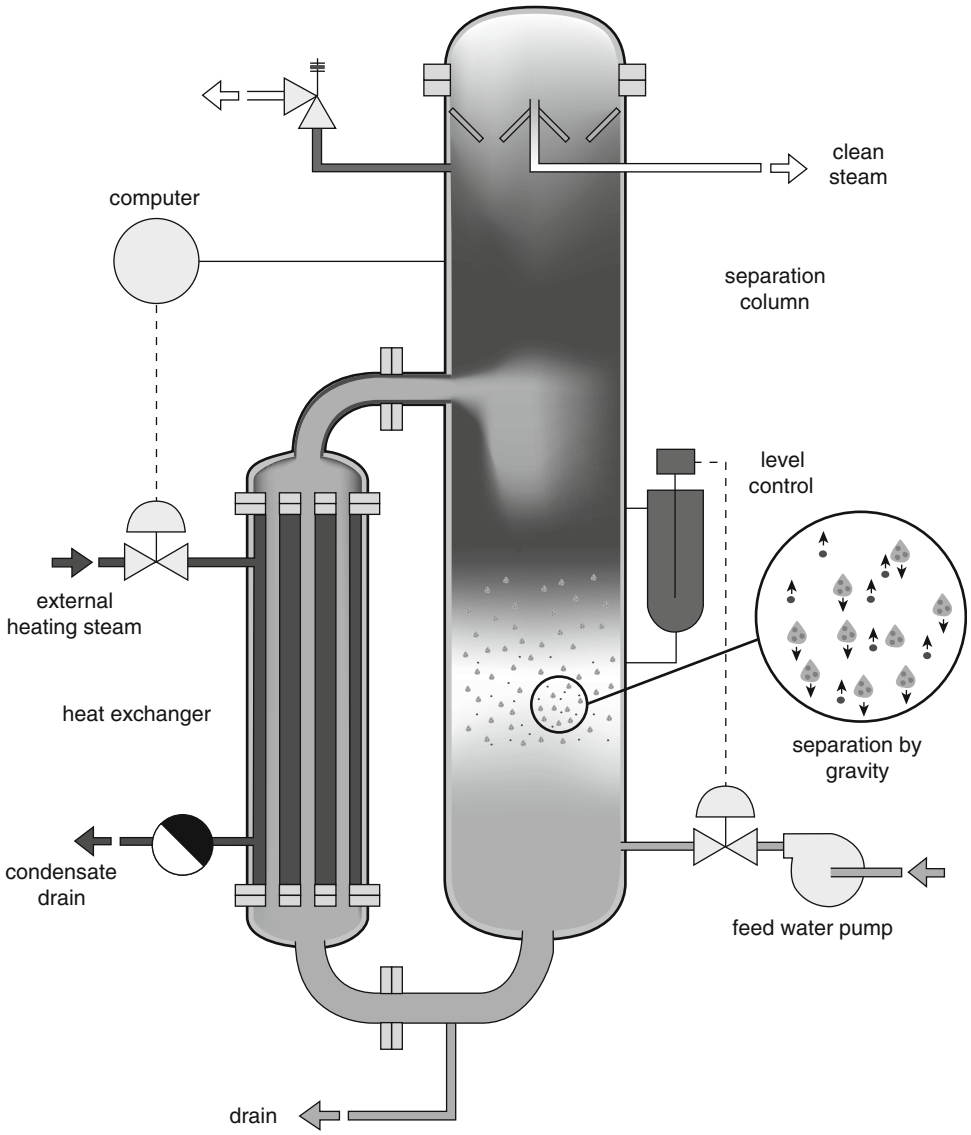

Fig. 28.5 Singular distillation column. Source: Recepteerkunde 2009, ©KNMP

28.5.2.2 Description

An ultrasonic bath contains water and creates waves from its walls with a frequency of more than 20,000 Hz. A container (usually glass) with solvent and the substance to be dissolved is placed in the water. The sound waves amplify in the water and pass, via the container wall, into the solvent. The powerful vibrations of the liquid increase the movement of dissolved molecules from the surface of the crystals into the solvent. This increase occurs at the micro level and does not lead automatically to a homogeneous solution. Therefore, the bulk of the solution should be stirred from time to time. The ultrasonic bath may include a bath that may be equilibrated at a fixed temperature by means of an electric heating source and thermostat.

28.5.2.3 Procedure

The same precautions about the water quality should be taken with an ultrasonic bath as with a water bath for heating purposes (see Sect. 28.5.5). Although ultrasound is not audible to the human ear, resonance tones are created within the audible range, which are quite annoying. Therefore, ear protection and placement in a separate room are advised.

28.5.3 Gas Stove and Gas Burner

28.5.3.1 Application

Gas stoves and Bunsen burners are used for quickly bringing to the boil water or aqueous solutions. However, accurate

Table 28.1 Qualities of various different heaters

Heater	Investment	Energy consumption	Speed	Use space	Thermostating	Built-in stirring
Gas stove	+	−	−	−	−	−
Electric heating plate	±	±	±	+	±	+
Heating lamp	±	±	−	±	−	−
Water bath	±	±	±	±	+	−
Microwave	−	±	−	−	±	−

+ favourable, ± moderate, − unfavourable

Table 28.2 Thermal conductivity of some materials

Material	Thermal conductivity coefficient ($W.m^{-1}.K^{-1}$)
Copper	380
Iron	50
Stainless steel	20
Glass	1
Water	0.6
Air	0.02

adjustment of the heat input is difficult and it is not possible to set the temperature. Both a gas stove and Bunsen burner do not take up a lot of space, but a gas supply is required. The room should be well ventilated because of the open fire, and no flammable liquids, vapours or gases should be present.

28.5.3.2 Description

The gas stove or Bunsen burner mixes natural gas with air to an optimally burning mixture. The tips of the flame reach temperatures of 1,500 °C. The produced heat is directed towards the container wall using a diffuser. Through the wall, conduction to the product occurs, in which the heat spreads by conduction and convection. Domestic gas stoves or a Bunsen burner usually are combined with a tripod. On top of the tripod, a metal gauze is used, sometimes with a pressed ceramic core or ceramic plate. The latter is the easiest to clean. The container should have a flat bottom for the proper conduction of the heat from the gauze or plate.

28.5.4 Electric Heating Plate, Immersion Heater and Heating Mantle

28.5.4.1 Application

Electric heaters can be applied in the same way as gas stoves or Bunsen burners. Since these heaters have no open fire, they are generally safer. A negative aspect is that they operate more slowly and have a lower efficiency. In general, electric heaters can be better controlled than gas burners, which means that overheating can be prevented more easily.

28.5.4.2 Description

An electric heating plate converts an electric current largely directed through resistance wires into heat. A cast iron, stainless steel, or ceramic plate conducts this heat to the container with the mass that should be heated. Ceramic has a few advantages, since it is lighter, heats faster and can be cleaned more easily compared to cast iron. Compared to stainless steel, it conducts heat better. However, heating of the plate requires time. The container should have a flat bottom for optimal conduction of the heat. Most heating plates can be adjusted to various levels of heating, which allows control of the temperature within certain limits. The heating plate can be combined with a magnetic stirrer, but these combinations have little stirring power. A heating plate uses little space, but requires an electricity connection.

An immersion heater consists of resistance wires embedded in ceramic material and mounted in a stainless steel spiral. The immersion heater should be placed in the liquid to be heated and is often connected to an immersion thermostat. For heating of large quantities the use of a container with a heating mantle is more efficient. The resistance wires are embedded in the mantle, thus the mantle conducts the heat to the product.

Another option is the use of a heating tape or blanket that can be wrapped around the container.

28.5.5 Water Bath

28.5.5.1 Application

The most important reason to choose a water bath for heating purposes, is the controllability of the temperature, since this cannot exceed 100 °C. Using a thermostat, the temperature can be controlled at any temperature between room temperature and 100 °C. With a cooling unit, lower temperatures are also possible.

28.5.5.2 Description

A water bath consists of a tank that is equipped with heating spirals with resistance wires, in which electricity is converted into heat. The tank is filled with water. The heated water conducts the heat to the container with the product, either by direct contact or through generated steam (‘boiling

water bath'). In principle, a water bath is equipped with a thermostat. The welds of the tank should be of good quality, otherwise leakage may occur as a result of calcification. The heating spirals are best embedded in the wall of the tank for the same reason. Tanks that consist of stainless steel can be used with purified water, which eliminates the risk of calcification. Purified water is too corrosive for less resistant metals. The shape of the container is not important, since both water and steam can cover non-flat surfaces well.

28.5.5.3 Procedure

The water bath should be filled to approximately two thirds of the volume with water. After incidental use, the bath should be emptied and dried after to prevent microbiological growth. When used daily, the water bath should be brought to 100 °C half an hour before use, and subsequently brought to the desired temperature. Moreover, the bath must be emptied and dried at least once in 2 weeks.

28.5.6 Heating Lamp

28.5.6.1 Application

A heating lamp may be applied for melting fats. Its advantage compared to a water bath is that a heating lamp bears no risk of bacterial contamination and contamination with water droplets. However, the surface of the fats is exposed to intensive radiation, to which the fat should be resistant. Moreover, the heat transfer is not controllable and the risk of overheating exists.

28.5.6.2 Description

A heating lamp converts electricity through a resistance filament into electromagnetic waves. These waves produce radiation heat that is absorbed by objects. The lamp is placed above the substance to be heated; a wide container is preferred for optimal heat transfer. The amount of heat cannot be regulated and depends highly on the distance from the lamp to the product. The lamp heats quickly after it is switched on.

28.5.7 Microwave

28.5.7.1 Application

Microwaves can be used to heat polar substances directly without the use of a medium such as air or water vapour to conduct the heat. Therefore, no energy is lost to the heating of the heat source itself and only little to the container with substance to be heated; the latter only heats up from heat coming from the content. Especially small quantities can thus be heated more quickly than with other methods. Its main application in pharmacies is selective heating of water or another polar solvent when heating of the other compounds or phase is undesirable, such as:

- Drying of herbs and eradication of vermin that may be present
- Drying and hardening of coatings
- Drying of granulates
- Regeneration of saturated silica gel being part of a container

A short heating time may be advantageous and meaningful because of a minimal temperature burden on the product.

28.5.7.2 Description

A microwave converts electricity into electromagnetic waves. The altering electromagnetic field sets molecules with a dipole, such as water, in motion. During this process, friction heat is produced. The electromagnetic waves have a frequency range of 100 to 1 million MHz, which corresponds to a wavelength of 0.03–300 cm. The efficiency of the conversion of electricity into electromagnetic waves is approximately 50 %. The energy source (microwave) is placed in a space (oven) with walls that are made of e.g. stainless steel, enamel or aluminium, which reverberate the waves. Most ovens contain a metal fan as well. This fan is not only meant to move the air in the oven, but also to mix the electromagnetic fields, in order to reduce the occurrence of nodes and antinodes. These hot spots may nevertheless occur as a result of the shape of the vessel in which it is heated, especially due to curved surfaces.

28.5.7.3 Procedure

For justified use of this heating method, the next points should be considered:

- The material that has to be heated and the container that is being used should be permeable to electromagnetic waves. Glass and many plastics are, but metal (e.g. aluminium foil) and melamine resin are not.
- The amount of energy that is required to heat the material depends on the polarity of the substance. Heating of less polar materials (such as paraffins) requires more energy (thus for a fixed setting of the microwave: more time) than polar materials.
- Microwaves penetrate about 3 cm into an object. Therefore, within larger masses the heat must be spread by conduction, which requires time.

The inside of the oven must be kept clean, in order for the surfaces to remain reflective. To prevent leakage of radiation the door must be kept clean as well and the closure must be checked.

28.6 Grinding, Mixing and Dispersing Apparatus

Mixing and dispersing are the most used preparation methods, see also Sects. 29.3–29.7. Mixing is achieved by axial, tangential or radial flow. These concepts are clarified in Fig. 28.6 and applied in the description of the apparatus. See Table 29.4 for the terminology of grinding, mixing and dispersing.

This section discusses subsequently the Stephan® mixer, the rotor-stator mixer, the planetary mixer, the mortar with pestle, the beaker mixer/blender, the three roll mill, the coffee grinder, the Topitec® mixer and Unguator® mixers.

28.6.1 Stephan Mixer

28.6.1.1 Application

The Stephan mixer is a combined mixing and dispersing apparatus. The brand name Stephan is used because of its specific construction and qualities. The apparatus can be used for the preparation of ointments, creams, emulsions, suspensions, gels, pastes, solutions, powder mixtures and granulates. The apparatus was originally developed for food processing.

The mixer is not suitable for grinding of crystalline substances. However, lumps and not too strong, large agglomerates can be broken up. For the mixing of powders it should be taken into account that the shearing forces are relatively weak compared to a mortar and pestle; they frequently fail to break up agglomerates.

28.6.1.2 Description

The Stephan mixer is available in different sizes, varying from 5 to 40 L for small scale preparations. The choice for the size will, not taking into consideration the available space in the pharmacy, depend on the volume of the batches. The vacuum version with a mantle is only a standard option for the smallest model; for the larger sizes it can be ordered as an optional feature. The larger sizes can be tipped over to facilitate the emptying of the bowl.

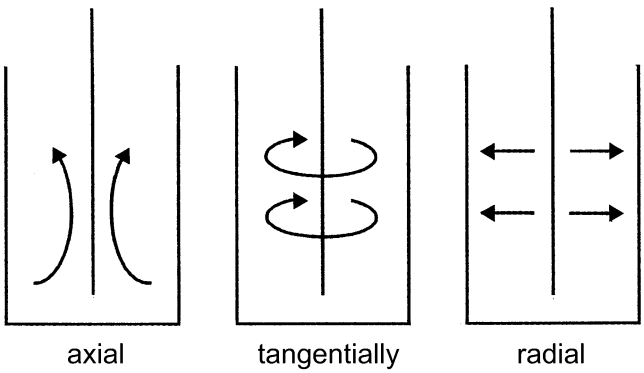

Fig. 28.6 Axial, tangential or radial flow. Source: Recepteerkunde 2009, ©KNMP

At maximum speed the mixer produces shearing forces at such an extent that they emulsify mixtures of water and oil. Only the rotor-stator mixer generates a higher shear force in fluids. During mixing an appreciable rise in temperature will occur, especially at higher speeds. If a mantle is available the contents of the bowl can be heated or cooled. The application of vacuum is relevant if air must be prevented from being whipped into the mixture.

The centrally mounted shaft is provided either with two stainless steel knives mounted in propeller position or with a mixing vane. The high rotation speed of the knives or the mixing vane down in the bowl results in an intensive mixing. The mixing vane provides a tangential and radial flow and additionally turbulence, See Fig. 28.7.

A plastic scraper, placed inside the bowl, facilitates scraping down the mass from the wall of the bowl, resulting in even better mixing.

The Stephan mixer requires a 380 V (3 phase) socket. The vacuum is realised with a small built-in vacuum pump. For the mantle a connection with a cooling water supply (usually tap water) and a drain is required.

28.6.1.3 Operating Procedure

The constituents to be mixed are being fed into the bowl with the mixing vane or the knives. When mixing fluids, the fluid with the least density is preferably fed in at the bottom. A fluid with a higher density, fed in on top of a fluid with low density will generate already a beginning of mixing as the heavier fluid will sink through the lighter one to the bottom. The mixing bowl is closed with the lid, not only to shield from splashing but also to be able to pull a vacuum as well as to fix the scraper that is mounted in the lid. If possible and desirable vacuum is applied subsequently. Mixing should start at low speed to prevent splattering of unmixed constituents against the inner side of the lid. Subsequently a higher speed is applied step by step. Depending on the consistency of the mass and the rate of filling it may be necessary to stir the mass in between by hand with a spatula. Be aware that insufficiently mixed mass may splatter onto the inner side of the lid. If emulsification is the objective the mixing vane should run at maximum speed for at least one minute. The precise adjustment of the apparatus depends on the nature of the preparation, the size of the batch and from the required sequence of adding the individual constituents. These adjustments have to be validated.

The shaft with the mixing vane should be greased regularly with a little soft paraffin. Additionally it is advisable to mount a non-return vessel between the bowl and the vacuum pump. This non-return vessel will collect any fluid that inadvertently could be sucked out of the bowl, keeping the vacuum pump dry and clean. Should, however, some fluid

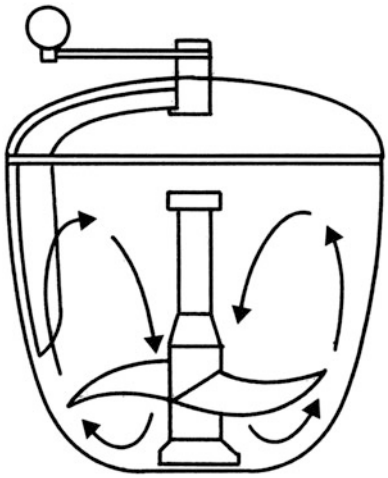

Fig. 28.7 Stephan mixer. Source: Recepteerkunde 2009, ©KNMP

enter the pump, at least the pump should run a couple of minutes 'dry' to prevent erosion. However in this case it is better to demount the pump and clean and dry all its parts.

Cleaning of the mixer seems to be easy, however this is must done quite meticulously. Almost all parts can be demounted and be cleaned separately. In any case extra attention is necessary for several connection points, the thermometer, the inner side of the pressure gauge and the inner side because they are provided with a rubber ring or contain a difficult cleanable screw thread. The apparatus does not contain its own drain, therefore the cleaning with soap water and the rinsing of the inner side requires a considerable amount of time.

The apparatus requires relatively little maintenance. For periodical servicing of the engine, the bearings, the vacuum pump and the seals of the shaft a specialised mechanic is necessary.

28.6.2 Rotor-Stator Mixer

28.6.2.1 Application

The rotor-stator mixer is used for the preparation of suspensions, emulsions and solutions. The apparatus is not suitable for mixing high viscosity fluids neither for any grinding of crystalline particles. For dissolving relatively easily soluble substances it is easier to apply a mixer with a mixing vane or a magnet stirrer instead. Keeping a suspension homogeneous during filling is better achieved with a stirrer with a well-designed mixing vane than with a rotor-stator mixer. The rotor-stator mixer is a dispersing apparatus in the first place, also suitable for breaking up agglomerates. Rotor-stator mixers may be suitable for the preparation of suppositories. For conditions see Sect. 11.5.3.

28.6.2.2 Description

The rotor-stator mixer is a mixing and dispersing apparatus consisting of an engine with an axis on which a rotor is mounted. The rotor comprises a series of vertically placed knives. The rotor turns with a very small tolerance inside the stator comprising of a cylinder with slits. The rotor, spinning at high speed, pumps the product through the slits of the stator, see Fig. 28.8.

The mixer causes a tangential, a radial and an axial flow. The mixing and dispersive effect are very intensive at the moment that the product passes the mixing head. High shearing forces that are required for dispersing, result from the narrow slits of the stator, the friction among the particles in the fluid and from the reduced space between rotor and stator.

The high shearing forces occurring during mixing cause a considerable amount of heat, and thus cooling may be necessary. However this heat can also be used for improving the rate of dissolution.

Optimal Speed and Mixing Effect

Increasing the spinning rate will raise the tangential flow rate and thus extending the chance at creating a vortex. Air will be sucked into the product and part of the added energy is lost in establishing the vortex. At a lower speed the chance of insufficient dispersive action and mixing exists. So the optimal spinning speed is the one where a vortex just evolves. This could imply that the mixing effect in the body of the product might be less intensive. Therefore, the volume of mass determines the size of the rotor-stator mixer. The supplier gives rough outlines for this. As a rule of thumb the rotor-stator mixer can run effectively if one third of the shaft is submerged in the product. If the shaft is inserted too deep into the fluid the product might be too close to the upper bearing with the risk of contamination and damage to the engine. Some models are provided with an overflow opening in the upper part of the shaft. The fluid should not discharge from this opening. Anyhow the determination of the relation between amounts of mass to produce, the size and form of the mixing vessel and the choice of a rotor-stator mixer can only be achieved by validation of the mixing procedure. Additionally it could be considered to place the shaft slightly slanted or eccentrically in the vessel, or to move the vessel and its contents up and down under the rotor-stator mixer.

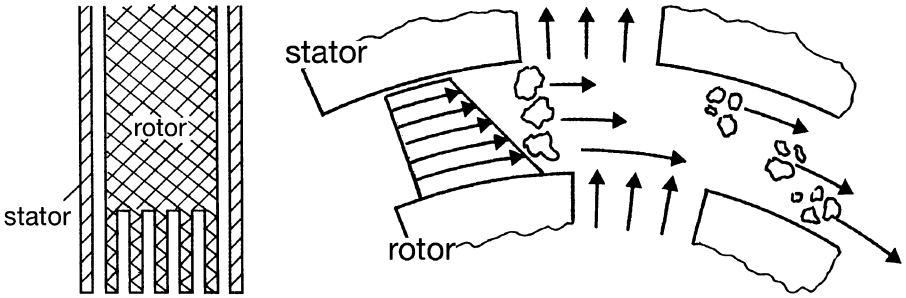

Fig. 28.8 Rotor-stator mixer, lengthwise section (**a**) and part of cross section (**b**). Source: Recepteerkunde 2009, ©KNMP

28.6.2.3 Operating Procedure

To control the possible noise nuisance the rotor-stator mixer should be placed in a separate area ('noise room'). The operator should bear ear protection.

> Noise levels are expressed in dB(A), an abbreviation for decibel-A. This sound level is adjusted for the frequency of the sound, because the ear is more sensitive for high than for low tones. Damage to hearing can occur from 80 dB(A). From this level the employer is required to provide hearing protection. Starting from 85 dB(A) employees are required to wear hearing protection. There are five types of hearing protection equipment. In increasing degree of effectiveness, these are: cotton wool, earplugs, earplugs, earmuffs and ear plastics. In the pharmacy equipment can be present at which hearing protection is mandatory: some rotor-stator mixers and tube closing machines. In the room where this equipment is used, there should be as few as possible people present during the preparation.

Large rotor-stator mixers and the accompanying vessels should be solidly mounted.

The rotor-stator mixer must never run dry. Without fluid, overheating occurs with risk of short circuits or affecting the dispersing head. The rotor-stator mixer generates a relatively high level of aerosols. To prevent the operator from exposure to those aerosols, the upper side of the vessel could be covered or placed under an exhaust.

Fill the vessel with the fluid in which other fluids or solid substances are to be dispersed. Place the shaft at the correct height (e.g. 1 cm above the bottom) in the vessel. Switch on the engine and gradually turn up the running speed. Be aware that switching on immediately at full power will raise strong reaction forces that might destabilise the placing. The fluid that is pumped by the rotor through the stator will be replenished at the down side of the head by hydrostatic pressure. Sometimes, the fluid that is sucked up can carry along the vessel which then might be sucked onto the dispersing head. Therefore, the vessel should be kept steady with a firm grip with the free hand. Glass vessels might easily break when being touched by the spinning mixer.

Next, the solid substances or fluids to be dispersed can be added; during this process the required speed might vary. Dispersing or mixing should be continued as long as is determined by the validation process.

Products that are difficult to disperse or to moisturise should be moistened in advance with a small amount of fluid; after dispersing the remaining fluid should be added.

When the mass is dispersed homogeneously the rotor-stator mixer should be turned off. Subsequently the shaft is pulled out and held above the product to drip dry. If necessary the shaft is wiped with a scrap card.

28.6.2.4 Cleaning

To enable adequate cleaning the stator has to be removed from the rotor. Larger rotor-stator mixers are equipped with an extra bearing near the dispersing head to prevent the long axis from swaying. A seal, e.g. a ring that cuts off any fluid from penetrating past the rotating axis, protects the bearing against the product. Seals are made from graphite or ceramic material. Seals made of graphite are preferred in blocking fluid penetration; however, they are more vulnerable. Ceramic seals are much more expensive. The seal is the most critical part as any product leakage, e.g. caused by an impairment during the cleaning process, will affect the bearing. Moreover, serious contamination of the product itself will occur from bearing grease, mixed with rusty product remnants, entering the product mass, past the seal.

Cleaning should done immediately after use by allowing the mixer to run in warm purified water with a small amount of detergent. Subsequently the mixer should run at least twice in a portion of fresh lukewarm purified water, until the rinsing water is clear and clean. This method is preferred if the rotor axis is equipped with an extra bearing near the dispersing head.

After each cleaning process the adequate function of the seal should be checked, e.g. using a piece of filter paper to test leakage on the axis past the seal. Additionally a shaft of this type should be demounted periodically by a qualified mechanic to check on any leakage traces. Parts that cannot be dried thoroughly after cleaning, e.g. because it is not suitable to demount the dispersing head, might be flushed with alcohol 70 %. Finally all parts should dry in the air. Drying in a stove or warm drying cabinet is not advisable because this will also dry the bearing grease.

Depending on manufacturers instructions an operator could demount the shaft. In that case all separate parts are cleaned with soapsuds prepared from soap and hot water. However, soap entering the parts with bearings should be avoided at any cost. Subsequently the parts are well rinsed with purified water and dried with absorption paper.

28.6.3 Planetary Mixer

28.6.3.1 Application

The planetary mixer is used for the preparation of creams, ointments, emulsions, suspensions, gels and light viscous fluids. The planetary mixer is developed primarily for the food preparation and thus not especially designed for pharmaceutical preparations. The shearing forces during mixing are considerably less than those of the rotor-stator mixer (see Sect. 28.6.2) and those of the Stephan mixer (see Sect. 28.6.1). This mixer therefore is not suitable for grinding particles or to break up agglomerates.

28.6.3.2 Description

The eccentrically placed stirring mechanism rotates around its own axis. The axis also makes a rotating movement in the vessel. Therefore, movement of the stirring vane is the same as a planet that rotates around its own axis as well as around the sun, hence the name planetary mixer, see Fig. 28.9. The mixer causes mainly a tangential and a radial flow. The mixing is very intensive.

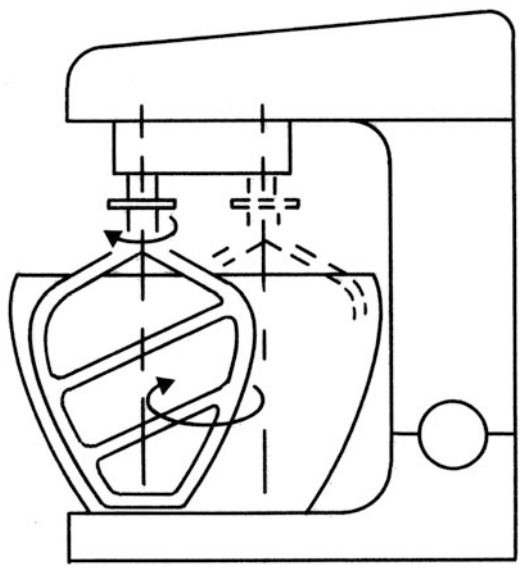

Fig. 28.9 Planetary mixer. Source: Recepteerkunde 2009, ©KNMP

There are mixers available with a mantle to heat, cool or isolate the contents of the bowl. The choice of the vane depends on the kind of product that is prepared. Most products will be prepared using the vane with the anchor form (also called "K-arm"). The so-called whisk vane is less suitable for fluid or semisolid products as this vane will easily beat in too much air. To prevent splashing product from the bowl during mixing some apparatus are equipped with a lid or splashboard that will completely or partly close off the upper side of the bowl.

Planetary mixers are available in different sizes, from kitchen apparatus to small industrial machines. The choice for the format of the mixer will, except from available space in the pharmacy, depend on the batch volumes. The apparatus can be cleaned easily, because both bowl and stirring vane can be detached from the apparatus. A maintenance agreement should be concluded, especially concerning larger mixers.

A relative disadvantage of planetary mixers is that they cannot run under vacuum. However, a good closing lid has advantages because it reduces the risk of microbiological contamination and of evaporation of water.

28.6.3.3 Operating Procedure

The stirring vane is attached to the apparatus and a part of the constituents to mix are transferred into the bowl. Fluids with the lowest density are preferably placed at the bottom of the bowl. When another fluid with higher density is placed on top, its gravity will already start the mixing process. Subsequently the mixer is switched on at low speed. The speed should then gradually be increased until the desired one. During mixing other constituents could be added. The speed never should be turned up to such a level that air is whipped in or the mass could spill over the rim of the bowl. This risk can be limited by placing a lid or splashboard.

In the case of viscous products the contents should be released from the wall with a scraper by hand, because in the immediate vicinity of the wall hardly any mixing takes place.

The mixing bowl and the stirring vane are usually cleaned by placing them in a washing machine.

28.6.4 Mortar with Pestle

28.6.4.1 Application

The mortar with pestle is a hand operated milling (pulverising), mixing and dispersing apparatus. The mortar is used for the preparation of ointments, creams, emulsions, suspensions, gels, pastes, solutions, triturations and granulates up to a scale that reasonably can be processed by hand. The brass of bronze mortar is also used for crushing plant materials.

28.6.4.2 Description

A mortar with pestle is a vessel widening to the upper side and a thick rod with a club form at the end, the pestle, see Fig. 28.10. A scrape card used for wiping off the mass of the wall is an essential attribute. A brass or bronze mortar distinguishes itself from the standard mortar in that the vessel usually is higher.

By shoving the pestle against the wall of the mortar a milling and dispersing effect results. Mixing takes place in primarily tangential direction. In semisolid and dry mixtures a more or less axial movement results from ladling the mass with a scrape card. This is hardly possible in fluid mixtures. Triturations should regularly be released from the wall and shovelled around with a scrape card. Additionally it is useful to tap the mortar, held a little slantwise, against the table top to recollect the powder.

Material

The mortar is usually made of porcelain ('stone' mortar'), melamine resin ('plastic mortar') or stainless steel ('metal mortar'). The pestle is made of smooth or rough porcelain or of smooth melamine resin. When a pharmaceutical substance is ground in a mortar some losses may result from 'sticking' to the wall of the mortar and the pestle or by being electrostatically charged and subsequently being drawn away by the air of any dust suction installation. Sticking to the wall is most pronounced in rough porcelain mortars. Electrostatic charging is expected to be most substantial in melamine resin mortars.

Traditionally, a porcelain mortar has either a smooth or a rough inner wall. A rough inner wall facilitates a more forceful rubbing, resulting in more friction; shearing forces then will be larger so a rough mortar is expected to be more suitable for pulverising than a smooth one. On the other hand pharmaceutical substances appear to stick more effectively to a rough wall ('into the pores'). Therefore, a general distinction in the effect of preparation in either a rough or a smooth mortar cannot easily be determined in practice. As a rule of thumb a rough mortar is used for pulverising pharmaceutical substances. A smooth one is more suitable for mixing and the breaking up of agglomerates.

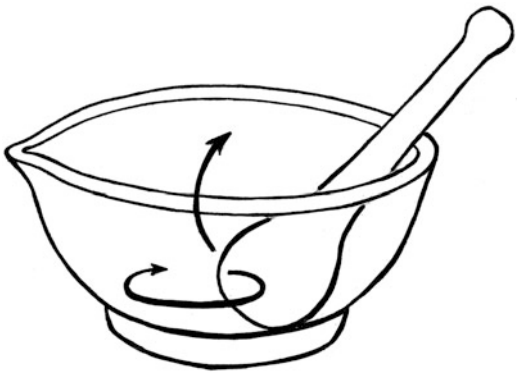

Fig. 28.10 Mortar with pestle. Source: Recepteerkunde 2009, ©KNMP

A melamine resin mortar is suitable for mixing and breaking up agglomerates, but not for pulverising. Additionally this kind of mortars should never be heated over 100 °C. Moreover coloured substances may give rise to difficult to remove smudges. A supplier suggests that stains may be removed by immersing the mortar in hot perborate solution at 80–90 °C.

A stainless steel mortar is suitable for mixing, not for pulverising. Additionally a stainless steel mortar lends itself for melting Hard fat for suppositories and fatty substances for ointments and creams. If necessary this mortar can withstand rather high temperatures. As a pestle only a melamine resin one should be used as a porcelain pestle might scrape off metal particles from the wall.

Furthermore plastic mortars and pestles are commercially available as a sterilised set. Disinfection and sterilisation of these kind of materials on a small scale takes validation and thus is inefficient.

> The material of the mortar has a substantial impact on the outcome of the preparation. An example is the preparation of Prednisone capsules 10–75 mg. In a rough porcelain mortar more substance 'sticks' to the wall (3–5 %) than in a smooth one (2 %). Moreover it has been shown that preparation in a melamine resin mortar causes losses resulting from electrostatic charging [11]. Using a stainless steel mortar results in no charging whatsoever.
>
> However, any general conclusions on the relationship between the material of the mortar and the attainable mixing quality are not possible.

28.6.4.3 Operating Procedure

For pulverising, a rough porcelain mortar with a rough pestle is necessary; an excess of pharmaceutical substance is pulverised and subsequently the prescribed amount should be weighed. Mixing usually is done with a smooth porcelain, melamine resin or stainless steel mortar. For mixing, the mortar should be sufficiently wide to facilitate scraping the sides and turning around the mixture. However, if the mortar is too wide it will result in a higher rate of loss. It is obvious that the total amount of constituents to mix will have an impact on the mixing time. However no suitable practical data on this issue are available.

If low dosed pharmaceutical substances, coloured substances or easily electrostatically chargeable substances are to be mixed in a mortar it is best practice to primarily

transfer a layer of bulking substance into the mortar, put the critical substance on top of that and finally cover it with another layer of bulking substance: the so-called wrapping method, see Sect. 4.5.1. If a porcelain mortar is rough and has large pores, the wall can be rubbed with excipient first, to block the pores. This is not necessary when a mortar with a smooth wall is used.

Mixing is achieved by stirring around the mass with the pestle. The stirring should be interrupted regularly to scrape the material from the wall with a scrape card. Powder mixtures should be shovelled around regularly and also the mortar should be tapped on the table slantwise too loosen the powder. Agglomerates are being broken up by vigorously rubbing by a suitable means (see Sect. 29.3). This should always imply small amounts, because otherwise vigorous rubbing is not possible.

28.6.5 Beaker Mixer/Blender

The blender may be used for small scale preparation of emulsions, suspensions and solutions. The apparatus is not suitable for grinding crystalline substances.

28.6.5.1 Description

The blender is a mixing and dispersing apparatus. At the bottom of the mixing beaker a mixing cross is situated consisting of four knives; two of them lying horizontally or are placed slantwise to the bottom; a second pair are placed slantwise upwards, see Fig. 28.11.

The mixing cross also causes a tangential and a radial flow and turbulence. During mixing a lot of air is whipped into the mass and after long mixing the temperature will increase.

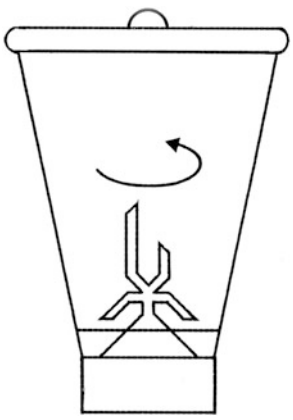

Fig. 28.11 Blender. Source: Recepteerkunde 2009, ©KNMP

Sometimes mixing cross and mixing beaker are one entity; in other cases the mixing cross is permanently attached to the engine block. Apparatus in which the mixing cross part can be detached from the engine are preferred because of the more easy cleaning of the mixing cross.

28.6.5.2 Operating Procedure

The mixing cross part is attached to the engine. Subsequently the beaker is screwed on top of it. The constituents to mix are transferred into the beaker. The beaker may only be filled up to half its volume as otherwise insufficient mixing will result.

To prevent splashing contents from the beaker it should always be covered with a lid. Subsequently the mixer is turned on. Sometimes it may be necessary to release the mass from the wall with a scraper. When the mixing beaker is detached from the engine block it is obvious that the mixing cross part should stay in place to prevent the contents from pouring out from the bottom. When the mixing cross part is one entity with the engine block the contents must be poured out before the beaker is detached. Extra attention should be paid to the mixing cross and the duct and the bearings of the axis during the cleaning process.

28.6.6 Three Roll Mill

28.6.6.1 Application

A three roll mill (or ointment mill) is used to disperse solid substances in a semi solid or thick fluid base. The constituents themselves should be mixed homogeneously in advance.

A three roll mill may be used:

- When the product mass is too bulky to be handled in a mortar.
- When the raw materials have ultra fine particles, such as zinc oxide, precipitated sulfur and substances indicated as 'micronised' (see Sect. 23.1.8). These powders have a strong inclination to form agglomerates. The three roll mill disperses those agglomerates in the semi solid base into the primary particles. After transferring through the three roll mill the mass should be mixed again (by hand or in a mixer) to distribute the particles evenly over the whole mass.
- To clear away whipped-in air. During the mixing of semi solid masses air is usually whipped in to some

(continued)

degree. This might result in the inability to fit the required mass into a tube. With the three roll mill the whipped in air is pressed out again from the mass.

If the transfer of a cream through a three roll mill is considered, it should be shown that the emulsion will not break.

28.6.6.2 Description

The three roll mill has, as its names already depicts, three rollers, usually made of ceramic material, having adjustable mutual clearances, see Fig. 28.12.

The mutual rotation speed of the rolls is, independent of the adjustments of their position, always different. Thus when a semi solid mass with incorporated agglomerates are transferred between the rolls and subsequently are transported from the slower to the faster roll, shearing forces are being exerted on the agglomerates, breaking them up into the primary particles.

The distance between the rolls can be reduced up to a minimum of 20 μm, thus principally enabling the grinding of crystalline particles to this size. Whether this is appropriate should be determined for each individual product. Commonly preparations in the pharmacy will use raw materials with the required particle size.

At the end of the milling process the mass is removed from the last roll with the mounted scraper. The scraper (drain board) is made of stainless steel or plastic.

28.6.6.3 Operating Procedure

In case of processing creams and other products that contain volatile substances evaporation should be considered. This evaporation might occur in an irregular way, thus necessitating final mixing. The degree of evaporation will depend on the duration of the process and thus from the batch volume.

Transferring a product through a three roll mill will cause losses. So if the resulting mass is an intermediary product used in another preparation process, this loss should be taken into account.

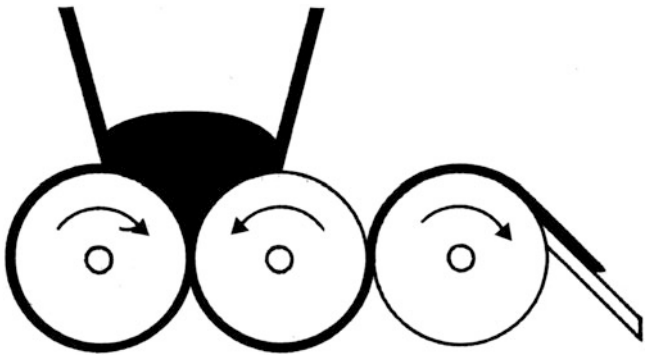

Fig. 28.12 Three roll mill. Source: Recepteerkunde 2009, ©KNMP

Description Three Roll Mill Exakt®, Type 35 Resp. 50

Shiftable guides are used to adjust the working width if small volumes are to be processed.

The rollers are subsequently adjusted to their smallest slit width (position I). A small volume of product is then transferred between the back and the centre roller. If the mass is not or difficult to transport the slit width is increased until the mass appears on the scraper plate. Subsequently the slit width is narrowed again as far as possible to maintain a minimum of transport. This procedure will attain the highest possible shearing forces. With rotating rollers the rest of the mass is transferred either with a scrape card or a spatula onto the back roller by wiping off in the opposite rotation direction of the roller, or the mass is transferred into the loading funnel.

The processed mass is collected in a mortar and then again meticulously mixed.

To check the mass for any agglomerates, a couple of samples are randomly taken from the mass, flattened between two glass slides and then assessed by examining it against light. If agglomerates are still visible the mass is transferred once more through the three roll mill.

28.6.6.4 Cleaning

The apparatus should be cleaned immediately after use. The cleaning procedure has to be validated with a well designed procedure based on a worst case situation. If cleaning of a specific product or substance appears to be notoriously difficult, the product may play a role in the cleaning validation. Cleaning starts with pulling the plug from the socket. Also the funnel (if applicable) the guides and the scraper are removed. All parts are cleaned (using detergent and lukewarm water) and well dried. Subsequently the rollers are adjusted to their greatest slit width (position III). The rollers can be rotated by hand by means of a knob at the left side. Never run the rollers, engine-driven, during cleaning. The main part of remaining mass is then removed using a tissue.

The cleaning of the rollers is done with a tissue drenched with water in case of a water-soluble mass, or with a tissue drenched with liquid paraffin in case of a fatty mass. The flanks of the rollers and the places just below them must not be forgotten.

Finally the rollers should be wiped off and dried thoroughly with another tissue.

Ether or other inflammable organic solvents should never be used for cleaning; Switching on the motor may elicit a spark and cause a fire.

After cleaning the guides, the scraper and if applicable the funnel, are mounted again. All parts should be completely dry. Finally the apparatus should be covered with a dust cover.

At least once a year maintenance is required.

28.6.7 Coffee Grinder

28.6.7.1 Application

In some instances a coffee grinder might be used in the pharmacy to pulverise (coated) tablets to process them into capsules. The application is contentious because the milling process cannot be controlled very well and the cleaning process cannot be validated either. The apparatus is discussed because nevertheless in pharmacy practice applications for the coffee grinder do exist. The only small scale alternative for milling and mixing of powders is the mortar, having the drawback that fragments might spill from the mortar and the result might not be fine enough. This is especially applicable for hard (coated) tablets. The coffee grinder may be used for mixing powders as well. It has the advantage, over hand-operated mixing, of being fast and intensive, although also segregation is reported to evolve sometimes. A drawback however is that mixing may cause unintentional grinding and heating.

If a coffee grinder is used for one of the purposes described it must be validated that this way of processing will actually yield a product that meets all requirements.

28.6.7.2 Description

In principle the coffee grinder is a beating mill. Grinding is realised by strokes of the knives that spin with high speed down in the milling space. A fine powder with a narrow particle size distribution is provided.

28.6.7.3 Operating Procedure

Reproducible milling and thorough cleaning are major points of attention. The efficacy of milling depends on the filling rate and the duration of milling, so this should be determined and documented for each individual substance. Variations in starting material properties, losses by atomised ultra fine particles and temperature increase should be considered. If mixing is aimed at, it should be assessed if the grinding and the temperature increase are acceptable and if a homogeneous blend will result.

Additionally the possibility of dust explosions should be considered. This is of special concern in a mixture of high concentrations of substances with elevated explosion risk. Usually substances of this type in the pharmacy are being offered as 'phlegmatised', which means that they are premixed with excipients that extinguish their explosion risk (such as benzoyl peroxide hydrated 25 % water and nitroglycerin with 40 % lactose).

28.6.7.4 Cleaning

The apparatus should be cleaned thoroughly to prevent any cross contamination. This procedure should be validated. Substances which dissolve slowly may play a role. A suitable procedure could consist of the following steps:

- Wipe the empty mill (including the knives) with tissues drenched in water.
- Repeat this with tissues drenched in ethanol 70–96 %.
- Then let the grinder run with microcrystalline cellulose. The cellulose acts in this situation as a pharmaceutical inertial cleaning powder.

28.6.8 Topitec and Unguator

28.6.8.1 Application

The Unguator and the Topitec are mixing apparatus for semisolid preparations. Mixing is executed inside the final container, see Fig. 28.13. The mixing process can be programmed after validation. During the mixing process the operator will hardly be exposed to substances.

28.6.8.2 Description

A mixing disc or propeller is mounted to a bar driven by a stirring engine. The bar is guided through the lid of the container or through the movable bottom. When placed inside the mixing vessel (final container) this mixer cause, predominantly, a radial flow. Axial and tangential flow should be created by moving the vessel up and down.

28.6.8.3 Topitec

Three types of the Topitec are available. The most simple one is the Basic. The mixing vessel should be moved up and down by hand, which precludes standardisation of the preparation method.

The vertical movement in the type Automatic is executed automatically. The preparation programs (rotational speed and mixing time) are adjustable and can be stored in a memory. With the Automatic amounts up to 1 kg can be produced and the apparatus can be cleaned easily. The movement in the type Touch is also executed automatically.

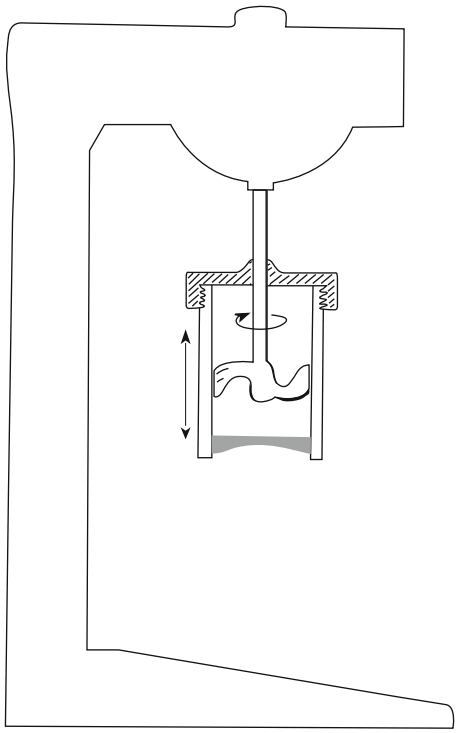

Fig. 28.13 Unguator, schematic. Source: Recepteerkunde 2009, ©KNMP

28.6.8.4 Unguator

Of the Unguator three types are available: B/R; e/s and 2100. The B/R model requires moving the mixing vessel up and down by hand, which precludes standardisation of the preparation method.

The vertical movement in the type e/s is executed automatically. Rotational speed and mixing time are adjustable and programmable. With this type up to 500 g can be produced in one process. In the type 2100 up to 1 kg can be prepared and numerous preparation processes can be stored and reproduced for repeated execution.

28.6.8.5 Preparation Method

The suitability of the apparatus should be validated for each formulation and batch size. The following points of attention can be given, with reference to dispersion and mixing by hand with mortar and pestle (see Sect. 28.6.4, see also Sects. 29.2–29.7 on the basic operations on dispersing and mixing):

- Control of the product is not possible during processing. The visual control of homogeneity in the final product (and for instance the surface of the mixing disc or propeller) requires more attention.
- Physical stability may be challenged because of the high rotational speed of the mixing disc or propeller.
- Heating may occur due to mixing which may increase degradation of heat labile substances and may cause supersaturation (see Sect. 18.1.6).

The DAC/NRF [12] issues following guidelines:

- Never mix any coarse or fine crystalline substances with the cream or ointment; just very fine pulverised, preferably micronised, solids or suitable concentrates (see Sect. 29.1.8) should be used.
- Stir if necessary the active substance intensely with a small amount of base as a premix, comparable to the first step in geometric dilution using mortar and pestle (see Sect. 29.3.3).
- Apply the wrapping method: first transfer half of the basis into the container, than add the active pharmaceutical substance and finally introduce the rest of the base.
- Remove enclosed air as far as possible before mixing.
- If heating is involved stir gently and repeatedly within the cooling-off time.
- Don't process heat labile preparations.

Premixing in the container may be advantageous if insufficient homogeneity is obtained, especially when processing of low concentrations. The active substance is at first mixed with 5–10 % of the base and subsequently the rest of the base is introduced. Another option is mixing at different rotational speeds: first at about 500 rpm and then at a higher speed.

Some creams are known to lose viscosity by mixing with this type of apparatus.

28.6.8.6 Testing and Validation

Validation has been described in [13]. The risk of inhomogeneity is most prominent with more viscous bases and with low dosed active substances.

Every formulation and batch size should be related to a specific rotational speed and mixing time. These should be documented and their correct application warranted. Samples should be taken from the most critical places in the container: near the nozzle, at the bottom and in the centre of the mixing disc or propeller. The centre of the mass is a critical place as well: the mixing effect of the mixing disc or propeller sometimes fails at that particular place.

Validation is best started with a limited number of typical preparations. With experience from the results the range of products can be expanded gradually. Colouring agents may be used to indicate homogeneity, however it cannot replace the analytical assay of content regarding active substances with a variety of particle sizes or other properties. The Topitec and the Unguator are mainly used for individual preparations; a small overproduction could be used for continuous validation.

28.6.8.7 Packaging and Shelf Life

The mixing vessel is the container in which the product is dispensed to the patient (see Sect. 24.4.7). This container is not air and light tight which has to be taken into account. Substances that are vulnerable to oxygen or light may

degrade. Products containing dithranol, tretinoin or isosorbide dinitrate, therefore should be packed in aluminium tubes immediately after the mixing process.

A series of container sizes are available. For the Unguator type containers several attachments can be supplied, i.e. cannulas for more accurate dosing. To push or screw in the bottom of the container requires quite some force: this will not work for all patients. The solution is then to pack in aluminium tubes instead.

28.7 Filling and Apportioning Apparatus

When the bulk mass is ready it has to be divided into portions with the quantity of one dose (capsules, suppositories or powders) or one dispensing unit (bottles or tubes).

This section will discuss subsequently:

- Filling apparatus for fluids
- Suppository molding apparatus
- Capsule filling and closing apparatus
- Tubes filling apparatus

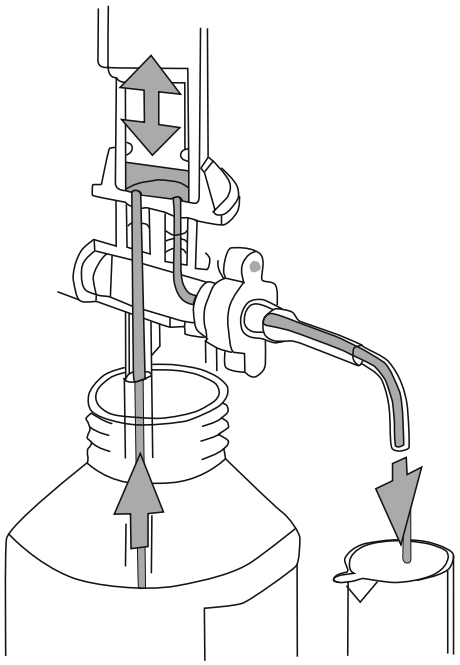

Fig. 28.14 Dispenser. Source: Recepteerkunde 2009, ©KNMP

28.7.1 Small Scale Filling Apparatus for Fluids

28.7.1.1 Application

Devices that are used to deliver a fixed volume per container are called dispensers or filling pumps. Apart from these, pumps are used e.g. to transfer the product from one vessel to the other.

Fluids that are portioned out in a pharmacy usually are solutions for external use and oral liquids. However, emulsions, suspensions and light viscous fluids are also being portioned out with dispensers or filling apparatus. Apportioning of suspensions and emulsions always should be executed under continuous stirring.

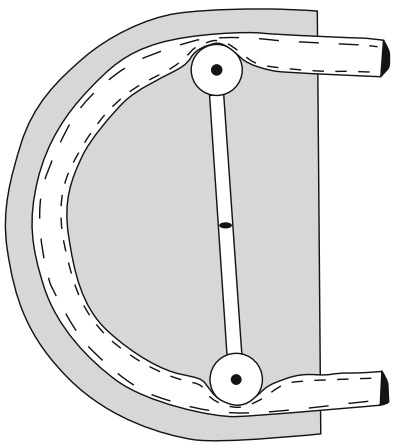

Fig. 28.15 Peristaltic tube pump (principle). Source: Recepteerkunde 2009, ©KNMP

28.7.1.2 Description

The filling apparatus in the pharmacy usually is a dispenser or a peristaltic tube pump, see Figs. 28.14 and 28.15. For filling very tiny batches an injection syringe may be suitable as well.

Requirements for a dispenser or pump are:

- The dosing must be accurate, correct and reproducible.
- The apparatus or tubing should not discharge any foreign substances or particles (this should be documented for each apparatus).
- The apparatus, tubing or the filling process should not be a source of microbiological contamination.
- The material that has immediate contact with the filled product should neither adsorb nor absorb any substance.
- Parts that are in direct contact with the product should be designed for easy cleaning and drying and if necessary should be autoclavable.
- Appliances such as hoses should be economically efficient in use.

28.7.1.3 Dispenser

A dispenser is a semi-automatic dosing and filling apparatus, allowing fixed volume dosing by hand. The apparatus consists of a glass cylinder, in which a piston is mounted.

The piston is moved up and down by hand. The stroke can be adjusted to the desired dosing quantity.

The choice of the size will, apart from available space, depend on the quantities that should be filled per stroke and from the desired filling speed.

Most dispensers may be designed for laboratory use which might involve that general principles of hygienic design are not or insufficiently met. So all parts should be dismounted after use and be cleaned, rinsed and dried. For critical applications a cleaning validation is required.

Maintenance is usually carried out within the department. However availability of spare parts is required.

Dispensers are available in different dosing ranges, e.g. from (small volume) 0.4–2.0 mL, increasing to (large volume) 300 mL. The material in direct contact with the product usually consists of inertial glass (piston, cylinder) and Teflon® (nozzle, suction hose). Some dispensers are made suitable for the dosing of aggressive fluids by a specific choice of materials.

The product is transferred into a pharmaceutical grade holding flask of which the screw thread fits onto the dispenser from which a Teflon suction hose stretches to the bottom of the flask.

The cylinder is stripped from air bubbles by pumping the piston a number of times.

The empty unit to be filled is placed under the plastic nozzle. Thereafter, the adjusted volume is dosed by moving the piston up and down by hand.

28.7.1.4 Peristaltic Pumps

Apart from the dispenser the peristaltic tube pump is generally used as a filling apparatus for liquids. Lower pressure peristaltic pumps typically have dry casings and use rollers along with non-reinforced, extruded tubing. This class of pump is sometimes called a 'tube pump' or 'tubing pump'. Pumps that work with higher pressure and (reinforced) hosing are called hose pumps.

This tube pump facilitates the automation of the filling process. The most simple model is actuated by a foot switch. In more automated filling systems the empty container is placed under an electronic eye, actuating the pump, to fill the required volume.

Peristaltic pumps have no valves, seals or glands to leak, clog or replace.

The pumped fluid does not touch the pump itself – it is in contact only with a high-pressure, flexible hose or tubing, thus eliminating the risk of the pump contaminating the fluid, or the fluid contaminating the pump. Maintenance is confined to a periodic hose change, which takes minutes. Peristaltic pumps can run dry, reverse their direction of flow, and are self-priming. A tube pump is an example of a peristaltic pump for accurate dispensing. In pharmacy practice it can be a more or less pulseless, small or medium size bench top pump. It has manual or semi-automatic control. It has the principle of a positive displacement pump, used for dispensing a variety of solutions for oral, parenteral or external use and of different viscosities. They are easy to install and after training simple to operate.

For all pharmaceutical applications a hygienic design of the hose pump including hosing is very important to prevent microbial growth in the tubing. For parenteral use membrane filtration in the filling line is recommended to prevent foreign particles entering the parenteral finished product.

The heart of a hose pump is the rolling pump head. Usually this will be a precision multi-roller pump head for accurate flows. The fluid is being drawn into the pump, trapped between two shoes or rollers and finally being expelled from the pump. The complete closure of the hose which is squeezed between a shoe and the track, gives the pump its positive displacement action, preventing backflow and eliminating the need for check-valves when the pump is not running.

The operator has to place special pump head hosing or special silicone dispensing hosing under the rollers of the pump head. The tubing to be fixed in the pump head can be either a separate short piece of special pump head tubing or it can be the tubing hose itself (in one piece). The pump head section divides the tubing in a suction part and a dispensing part. Fixating points in the pump head prevent the tubing in the pump head from sliding and moving during pump action. The pump head itself consists of several hard hose rollers that revolve within a C-shaped recess in which the silicon pump hose tightly fits. The rollers squeeze the pump hose by rolling over, resulting in a peristaltic pump action with a suction effect. The rolling speed can be chosen by the operator. At the suction side an extension hose made of a pharmaceutical grade rubber might be attached to the silicon hose to dip into the stock vessel. This extension hose should be rigid to prevent it from collapsing during suction. The rubber material should be compatible with the product. That extension hose must be autoclavable as well. This hose should have a stainless steel notch at its end to prevent the suction hose from sticking to the wall of the vessel during suction. At the dosing side of the pump a compatible and autoclavable hose is mounted with, at its end, a filling needle (nozzle) made of stainless steel, to be fixed in a holder above the package to be filled. The filling needle can be sterilised or cleaned and stored dry.

Some special hose pumps are equipped with a double pump head. This is to buffer the pulsing action by synchronising both pump heads in such a way that a more steady flow arises at the filling process. A drawback is that the assembling of such a pump configuration requires a lot of training of the operator and a good management of the (sterilised) materials as well.

Per product the specific pump (tubing) parameters and any other adjustable variables should be well documented, for instance pump speed, pump tubing specifications, type of pump head and specifications of extension tubings for the suction side and for the dosing side.

28.7.1.5 Pump Tubing

Both the inner diameter and the wall thickness of the pump tubing are of great importance. The manufacturer supplies obligatory guidelines. The supplier should deliver the tubing in a well labelled box, with a clear description about diameters and application purpose. Per pump model a set of tubing formats should be introduced, varying from large to small. The large ones dose more fluid per unit of time than the small ones.

Only qualified silicone pump tubings should be used. Any tubing, not specifically designed for tubing pumps might have a poor chemical and physical material quality soon resulting in internal abrasion. This could lead to contamination of the product and to inaccurate dosing. For the dosing of parenterals some producers recommend the 'platinum cured' tubing. This rubber quality has a relatively low wearing off of extractable components.

The tubings when mounted on the pump, should be pre-rinsed with the product to be filled. This is to prevent dilution of the product by retained condensation water after sterilisation and to saturate any possible adsorption sites.

Pump tubings may easily adsorb substances, which could cause cross contamination or staining of the tubings. This problem may be approached differently:

- By single use tubings
- By using dedicated tubings
- By cleaning the tubings after use

The single use of tubings seems to be quite expensive. However it may be an acceptable option when put in the perspective of the efforts coming with both other options.

Using dedicated tubings requires:

- Cleaning, rinsing and drying after use (or sterilising as a more reliable process than rinsing and drying). Drying may occur in drying hot air cabinets. The assessment of the correct drying time however is not easy; as a consequence tubings might stay too long inside the hot drying cabinet. For sterilisation the best practise may be to let the tubing drip dry after the last rinsing phase, as far as possible, subsequently wrapping it into a special sterilisation-laminate pouch and finally steam-sterilise it. The steam will, by means of the vacuum pulses preceding the sterilisation process, penetrate the tubing fully and sterilise it externally and internally. Verify the sterilisation temperature recommended by the producer of the tubing. This should be at least 121 °C.
- Storage of a large pile of laminate pouches with packed, sterilised tubings and filling needles
- Documenting the use of every tubing in order to remain within its shelf life

Cleaning tubes after use requires, in excess of these requirements, the validation of the cleaning process, which is practically unfeasible.

Needles and nozzles should be cleaned very thoroughly regarding their tiny apertures. The effectiveness of the cleaning should be validated.

28.7.2 Suppository Molding Apparatus

28.7.2.1 Application

Suppository molding apparatus are used to produce comparatively larger batches of suppositories. In the pharmacy this will usually amount to 250–1,000 suppositories per batch. The apparatus is denoted as *hand-operated* if the apparatus is just designed to keep a relatively large amount of suppository mass homogeneous and at the right temperature during molding. The actual dosing and placing of suppository molds below the dosing point is hand-operated, in that case. If the dosing is executed automatically the apparatus is denoted as *half-automatic*. With a *fully automated* apparatus also the transport of molds below the dosing point is automated.

28.7.2.2 Description

A Suppository molding apparatus (see Fig. 28.16) consists of the following components:

- A double-walled metal or glass vessel in which the suppository mass is contained
- A water reservoir in the casing of the vessel which is kept at the desired temperature by a heating coil and a thermostat
- A stirrer placed inside the vessel to keep the mass homogeneous during molding
- A dosing point, equipped with a tap or an automatic dosing mechanism, heated or not
- A number of holders for strips of plastic suppository molds, optionally with an automated transport mechanism and a foot switch

The calibration of the temperature probe and the accuracy of the temperature adjustment of the suppository mass are critical for the process. Additionally the cooling rate near the dosing point is critical as the mass might solidify prematurely.

The water reservoir is at an ideal temperature for microorganisms to grow. Therefore effective measures should be taken to prevent microbiological contamination. The indications in Sect. 28.5 apply.

The (half) automated apparatus, in principle, facilitate a more reproducible method of working than hand operated apparatus.

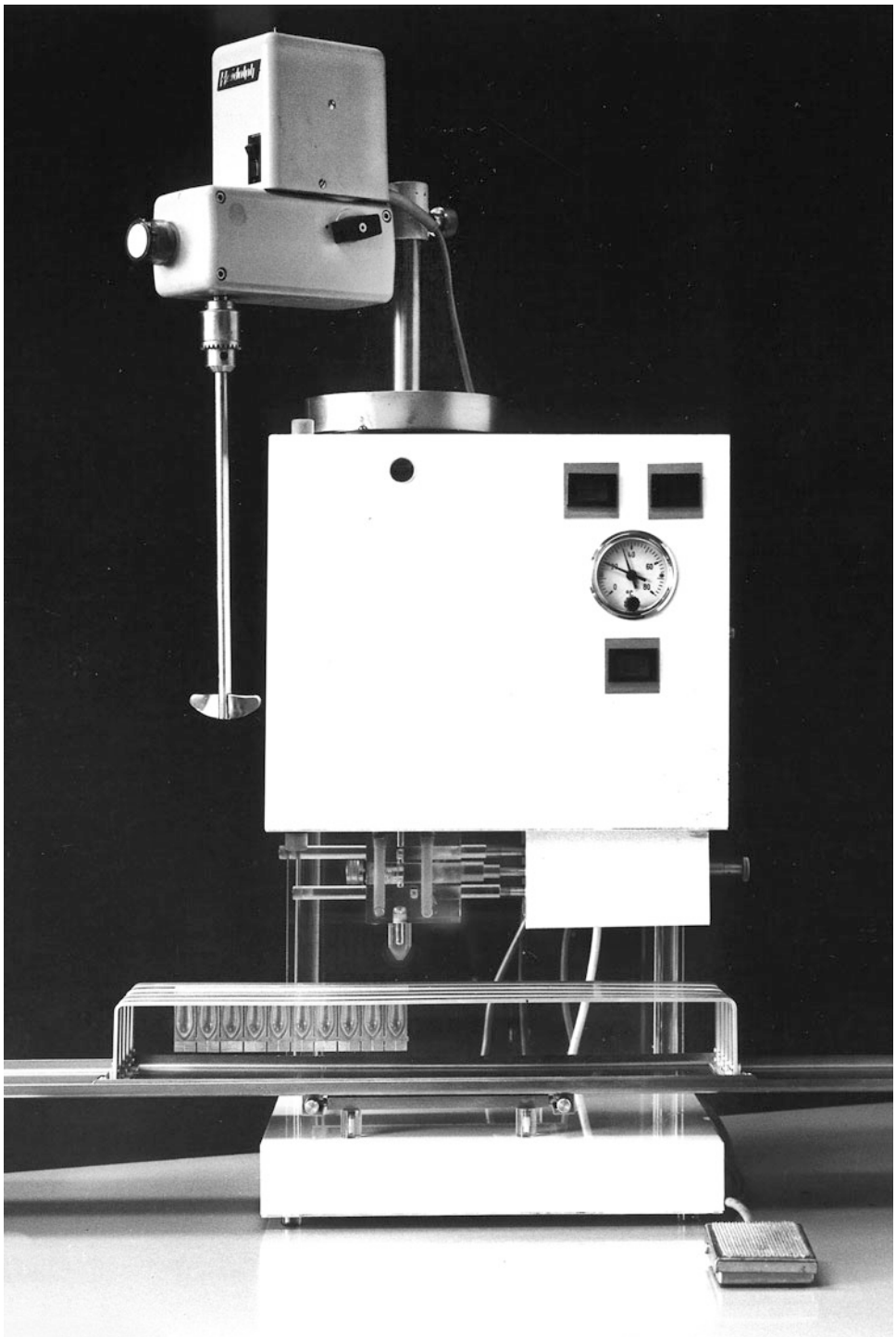

Fig. 28.16 Suppository molding and pouring apparatus. Source: Recepteerkunde 2009, ©KNMP

28.7.2.3 Operating Procedure

Either suspension suppositories or suppositories with dissolved active substances can be molded with the suppository molding apparatus. Preparation of suspension suppositories is the most common, however it is also the most critical process, as is discussed elaborately in Sect. 11.5. Dispersion of larger quantities of active substance is best performed by using a rotor-stator mixer, which cannot be executed within the suppository molding apparatus. An alternative way of dispersing is triturating the powder with molten base in a mortar and add it to the rest of the molten mass in the apparatus vessel. The blade stirrer of the molding

apparatus is only suitable to keep the pre-dispersed suppository mass homogeneously during the phase of molding; no dispersion can be achieved.

The mass should be mixed continuously during molding. A rotor-stator dispersing apparatus is not suitable for this purpose as it whips air into the mass and its mixing is insufficient.

The shape of the stirring blade, the position of the stirrer in the vessel and the stirring speed all have decisive impact on the efficacy of the mixing process. The stirring blade should be placed as close above the molding drain as possible. The stirrer should be pre-adjusted, and re-adjusted during the molding, at such a speed that no air is whipped into the mass [14–16].

A suppository molding apparatus should be subjected to initial and periodical qualification and the molding process to validation. The precise method to execute the PQ depends on the formulation and batch size. A worst case scenario should always be defined and test processes should be executed with a suitable formulation. The test product should be mainly examined on content uniformity, weight uniformity, and appearance.

28.7.3 Capsule Filling and Closing Apparatus

28.7.3.1 Application

The small scale preparation of capsules (see also Sect. 4.6.3) is performed with hand operated capsule opening, filling and closing apparatus for small batches.

Per single batch a portion of 50, 60 or 100 capsules can be prepared; larger batches can be made by reiterating the filling of the single batches. The production capacity per hour is at maximum about 1,000 capsules.

Large scale capsule filling machines are not commonly used in pharmacies. They may require a different design of the powder mixture because the way of operating requires a better flowability.

If large batches of oral dosage forms are necessary, usually the production of tablets is considered. Tableting machines for relative small batches are commercially available, e.g. Korsch XP1, Manesty B4, Optima 3000, Riva-Piccola.

28.7.3.2 Description

A hand-operated capsule opening, filling and closing apparatus consists of a rectangular metal frame with below and above four horizontal plates, see Fig. 28.17.

The lower plate can be moved up and down relative to the frame. The upper plate is mounted with a hinged transparent cover that can be fixed. The upper plate, as well as the middle plates, is perforated with 50–100 holes for the capsules. Apparatus brands that are used frequently are Capsunorm® (plastic type), Feton® (plastic type), Loeco® (polycarbonate), Loetschert® (aluminium), Optima® (aluminium) and Profill® (aluminium). The overall width of the holes depends on the capsule size. Each apparatus is dedicated to a fixed capsule size. The holes in the upper plate are tapered to the underside, so only the lower halves of the capsules fall through, see also Fig. 28.18.

The holes in the two middle plates are smaller and have the same size as the smaller lower halves of the capsules. The lower middle plate can be moved slightly in horizontal direction relative to the upper middle plate resulting in slightly displaced holes relative to each other. The lower middle plate can be fixed in its shifted position by means of two clamp screws, thus fixing the lower halves of the

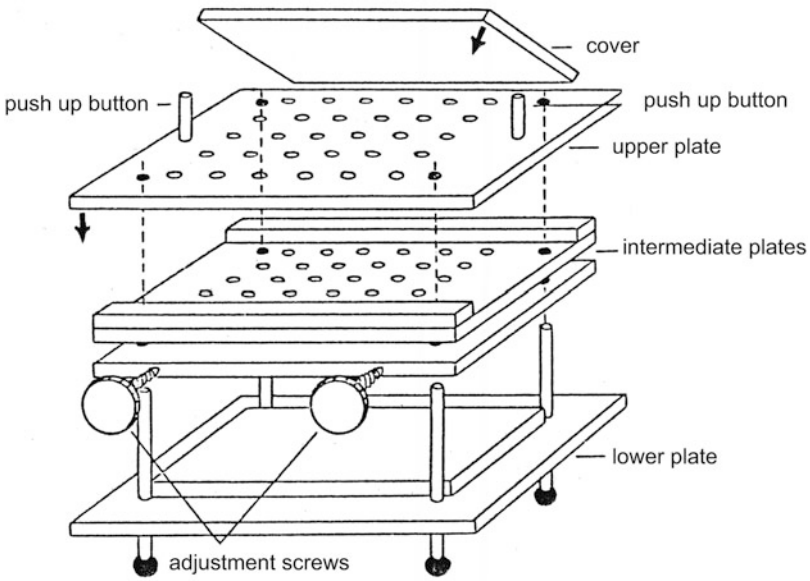

Fig. 28.17 Hand-operated capsule filling and closing apparatus. Source: Recepteerkunde 2009, ©KNMP

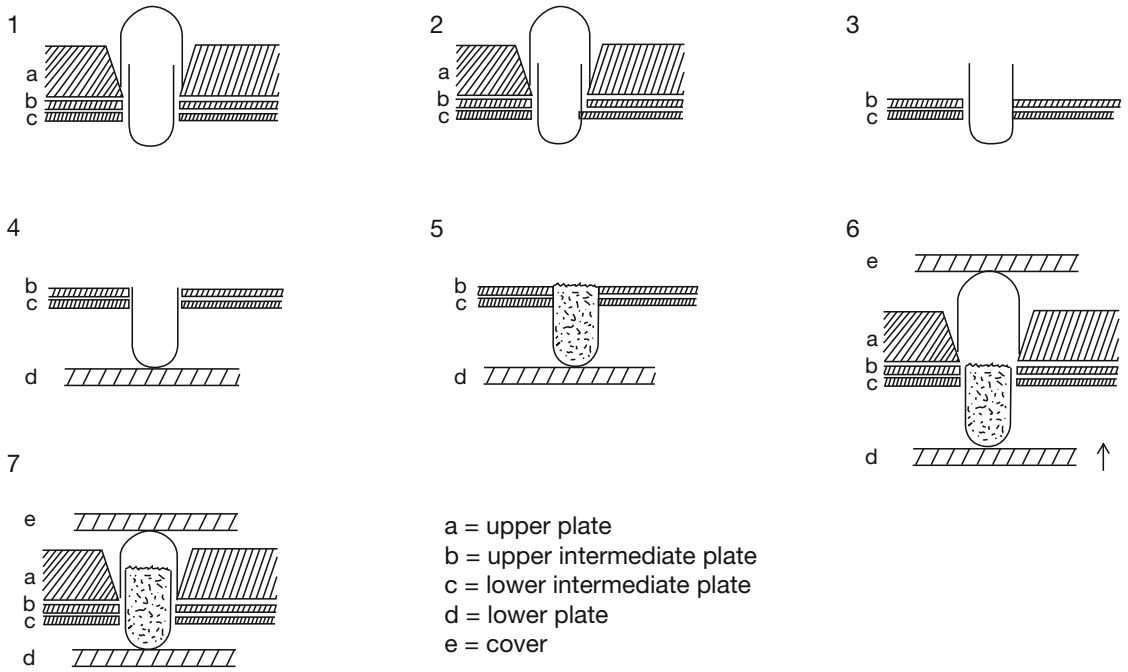

Fig. 28.18 Filling of hard gelatine capsules. Source: Recepteerkunde 2009, ©KNMP

capsules and facilitating the separation of the upper halves all at once.

The upper middle plate is equipped with an edge that contains the powder during its spreading over the plate. After filling of the lower half of the capsules the upper half is placed and the capsules are closed.

Issues to consider at the purchase of a capsule filling and closing apparatus are, ease of use and sustainability. However apart from this there are additional issues:

- Material of the plate sets; the plate sets are made of aluminium or plastic; plastic plates are not resistant to hot water cleaning; the plates might warp easily. The process, cleaning instructions and the periodical assessment should be adjusted appropriately.
- The option of using capsules arrayed on card; the efficiency of these cards may outweigh its extra costs.
- The option of the use of a capsule sorting apparatus; this is an empty capsule "orienter" to drive the capsules in the right position.
- A tamper, powder spreader or disposable plastic powder spreading card might be practical for powder distribution and filling in some cases; however be careful: the use of these and other devices must always be standardised and validated. Otherwise the process might not be reproducible enough.

28.7.3.3 Operating Procedure

The preparation of hard gelatine capsules covers four steps: insertion, opening, filling and closing, see Fig. 28.18.

If less than the apparatus capacity of 50 or 100 capsules is being prepared, the unused openings of the apparatus should be covered, for instance with tape.

If the insertion of loose capsules is done by hand, gloves (unsterile) should be worn to avoid any contamination of the capsules. Wearing gloves is recommended anyway to avoid exposure of the skin with hazardous substances (see Sect. 26.4.3).

Insertion by means of a capsule sorting apparatus is executed, in principle, quicker and more hygienic, although the apparatus does not always function flawlessly. Capsules arrayed on a card can be inserted quickly, hygienically and faultlessly. The card is placed, with or without an adapter, and using a little bar the capsules are pressed out off the card into the holes of the apparatus. A card may have the disadvantage that the choice of the capsule type itself is limited.

28.7.3.4 Cleaning

After use the apparatus must be cleaned thoroughly to prevent cross contamination. The upper plate and both middle plates are removed from the frame. The plates should be cleaned with a soap solution. Plastic type plates may not be resistant to hot water as is the case with the Capsunorm and Feton apparatus: the water temperature should not exceed 40 °C.

All parts are rinsed with clean water subsequently; if the hardness of the water could result in scaling, purified water is to be preferred. Drying should be done using a clean, non-fluffing cloth or piece of tissue paper.

The apparatus should dry further in the air, possibly near a heater or in a stove. The Capsunorm and the Feton apparatus may only dry in air.

The apparatus support is cleaned by means of a moist cloth.

Frequent maintenance is very important for the preparation of good quality capsules. By the frequent tapping of the apparatus onto the worktop or by a too rough (warm) way of cleaning, the apparatus can easily be dislocated or the plates could warp. As a consequence the upper rim of the lower halves of the capsules might not align everywhere with the upside of the upper middle plate. This can be detected by careful visual inspection.

A regular test to assess whether the capsules apparatus still works correctly is described below:

- Insert empty capsules in the apparatus and remove the upper halves;
- Check if the upper rims of the lower halves level exactly on or at the most a fraction of a millimetre below the upside of the upper middle plate;
- If the alignment is not levelled, e.g. by the frequent tapping of the apparatus onto the worktop, the lower plate should be adjusted. At the Capsunorm and the Loetschert-apparatus this is done by means of setscrews at the legs, using a small key or not. For the Feton-apparatus the legs have to be unscrewed followed by placing extra rings at the hexagonal parts of the legs;
- After adjusting, the apparatus is assessed for its functioning by the preparation of a batch of 60, respectively 100 capsules with, for instance, microcrystalline cellulose. Subsequently the relative standard deviation and the mean of weights of the content of the capsules is determined. If the relative standard deviation exceeds 1.5 %, or the deviation of the mean of weights from the theoretical weight exceeds 1.5 %, the functioning of the apparatus should be investigated. The variation of weights of the empty capsules should be taken into account;
- Results should be logged on a maintenance card, a logbook or in a journal.

If the apparatus is dislocated, capsules will be filled irregularly and a too large a variation of weights is the result. In that case the position of the lower plate should be re-adjusted. Subsequently the test should be re-executed.

When examining the test results the outcome not only depends on the quality of the apparatus but also on the experience of the operator.

It is also possible to document the operator qualification for the preparation of capsules using a pre-approved apparatus.

28.7.4 Tube Filling Apparatus

The filling of tubes can be executed by hand, with simple tools and with larger apparatus. The following tools and apparatus are described:

- Polypropylene film or paraffined weighing paper plus spatula (filling by hand);
- Piston-cylinder apparatus, simple (for a few dozens of tubes);
- Piston-cylinder apparatus with hand wheel (dozens to hundreds of tubes);
- Apparatus with a pumping mechanism (larger batches; not discussed in this Chapter).

28.7.4.1 Polypropylene Film or Weighing Paper

Application

Propylene film or weighing paper is used to fill an amount of ointment or cream into a tube by hand by pushing the substance with a spatula into the tube.

Operating Procedure

The chosen amount of ointment or cream is put onto the film like a sausage. The film is rolled around the 'sausage' subsequently and the whole is slid into the tube. After flattening the open end of the tube firmly with a spatula the film is pulled out of the tube again. Film is preferred over weighing paper with creams and water containing ointments, as paper could attract too much water. For closing the tube neatly a pair of tube squeezing pincers should be used.

Operating Procedure for Aseptic Preparation

Filling of e.g. eye creams should be carried out aseptically.

See Sect. 12.7.3 for the preparation method including filling of tubes with a syringe. If the filling has to be done by hand the polypropylene film is preferred as this can be steam sterilised. The drawback of this filling method is the relatively large risk of direct or indirect contact of the product with the hands of the operator. Additionally at the filling of more than one tube each portion must be weighed onto the film. This requires the placement of an electronic balance in the LAF-workbench, with special attention to aseptic working with this in the laminar airstream (see Sect. 28.3.5).

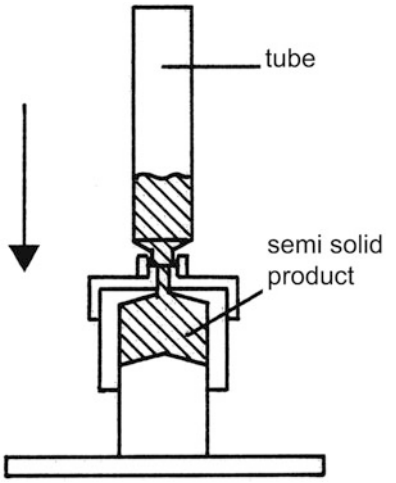

Fig. 28.19 Schematic drawing of a piston-cylinder apparatus

28.7.4.2 Piston-Cylinder Apparatus, Simple

Application

The piston-cylinder apparatus is suitable for the filling of some dozens of tubes, see Fig. 28.19.

Description

The piston pushes the mass through the threaded opening of the cylinder into the empty tube screwed on top of that. The synthetic material is resistant against almost all ointment ingredients, though not against long-lasting contact with most organic solvents. Phenols, tar preparations, alcohol and acetone do not affect the material. The apparatus can be steam-sterilised (15 min at 121 °C).

Operation Procedure

Using this apparatus requires less operator experience and skill than the hand operated method with film or paper, however cleaning requires much attention.

First the right amount of product must be brought into the cylinder. Especially with the handling of thick masses attention should be paid to avoid the introduction of air bubbles during filling, as in that case insufficient ointment will be filled into the tube. This can be achieved by tamping down the cylinder with the mass several times during the filling. While handling masses with a thin consistency, a closing cap should be placed on the cylinder opening during the filling process to prevent leakage. When the consistency is too thick it can be an awkward task to push the mass through the neck of the tube.

The loss remaining after one filling procedure depends on the used amount and the type of mass and usually ranges from 3 to 7 %. During stock preparation this should be taken into account by weighing in some 5 % excess at the first filling of the cylinder. For this reason the apparatus is less suitable for transferring small quantities (<50 g) into a tube.

For several tube sizes adapters and screw joints are available, however the cannula of an eye cream tube is too narrow to press the cream into the tube. This problem can be solved by mounting a (metal) filling pipe onto the cylinder over which the rear side of the eye cream tube fits. Consequently the tube will be filled from the open end. This kind of filling pipe is available. To monitor how far the eye cream tube can be filled, a mark should be applied.

28.7.4.3 Piston-Cylinder Apparatus with Hand Wheel

Application

The piston-cylinder apparatus with hand wheel is suitable for some dozens to hundreds of tubes per batch, see Fig. 28.20.

Description

The piston-cylinder apparatus is made of stainless steel. It is available in sizes/volumes of 1–3 L, with tube filling pipes for several tube-opening sizes, see Fig. 28.20.

Operation Procedure

The cream or ointment is transferred into the cylinder-shaped vessel. By bringing down the piston using the hand wheel the cream or ointment is pressed into the tube which has been slid over the outflow opening. At the filling pipes ring marks are applied to provide equal filling of the tubes, see Fig. 28.20.

During cleaning the bleeding valve in the piston should always be demounted as well.

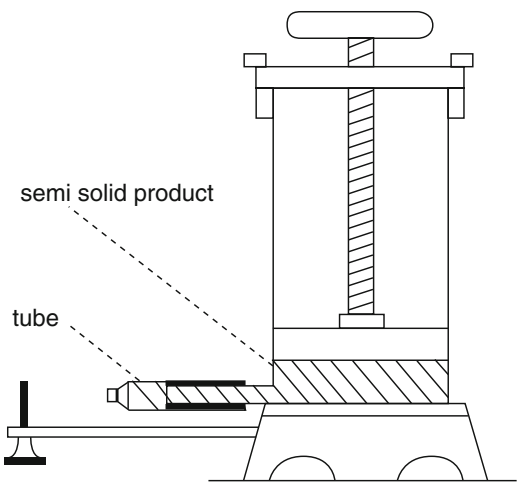

Fig. 28.20 Schematic drawing of a piston-cylinder apparatus with hand wheel. Source: Recepteerkunde 2009, ©KNMP

28.8 Cleaning Apparatus (Dishwasher)

28.8.1 Application

A washing-up machine is used to clean all utensils (implements and parts of preparation apparatus) which have such a form and dimension that they fit into the washing-up machine and can be placed in such a way that all surfaces will be reached by the detergent solution during the washing process. Additionally the utensils must be resistant to the treatment, the cleaning temperature and the used detergents.

28.8.2 Description

A professional washing-up machine will achieve the following:

- Mechanical removal (along with destructive effect of heat) of micro-organisms, however this is not a sterilising cycle
- Removal of nutrients for micro-organisms
- Removal of remainders of any products

In general mechanically cleaning and rinsing is the preferred method because it is easier to be standardised. Visible product residues are best removed by hand using absorbing paper.

The machine washing-up cycle consists of pre-rinsing, cleaning, post-rinsing (several runs, the last of them preferably using purified water) and drying. A professional washing-up machine should have a built-in dryer. Furthermore the water temperature of the main program should be 65 °C or higher.

Some professional washing-up machines log the cleaning and rinsing process parameters.

28.8.3 Operating Procedure

The removal of visible product residues should preferably be done immediately after the preparation process and the mechanical cleaning should be done within one day. This so-called 'pre-cleaning hold time' should be assessed in advance and be warranted in practice. After all, residues that are left during a longer time might be hard to remove effectively by a standard cleaning process. Additionally micro-organisms may grow.

A load scheme should be available in order to clean the utensils in a standard way. So called rinsing shadows must be prevented: surfaces which aren't reached during the cleaning process because they are covered by other objects. The load scheme should also prevent placing objects in such a way that upward situated cavities collect rinsing water that will remain. The load scheme, the chosen washing-up program and the nature and quantities of detergents and, if applicable, neutralising products, should be documented in advance to guarantee a clean product.

Validation of the cleaning process has to be done before operating. As difficult to clean objects utensils contaminated with zinc oxide paste (if desired with 3 % brown iron oxide) can be recommended. The validation should be repeated periodically, e.g. yearly, or at any time utensils are not clean after washing up or when new utensils are introduced. Results should be documented.

For adequate cleaning an alkaline detergent is necessary, preferably designed for laboratory use. Household agents will not always clean sufficiently [17]. The detergent must be dosed in accordance with the initial validation tests.

Prior to use, the sieves must be checked on possible residues of the proceeding run. Utensils must be placed in such a way that water from the spray nozzles will effectively hit the dirty parts. In general, this means that the most contaminated part should be directed downward.

Utensils with hollows or cavities should be placed in a slanted position otherwise water cannot drip off. High and narrow utensils should be placed directly over the spray. Loading procedures are necessary to put utensils in the machine that either have difficult to access places or aren't resistant to the temperatures or chemicals in the machine.

Vulnerable utensils should not be placed against other ones.

To guarantee an adequate cleaning the machine should not be overloaded. Neither objects should contain any caked dirt, which should be removed by pre-cleaning any residues directly with absorbing paper and by enforcing the pre-cleaning hold time. This pre-cleaning also prevents the sieves of the machine from clogging.

The correct operation (program choice, dosing of detergents and neutralising agents, logging of runs) should be incorporated in an operating instruction. This should include the instruction that after every run each utensil is checked for its cleanliness and dryness. The washing-up machine should preferably not be started at the end of a Friday afternoon because in that case any water residue will remain in place for a couple of days, increasing the risk for microbial contamination.

28.9 Apparatus for Cooled Storage

28.9.1 Application

Cooled storage (refrigerators, cold stores and freezers) is necessary in every pharmacy. For some medicines, e.g. certain vaccines, a common refrigerator is not sufficiently specified. The pharmacy refrigerator for licensed products is part of the so-called cold chain, see also Sects.

36.9 and 37.3. The producer or wholesaler usually will store medicines that should be kept 'cool' in large cold stores with a temperature control. The cold chain should warrant that storage conditions will be maintained during transport and temporarily storage.

28.9.2 Description

A pharmacy refrigerator should maintain a temperature of 2–8 °C. A freezer has a temperature of −18 °C as maximum. No standard applies for a minimum temperature. However it might be useful to define some minimum temperature, e.g. −30 °C, because a lower temperature can indicate a malfunction.

A refrigerator without internal freezing compartment will best meet the temperature requirement of 2–8 °C; next to a freezing compartment a temperature zone below 0 °C might arise. Automated thawing is undesirable as well if the refrigerator has only one evaporator, because this will raise the temperature every now and then to have frozen moisture thawed and drained away. A good refrigerator is provided with forced air circulation to achieve an even temperature and with a thermostat to control the temperature at 4 °C. Some refrigerators are equipped with specific provisions for monitoring. Other have an external temperature display or a logging function.

If there are several refrigerators placed together in one room it is advised to connect them to different electricity groups to diminish the consequences of any failures.

If the stock of cooled products requires considerable space it should be decided whether several refrigerators or one cold store is preferred. Several refrigerators usually are energetically less favourable then a cold store. However in case of a failure of one refrigerator it might be an advantage to have spare capacity in the others. In a cold store the risk of failure might be abated by installing a redundant pair of compressors. A cold store should be installed, validated and controlled in a similar way as a refrigerator.

28.9.3 Operating Procedure

28.9.3.1 Installation

The instructions of the manufacturer should be followed carefully. Usually this means that a stabilisation time should be observed of 24 h after initial installation or after a removal. Then, after switching on, the temperature and the mutual temperature differences should be measured at a sufficient number of different places in the empty refrigerator.

Subsequently these measurements are to be repeated in a three-quarter filled refrigerator, again at a number of places according to a comparable scheme.

All measurements can be executed in two different ways:

- Using minimal two calibrated minimum/maximum thermometers or
- Using a calibrated temperature-data logger.

The use of calibrated electronic temperature-data loggers have many advantages over the use of minimum/maximum thermometers as the course of the temperature over time can be measured and recorded.

Some data loggers are able to indicate whether the temperature fall below 2 °C or rises over 8 °C by a light signal.

The refrigerator can be used after the correct functioning has been established.
Criteria for approval are:

- All measured temperatures have to be between 2 °C and 8 °C, both in the empty and in the three-quarter filled refrigerator;
- Minimum and maximum temperatures, measured at one location, should not vary more than 6 °C;
- The measured mean minimal temperature should not differ more than 6 °C from the measured mean maximum temperature.

If these criteria are not met, arrangements should be made and subsequently the measurements of temperatures and temperature-differences should be repeated.

The thermostat adjustment to achieve the correct functioning should be documented.

28.9.3.2 Use

Relevant points in the use are:

- The control of cooling provisions need continuously attention. Household provisions are not sufficient.
- Current interruptions or a failure in the closing of the door might cause unacceptable deviations of the temperature.
- The refrigerator should never be filled for more than three quarter of its capacity. This filling rate leaves sufficient space for an adequate air circulation, providing a homogeneous temperature distribution.
- Product should not be placed against the back wall; this disturbs the air circulation and, in case of an automatic thawing refrigerator, ice might built up against the back wall.

28.9.3.3 Cleaning

For cleaning no scouring agents or alkaline detergents should be used as the plastic parts might be affected. By cleaning each shelf individually it is possible to keep the contents of each shelf or drawer cool during cleaning. The contents can be stored temporarily on a different shelf or in another drawer.

Another possibility is the use of a cool box; in that case direct contact of the product with the freezer packs should be avoided to prevent any local freezing. The freezer packs belong in the upper part of the box, preferably inside the lid, because otherwise the temperature inside the box will not fall below 15 °C.

28.9.3.4 Thawing (for Non Automatic Fridges)

The timing and frequency of thawing of the refrigerator is determined by the thickness of the ice built-up onto the cooling elements. With a thick ice sheet it takes considerably more energy to cool. However thawing and cooling costs energy as well. A rule of thumb for thawing is to do it when the ice sheet has grown to 1–2 cm. Another possibility is thawing with a closed door. In that case the contents are kept in the refrigerator. Leaking meltwater should be collected in such a way that the products remain dry. A drawback is that cleaning cannot take place at the same time. Finally it can be considered to remove all products from the refrigerator and stack them in a cool place wrapped in isolating material such as a woollen cloth. The low temperature can be retained for some time in this way.

28.9.3.5 Monitoring

The required temperature should be verified continuously. The temperature can be recorded continuously using two temperature sensors. One of these has to be placed in the coldest place and the other in the least cold place, which are determined during validation. The use of only one moveable temperature sensor can be justified if the temperature differences in the refrigerator are almost negligible at the several measurement places.

The temperature sensor used to control and monitor or both is preferably placed in a holder, e.g. in a little cardboard box or better in a vial filled with glycerol. By this method the reaction of the sensor to the opening of the door can be buffered. Electronic data loggers can provide continuous recording.

Pharmacy employees have to check the temperature every time they open the fridge and proceed in accordance with alert and action levels of the temperature. By this procedure any failure during operating hours can be detected easily. However the connection of a cooling system to a building control system raising an alarm any time the temperature fails to stay within its prescribed boundaries is to be preferred.

Procedure in Case of Failure

Failures can arise by any break down of the refrigerator (e.g. power failure). A failure is defined if the temperature rises (has risen) over 10 °C or fall (has fallen) below 2 °C.

Several causes of failure can be discerned:

- The door does not close very well or has been left open for a prolonged time (the most common interruption of the cold chain in community pharmacies seems to be caused by an open door).
- The thermostat is not adjusted correctly.
- A power failure has occurred.
- The refrigerator does not function well: e.g. a specific part has broken down (thermostat switch, ventilator, automatic thawing mechanism or compressor failure).

A temperature calibration should be executed each time any doubt has risen about the temperature.

The consequences of a failure to the product are based on the maximum temperature and the duration of the failure. The duration of a power failure can be retrieved from the energy company. Producers of licensed medicines usually have specific information to assess the gravity of the interruption of the cold chain.

It is suggested to investigate the increase of the temperature in some situations in order to have an indication of the possible damage when disturbances have occurred:

- A power interruption of at least 12 h.
- A defective thermostat while the ventilator keeps running.
- Leave the door ajar 1 cm for at least 12 h.

Measurements best be executed in a closed, empty refrigerator as a worst case in relation to the rate of temperature increase.

As a preventive measure the purchase of an emergency power supply might be considered. This could consist of an apparatus with a back-up time of e.g. 8 h, producing 230 V from closed gel batteries, built-in into the refrigerator or installed outside of it.

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Basic Operations

29

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Contents

Abstract

Weighing, volume measuring, particle size reduction, dispersing, dissolving and mixing, including checking each step, are key issues in all pharmaceutical preparation processes. Accuracy, precision and measurement uncertainty are essential concepts in performing these basic operations. In this chapter the background to basic operations in pharmacy preparations is provided, good practices are discussed and examples from practice are given as illustrations. The concept of Minimum weight and metrological control are discussed. It is shown how to choose the proper method for optimal performance in practice. As equipment and utensils for weighing and measuring are closely linked to the operations they are also discussed. They encompass balances, receivers for weighing, devices for volume measuring, mortars and mixers. Particle size reduction and de-agglomeration are discussed in relation to mixing and dispersing. A proper understanding of these techniques significantly influences the quality of a pharmacy preparation and thus the required pharmacotherapeutic outcome.

Keywords

Dispersing • Dissolving • Mixing • Particle size reduction • Volume measurement • Weighing • Agglomerates

Based upon the chapter 'Wegen, meten en mengen' by Herman Woerdenbag, Yvonne Bouwman-Boer and Erik Frijlink in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_29,

29.1 Weighing and Volume Measuring

Weighing is determining the mass of an object or of a quantity of substance. In pharmaceutical preparation processes it is usually the accurate weighing out of a set amount of a substance. A weighing instrument is a measuring instrument to determine the mass of an object by using the action of gravity on that object [1]. Analogously, volume measurement in pharmaceutical preparations is the accurate measurement of a given volume of a required material, which is usually a liquid. But also the powder mixture for capsules is prepared by volume. Historical information on weighing and volume measuring in pharmaceutical practice as well as pharmaceutical calculations can be found in general textbooks [2, 3].

The basic good performance of weighing and volume measuring depends on choosing the right equipment, using it in a careful and correct manner and maintaining it in good order.

29.1.1 Required Accuracy and Precision

Describing measuring means caring about measurement uncertainty, which is a universal concept. The universal and very useful document on measurement uncertainty is the Guide to the Expression of Uncertainty in Measurement (GUM) [4]. In this chapter the concepts of measurement needed for preparation and manufacturing of pharmaceutical preparations are dealt with, in a concise, though justified, way. For more profound scientific information the aforementioned GUM [4] is highly recommended.

29.1.1.1 Concepts of Accuracy and Precision

Accuracy and precision are essential concepts for weighing and volume measuring in pharmaceutical preparation processes. Accuracy represents the degree of the closeness of a measurement to the actual or true value (the standard or reference). Precision (also called reproducibility or repeatability) is defined as the degree to which repeated measurements under the same conditions yield the same results. It is the refinement in a measurement, calculation or specification, represented by the number of decimal figures given. Accuracy and precision are visualised in Fig. 29.1. See also Sect. 20.2.2. For the sum of inaccuracy and imprecision the terminology ‘measurement uncertainty’ is used, e.g. by the Joint Committee for Guides in Metrology (JCGM) [5, 6].

29.1.1.2 Required Accuracy and Precision

In relation to preparation in the pharmacy, weighing is used in the preparation process and in Quality Control. Firstly measurement uncertainty is dealt with in relation to Quality Control.

For Quality Control purposes the required measurement uncertainty is set by the Official Medicines Control Laboratories (OMCL) Network of the Council of Europe. The measurement uncertainty for analytical weighing is

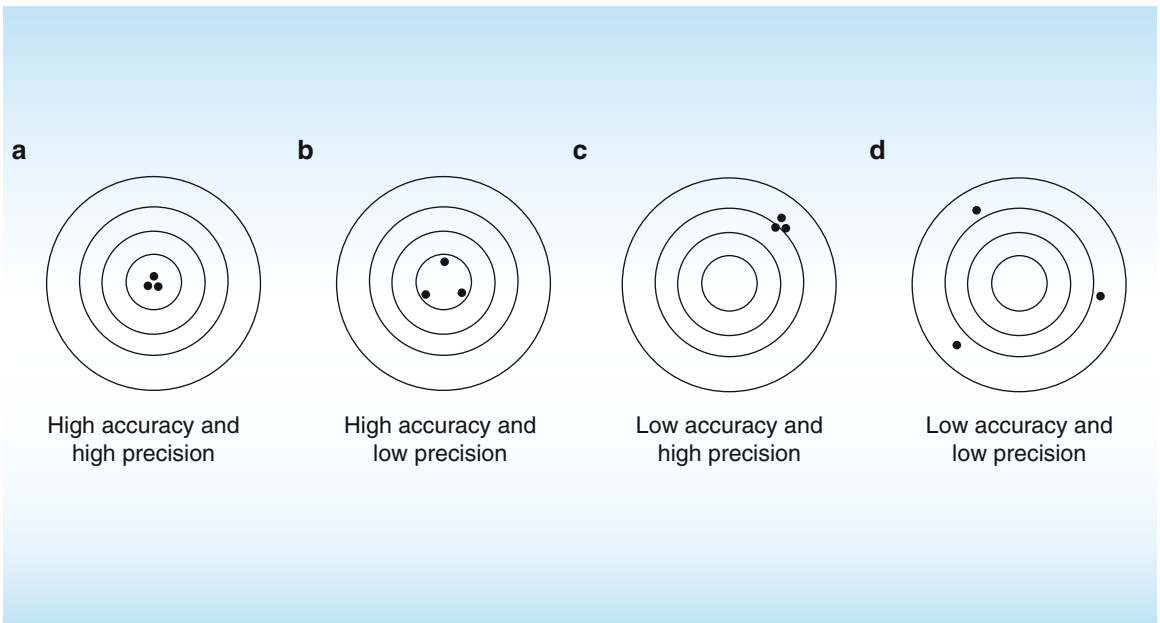


Fig. 29.1 Schematic representation of accuracy and precision. (**a**) High accuracy and high precision, good balance in repeatability; (**b**) High accuracy and low precision, measured values are wide-spread; (**c**) Low accuracy and high precision, good balance in repeatability; (**d**) Low accuracy and low precision, measured values are wide-spread. From Radwag [7] with permission

considered to be satisfactory if three times the standard deviation of not less than ten replicate weight measurements, divided by the amount weighed (at approximately 50 % of the maximum capacity of the balance), does not exceed 0.001 [8]. For comparison: USP gives a requirement for weighing tolerance (based on the requirement for repeatability as the most determining uncertainty at small weights) for "materials that must be accurately weighed" [9] which is 0.1 % for two times the relative standard deviation of 10 times weighing a test weight.

For the preparation process, no official requirement is known to the authors, so it has to be derived. Most preparation processes start with accurately weighing the required amount of active substance(s) and excipients or with measuring them by volume. Several process steps, such as transferring or mixing, may cause loss of active substance or excipients due to spillage, exhausting, adsorption. Usually this leads to a deviation of the actual content from the required content. It depends on the type of processing and the properties of the involved active substances and excipients, whether the resulting mean content will be lower or higher than 100 %. Especially in small-scale preparation any small process imperfection may lead to a noticeable deviation in content, which is acknowledged by the somewhat less rigid requirements to mean content of pharmacy preparations compared to licensed medicines. Taking this into account, one may argue that weighing and volume measuring should negligibly contribute to these deviations because it is relatively easy, especially for weighing, to perform these process steps accurately and precisely. Due to the small obtainable uncertainty in weighing and measuring, other processes can use up the 'uncertainty budget' [9]. It immediately follows however that they should not be executed so accurately and precisely that it hampers an efficient performance of the preparation process.

Although uncertainty in weighing and measuring can be small, it is worth knowing 'how small' for purposes of:

- Using the right balance and the right volume measuring device;
- Knowing the minimum weight (M_{min}) that can be weighed on that balance and the minimum amount to be measured with the volume measuring device.

Mean content of pharmacy preparations is required to be between 90 % and 110 % (see Sect. 32.6). If one would reckon with instability during storage and the need to have a feasible shelf life, further narrowing this to 95–105 % for the mean content immediately after preparation is reasonable (see Sect. 22.4.1). This can be interpreted as there being an uncertainty range of maximal 5 % for weighing and measuring. However it may be more reasonable to leave some room for other processes contributing to the deviation of the mean content.

A maximum deviation of 5 % from the mean content would lead to a maximum allowed weighing uncertainty of 0.018, expressed as most probable standard deviation. To obtain this value all four components contributing to uncertainty (see next section) are taken into account. This requires specific mathematics and reasoning, which are explained in [10]. The value of 0.018 results from a recalculation with a 5 % deviation of the mean content instead of the original 7 % allowed. To leave some room for other processes, to be memorable and to give a clear comparison to analytical weighing a true standard deviation σ of 0.01 could be proposed. As said, OMCL requires 0.001 for analytical weighing. For comparison with the requirements for the mean content it should be realised that this standard deviation (sd) corresponds with a relative standard deviation (rsd) of 1 % at the minimum amount to be weight M_{min}. This standard deviation of 1 % corresponds subsequently to most measurements being within 2–3 times that sd from the mean, so to a maximum deviation of 2–3 %. This deviation rapidly decreases with weighing larger quantities: to 1–1.5 % at weighing of two times the M_{min} and so on. How to assess the Minimum weight in practice is further derived in Sect. 29.1.3.3.

Maximal measurement uncertainty at volume measurements could be calculated as well. However volume measurements are generally only performed as second choice if weighing would pose too many drawbacks for the reliability of the preparation process (see Sect. 29.1.2). Therefore, the acceptable measurement uncertainty for volume measuring depends strongly on the nature of the process in question. Usually only inaccuracy is taken into consideration. It is limited by requiring a minimum filling of the device to be used, as is explained in Sect. 29.1.7. More exact calculations would be irrelevant.

29.1.2 Weighing versus Volume Measuring

The measurement uncertainty of weighing will usually lead to a deviation due to inaccuracy and imprecision of not more than 1 % [10]. Volume measurements however, may show a deviation of 1.5 % under the most favourable conditions. Under less favourable conditions this can easily rise to 3 % or more (see Sect. 29.1.7).

Weighing has three advantages over volume measuring:

- Greater accuracy and precision to be achieved so smaller quantities can be handled.
- The read-out of a weight is less subjective than of a volume.
- The use of an electronic balance offers the possibility to record the result of a weighing objectively, by connecting to a printer or a computer programme (in-process control).

Viscous liquids can be accurately weighed but are difficult to be measured on a volume basis. Consider, for example, Chlorhexidine Digluconate Solution (Ph. Eur.), which is a rather viscous solution. In an investigation of chlorhexidine containing preparations, prepared in Dutch pharmacies, it was shown that chlorhexidine solution measured by volume often resulted in too low concentrations of this ingredient. This was caused by the adherence of the solution onto the measuring device. For instance, the average content of a chlorhexidine mouth wash (Table 29.1) in samples prepared by volume measuring was 3 % lower than in those prepared by weighing. This formula of Chlorhexidine mouth wash was then redesigned so as to give the weight of the required amount of chlorhexidine solution instead of the volume.

Table 29.1 Chlorhexidine Digluconate Mouth Wash 0.2 % [11]

	FNA
Chlorhexidine digluconate solution	10.65 g
Ethanol (96 % V/V)	70 g
Peppermint oil	3 dr
Sorbitol liquid, crystallising	535 g
Water, purified	493 g
Total	1109 g (= 1000 mL)

For some steps of the preparation processes, however, weighing is not or hardly possible or volume measurement has advantages for reasons that outweigh inaccuracy. Examples include: the adjustment to volume of large amounts of solutions, working in a laminar flow cabinet, and preparing parenterals prior to administration on the ward.

If a preparation is carried out in a small working space with conditioned airflow (laminar flow cabinet, safety cabinet, isolator), a balance cannot be too big and must be protected to weigh free from draft. Those balances are suitable to weigh ingredients but not to determine the final weight of a preparation, for instance a measuring cylinder with eye drop solution. The final step will therefore be filling up to volume and not to weight.

If a large vessel (e.g. 50–100 L) is used for a preparation process, this may be carried out on a volume basis. In that case the volume is determined using a calibrated vessel with volume marks or by using a calibrated rod. Newly bought vessels are equipped with load cells (transducers that convert force into an electrical signal) so that weighing can be performed.

The nurse who prepares parenterals prior to administration to a patient sometimes only needs a small part of an injection solution from an ampoule or has to take the appropriate amount from the ampoule for further dilution to achieve the appropriate dose. She will take out the desired volume from the ampoule with a syringe and probably use other syringes for further dilution (see also Sect. 29.1.7).

In pharmacy preparation, volume and weight of liquids sometimes have to be converted into each other through the relative density.

Syrups do not contain active ingredients. They are not administered as such but serve as a vehicle because of their flavouring and sweetening properties. Since the density of syrups is high, the volume in mL will not equal the weight in grams. Syrup BP contains 667 g sucrose and purified water to produce 1,000 g. The density is 1.315–1.333 g/mL, yielding a sucrose concentration of about 64.6 %.

Benzalkonium chloride is available as Benzalkonium Chloride Solution (Ph. Eur.) which contains a mixture of alkylbenzyldimethylammonium chlorides in water at a concentration of 500 g/L (50 % w/v). If the final concentration of benzalkonium chloride in a product has to be 0.01 % (either w/v or w/w), for 1,000 mL of the preparation 100 mg of benzalkonium chloride is required. Volume measuring would require 0.2 mL of the Benzalkonium Chloride Solution (50 % w/v) to be taken which cannot be performed with adequate accuracy because of its high viscosity. For weighing instead, the density of the solution has to be known. Density may be taken from the product certificate issued by the manufacturer or it has to be measured. If the density would be 0.9805 g/mL (as measured) one should weigh 196 mg of the 50 % Benzalkonium Chloride Solution for 1,000 mL of the solution to be prepared.

If minor amounts are to be used of an excipient, such as an essence or an essential oil in liquid oral preparations, the required weight should be known as well, regardless of the fact that a limited variation in quantity has no essential influence on product quality. A pharmacist can convert the weight into droplets if such small quantities of the product are prepared that weighing is not practical. In such cases the

required quantity on a preparation worksheet can be stated in droplets instead of weight.

Other examples from practice are the preservation of eye drops and the addition of a vitamin solution.

The combination of benzalkonium chloride and betaphenylethanol in final concentrations of 0.05 g/L and 4 g/L, respectively, is sometimes used to preserve eye drops (but with care and restrictions as betaphenylethanol often causes irritation). In that case, for the preparation of 10 mL of 0.5 % Atropine sulfate eye drops, 0.5 mg of benzalkonium chloride and 40 mg of betaphenylethanol are required. The preservatives can be added to the prepared solution by droplets as follows: the amount of 40 mg of betaphenylethanol corresponds to two drops of this liquid preservative; benzalkonium chloride is used as a 0.5 % stock solution: five drops (100 mg of the stock solution) are needed.

An oily concentrate of vitamin A contains 1,000,000 IU/g of the active substance, corresponding to 34,500 IU in one drop. If 25 g of an ointment should contain 120,000 IU, it means that four drops of the concentrate should be added. If better precision is required the concentrate should be diluted with an appropriate oil and added to the ointment by weight.

In the case of the preservation of eye drops this may be an acceptable approach especially because it may decrease the number of process steps in aseptic handling, although using a sterile stock solution with accurately weighted substances is definitely to be preferred. For active ingredients such as vitamin A, for which a content of 90–110 % is required, it may result in the final product not meeting the requirements.

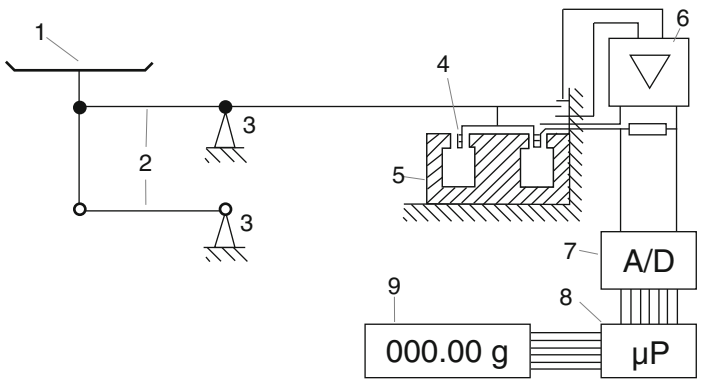
29.1.3 Physical Principles of Weighing

For weighing in the pharmacy a balance is used. Two types of balances exist: electronic (principle: comparison of force) and mechanical (principle: comparison of mass). Most balances in European pharmacies are electronic balances.

29.1.3.1 Electronic Balance

The principle of an electronic balance is electromagnetic force compensation: the force of the mass to be weighed is compared with an electromagnetic force. The electronic balance has a magnet, a coil and a load carrier that is mechanically connected to the coil. Under the influence of load on the load carrier the coil drops into the magnet and the current through the coil must be amplified to reach the starting position (equilibrium) again (see Fig. 29.2).

Two types of electronic balances exist. For the first, the difference in current between the loaded and unloaded state is a measure for the weight, the working of the second is based on electrical resistance.



1 weighing pan
2 parallel pair of levers
3 fulcrum
4 coil
5 permanent magnet
6 precision resistance
7 A/D converter
8 microprocessor
9 digital read-out

Fig. 29.2 Principle of a balance with electromagnetic force compensation. The structure is based on a lever. Typically, the weighing pan with the item to be weighed is attached to one end of the lever. A coil that generates an electromagnetic force is attached to the other end of the lever. Source: Recepteerkunde 2009, ©KNMP

Most electronic balances are provided with an adjustable integration time and stability indicator (that releases the weighing result). These functions decrease the influence of draft and vibrations on the weighing result. The integration time is the duration of the measurement cycle of the balance, and the result of the measurement is read out when the balance indicates 'standstill'. This is indicated by means of a signal lamp or the passing on of the read-out result to a printer. A longer integration time may occur if the weighing is disturbed by draft and vibrations.

29.1.3.2 Mechanical Beam (Equal Arm) Balance

The principle of a mechanical balance is based on comparison of mass. The mechanical beam balance may be present in the pharmacy as a back-up. The equal arm balance is three-knife yoke balance (see Fig. 29.3). The object to be weighed is placed on one scale and it is brought into balance with different calibrated weights on the other scale.

Before use, levelling and zero position should be checked. Levelling can be set using the adjusting screws. If the scales are clean but the pointer does not indicate zero in the unloaded state, the balance should undergo service. Such deviation should never be abrogated with the adjusting screws or by pieces of paper put on the weighing scales.

After use, the weighing scales should be cleaned when necessary. Maintenance consists of cleaning the knives, the pans and the loose weights and checking whether parts that are worn by the (mechanical) use should be replaced. The set of weights, when used regularly, should be recalibrated regularly, depending on applicable national laws. If the balance is used for emergencies only, it is recommended that the weights be sealed after recalibration and stored under dry conditions to avoid corrosion occurring.

When using a beam balance the extent of any deviation is not known. At the end of the weighing the pointer should be positioned exactly in the middle of the scale. If this is not the case, the extent of the deviation is unclear.

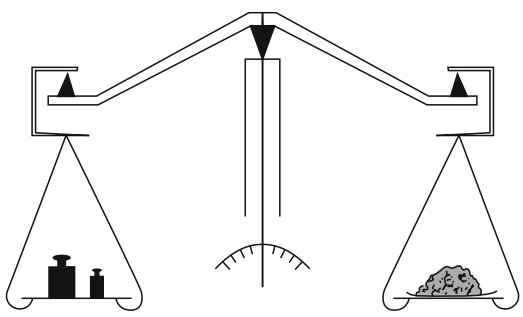


Fig. 29.3 Principle of a mechanical beam balance. Source: Recepteerkunde 2009, ©KNMP

29.1.3.3 Weighing Uncertainty at Preparation

To obtain the allowed weighing uncertainty the contribution of all components that are related to the weighing at preparation have to be summed up. Four components are contributing to weighing uncertainty [10]:

1. Intrinsic inaccuracy and imprecision of the balance
2. Imprecision due to the imperfect placement of the balance in practice
3. A difference between the value at which the weighing is read out and the quantity to be weighed according to the preparation worksheet
4. Reading out before the balance has stabilised sufficiently

The intrinsic inaccuracy and imprecision of an electronic balance will be given by the manufacturer's balance specifications, see further Sect. 29.1.4.

To keep inaccuracy and imprecision of a balance to their intrinsic (or ideal) values, a balance should be placed completely free from disturbances. However in pharmacy preparation imperfect placing is the rule. By using a stability indicator the additional imprecision due to imperfect placement can be restricted but it is generally acknowledged that the additional imprecision due to imperfect placement has to be monitored (see Sect. 29.1.6).

The third deviation is caused by the fact that the weighed out quantity never exactly equals the quantity that should be weighed according to the preparation worksheet. It is therefore important to determine what deviation is allowable. For instance, weighing out to meet exactly the target amount will take a lot of time. With a maximum deviation of 1 % from the target amount, weighing in small-scale preparation can be executed conveniently. Setting this deviation is also necessary for programming the stability control for accepting the weighing result and releasing it for the printer.

The fourth deviation is usually an operator's deviation; impatience may lead to reading out before the balance has stabilised sufficiently. If the balance is connected to a printer, this impatience will be to no effect as the printer will only accept results between ± 1 % (or any other set value). If impatience occurs the reason for it should be checked as it may be due to technical problems (see also Sect. 29.1.5). If the balance is not connected to a printer the operator has to calculate the maximum allowed deviation of the result from the target amount. It is safer, however, to express it in the number of decimal figures in the amount on the preparation worksheet. If, for instance, the amount to be weighed is specified as 7.0 g, the weighing can be stopped when the weighing result lies between 6.95 and 7.05 g. Within that range the deviation from the quantity to be weighed will be less than 1 %. If a deviation of less than 0.5 % is desirable, the target amount in the protocol should be specified as: 7.00 g. For example, '1.00 kg' implicates

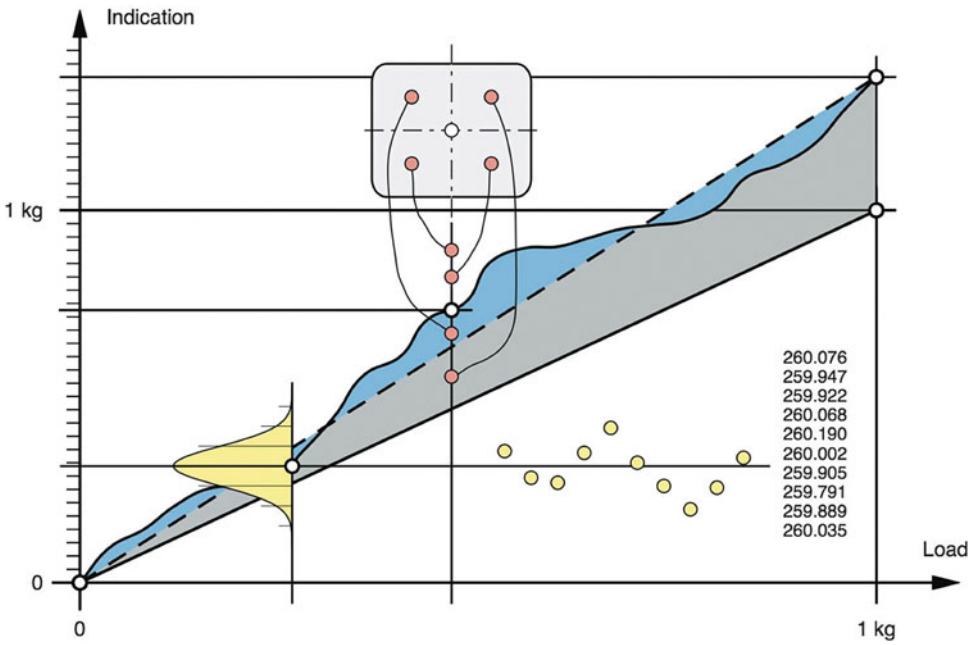


Fig. 29.4 Properties of weighing instruments: The dashed line with the associated grey area represents the sensitivity offset of the instrument, superimposed is the nonlinearity (blue area, indicating the deviation of the characteristic curve from the straight line). The red circles represent the measurement values caused by eccentric loading, and the yellow circles represent the distribution of the measurement values due to repeatability, from Mettler-Toledo [13] with permission

that a larger deviation is permitted than for '1,000 g' (5 g and 0.5 g respectively). Thus, the number of decimals places has a practical meaning [12].

> The BP describes the accuracy requirements as follows: Quantities are weighed or measured with an accuracy commensurate with the indicated degree of precision. For weighings, the precision corresponds to plus or minus 5 units after the last figure stated (for example, 0.25 g is to be interpreted as 0.245 g to 0.255 g). For the measurement of volumes, if the figure after the decimal point is a zero or ends in a zero (for example, 10.0 mL or 0.50 mL).

To find out if the total influence of these deviations on the mean content is still within the set amount of 5 %, all deviations have to be accumulated. Weighing deviations may compensate for each other so straightforward totalling limit values will reflect an extremely worst case. Combining deviations that have a different mathematical type is essentially an addition of quadratic standard deviations (variances), but only after limit values have been turned into standard deviations according to their specific statistical distribution. This propagation (or accumulation) of uncertainties is elaborated in Sect. 5 and Annex E.4 of [4] and applied to small-scale preparation in [10].

Intrinsic measurement uncertainty, as has been said (Sect. 29.1.1), can be differentiated in inaccuracy and imprecision. The intrinsic inaccuracy of an electronic balance is caused by deviations from sensitivity, linearity and eccentricity. Sensitivity is defined as the change in weighing value divided by the change in load, usually measured between zero and the capacity of a balance. Linearity is the ability of a balance to follow the linear relationship between a load and the indicated weighing value. Eccentricity is the deviation in the measurement value caused by eccentric loading (asymmetrical placement of the load). Figure 29.4 illustrates these uncertainties.

Intrinsic imprecision is also called repeatability and is usually determined included in total repeatability. Intrinsic measurement inaccuracy is checked by calibration.

For analytical balances and microbalances the contribution of the components to measurement uncertainty are very different. For the lower weighing range, repeatability is by far the most important. For precision balances and industrial scales, this is less prominent. But testing frequencies (see Sect. 29.1.6) are, via risk assessment, for these balances are largely determined by checking repeatability and sensitivity.

29.1.4 Selection of an Electronic Balance

29.1.4.1 General Selection Criteria

The relevant classes of balances for pharmaceutical purposes are: semi-micro-balances, analytical balances, precision balances and platform or industrial balances [14]. They are categorised by their capacity and readability (Table 29.2):

Table 29.2 Categorisation of balances for pharmaceutical purposes

Type	(typical) Capacity	(typical) Readability	Remarks
Semi-micro	30 g	0.001 mg or 0.002 mg	With an enclosed draft shield
			For quantitative analysis in the laboratory only
Analytical	500 g	0.1 mg or 0.01 mg	With an enclosed draft shield
			For small-scale preparation and for quantitative analysis
Precision (or top pan)	20 kg	0.001 g or greater	For production, and for general weighing in the laboratory
Platform	1,000 kg	0.1 g or greater	For industrial production

The selection of a balance may be determined by:

- Weighing range
- Required precision and accuracy
- Metrological approval of the model
- The shape and area of the weighing pan
- The area and height of the weighing chamber, e.g. are containers to be weighed on the balance
- The power supply required, e.g. 115 V, 240 V or battery powered

All balance types for pharmacy preparation preferably have an automatic internal calibration option and can operate in connection with software functions, e.g. for in-process control. The balance should be equipped with a stability indicator so that the weight is only registered or printed after stabilisation of the balance. Draft shields are important, especially for weighing in controlled (ventilated!) environments. Special functions such as piece counting (for counting tablets or capsules; the so-called 'pill counter') may be advantageous.

29.1.4.2 Metrological Approval

For pharmacies (as opposed to industries) it is legally required [1] to use balances under metrological control of the model. So when buying a balance, it should be verified if the model can be supplied under metrological control.

> The manufacturer produces the instrument in accordance with the product specification. The CE marking and the supplementary metrology marking are affixed by, or under the responsibility of, the manufacturer onto the instrument during the fabrication process as proof of conformity with the EU directives. The manufacturer must have had such a metrological control carried out by one of the competent authorities of the Member States of the European Union, called a notified body. Details are described in [1, 15]. Balances used in pharmacies are defined as 'non-automatic weighing instruments' according to the European law, meaning that they require the intervention of an operator during weighing [1, 15].

Measuring instruments subject to metrological control undergo metrological inspections by the competent authorities: a notified body. The specific requirements have been entered in the regulations.

The EU directive distinguishes four accuracy classes for balances: I (special), II (high), III (medium) and IIII (ordinary). The balances used in pharmacies' practice usually belong to the accuracy classes I and II. In the pharmaceutical industry (for large-scale preparations) also technical balances (platform balances) of class III may be used [1].

The accuracy classes are characterised by their corresponding measurement uncertainties, expressed in specific parameters:

- The verification scale interval "e", representing the operational deviation limit in the lower parts of the weighing range.
- The actual scale interval "d" (readability, the smallest digit that can be read out from the display).
- The minimum capacity "Min", the metrological lower limit of the weighing range.
- The maximum weighing capacity "Max", being the upper limit of the weighing range. Weighing of a quantity exceeding the maximum weighing capacity may damage the balance.

A typical e-value for an analytical balance (accuracy class I) is 0.001 g, indicating an operational inaccuracy limit of ± 0.001 g in the lower part of the weighing range. For less sensitive precision balance (accuracy class II) a typical e-value is 0.1 g.

The measurement uncertainty these parameters are applying to is the 'intrinsic' one: based on an ideal, disturbance-free placement of the balance. Ideal placement may be attained in a laboratory situation but usually not in a pharmacy production environment. For selection of the appropriate balance these parameters may be helpful, although there is not much advantage above the usual categorisation as is reflected in Table 29.2.

But measurement uncertainty in practice has to be checked by investigating the actual repeatability leading to a Minimum weight M_{min} in practical circumstances, as opposed to the metrological minimum capacity 'Min' (see Sect. 29.1.5).

29.1.5 Installation and Minimum Weight

29.1.5.1 Installation

In order to work under optimal conditions a balance should stand stable, preferably in a weighing room or on a weighing bench, on a solid, level, nonmagnetic surface that minimises the transmission of vibration. A balance should be shielded from big changes in airflow or draft (laminar flow, air exhaust, radiator, open door or window, passage area) and temperature (direct sunlight, radiator). Humidity must be constant, preferably between 40 and 60 % RH. A low humidity will increase the effect of static electricity. The positioning should be free from electromagnetic fields, static electricity (due other equipment) and vibrations, e.g. by construction work or traffic passing [9, 16].

Prior to installation and release for use, it is recommended to check all the requirements set during the selection of the instrument. Secondly a full calibration (involving sensitivity, linearity, eccentricity and repeatability over the entire operation range of the balance) should be performed before putting into service. This is done at the location where the balance is used [9].

A balance should be adjusted for each location where it is used. Weight varies slightly according to latitude, altitude, temperature and pressure. A measuring instrument must therefore be adjusted for the particular part of the country (gravitational area) where it will be used. In a small country like the Netherlands, eight gravitational areas are distinguished. When moving to another part of the country or the world, a balance may enter into a different gravitational area and requires re-adjustment. By using an internal calibration this adjustment is not necessary.

Finally, the minimum weight in practical circumstances M_{min} should be assessed.

29.1.5.2 Concept of Minimum Weight

The Minimum weight M_{min} describes the lower limit of the balance below which the required weighing tolerance (accuracy) is not adhered to [9]. Or put differently: one has to weigh at least this amount of material in order to meet a limit of uncertainty that satisfies the weighing accuracy requirements specific to the process involved [12]. The Minimum weight M_{min} is specific for the process for which the weighing is used. M_{min} is to be distinguished from the metrological Min = Minimum capacity (see Sect. 29.1.4), which is a technical specification of the balance itself.

With regard to Quality Control the M_{min} can be derived from the allowed measurement uncertainty given by OMCL or USP.

USP uses the following equation for the minimum weight [9]:

$M_{min} = (k \times s)$/required weighing tolerance; k being a 'coverage factor' and s being the standard deviation of 10 weighings.

Using 0.10 % as the weighing tolerance for materials that have to be accurately weighed (see Sect. 29.1.1) the equation amounts to: $M_{min} = 2{,}000 \times s$. Note that repeatability is taken as the measure for uncertainty. This is allowed at low loads as repeatability is dominating the contributions of non-linearity, sensitivity or eccentricity [9].

For preparation processes, the required weighing uncertainty was derived in Sect. 29.1.1 and expressed as a maximum standard deviation γ_w of 0.018. Via $\gamma_w = \sigma_w/M_{min}$ and $\sigma_w = 1.59 s_w$ (n = 10) this leads to a M_{min} of about $100 \times s$; s being the standard deviation of 10 replicate measurements of a practical and relevant load. For an approach that leaves more room for other processes contributing to deviation from the mean content, as said (Sect. 29.1.1), γ_w of 0.01 could be used. This would result in a M_{min} of about $150 \times s$.

As a conclusion, M_{min} for preparation purposes is to be determined by performing 10 replicate weighings of a practical, relevant object such as usual receivers: a mortar, a flask, a paper with a large surface. After calculating the standard deviation s_{10}, multiplication by a factor $100 - 150$ will lead to the M_{min}

$$M_{min} = 100 - 150 \times s_{10}$$

However, theoretically M_{min} should never be less than about $80 \times d$, d being the scale interval, see Sect. 29.1.1. Due to rounding of the digital indication, the lower limit s_{min} of the standard deviation of a weighing is calculated as being $0.41 \times d$ for technical reasons [13]). This fact of a lower limit of s, is also taken into account in [17]. It will lead in the case of preparation to a minimal M_{min} of about $80 \times d$.

An alternative approach could be that the M_{min} is determined by an experienced operator and multiplied by a safety factor of 2 (or even a higher number) to account for all future variations [13].

29.1.6 Operation and Maintenance

29.1.6.1 Operation of a Balance for Pharmacy Preparation

A clean balance that is in a completely level position should be used. In all cases the balance chosen should be appropriate for the quantity to be weighed and for the accuracy needed.

The first step is to switch on a balance. Depending on the type of balance a warming-up period should be taken into

account. The balance should reach thermal equilibrium after being connected with the power supply. If the balance is in the standby mode (which is generally recommended when a balance is used regularly) the electronics are still energised and no warming-up period is necessary.

It should be checked to see if the balance is levelled. If this is not the case, the balance should be aligned using the adjustable feet while monitoring the level indicator. It should be checked that the balance displays exactly zero at the start of each weighing (stability indicator, Sect. 29.1.3.1). The balance can then be tared.

The allowed difference between the quantity to be weighed and the actual weighed quantity, for instance 1 % (see Sect. 29.1.3.3), can be incorporated into a weighing programme. It may also be indicated in the worksheet by the number of decimals of the quantity to be weighed (see Sect. 29.1.3.3).

Strong (electro) magnetic fields and static electricity may disrupt the operation of an electronic balance. For example, Plexiglas draft shields, protective plastic covers or plastic weighing trays can be charged to such an extent that it influences the weighing result. In that case there is a large fluctuation of the figures that indicate the weighing result, especially when moving the charged object above the weighing scale. Avoid weighing vessels made of plastic when atmospheric humidity is below 30–40 %. The risk of electrostatic charges is greater under these conditions. This leads to inaccurate weighing results.

A deviation may be caused by the presence of a stir bar in the vessel into which the weighing is done. Therefore, a stir bar should preferably be removed from the vessel before weighing. If any deviation is remaining despite sensible actions, consultation of the supplier is necessary to be able to undertake the proper corrective action.

Temperature is one of the most important factors of a weighing process. For balances equipped with an automatic adjustment system, the balance precision restoring process is carried out automatically, with consideration of temperature as time changes. However, this concerns only temperature of the environment. One must not weigh hot or very cold objects on the balance. Hot objects will give erroneously low readings due to buoyancy of hot air, while cold objects will give high readings. Therefore, after removing the weighing vessel from a drying oven or dishwasher, allow time to cool before placing it on the balance. Analogously products taken out of the refrigerator should adjust to room temperature before they can be properly weighed.

A beaker taken from a water bath should be dried on the bottom before it can be placed on a balance scale.

Weighing vessels must be put in the centre of the weighing pan to prevent influence of eccentricity.

Finally, health and safety precautions at weighing procedures generally brings with it the wearing of gloves as a measure that is easy and good practice for all materials, but especially for the toxic ones (see Sect. 26.4.3). Because usually powdered substances are weighed, decreasing the exposure by inhalation is relevant. The use of an exhaust at the back of the balance is preferred, but expensive. The use of a safety cabinet or isolator could even be necessary. As an alternative in specific situations qualified nose-mouth masks or respirators can be worn. The best measure to decrease exposure is to use fluid or semisolid triturations of the active substance instead of the powder form (see Sect. 29.5).

29.1.6.2 Utensils for Weighing

For weighing out ingredients, a range of paper sheets, vessels and containers, spatulas and spoons are available. All receivers must be clean, dry and inert. The total weight of the receiver plus the substance to be weighed must not exceed the maximum capacity of the balance. If the repeatability and hence the M_{min} has been determined (see Sect. 29.1.5.2) with the usual, probably large, receivers (as is recommended), small quantities can be weighed from $M_{min,}$ if necessary also in those receivers.

The choice of the receiver is mostly determined by the ease for the preparation process concerned. Solids are often weighed on (paraffin) paper or in the processing vessel itself. Weighing polystyrene boats, antistatic weighing canoes or greaseproof paper are used as receivers as well. After transferring the solid from a weighing paper, hardly visible residues may still remain. By re-weighing the receiver and residuals the loss can be controlled to an acceptable level. The actual quantity added can also be determined through weighing the original container before and after the extraction. By weighing directly into the preparation vessel no loss occurs through transfer. Small amounts of powder can eventually be weighed on filler substance, but this harbours the risk that an excess cannot be removed in the case that too much of the substance is weighed. It is a matter of skills and experience.

Semisolids are weighed on greaseproof paper or cellophane. To prevent loss, a small amount of a substance can be weighed on a bit of the ointment base into which it will be incorporated (see above).

Compatibility with the receiver should be checked especially with fluids. Spatulas and spoons made of stainless steel may interact with substances such as chloral hydrate or iodine. But for the short contact time involved in the weighing procedure these interactions don't appear to be relevant. Plastic spatulas may cause a problem with electrostatic charge. Also with some substances discolouration of the plastic occurs so disposable spoons are increasingly used.

For liquids that are best weighed droplet-wise, vials with a drop dispenser (dropper) are suitable. By varying the position of the vial, the droplet size can be easily adjusted.

An accurate weighing of volatile solvents or solutions (alcohol, ether, methylene chloride) is still an unsolved problem. Evaporation occurs and the readings change constantly showing decreasing weight. The read-out of the weight should be performed only if the vial is closed.

29.1.6.3 Maintenance

Balances should be protected from damage, cleaned with great care and checked periodically. The weighing chamber and weighing pan should be kept clean (using conventional window-cleaning fluids, lint-free cloths), only clean weighing vessels should be used, contaminants should not be brushed into potential openings and all removable parts should be removed before cleaning.

All balances should be regularly calibrated and monitored for their performance. The applicable frequency of such tests should be based on risk assessment: the higher the impact of deviations, the more often testing should take place. Calibration is to be performed by the user either manually (with an external calibration weight) or using the internal calibration.

Calibration of a balance by an automatic internal calibration weight can be easily and regularly performed. Although it only indicates intrinsic accuracy and precision, which is not expected to change easily, it will indicate gross deviations as well, also those of the most important contributor to uncertainty: repeatability [13]. Repeatability and thus M_{min} depends also on environmental circumstances that may differ. Change of location, levelling the balance, major changes in temperature, humidity or air pressure make calibration and determination of M_{min} particularly important. When large deviations are noticed, the manufacturer has to adjust the balance.

So, calibration is to be performed daily and repeatability (leading to $M_{min,}$ see Sect. 29.1.5.2) should be determined regularly as well, for instance weekly. For repeatability also the alternative approach as described in Sect. 29.1.5.2. can be used. All other specific checks can be better performed at a technical service.

Balances that are broken or not qualified should be removed from the pharmacy or clearly marked.

29.1.7 Volume Measurement

29.1.7.1 Accuracy and Precision

Volume measuring means the exact determination of a defined volume of a liquid (or of a powder mixture in the case of preparing capsules). Devices for measuring of volumes for pharmacy preparations include: graduated pipettes (traditional or automatic), syringes and graduated cylinders. Beakers, Erlenmeyer flasks and medicine bottles are not fit for volume measurement, even if they are graduated. During pharmacy preparation processes all observed volumes are recorded on the batch preparation record as in-process controls.

As explained in Sect. 29.1.2 for preparation processes weighing is generally preferred to volume measurements, because a better accuracy and precision can be obtained.

When measuring a volume the following deviations (see also Sect. 29.1.1) are distinguished:

- Inaccuracy of the measurement devices
- Inaccuracy due to a temperature other than 20 °C
- Imprecision of the read-out

For the accuracy of volumetric measurement devices, ISO standards apply which are mentioned at the description in the next subsections.

Under ‘room temperature’ conditions, the temperature only has a small influence: 5 °C deviation of the calibration temperature of 20 °C results in a deviation of 0.1 % in the volume, based on the relative density of water. Warm or hot liquids cannot be measured accurately.

The imprecision of the read-out can be made as small as possible by choosing a graduated pipette, syringe or measuring cylinder with a nominal capacity as near to the volume to be measured as possible. For example: a volume of 0.5 mL should be measured by a 0.5 mL automatic pipette or with a 1.0 mL traditional graduated pipette. A volume of 21 mL should preferably be measured with a 25 mL graduated pipette or a measuring cylinder of a nominal volume of 25 mL.

29.1.7.2 Graduated Pipettes

Graduated pipettes must only be used for liquids that behave like water. They are calibrated on dispensing water, so that rinsing afterwards is not necessary. Graduated pipettes must meet ISO standards (International Organization for Standardization) [18]. The inaccuracy is limited in this way. The volume is read at eye level, at the bottom of the liquid surface (meniscus). The pipette is held vertically with the tip against the sloped wall of the receiving container and allowed to flow out vertically. Liquids should never be aspirated by mouth. Aspiration devices such as rubber balls are used in practice for sucking up fluids to be pipetted. Automatic pipettes, however, are by far to be preferred for this purpose.

When using graduated pipettes for more viscous liquids, an additional inaccuracy must be taken into account. Viscous fluids are therefore preferably weighed (see Sect. 29.1.2).

29.1.7.3 Syringes

In the framework of pharmacy preparations syringes are mainly used for measuring non-aqueous fluids and to make dilutions for parenteral administration on the ward. Especially for the latter application it is important to take the

attainable accuracy into account, according to ISO standards for syringes [19]. The size of a syringe for measuring a required volume should be carefully chosen

To make parenterals ready to administer, sometimes dilutions are to be made (see also Chap. 13). The deviation of the volume to be measured decreases with the increasing degree of filling of the syringe used. From the viewpoint of the pharmaceutical preparation a deviation of no more than 5–10 % is recommended (see Sect. 29.1.1). This recommendation, however, may require an additional dilution step to be performed. This increases the risk of microbiological contamination and calculation errors. Therefore risk assessment is necessary to decide which measurement accuracy is accepted in practice.

The dose to be administered should also be measured. Also for this purpose the volume of the syringe to be used should be as close as possible to the required dose (volume). To achieve this, the injection fluid can be diluted, but when administered to neonates this is not common practice because fluid restriction in this patient group is more important than ultimate dose accuracy. In practice for example, a 1 mL syringe is preferably used for the administration of 0.6 mL (or even less), but a 2 mL syringe is taken if a 1 mL is unavailable.

As an illustration the following clinical case may be considered. For the preparation of a parenteral infusion solution at the neonatal ward, an antibiotic injectable solution for adults has to be diluted. It was calculated that 0.6 mL of the 'adult' solution should be diluted to 10 mL with 0.9 % NaCl infusion solution. The dilution should preferably be prepared in a 10 mL syringe that subsequently could be installed in a syringe infusion pump. However, 0.6 mL of the concentrated antibiotic solution cannot be accurately measured with a 10 mL syringe, which does not even bears markings with 0.1 increments. A 1 mL syringe was used to sample 0.6 mL of the concentrated antibiotic solution and to transfer it to a 10 mL syringe. This process was checked for accuracy and repeatability. With six 1 mL syringes, each syringe used six times, '0.6 mL' water was sampled and weighed. The average weight was 0.63 g and the standard deviation (n = 36) was 0.025 g. So the inaccuracy (deviation from the nominal volume as a property of this batch of syringes) was 0.63–0.6 = 0.03 g = 0.03 mL which corresponds to a relative inaccuracy of 5 %. This is within the ISO norm (see further down). Assuming the six syringes being identical, the standard deviation of 0.025 g reflects the repeatability (imprecision due to handling). A single volume measurement may be affected in a worst case (imprecision having the same sign as the inaccuracy) with an inaccuracy of 0.03 mL as well as an additional deviation of about 2 times the standard deviation 0.025 g = 0.08 mL. This correspondences with a worst case relative deviation of about 13 %; which will be quite acceptable compared to clinical risk.

When a syringe is used to deliver a given volume, the liquid is expelled quantitatively with the piston. Depending on the type of operation performed, the dead volume of the syringe and the needle (if used) should be taken into account. This is for instance the case when a volume of a liquid is measured in a syringe, after which it is diluted by aspiring a volume of another liquid into the same syringe [20, 21]. To minimise dead volume deviations, smaller volumes are better aspired with a separate syringe and added to another syringe which contains the diluent. The dead volume can be calculated from the difference in weight of a syringe (with needle) before use and after the liquid has been expelled. The dead volume is, of course, not applicable if only a fraction of a liquid present in the syringe is measured (for example, if from a syringe filled up to 10 mL only 5 mL is expelled) or even when a measured volume is fully expelled.

Accuracy and precision is best if syringes are used with a capacity as near as possible to the quantity to be measured. Filling a syringe that is meeting the appropriate ISO norm (7886-1) [22] to more than 50 % of its capacity will result in an inaccuracy not exceeding 5 %. If the filling degree is around 20 % the inaccuracy will rise to 10 % and filling to not more than 10 % may lead to an inaccuracy of about 20 %. Imprecision depends very much on individual handling, but will be smallest when the capacity is nearest to the quantity to be measured.

What is considered acceptable depends on the purpose or application. A risk assessment should reveal whether a lower deviation obtained by stepwise dilutions offsets the higher risk of bacterial contamination introduced by the higher number of handlings, see also Sect. 31.3.2).

29.1.7.4 Measuring Cylinders

The measuring cylinders that are used in pharmaceutical preparation processes have to comply to international standards for graduated measuring cylinders (ISO norm 4788) [23]. A measuring cylinder is calibrated either to contain or to deliver (marked 'TC' (to contain) (or 'IN') or

'TD' (to deliver) (or 'EX') accordingly). For preparation purposes a cylinder to deliver the liquid may be most appropriate. The volume is read out at eye level. For measuring viscous liquids, the measuring cylinder has to be rinsed afterwards with another fluid (such as water) used in the preparation process because the nominal volume is related to the volume that is contained in it. If there is no liquid in the preparation to rinse a measuring cylinder with, it should not be used. Instead a syringe can be used. If rinsing is impossible because of too high the viscosity, the liquid should be weighed (see also Sect. 29.1.2).

The inaccuracy of measuring cylinders have to meet ISO requirements as well. The inaccuracy is limited to 5 % when using at least 40 % of the nominal capacity of cylinders ≤50 mL, and at least 20 % of the nominal capacity of 100–2,000 mL cylinders. For preparation purposes there will be hardly any reasons for not aiming at a maximum inaccuracy of 5 %, realising the requirements for the mean content (see also Sect. 29.1.1).

29.1.7.5 Preparation Vessels

Medicine bottles are often provided with a graduated mark. It is intended, and accurate enough, to measure a quantity to be dispensed to the patient. To adjust the volume during a preparation process it is too inaccurate. This may also apply to the reconstitution of an antibiotic oral mixture in a bottle provided by the manufacturer. In this case it is also relevant that the meniscus cannot be accurately read due to foaming of the mixture. Separate measuring or weighing of the required quantity of water is the right approach.

In very large preparation containers a calibrated rod or mark indicates the volume (as an alternative to load cells). In a calibrated rod a dash can be accurately notched.

With a calibrated rod that is suspended centrally above the liquid in a preparation container, the level is readable at ≤1 mm. In a container with a capacity of 100 L and a diameter of 50 cm, a difference of 1 mm in height corresponds to 0.2 % of the volume. If a calibrated rod would be used along the side of the container, the mistracking may be 3 mm (by 'creep' of water against the wall). This corresponds to a deviation of 0.6 % of the volume.

29.1.8 Non-Directly Weighable Quantities

Especially in the case of extemporaneous preparations, it may happen that the quantity of an active substance or excipient to be processed lies below the minimum weight M_{min} (see Sect. 29.1.5) of the most sensitive balance available: a non-directly weighable quantity. The best procedure is to prepare a larger batch of the preparation than necessary and to reject what will not be dispensed. However, this may not be economically feasible, in which case there are two (less good) alternatives: trituration/dilution, or starting from another preparation or licensed medicine with a low concentration of the active substance required.

29.1.8.1 Triturations and Dilutions

A trituration of a powdered active substance is obtained by mixing (see also Sect. 29.4.3) with an excipient (for instance lactose) in a ratio that is easy for calculation when creating a batch preparation worksheet (1:10; 1:100). The excipient can also be a semisolid substance such as white paraffin, with which simultaneously a deagglomeration can be accomplished.

Salicylic Acid Trituration 50 % DAC [24] is an example of a trituration with semisolid excipients. The composition is given in Table 29.3.

Table 29.3 Salicylic Acid Trituration 50 %

Salicylic acid	50 g
Paraffin, liquid	10 g
Paraffin, white or yellow soft	40 g
Total	100 g

The preparation method consists of three subsequent steps: (1) grinding of salicylic acid, (2) triturating salicylic acid with liquid paraffin, (3) mixing the salicylic acid – paraffin mixture with white or yellow soft paraffin.

In case of a dilution, the active substance is dissolved in a suitable liquid to obtain a concentration that is easy for calculation when creating a batch preparation worksheet.

The risk of calculation errors, inhomogeneity and instability with preparing triturations and dilutions is probable and therefore, an analytical control is advised.

The content of active substance in a dilution or a trituration must be low enough, to ensure that a volume can be measured with sufficient accuracy from a dilution, and a quantity can be weighed with sufficient accuracy from a trituration. For the sake of homogeneity, the content of the trituration should however be as high as possible.

When designing dilutions, the solubility of the active substance should be known and stability and preservation should be taken care of if the dilution is stored. When designing triturations, similar aspects as in the preparation of a powder mixture for capsules must be examined:

adsorption to fillers, physico-chemical changes due to trituration, homogeneity. The same aspects apply to semisolid triturations. Chemical and physical stability (demixing, evaporation) and interactions have to be investigated if the trituration is stored. If a trituration is kept in stock, appropriate measures must be taken to avoid mistaking the trituration for the pure active substance.

For each specific dilution or trituration a batch preparation worksheet (see Sect. 32.4) must be designed. The in-process controls are the same as for the mixing of substances.

As a conclusion, chose a 10- or 100-fold trituration respectively, a 10-, 100- or 1,000-fold dilution, so that the quantity to be weighed or the volume to be measured lies above the minimum weighable or measurable quantity. An excipient has to be used that does not affect the therapeutic and biopharmaceutical properties of the preparation, nor its stability. An excipient, already used in the preparation, might be a good choice. The trituration is made by grinding (in case of a solid) or trituration (in case of a semisolid) and mixing of the powder substances. A dilution is made by dissolution.

29.1.8.2 Starting from Pharmaceutical Preparations

Weighing a (ground) pharmaceutical preparation instead of the pure raw material may be necessary if a very small amount of active substance – below the minimum weight M_{min} – is needed. Tablets or capsules may be used, in which the active substance is contained in a low concentration, and ground. Counting substitutes weighing and mixing becomes easier because of the larger bulk volume and may lead to less exposure (see Sect. 26.5). Caution should be exercised, however, as the content of active substance in the few tablets or capsule that are ground may differ, sometimes considerably, from 100 %. Also to be borne in mind is the presence of excipients in the preparation which can affect the release rate when used in a new formulation (e.g. a tablet that is used in preparing low dose suppositories). The feasibility of tablets and capsules for this procedure is further discussed in Sect. 4.10.7. The use of tablets or capsules as starting material is discussed in Sect. 4.5.1.

29.2 Particle Size Reduction

Single crystalline or amorphous particles are called primary particles, agglomerates are secondary particles. Particle size can be reduced by reducing primary particles, or by splitting secondary particles into primary particles (dispersion of agglomerates). In this section the importance of particle size for the quality of the medicine is discussed and two methods of reducing primary particles are highlighted: mechanically (by grinding or milling) and by using physico-chemical methods: the solution method (solvent deposition method, see Sect. 29.2.3) and the precipitation method. Dispersion of agglomerates is discussed in Sect. 29.3. See Table 23.3 for the terminology of the degree of fineness of raw materials and Sect. 23.1.8 for measurement of particle size.

29.2.1 The Purpose of Particle Size Reduction

For pharmaceutical or biopharmaceutical reasons, or both, requirements for the particle size are set for many active substances and excipients. See Sects. 16.1.2 and 23.1.8.
Particle size reduction may be advantageous:

- For the uniformity of content and dose accuracy. Particle size reduction increases the number of particles per unit of weight and thereby the homogeneity of the mixture.
- For the stability of a suspension. Smaller particles have a lower sedimentation rate.
- To prevent demixing. By striving for a particle size that is approximately equal for all components, demixing is prevented.
- To enhance the dissolution rate of poorly soluble substances. Poorly soluble substances dissolve faster as the particles are smaller (see Sects. 18.1 and 16.1.4).
- To prevent irritation upon contact of the particles with the skin, eye or mucous membranes.
- For a smooth appearance (in ointments).
- To avoid high local concentrations (in ointments and suppositories).

Particle size reduction may also have drawbacks:

- Increasing the particle surface increases access by water vapour or oxygen which may accelerate degradation.
- The flowability of the substance is deteriorated.
- If only the particles of the active substance are reduced and the excipient particles remain larger, demixing will be favoured.
- Wetting becomes more difficult, making a substance harder to dissolve or more difficult to bring into suspension.
- Tendency to uncontrolled agglomeration.
- Electrostatic properties increase.
- Inhalation of particles in dust.

When designing a formulation, the requirements for the particle size may be conflicting. In practice, one must often be satisfied with a compromise.

Tetracycline hydrochloride comes in two different grades: 'micronisatum' (microcrystalline) and 'ponderosum' (the pressed form). Microcrystalline tetracycline is finer, easy to disperse in a cream or ointment base but less stable because of its larger surface in contact with water. Preparations containing the microcrystalline form have a relatively short shelf-life. The pressed quality has a considerably better flowability and is more stable, but when processing it into a cream or ointment base much more attention should be paid to get a homogeneous distribution.

In the preparation of Paracetamol-codeine suppositories FNA (Table 11.5), paracetamol (45) is used as small particles because they provide a faster release rate [25]. In addition, the small particles sediment less rapidly during the preparation of the suppositories. Particles with this degree of fineness, however, establish a poor flow and have a high bulk volume. This makes them unsuitable for processing into capsules. For this purpose the paracetamol quality (90–500) is used. For sieve ranges in relation to particle size see Table 23.3.

29.2.2 Grinding

Many raw materials are available in a quality that is sufficiently fine for pharmaceutical preparation. If mechanical particle size reduction is still needed, this is done manually by grinding in a rough stone or porcelain mortar, using a stone pestle. However, this is only useful for substances with primary particles larger than about 100 µm. For finer materials there is a considerable risk of agglomerates being formed. By grinding in a mortar often no particles smaller than about 50 µm are obtained. Using small impact mills, for example a beating mill (coffee grinder, see Sect. 28.6.7), finer powders with a narrow particle size distribution can be obtained.

If the primary particle size is >180 µm (or in case of doubt) first an excess is ground in a rough stone mortar to obtain the correct particle size (see Sect. 28.6.4). Excess material (usually depending on a size of mortar) is used, the required quantity weighed and the remainder is thrown away (not put back into the container), in order to avoid possible contamination. Tablets can be ground in the same way.

On an industrial scale, micronisation of substances is often achieved with a jet mill. The strong air current in this device results in electrostatic charging of the particles, making them more difficult to be moistened. This can also lead to agglomerate formation. This phenomenon is called tribo-electrification. During the grinding of very hard materials, such as borates, particles (plastic or metal) of the grinding equipment may contaminate the powder. These are visible as an impurity when the substance is dissolved and may even hinder wetting. In contrast to other mills, contamination with metal particles in the jet mill is very rare.

Grinding in the presence of a liquid or semi-liquid (wet grinding) can be as effective as dry grinding and may have the advantage of preventing electrostatic charging that may cause agglomeration, stickiness or 'jumpy' behaviour.

When metronidazole (crystals 500–600 µm) for the preparation of a fat-based eye ointment is made into a paste in a mortar with a few drops of paraffin, the particles are 20–70 µm in size after 1 min of mixing. After 15 min of mixing, a powder is achieved with particles less than 10 µm in size. To obtain such a particle size reduction without the paraffin is difficult since the powder escapes from the mortar due to its strong electrostatic properties. If a hydrophilic ointment base is used, glycerol may be considered to triturate the metronidazole with.

29.2.3 Physico-chemical Particle Size Reduction

Physico-chemical methods for particle size reduction comprise methods wherein the substance is first dissolved and then precipitated in a finer form during further processing. This has the advantage that it is independent of the fineness of the starting material and that the formation of small agglomerating particles is largely prevented. Two methods are distinguished: the solution method and the precipitation method.

The names 'solution method' and 'precipitation method' are actually not very well chosen. Indeed, in the precipitation method the active substance is first dissolved, while in the solution method the substance is also precipitated, but onto

a solid substance as a carrier. For the latter, the term 'solvent deposition' is applied as well [26].

29.2.3.1 Solution Method or Solvent Deposition Method

In the solution method or solvent deposition method, the active substance is dissolved in a volatile solvent. The solution is triturated dry on a powder (carrier material) that is insoluble in the solvent. After evaporation of the solvent, the substance is evenly and finely divided over the surface of the carrier, in a non-agglomerated form.

The solution method is, for example, suitable for the preparation of capsules with a low dose of active substance. But the method can only be applied if:

- The active substance is sufficiently soluble in a quantity of non-toxic volatile solvent that can be evaporated within a reasonable time (most often ethanol is used).
- The active substance is stable in solution.
- There is sufficient carrier material in proportion to the amount of active substance that is divided, as otherwise agglomerates of the active substance may occur.
- The crystal form of the active substance is changed by dissolving and precipitation, but the stability and the dissolution behaviour may not be altered.

Furthermore, it must be ensured during the preparation process that:

- The dissolved active substance does not remain on the wall of the mortar and pestle.
- There is no (toxic) solvent residue remaining in the mixture.
- The solvent is properly exhausted because most suitable solvents are flammable and explosive and toxic to the compounder.

This method is known as 'solvent method' for the preparation of low dose capsules, and is further described in Sect. 4.5.1. The method brings about not only particle size reduction and deagglomeration but is also used for the preparation of triturations of low-dose active substances (see also Sect. 29.1.8).

The solution method proved to be useful for capsules with a low dose ($\leq$5 mg per capsule) of colchicine, diazepam or ethinylestradiol. Colchicine and diazepam are sufficiently soluble in dichloromethane, after which it is precipitated on microcrystalline cellulose, which also serves as a filler for the capsules. Ethinylestradiol is soluble in acetone and is precipitated on lactose, which is used as a filler here. In all cases, an amount of solvent is taken in which the active substance dissolves and by which half of the powder mixture on which the active substance is precipitated can be moistened. The active substance is dissolved in the solvent in a mortar with a smooth wall. Half of the filler is added and the powder is mixed until dry and the smell of the solvent no longer detectable. The powder mixture is then taken from the mortar. Because the active substance can deposit and / or crystallise on the mortar wall, mortar and pestle are subsequently wetted with the solvent and the other half of the filler is mixed therewith. Once the smell is gone, both portions of powder mixture are mixed and the capsules filled.

The solution method can also be used for the achievement of a homogeneous mixture in the mixing of solids with a poor mixing ratio. Also for colouring a powder, this method is very suitable. Much less dye is necessary: if the colouring agent (see Sect. 23.11) is homogeneously dispersed on a carrier, the colour will be much more intense than when the dye particles are distributed between other particles.

Triamcinolone acetonide in dermal preparations is processed as a trituration with rice starch (1:10). Here, the particles of triamcinolone acetonide are reduced in size firstly by dissolving the substance in a volatile solvent, after which this solution is rubbed until dry with rice starch. The resulting particles of triamcinolone acetonide of about 5 μm are in this way mixed with and held apart by the starch particles. By pulverising triamcinolone acetonide as such in a mortar such fineness of particles is not achieved. Moreover, agglomerates will be created. Also rubbing the solution until dry without rice starch does not yield a good result. Not only agglomerates will be recreated, but part of the triamcinolone acetonide will crystallise in a coarser form.

29.2.3.2 Precipitation Method

The precipitation method may be used when an active substance with too large particles has to be processed in a suspension. In this method the active substance is first dissolved, and then after changing the medium into the final composition, the active substance will precipitate, in a more finely divided form.

To (temporarily) dissolve an active substance for the precipitation method, the following methods are applicable:

- Temperature rise
- pH shift
- Dissolution in only one of the components of the final medium

Two examples, concerning the processing of active substances in an oral suspension.

If sulfonamides have too large particles, first the corresponding soluble sodium salt is prepared in aqueous medium with sodium hydroxide. Then, by adding citric acid solution the sulfonamide finely precipitates.

Tetracycline hydrochloride dissolves partially in water and then degrades quickly. Moreover, the pH of such a solution is very low (about 2) which is too low for an oral liquid. By adding sodium citrate the pH is increased to about 6. Tetracycline precipitates finely divided and the dissolved fraction is as small as possible. This method can be used as well to prepare a cream containing tetracycline.

In Polish pharmacies the most popular method to obtain very small particle sizes is a combination of the precipitation method with grinding: the substance is dissolved in a porcelain mortar in a very small amount of ethanol or even ether and rubbed with a pestle until the solvent evaporates. When the solvent evaporates, precipitation occurs and the crystals are immediately pulverised. Not using a carrier however increases the risk of agglomeration of the fine particles (see Sect. 29.3.2).

29.3 Dispersing Agglomerates

29.3.1 Orientation and Definitions

Primary particles may form agglomerates under the influence of moisture, electrostatic or Van der Waals forces. The tendency to form agglomerates increases with decreasing particle size, as is seen in many micronised active substances. Lipophilic substances exhibit a stronger tendency to agglomerate than hydrophilic substances. Agglomerate formation is often the cause of poor flow of a powder mixture. The dispersion of agglomerates improves the flowability. For further reading see [27].

When processing agglomerating substances, agglomerates must be dispersed and re-agglomeration prevented. For the dispersion (shear) forces are needed, but the medium in which the agglomerates are dispersed should ensure that dispersed primary particles remain separate. For that purpose interactions have to be offered that replace the interactions that lead to agglomerate formation. If dispersing of agglomerates occurs by trituration and dispersing into a medium, the cohesive interaction between the particles of active ingredient is replaced by adhesive interaction between active ingredient and excipient.

If out of habit or 'to take out lumps' a very fine active substance is rubbed in a mortar while not adding a suitable medium, agglomeration may be increased. As a result, it takes much more effort to disperse them in a medium afterwards. The right approach to get rid of visible lumps is to press them gently by hand (between two papers, e.g. for sulfur), with a plastic pestle or with a brush and sieve.

The term trituration is used if a solid substance is firstly mixed with just enough of the liquid (or of the semisolid) in a formulation and subsequently gradually mixed with the rest. This is usually done in a mortar with pestle. With trituration agglomerates can be properly dispersed.

Table 29.4 summarises the terminology used on particle size reduction, mixing and de-agglomeration.

29.3.2 Selection of the Medium

The medium used to disperse agglomerates must be selected so that no re-agglomeration occurs. The choice of medium also depends on the pharmaceutical dosage form that is prepared. Agglomerates can be dispersed in another solid, in a liquid or semisolid. Examples of solid medium are lactose for de-agglomerating morphine hydrochloride processed in suppositories, and rice starch for triamcinolone acetonide (processed in dermal preparations). Examples of a liquid medium are propylene glycol in the processing of miconazole nitrate or hydrocortisone acetate as an addition to dermatological bases, or a mixture of propylene glycol and water for the processing of carbomer in the preparation of a gel. Miglyol 812 ® (Triglycerida saturata media), a mixture of medium chain triglycerides, is a low viscous lipophilic substance that is very suitable to de-agglomerate solids. Semisolid substances and preparations that can be used as a medium include molten suppository base (the standard method for the preparation of suspension suppositories) and cream bases.

The uniformity of content of suppositories with morphine hydrochloride 20 mg in a fat base is considerably improved by triturating the morphine hydrochloride first with 100 mg of lactose or mannitol [28]. It is likely that the agglomerates of morphine hydrochloride are 'ground' between the crystals of lactose or mannitol into smaller primary particles.

Zinc oxide is better wetted by oil than by paraffin. Therefore, it is relatively easy to disperse Zinc oxide in oil, and more difficult in liquid paraffin [29].

Table 29.4 Overview of the terminology used in relation to particle size reduction, mixing and de-agglomeration

Topic	Term	Description
Particles	Primary particles	Particles that consist of a single crystal
	Secondary particles	Particles are agglomerates
Particle size reduction	Milling	Particle size reduction by (different) forces
	Grinding	Milling a substance by hand
	Wet grinding	Grinding with an amount of liquid as small as possible for reasons of: preventing agglomeration, augmenting milling efficiency (grease effect) or for occupational safety and health reasons (to prevent the creation of dust particles)
	Pulverising	Smashing a material into a powder
	Comminuting	Reducing to powder (US)
Mixing and de-agglomeration	Dispersing	Distributing primary particles in a medium; may simultaneously lead to the breaking up of agglomerates (de-agglomeration)
	Geometrically dilution (Triturating)	Mixing using the ratio 1:1 repeatedly
	Mixing (= blending)	Putting substances together to get a homogeneous distribution
	Rubbing	Intensely mixing (triturated) powders with a semisolid or liquid on a surface to obtain a smooth mixture
		Making into a (thick) paste
		Levigating (US)
	Triturating	Mixing a solid with a solid, semisolid or liquid substance in such a ratio and intensity that agglomerates are dispersed (de-agglomeration); de-agglomeration may take place if the right medium is chosen

29.3.3 Dispersion Methods

Agglomeration might be the cause of poor flowability, for instance of a powder mixture for filling of capsules or tablet dies. The addition of anhydrous colloidal silica (Aerosil 200V) may be effective for the dispersion of agglomerates. Silica is added to 0.5–1 % (w/w) of the total weight of active substance and excipients.

Flowability can be measured (quantitated) by determining the angle of repose, flow through an orifice or tapped and bulk density [30].

For dispersion of agglomerates amid another substance usually a (non-rough) pestle and mortar, an three roll mill (ointment mill, see Sect. 28.6.6) or a rotor-stator mixer (see Sect. 28.6.2) are used as a tool. Sometimes a beaker mixer/blender (Sect. 28.6.5) or the Stephan® mixer (Sect. 28.6.1) is used). Trituration of an active substance with eye ointment base is done in a stone mortar with a stone pestle because a lot of force is needed. Sometimes it is possible to disperse agglomerates on an ointment tile with a spatula, but a drawback is that no great force can be exerted. For the dispersion of a solid substance amid other solids, a plastic or metal mortar can be used.

To choose the most appropriate method for dispersing agglomerates some basic rules are given:

- For small quantities, it is first investigated whether trituration with the medium in a mortar yields the required dispersion.
- A raw material having very small particles with a high tendency for agglomeration points to the use of an ointment mill if a semisolid can be used.
- If the percentage of solids in ointments is more than about 10 % or if the batch size exceeds 200 g the use of an ointment mill is preferred.
- A rotor-stator mixer requires a sufficiently large volume and is unsuitable for viscous and foaming media.

The choice of the mixing tool which is able to reduce particle size and to eliminate agglomerates depends of the physical characteristics of the preparation. The most suitable ones are:

- For powders: mortar, mechanical mill, blender.
- For liquid suspensions: rotor-stator, Stephan mixer, other mixers (e.g. Unguator®).
- For suspension-type semisolids: mortar, mixer, ointment mill, spatula.
- For emulsions: rotor-stator mixer, high pressure homogeniser, ointment mill.

29.4 Mixing of Solid Substances

29.4.1 Orientation

A characteristic feature in mixing solid substances is that temporary expansion is necessary. After mixing, demixing may occur when the mixture is brought into motion.

Mixing of solids takes place in the pharmacy in the preparation of capsules, single-dose powders and multidose powders. But also in the preparation of suppositories and dermal preparations solids may first be mixed together before they are combined with the base. A common reason for this is that mixing solids may give an opportunity to:

- Disperse agglomerates (morphine hydrochloride with lactose)
- Making carbomer hydrophilic ('hydrophilise') with disodium edetate and trometamol)
- Improve handling (paracetamol (45) with anhydrous colloidal silica)

In the next sections two types of mixing of solids are discussed: random mixing and ordered mixing. In practice, the mixing process mostly consists of a combination of the two. Dispersion of agglomerates may precede the mixing of solids or it may take place simultaneously [26].

The actual mixing (geometrically dilution method and wrapping method) is discussed thereafter. The best mixing quality is obtained when the mixing ratio of two solids is 1 to 1 (geometrical dilution), and the particle size is equal. A large mixing ratio, and a large difference in particle size, will lead to a long mixing time to obtain a homogeneous mixture [2].

29.4.2 Random Mixing

The term random mixing is used when the particles to be mixed show no cohesive or adhesive forces to each other. The best attainable mixing in that case is a statistically random mixture (see Fig. 29.5). A fully homogeneous and regular mixture (Fig. 29.6) is impossible to obtain in practice.

In a random mixture the probability that a sample contains a certain amount of active substance is equal throughout the entire mixture. This probability is proportional to the fraction of active substance present in the mixture. Theoretically, this applies only if the particles of the substances in the mixture have the same shape, size and density, and if there are minimal surface forces in action such as moisture, electrostatic charge, or, for small particles, Van der Waals forces.

The variation of the fraction of component (an active substance) in a random mixture can be calculated using the formula: [27]

$$\mathrm{rsd} = (\mathrm{p}(1 - \mathrm{p})/\mathrm{n})^{½} \times 100\ \% \qquad (29.1)$$

where rsd = relative standard deviation, p = the fraction of active substance of the mixture and n = the total number of particles per sample.

With this formula the influence of the number of particles and the mixing ratio on the theoretically achievable homogeneity can be demonstrated. If the number of particles (n) in the mixture increases, the relative standard deviation will decrease. With an equal number of particles in a sample, the rsd strongly increases as the fraction of active substance (p) in the mixture decreases.

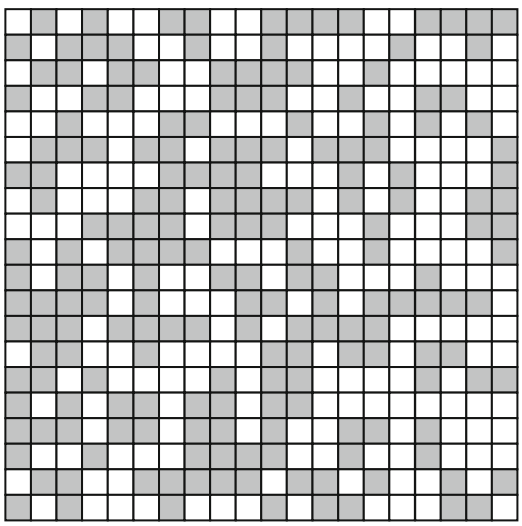


Fig. 29.5 Statistically random mixture (from Twitchell [27], with permission)

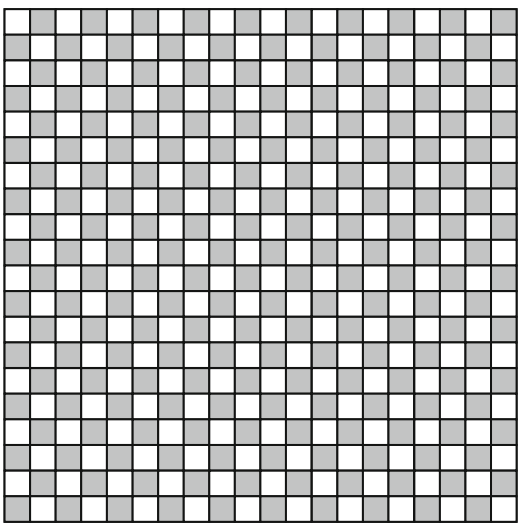


Fig. 29.6 Fully homogeneous and regular mixture (from Twitchell [27], with permission)

Suppose that the rsd for mixing must not exceed 5.0 % to meet the requirements for content uniformity. If an active substance is mixed with an equal number of particles of another substance ($p = 0.5$), a total of at least 400 particles per dose unit will be present at the best attainable mixing. To a mixture of 1 % of active substance ($p = 0.01$), the number of particles per dose unit has to be 40,000 or more to meet the same requirement. From this calculation it appears that in case of an unfavourable mixing ratio (p is small) more particles in the sample (i.e. smaller particles) are needed.

29.4.3 Ordered Mixing

When a substance consisting of very small particles is mixed with a substance consisting of larger particles, adhesion forces between the small and large particles may start to play a role. The smaller particles will be distributed onto the larger ones, which act as a carrier. The mechanism for this may be incorporation of the particles in irregularities on the surface of the carrier or, for larger quantities of the active substance, formation of a film of small particles on the carrier material. Both electrostatic and mechanical forces take part in this distribution [27].

This phenomenon is designated as ordered mixing, although random distribution plays a role here as well. When ordered mixing can be used a very good mixing quality is obtained, with less chance of demixing compared to random mixtures.

But with ordered mixing demixing is possible as well:

- If there are insufficient sites for adhesion at the carrier.
- If the particles of the carrier largely differ in size; the carrier particles will demix and because carrier particles of various sizes adsorb different amounts of active substance, this demixing may result in a considerable variation of the amount of active substance per unit weight.
- If another substance is added to the mixture that competes with the adsorbed active substance particles: a fraction of the active substance can be released if there are insufficient interaction sites on the carrier particles for both.

For some capsule preparations in pharmacies ordered mixing may be the case. Mixing as the result of the solvent method may be considered as such (Sect. 4.5.1).

29.4.4 Mixing Methods

Three methods of mixing of solids are distinguished:

- Diffusive mixing: the particles roll on top of each other under the influence of the gravity
- Convective mixing: portions of the powder mixture move in relation to each other
- Mixing under the influence of shear forces

(see also Sect. 28.6)

Shear forces are especially important when dispersion has to be achieved during mixing. The shear forces in low shear mixing equipment (mixing cube, Turbula® mixer, Stephan mixer) are weak and are sometimes insufficient to disperse agglomerates. In a mortar with pestle and in medium shear mixers (e.g. Nauta® mixer) or high shear mixers (e.g. IKA® mill) the shear forces are often big enough. In exceptional cases joint grinding of materials (co-milling) is necessary to reach adequate mixing.

For good mixing, preferential directions must be avoided. This can be achieved by combining the three above mentioned modes in a mixing process. A preparation worksheet should give sufficient details on the mixing procedure:

- Degree of filling, respectively the size of the mortar: in a mixing device there must be sufficient space for expansion of the powder mixture and therefore it may not be filled to more than two-thirds
- Order of adding substances
- Quantities to be added for each mixing step
- Mixing speed (if the process is automatic)
- Mixing time: as a consequence of mixing too long, separation of the mixture can occur [30].

For information on mixing equipment, see Sect. 28.6.

29.4.4.1 Geometrical Mixing and Wrapping Method

The mixing of powders in a pharmacy is typically done in equal parts using a mortar and pestle together with a spatula (geometrical dilution technique) [2]. It can be considered as a combination of convective mixing and mixing under the influence of shear forces. Firstly, the substance available in the smallest amount is mixed in the mortar with (as a rule) an equal amount of the substance available in the second smallest quantity. Subsequently as much substance as is already present in the mortar is added, etcetera, until all ingredients are well mixed. If only one active substance is processed, it must first be mixed with an equally large amount of filler. By applying this method of mixing, diffusive and convective mixing alternate. It provides the best mixing quality. Moreover, in this way, the small fraction is maximally involved in the mixing process. Sometimes this method of mixing (in a mortar) is applied as a first step (pre-mixing), preceding mixing with mechanical mixers.

Using a Turbula® mixer mixing starts with shear forces, followed by a combination of (low) shear forces and diffusive mixing.

Many modern active substances show strong agglomeration, the powder is electrostatic and jumpy. When mixing, the agglomerates must be dispersed simultaneously. However, before such substances have been mixed with other substances they already adhere to the wall of the mortar or the pestle or disappear from the mortar with the airflow in the dust exhaust hood. Without precautions loss of these active substances occurs during mixing in the mortar and in other open vessels. The loss can be prevented by wrapping the active substance between two layers of filler first, prior to mixing and the dispersion of agglomerates. This is called the wrapping method. Subsequently the principle of geometrically mixing is applied. When a stainless steel cube mixer is used, there is no essential difference between mixing with and without wrapping packing the active substance.

In extemporaneous preparation, the mixing time in a mortar is frequently determined by visual assessment of the mixture after the procedure has been validated. Usually a mixing time of powders in a mortar should not be shorter than 3–4 min. For larger scale preparations the required mixing times have to be assessed by analysis and validated. Mixing times may differ quite a lot, depending on material properties, such as particle size, mixing ratio and volume of the powders.

29.4.4.2 Demixing

Demixing counteracts the achievement of a homogeneous mixture. The extent to which and the ease with which separation can occur is dependent on material properties, the mixing method applied and external influences during storage and transport.

External influences that may cause demixing are gravity, movement, fall and vibrations. When a powder mixture is stocked, e.g. a trituration, it must be examined whether demixing occurs. This also applies to a possible transport thereof. Cutaneous powders may demix as a result of the shaking movements applied during use.

Substance properties are an issue in the following ways of demixing:

- Differences in particle size lead to separation in poorly flowing mixtures.
- Differences in density lead to separation in well flowing mixtures.
- Differences in the shape of the particles and in electrostatic charge can lead to demixing.

The mixing method may cause demixing in the following ways:

- The occurrence of preferred movements in the mixing process itself. When mixing in a mortar and pestle, for example, it is necessary to alternate horizontal (diffusive) mixing by alternate (convective) mixing with a spatula. Good mixers are so designed that preferred movements do not occur. The mixing process should be abruptly

An example of the effect of mixing time for Benzocaine (as a model substance) is illustrated with microphotographs (Fig. 29.7). Benzocaine (crystalline particles in a range of 50–250 µm) (left) was pulverised in a porcelain mortar for 1 min. The particle size was reduced to an average of 26 µm (range 10–40 µm) (middle). Continuing pulverisation for 10 and 15 min reduced the particle size to an average of 5 µm (range 2–8 µm) and 2.5 µm (range 1.5–3.5 µm) respectively (right picture).

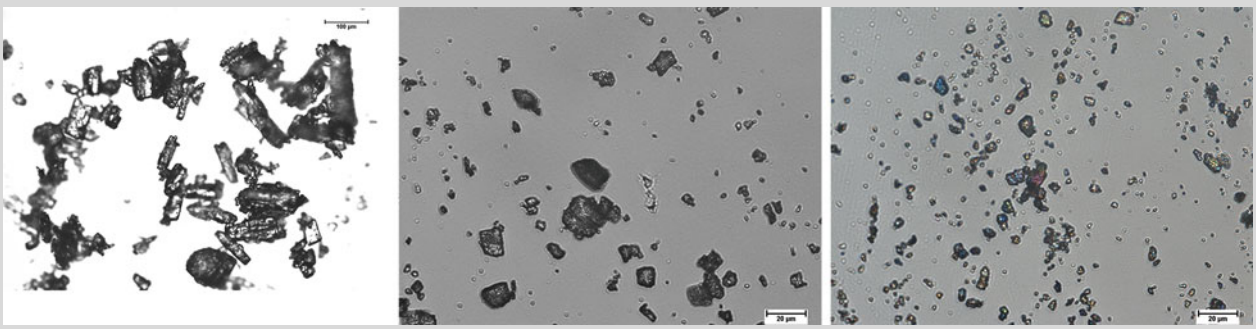


Fig. 29.7 Particle size reduction of benzocaine in relation to mixing time. Left picture: no pulverisation; middle picture: 1 min pulverisation in mortar; right picture: 10–15 min pulverisation in mortar. © Department of Pharmaceutical Technology GUMed Gdansk.

Table 29.5 Basis for Cutaneous Powder [31]

Zinc oxide	10 g
Talc	90 g
Total	100 g

Preparation: Mix zinc oxide and talc and pass through sieve no. 90. Mix again

ended. Slowly reducing the forces in one of the directions can lead to demixing.

- Also good flowability can lead to demixing. Particles flow too easily past each other, making them demix by difference in density or particle size or both.
- When sieving a mixture (sieve sizes in Sect. 23.1.8), the particles of various substances may pass the sieve openings with different speed, mainly because of differences in size and shape. As this may cause demixing, remixing is needed after sieving, As an example Basis for cutaneous powder FNA is mentioned (see Table 29.5), in which preparation talc and zinc oxide are mixed, sieved and mixed again.

29.5 Dissolving Solid Substances

Dissolution in aqueous environment is a prerequisite for the absorption of any active substance. Furthermore, the solubility behaviour of an active substance may influence the choice of a pharmaceutical formulation.

Dissolution of a solid into a liquid can, in principle, occur spontaneously by diffusion, but that may take quite some time. Once dissolved, a molecular distribution of the substances in one another exists (solution) and no separation will occur. Diffusion becomes progressively slower as the saturation concentration (solubility) is reached (Noyes-Whitney equation, see Eq. 18.1). The diffusion can be accelerated in a pharmacy preparation by shaking, swirling, stirring and eventually heating. Semisolid substances, such as fats and macrogols, nearly always have to be dissolved under heating (via melting).

The dissolution rate of a solid substance in a liquid can be increased in three different ways:

1. By first squeezing any lumps.
2. By using a quality with finer particles. This is only necessary when the substance dissolves extremely slowly.
3. By dry premixing (trituration) with a substance that is easily wetted by water. This means that the powder is temporarily hydrophilised.

Mixing with a well wettable substance is needed for poorly wettable substances that otherwise in contact with water will form lumps with a water inaccessible core.

Viscosity enhancers easily form lumps, after which they do not dissolve. To avoid this during a preparation, they must first be finely divided by trituration, by dispersing with a rotor-stator mixer or by sprinkling them slowly on the surface of the vigorously mixed water.

The way of processing cellulose derivatives depends on the type. Some should be moistened with hot water, in which they do not dissolve, and thicken only upon cooling. See Sect. 23.7.

If carbomer would be suspended in a mortar with water, it would result in a lumpy mixture. In the preparation of carbomer gel the carbomer is therefore processed in a different way. It is finely distributed with a rotor-stator mixer, or first (dry) mixed with the readily water soluble substances disodium edetate and trometamol (hydrophylisation). If this mixture is subsequently triturated with water, no lumps will occur. Alternatively, a carbomer gel may be prepared by adding carbomer in portions to vigorously stirred water or an aqueous solution followed by adding the alkaline solution. It is an advantage of carbomer, as opposed to cellulose derivatives, that it is easy to use for the preparation of a gel.

In pharmacy preparations, various methods are used to dissolve a solid substance in a liquid:

- Swirling in an Erlenmeyer flask
- Shaking or swinging in a closed vessel
- Stirring with a glass rod or spoon in a beaker or with a magnetic or mechanical stirrer
- Using an ultrasonic bath (sometimes)

If there are semisolid ingredients they can be dissolved in a metal mortar or in a porcelain dish while warming on a water bath. Inhomogeneity of solutions may look like trails or strings.

Heating has to be applied if saturated or supersaturated solutions are prepared (see Sect. 18.1.6). To create a nearly saturated solution, another approach starts with a medium in which the necessary concentration for supersaturation can be easily dissolved: using cosolvents or a different pH. In the first case, a small amount of solvent is used in which the substance is very soluble, after which it is filled up to volume with the desired solvent. In the second case, a pH is chosen at which a substance dissolves easily and then the solution is adjusted to the desired pH with acid or base.

Volatile substances should be added at the end of a preparation in order to limit the time they may evaporate. If we heat (gently) during the preparation process, the mixing vessel must be covered. This is required, for example, when sorbic acid, which is volatile with water vapour, is dissolved in water under boiling. Fragrances are added to a cold mass.

Sorbic acid is a preservative at a concentration of 0.1–0.2 % in, for example, creams. In order to obtain this concentration, sorbic acid should be present as a nearly saturated solution in the water phase. In preparation, sorbic acid thus must be dissolved in water under boiling. An alternative method is to start with the good water-soluble potassium sorbate followed by acidifying the cream, yielding a pH at which sorbic acid is present in its acid form. A third way is to dissolve sorbic acid initially in a small amount of ethanol, followed by mixing with the cream.

In manufacturing, parabens are often added as solutions in ethanol.

The addition of a solid substance in solution to an intermediate or to another medium is applicable only if it is fully soluble in the complete product at its storage temperature. A substance for which this does not apply will crystallise in the product, and this can lead to an uneven distribution of the active substance. Such substances should be processed like insoluble substances.

In the preparation of Triamcinolone Ointment 0.1 % FNA (Table 29.6) triamcinolone acetonide is dissolved in propylene glycol, 100 mg per 10 g. Upon addition of other ingredients (wool fat and white soft paraffin) triamcinolone acetonide remains dissolved. In the preparation of Triamcinolone acetonide Cream 0.1 % FNA (Table 29.7), the same method, however, would lead to crystallisation of triamcinolone acetonide coming from propylene glycol in a propylene glycol-water mixture in which it is considerably less soluble. In this preparation, triamcinolone acetonide as a powder must therefore be triturated with the cream base.

Table 29.6 Triamcinolone Acetonide Ointment [32]

Triamcinolonacetonide	0.1 g
Propylene glycol	10 g
Wool fat	10 g
Paraffin, white soft	79.9 g
Total	100 g

Table 29.7 Triamcinolonacetonide Cream [33]

Triamcinolonacetonide, micronised	0.1 g
Sorbic acid	0.2 g
Cetomacrogol emulsifying wax	15 g
Decyloleate	20 g
Sorbitol liquid crystallising	49 g
Water, purified	60.7 g
Total	100 g

29.6 Mixing of Liquids, Semisolid Substances and Molten Solid Substances

As with dissolving of solid substances, the mixing of liquids that dissolve in each other, occurs spontaneously by diffusion. This process is slower with semisolids and molten substances. If the mixture is homogeneous, no separation will occur. Diffusion can be accelerated by shaking, swirling, stirring and heating.

In pharmacy preparations the same methods are being used as for dissolving substances. Mixing of fluids becomes more difficult with increasing viscosity and with increasing differences in density.

Vitamin K oral solution is prepared by mixing the viscous raw material phytomenadione with refined arachis oil. It appears to be difficult to obtain a homogeneous mixture with swirling small quantities in a bottle. The right approach is firstly getting phytomenadione, kept in the refrigerator, to room temperature, to decrease its viscosity. Mixing is best performed in a transparent vessel (e.g., a conical flask) which enables the homogeneity to be checked by the naked eye. If not homogeneous yet, the liquid may show trails or strings.

Semisolid or solid fatty substances are mixed by melting them together in a metal vessel on a water bath, or under a heating lamp. The use of a microwave oven is not a good option, since the process is not easily controlled. Liquid and semisolid substances can be mixed without heating when the semisolid is not too tough. After melting, the mass is stirred until cool to obtain a homogeneous mixture. Inclusion of air must be avoided as much as possible in order to prevent oxidation of the fats. The Unguator and the Stephan mixer (with vacuum) are suitable devices for this purpose (see Sects. 28.6.8 and 28.6.1).

During intensive mixing, particularly when surfactants are present, substantial aeration and foaming may occur. If the preparation is viscous or semisolid it will take a long time to remove the enclosed air. Leaving the product under vacuum or applying vacuum during the mixing process may be necessary to avoid oxidation of the active substance due to air present in the preparation.

29.7 Dispersing in Liquids and Semisolids

In this section the preparation of disperse systems or dispersions is discussed. Dispersions are mixtures consisting of a (liquid or solid) substance that is finely divided into another (liquid or semisolid, see Sect. 29.7.1) substance.

Liquid and semisolid disperse systems are distinguished. The act of preparing a dispersion is called 'to disperse'. The term dispersing is used to indicate that a solid or liquid substance is mixed with a liquid or a semisolid substance to obtain a two-phase system, an emulsion or a suspension (see Sect. 18.4).

In pharmacy preparations several different types of disperse systems are found. Liquid dispersions are dispersions in which a solid substance is dispersed into a liquid substance, such as suspensions for cutaneous applications and oral suspensions, and dispersions in which a liquid is dispersed in a non-miscible liquid, such as emulsions and solubilisations.

Suppositories are semisolid dispersions in which a solid substance is dispersed in a (melted) semisolid base at the time of preparation. In the following paragraphs the dispersion of a solid into a liquid and a semisolid substance as well as the dispersion of a liquid into a non-miscible liquid will be discussed.

29.7.1 Dispersing a Solid into a Liquid

Dispersing a solid into a liquid may be done by trituration in a mortar (see Sect. 29.3). The first step in the preparation is usually the dispersion of agglomerates and wetting of the particles. Then the active substance should be homogeneously distributed into the entire preparation. Dispersion can also be done by vigorous mixing with a rotor-stator mixer. This method is mainly used if the solid is added at once or in parts, to all of the liquid (or all of the semisolid).

The dispersion of a solid into a liquid can be found in dosage forms such as mixtures, dermatologic preparations, suppositories, enemas, and eye drops. Characteristic for this process is the requirement of energy to obtain a homogeneous mixture; furthermore, often separation occurs upon storage. This does not apply for suppositories, ointments or creams, which during the preparation are a dispersion of a solid into a liquid, but, once solidified, form a semisolid dispersion.

A liquid suspension is an unstable system and as a dosage form, it should not sediment (settle) too fast. By simply shaking, a homogeneous preparation should be produced that remains homogeneous sufficiently long to assure that the right dosage can be measured. The factors causing sedimentation in suspensions can be derived from Stokes' law (see Eq. 18.11 in Sect. 18.4.2.1). Too large particles of active substance and too low viscosity of the medium are the most important factors causing fast sedimentation of the particles. To obtain a stable suspension, the particles should be reduced in size or agglomerates should be dispersed as much as possible, or both. The viscosity of the medium can be increased if necessary. At a high concentration of active substance, the particles will hinder each other in their movement. As a result, the viscosity of the preparation increases and the risk of sedimentation decreases.

Also at the end of the manufacturing process, e.g. at the phase of filling in the package, separation by sedimentation is a crucial point. Then, keeping a suspension homogeneous by stirring is most critical since sedimentation quickly leads to differences in content. Inhomogeneity can be avoided by continuous mixing during the filling process or by mixing each time before, e.g. the next bottle or suppository, is filled. In the preparation of suppositories mixing in a mortar (mainly consisting of horizontal movements) with the molten suppository base is not sufficiently effective for this purpose. Sedimentation, and thus deviations in the content of suppositories, is not prevented in that case.

The method of preparation applied for a suspension depends on the formulation. Therefore it is referred to the following relevant Sects.: 11.5.3 for suppositories, 5.5.4 for suspensions for oral use, 12.6.2 for cutaneous preparations and 13.5.7 for suspensions for parenteral use.

29.7.2 Dispersion of a Solid into a Semisolid Substance

Mixing solid substances with semisolid substances in which they do not dissolve is mainly seen in creams and ointments. The first preparation step usually consists of the dispersion of agglomerates by triturating in a mortar (see Sect. 23.3). Then a homogeneous distribution of the active substance in the semisolid base is gained by geometrically dilution and triturating. Characteristic for this mixing process is that energy is needed to obtain a homogeneous mixture.

In pharmacy preparations, a mortar with pestle or mechanical mixing equipment is used for the dispersion of a solid into a semisolid. A mortar with pestle is normally not suitable for mixing quantities exceeding 500 g especially if the consistency is relatively tough. When mixing in a mortar, as a rule of thumb portions of the semisolid base are added to the solid while continuously mixing. When using an ointment mill to disperse agglomerates, mixing occurs locally, whereas in the entire preparation separation may occur. For this reason the preparation should always undergo a second mixing following the use of an ointment mill.

A fine homogeneous concentrate of 50 % salicylic acid in soft paraffin can be made using an ointment mill. With this concentrate lower concentrations of salicylic acid in soft paraffin can be prepared efficiently without using an ointment mill. See Table 29.2 (Sect. 29.1.8).

29.7.3 Dispersion of a Liquid into a Non-Miscible Liquid

The dispersion of a liquid into another liquid with which it is immiscible to obtain a sufficiently physically stable product is only possible by emulsifying or solubilising, using surface-active substances (tensides, surfactants). This process is applied in the preparation of creams and solubilisations. In oral emulsions surface-active substances are not used, but instead viscosity enhancers that possess little surface activity. Below the preparation of emulsions and solubilisations is briefly discussed.

The factors that have an impact on the physical stability of emulsions, can be derived from Stokes' Law. It shows that the following methods are, in principle, useful for problems with creaming or sedimentation (see Sects. 18.4.2 and 18.4.3):

- Finer distribution of the dispersed phase
- Increase the viscosity of the medium
- Reduction of the difference in density between the two phases

In the practice of pharmacy preparations, it is usual to try to distribute the dispersed phase more finely with a rotor-stator mixer or a simple mechanical (paddle) mixer (pourable emulsions), or, for semisolid emulsions, with a mortar and pestle or a mixing device. Magnetic stirrers are unsuitable. Impaction of air should be avoided because the liberation of air bubbles can accelerate the creaming process (in case of pourable emulsions) and promote possible oxidation of the lipid base or of an active substance. A Stephan mixer with vacuum (see Sect. 28.6.1) is a suitable device for the preparation of emulsions without inclusion of air.

Emulsions for oral use cannot be prepared with a surfactant, because at high doses these substances are harmful for the gastro-intestinal tract and have an unpleasant taste. Emulsions for oral use are stabilised with viscosity enhancers. Such emulsions are less stable than emulsions prepared using surface active excipients and can quickly show creaming. Creaming is a reversible process, while coalescence leads to large droplet sizes of the internal phase and to breaking of the emulsion causing the oil phase to float on top. (Intensive) shaking may restore a creamed emulsion but neither coalescence nor phase separation may be reversed.

One of the best known solubilisations prepared in a pharmacy is that of an oily solution of a vitamin in water. First, polysorbate 80 as a surfactant is mixed with the oil (containing the vitamin). Then it is mixed with sugar syrup by which micelles of polysorbate are formed in which the oil is solubilised (see Sect. 18.3.3). During the mixing little force is used. If mixing is done too intensively, the micelles are broken and a milky product (emulsion) is formed.

The method of preparation applied for an emulsion or a solubilisation depends on the composition of the preparation. Therefore it is referred to the following relevant Sects.: 5.5.5 for emulsions for oral use, 5.5.6 for solubilisations for oral use, 12.6.1 for cutaneous preparations, and 13.5.7 and 13.9.2 (emulsions for parenteral use).

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33. Triamcinolonacetonidecrème FNA (jaar 2013) Formularium der Nederlandse Apothekers. Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP), Den Haag

Sterilisation Methods

30

Marco Prins and Mattias Paulsson

Contents

Abstract

This chapter discusses sterilisation methods and equipment for the sterilisation of medicinal products, medical devices and utensils. Sterilisation is an active, validated process in order to kill micro-organisms. It is the most critical step in the preparation of sterile products. The achievement of the absolute state of sterility cannot be demonstrated, sterility can be defined only in terms of probability.

Classical sterilisation techniques using an autoclave and saturated steam under pressure, hot water or dry heat are practical and reliable. Other reliable sterilisation methods include membrane filtration, ionising radiation sterilisation (gamma and electron-beam radiation) and gas sterilisation (ethylene oxide, formaldehyde). Sterilisation equipment (autoclaves, membrane filters, and other sterilisers) is often used in industrial manufacturing, in preparation in pharmacies, and in other healthcare establishments. Standard sterilisation processes are described in the Ph. Eur., in other current Pharmacopoeias, in ISO standards and National guidelines.

The efficacy of any sterilisation process depends on the nature of the product and container, the extent and type of any contamination before sterilisation, the production and sterilisation conditions. Pre-cleaning of materials and pre-filtration by membrane filtration result in a low bioburden. Process validation, quality assurance and quality control are necessary to secure sterility.

Keywords

Sterilisation • Autoclave • Sterile products • Saturated steam • Hot air • Dry heat • Radiation • Ethylene oxide • Hydrogen peroxide • Plasma • Membrane filtration • Gas sterilisation

Based upon the chapter 'Sterilisatiemethoden' by Frits Boom, Ewoudt van de Garde and Philip de Vries in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_30,

30.1 Introduction

Sterility is the absence of viable micro-organisms [1]. Sterilisation is an active, validated process in order to kill micro-organisms. It is the most critical step in the preparation of sterile medicinal products, sterile medical instruments and sterile pharmaceutical utensils. These methods are used to obtain sterile medicines, active substances, medical devices or devices used in pharmaceutical production equipment. Sterilisation of healthcare products makes use of many specific terminology; this may be found in ISO [2] as well in the EU-GMP Annex 1 [3].

30.2 The Death of Micro-Organisms

The death of micro-organisms during sterilisation processes usually follows first-order kinetics when the population is homogeneous, which means that during every unit of time the same fraction of micro-organisms is being killed. This kinetics can be described by the following equations:

$$dN/dt = -kN \tag{30.1}$$

or after integration

$$N_t = N_0 e^{-kt} \tag{30.2}$$

or

$$\log(N_t/N_0) = -kt/2.3 = -t/D \tag{30.3}$$

In these equations N is the number of living micro-organisms at time 0 and time t respectively, k is the first-order reaction constant, and D is the decimal reduction time.

When the logarithm of the number of surviving organisms is plotted against sterilisation time in a semi-logarithmic graphic, a straight line is obtained (see Fig. 30.1).

When the number of surviving micro-organisms is plotted directly (not logarithmic) against time, a curve is obtained which approaches the X-axis asymptotically with time. This means that theoretically the zero value is never reached. In time, the chance of a residual contamination with micro-organisms becomes smaller and smaller. Therefore, sterility, if defined as the absolute absence of micro-organisms, can never be guaranteed nor proved. The description sterility assurance level (SAL) is used instead [1]. It is the probability of a single unit being non-sterile after it has been subjected to sterilisation. It is important to note that when stating "1 container in 10^6 may not be sterile" this does not mean that it is acceptable for 1 container to be unsterile.

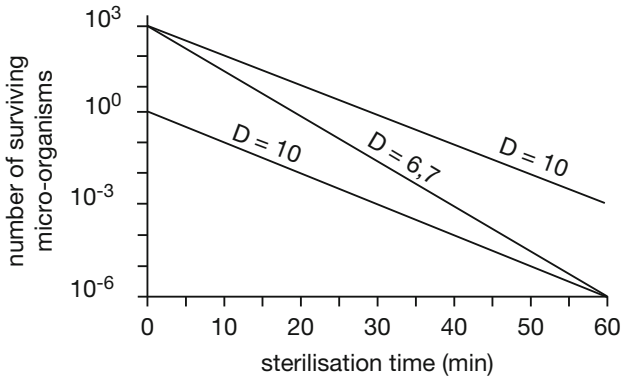

Fig. 30.1 Elimination curves of two types of micro-organisms with different D-values resp. micro-organisms with the same D-value but different initial contamination level at 100 °C heating temperature. Source: Recepteerkunde 2009, ©KNMP

SAL also describes the killing efficacy of a sterilisation process. A very effective sterilisation process has a very low SAL. A SAL of 10^{-6} corresponds to the probability of not more than one micro-organism present in 10^6 (one million) sterilised units of the product.

As for pharmacokinetics and reaction kinetics, rate parameters can be defined for sterilisation processes, such as the first-order reaction rate constant (k) with the dimension reciprocal time and the half-life ($t_{1/2}$). However, more commonly the term decimal reduction time or D-value is used. The D-value is the time required to inactivate 90 % of the present micro-organisms.

The D-value, half-life, and k are related as follows:

$$D = 2.3/k = 3.323\, t_{1/2} \tag{30.4}$$

The D-value is thus, like k and $t_{1/2}$, a measure for the resistance of the micro-organism to the sterilisation process that is applied. D is influenced by environmental factors and the state the micro-organism is in, especially the hydration state.

The D-value is always defined for a certain temperature and for a defined process. Table 30.1 presents a number of D-values for micro-organisms. Spores of *Bacillus* and *Clostridium* strains have the highest heat resistance.

Micro-organisms are killed faster at high temperature than at low temperature. In order to quantify the change in resistance of a micro-organism in response to a change in temperature, the Z-value has been introduced. The Z-value is the number of degrees of temperature increase required to decrease the D-value by a factor 10.

$$Z = (T_2 - T_1)/(\log D_1 - \log D_2) \tag{30.5}$$

In practice, the Z-value of a bacterial strain is calculated from the D-value at different temperatures (see Fig. 30.2). These D values are not absolute but depend on the method of

Table 30.1 Thermo-resistant micro-organisms; T = temperature of D-value, D-value see text [4]

Micro-organism	Medium	T (°C)	D-value (min)
Geobacillus stearothermophilus[a]	Water	121	2
Bacillus subtilis[a]	Air	160	5–10
Bacillus subtilis[a]	Water	100	11.3
Clostridium sporogenes[a]	Water	121	0.8–1.4
Clostridium botulinum[a]	Water	121	0.2
Non-spore-forming bacteria	Water	65.5	0.5–1

[a]spores of them

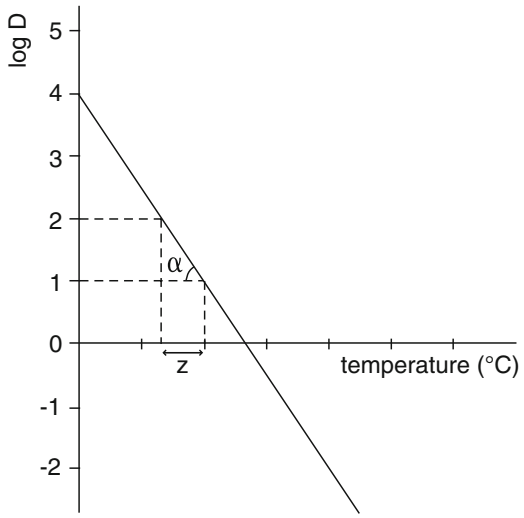

Fig. 30.2 Calculation of the Z-value from the relationship between the decimal reduction time D and the temperature. Source: Recepteerkunde 2009, ©KNMP

preparation of the spores. For precise calculations the D value must be obtained for each batch made from the supplier. This is particularly important where *Geobacillus stearothermophilus* is used as biological indicator.

30.3 Sterilisation Time

The sterilisation time that is required to obtain sterility at a certain temperature is dependent on the number and the resistance of the micro-organisms present in or on the product. An initial contamination with 10^6 of a certain micro-organism requires twelve decimal reduction times to obtain the SAL of 10^{-6}, see equation 30.3.

In theory two sterilisation processes can be distinguished: the overkill process and the bioburden process.

The overkill process is often used in daily practice and is based on the principle that the process should be sufficiently powerful to reduce a severe contamination with a very thermo-resistant organism, i.e. circa 10^6 spores of *Geobacillus stearothermophilus,* to the SAL 10^{-6}. The standard process for steam or hot water sterilisation in the Ph.Eur. is 121 °C for 15 min and complies with this requirement. The overkill method is used when the product can withstand excessive heat treatment such as an $F_o \geq 12$ without adverse effects. Bioburden and resistance data are not required to determine the required 'F_o' values.

The bioburden process is based on the initial contamination before sterilisation, and thus it is a tailored sterilisation process. Bioburden based sterilisation cycles are not commonly used in Europe. Prerequisite is that the number and thermo-resistance of the micro-organisms in the product are documented, based on which the customised sterilisation time can be calculated. An example can be found for parenteral solutions (for injection, for infusion) in reference [4]. In this example, N_0 is 1 (rounded up) and the D-value at 100 °C of the most resistant micro-organism is approximately 2 min. Using equation 30.3, it can be calculated that a SAL of 10^{-6} will be obtained after 12 min.

There are basically two possibilities for determination of the sterilisation time of the overkill procedure:

- The autoclave computer software waits for the temperature in the Pt-100 in the product on the coldest spot having reached the set maximum process temperature (for example 121 °C) and keeps the load at this temperature for a specified duration (15 min); after that the cooling phase starts.
- The autoclave computer software takes into account the elimination of micro-organisms during the heating and cooling phases and adds the time that the product is kept at the maximum process temperature. The total lethality (the elimination effect) is not only obtained during the sterilisation phase, but during the heating and cooling phase germs die as well. The phase of maximum process temperature can be shorter in that case (but shortening of the sterilisation time at maximum temperature is not used when not necessary). The contribution of these three phases and subsequently the total lethality of the sterilisation process are dependent on the Z-value of the micro-organism(s) concerned. Autoclaves are equipped with computer software that can easily calculate these parameters.

For both the calculation of the lethality during the heating and cooling phase and the comparison of sterilisation processes at various temperatures, the F-value has been introduced. The F-value of a sterilisation process at a certain specified temperature (not the reference temperature) is the number of minutes that a sterilisation process would need to last at a reference temperature (usually 121 °C) to obtain the same degree of elimination. This is expressed by the equation:

$$\log F^z_{T_1} = (T_R - T_1)/Z + \log F^z_{T_R} \qquad (30.6)$$

In which $F^z_{T_1}$ is the time at temperature T_1, and $F^z_{T_R}$ is the time with the same lethality at the reference temperature T_R and Z is the Z-value.

For example, if after the calculation of the contribution of heating and cooling a sterilisation is performed that corresponds to 15 min sterilisation at 121 °C, the F-value is 15 ($F_{121} = 15$).

The Z-value is a measure for the change in resistance of the micro-organism following the change in temperature. Therefore, the Z-value should always be mentioned in the notation of the F-value. For steam and hot-water sterilisation, usually a Z-value of 10 °C is used.

$F_{121°C}^{10°C} = 15$ thus means an F-value of 15 min at 121 °C calculated with a Z-value of 10 °C.

$F_{121°C}^{10\ °C}$ can also be simplified to F_0. In general, the F_0-value of a sterilisation process stands for the lethality of that process expressed as the time at 121 °C calculated with a Z-value of 10.

For hot air sterilisation, the influence of the temperature on the elimination of the micro-organisms is characterised by the Z-value as well. Moreover, the effectiveness of two hot-air processes can also be compared with the F-value.

30.4 Initial Contamination

The initial contamination, also referred to as pre-sterilisation bioburden, is the contamination of a starting material or product just before sterilisation or before a disinfection procedure is performed. The initial contamination depends on the degree of contamination of the starting materials (including water), the packaging material, the storage conditions, the storage time, the preparation processes, and the circumstances during production (hygiene). When filtration is not performed as a final sterilisation process but as part of the preparation (removal of particles and lowering of the bioburden by membrane filtration), the initial contamination is determined after filtration and measured in the filled container, ready for sterilisation.

Bacteria may negatively influence product quality even after thermal destruction, for example when pyrogens are formed from the destruction of bacteria (see Sect. 19.3.4). Therefore, it is essential to reduce the initial contamination as much as possible before sterilisation. This can be done by choosing starting materials with a low level of contamination, such as containers with sterilised water for injection, hot or freshly cooled water for injections in bulk or sterilised base solutions for the preparation of eye drops. Furthermore, the equipment and primary packaging should be clean, sterile, and pyrogen free and direct contact should be avoided between the product, critical unsterile spots on the primary packaging and the hands of the operator. To reduce the growth of micro-organisms and the development of pyrogens in the product that is to be sterilised, the time between filling the primary packaging and sterilisation should be kept short, usually maximal four hours. However this time period may be somewhat longer in special cases, according to a risk assessment.

Final filtration through a sterile 0.2 µm membrane filter is not only a sterilisation method, but also an effective way to reduce the initial level of contamination. A pre-filtration (often in-line) with a coarser pre-filter (for example 1.2 µm) is necessary to reduce coarser foreign particles and contamination and to prevent early clogging of the 0.2 µm membrane filter.

Because products that require sterilisation are often aqueous solutions, the initial microbiological contamination can easily be determined in the quality control laboratory by the membrane filtration method (see Sect. 19.6.3).

30.5 Terminal Sterilisation Methods

The sterilisation methods (methods of preparation of sterile products) described in the Ph. Eur. are terminal sterilisation methods and filtration [1]. See for filtration Sect. 30.6. In this section an overview of terminal sterilisation methods is given.

Terminal sterilisation methods are:

- Steam sterilisation (heating in an autoclave): steam sterilisation or sterilisation with hot water in a closed container, minimum 15 min at 121 °C ($F_0 = 15$). The humid heat denatures proteins and DNA of micro-organisms.
- Dry heat sterilisation: hot air sterilisation at least 2 h at a minimum of 160 °C. Dry heat at temperatures higher than 220 °C is used for sterilisation and depyrogenisation of glassware. Sterilisation by dry heat is mainly caused by oxidation of micro-organisms.
- Ionising radiation sterilisation: an absorbed radiation dose of at least 25 kGy. This method leads to breaks in the DNA of micro-organisms and, in presence of water, the formation of free radicals.
- Gas sterilisation including gas plasma sterilisation: Gas, penetrated with moisture, enters the material to be sterilised, which is followed by the elimination of the gas. The gas (ethylene oxide or hydrogen peroxide) alkylates the purine and pyrimidine bases in the RNA and DNA of micro-organisms.

All mentioned sterilisation methods allow for different conditions, as long as the procedures and precautions are chosen as such that a SAL of 10^{-6} is obtained [1]. However broad sterilisation experience, good knowledge of GMP and process validation are necessary to work with different conditions. In many pharmacies and industries the standard methods are used in practice.

30.5.1 Steam (and Hot Water) Sterilisation

The principle of steam sterilisation for medical devices, pharmaceutical products and utensils is based on heat transfer by hot condensing steam under pressure. The steam condenses in the autoclave to pure water, releasing at that moment its heat content. This is a very effective means of heat transfer. Furthermore, the mechanism of inactivation by saturated steam (denaturation of proteins) is also very effective. Therefore, steam sterilisation in an autoclave is the preferred method for medical devices, utensils and some pharmaceutical products. It is of critical importance that the steam in a steam autoclave is completely saturated and not superheated, because only then the sterilisation is effective. For the details of steam sterilisation reference is made to other textbooks and guidance, such as [4, 5]. The pressure of saturated steam at different temperatures is shown in Table 30.2.

It is important that either the steam can penetrate into the object to be sterilised (medical devices or utensils in dedicated steam sterilisation packaging), or that the object in a closed container contains water (content of an ampoule, bottle, vial or plastic bag with aqueous solution).

Also 'empty' sterile bottles must contain some water for injections (and be closed under vacuum) before they can be sterilised by steam or hot water. Without water inside only radiation or heat sterilisation is effective to sterilise an empty, washed and dried container.

30.5.1.1 Steam Autoclave or Steam Steriliser

The steam steriliser is commonly referred to as an autoclave. The simplest steam steriliser, however, is a pressure cooker. In a pressure cooker, the added distilled or deionised water is heated and eventually begins to boil. The steam that is formed pushes the air out through the vent valve in the lid. This is not a very effective process because the vent valve is in the upper part of the steriliser and it takes time to remove the air just by continuous boiling. Air is heavier than steam, so these gases are slowly removed by upwards displacement to the upper part of the pressure cooker.

In a steam autoclave air is more effectively removed by downward displacement which makes loading with more and differently shaped objects possible as well. After removal of the air, the valve is closed and the steam pressure gradually increases. A pressure control valve is used to set the desired pressure, and thereby the desired temperature, since these parameters have a fixed relation in the absence of air (see Table 30.2). For control of the temperature and duration of the sterilisation process a timer or Programmable Logic Controller (PLC) can be used. A PLC is part of the computer of the autoclave. In a PLC the routine programs are factory set and fixed, so for the process operator it is not possible to change them. The temperature-time course inside the steam steriliser is shown in Fig. 30.3.

Table 30.2 Temperature-pressure relation of saturated steam

Temperature (°C)	Pressure (kPa)
100	101
115	170
121	204
134	304

Manual control of a pressure cooker is not realistic and GMP compliant in practice because it does not result in a reproducible process. Moreover incidental manual control by an operator is only allowed with the authorisation of a competent person. GMP compliant autoclaves are entirely computer-controlled using multiple pressure and temperature sensors. Processes for control and operation administration are validated.

30.5.1.2 Process Description of Steam Sterilisation for Medical Devices

In contrast to the sterilisation of liquids in closed containers, medical devices, such as surgical instruments, require the sterilising steam to penetrate through the packaging material to reach the surface of the device. The steam condenses on the cold surface, thereby transferring heat to the medical device, which results in heating up to the sterilisation temperature. The result is that both the medical device and the packaging become wet. Since wet packaging is not a barrier to micro-organisms, the packaging should be dried during and at the end of the sterilisation process. Moreover, the sterilisation agent (steam) should be dry and saturated, which means that the steam should not contain any air.

30.5.1.3 Packaging Medical Devices

The packaging of medical devices after cleaning and before sterilisation should protect the content (against contamination) as well as (during sterilisation) allow for removal of air and penetration of steam. The classical and most often used packaging material is sterlisation paper. Instrumentation kits are wrapped in sheets of sterilisation paper or non-woven materials that are subsequently sealed with sterilisation tape, which usually has a sterilisation indicator.

Smaller instruments are packed in sterilisation bags, which are made of sterilisation paper and transparent plastic. Sterilisation bags are sealed with equipment designed for the purpose.

The sealed packaging has a defined shelf life during which it should protect the sterilised content against contamination [5]. The user should be able to open the packaging aseptically.

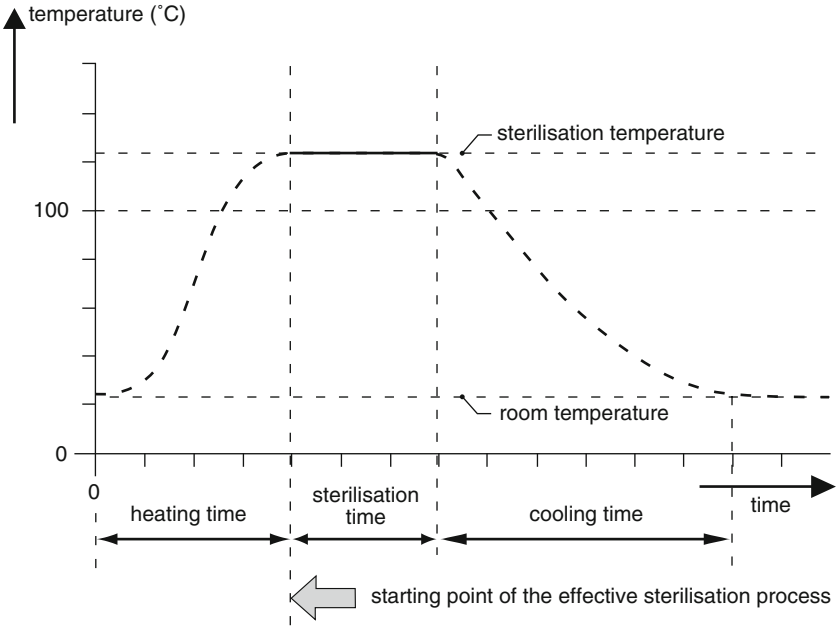

Fig. 30.3 Temperature-time course (temperature profile) during a sterilisation process in an autoclave (Reprinted with permission of the publisher [9])

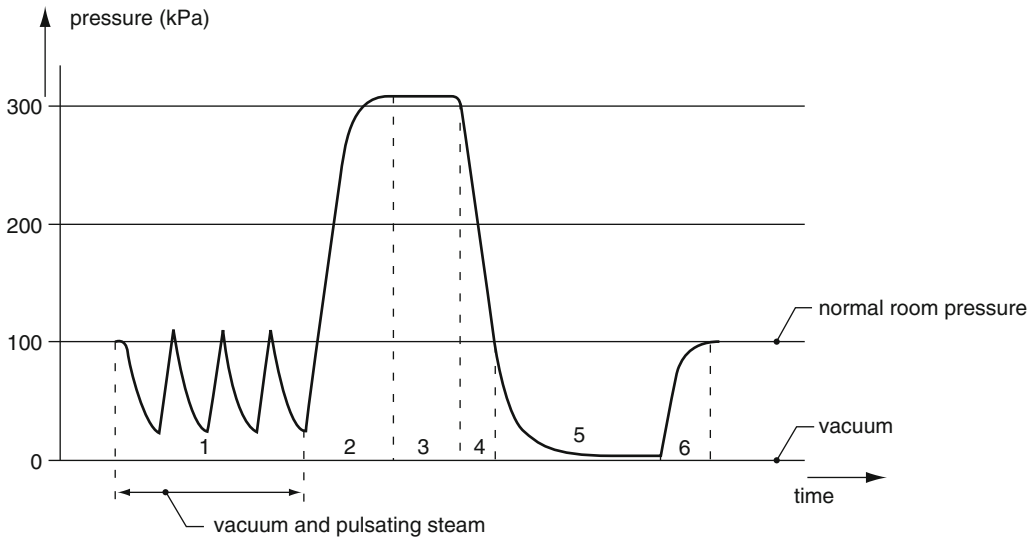

Fig. 30.4 Sterilisation process for medical devices (Reprinted with permission of the publisher [9])

30.5.1.4 Process Description of Steam Sterilisation of Aqueous Pharmaceutical Products

The steam sterilisation process is pressure-controlled and temperature-monitored. The most important steps in the steam sterilisation process are (see also Fig. 30.4):

1. Removal of air by repeated pre-vacuum
2. Heating/building up pressure by steam inlet
3. Sterilisation in dry saturated steam
4. Removal of the steam
5. Drying by post-vacuum
6. Letting in air until atmospheric pressure

During the steam sterilisation of aqueous liquids in closed containers (infusion bottle, bag, injection vial, ampoule, etc.), saturated steam has to heat the container and product inside the container. Steam condenses first on the colder surface of the container, which is the method by which heat is transferred to the aqueous content. In this way, every water containing container becomes a unique steriliser itself.

Sterilisation of aqueous liquids in closed containers by the traditional steam sterilisation process has some advantages and some important disadvantages:

The advantage of steam is that closed glass ampoules, glass injection vials and glass infusion bottles can be sterilised effectively. Filled and closed ampoules for injection are sterilised upside down in perforated stainless steel cassettes in streaming saturated steam. After sterilisation the steam autoclave is brought to vacuum. The vacuum dries the outside of the ampoules. This is used as leak test as well, because leaking glass ampoules will lose their content in the vacuum phase. The result is an empty container, which will be detected in the visual quality control process after sterilisation.

A disadvantage is that a higher pressure is created within the container than outside, which may result in quick, unwanted massive deformation or damage of the heated container, especially when the containers are made of polypropylene/polyethylene, flexible multilayer material or PVC. This may be prevented by adding extra air as supporting pressure into the steam autoclave before the sterilisation process starts. However, the difference in density between steam and air may easily lead to segregation due to a non-homogeneous temperature distribution within an autoclave. Therefore such autoclaves require greater control. Another disadvantage is that the sterilised pharmaceutical load stores a lot of heat. Natural cooling of the hot load under pressure after steam sterilisation takes a very long time in the absence of cooling water, especially when the steriliser is well insulated. The product temperature of liquids in closed containers remains high in a steam autoclave for a too long period. This might result in too much degradation of the content. These disadavantages of the use of steam sterilisation for the sterilisation of aqueous liquids in closed containers can be overcome by using hot water sterilisation instead. Plastic containers (plastic bags and bottles for parenterals use) are sterilised in hot water sterilisers with air pressure support in the sterilisation chamber. Also ampoules, glass vials and glass infusion bottles can be sterilised in a hot water autoclave.

30.5.1.5 Hot Water Sterilisation

Hot water sterilisers are also called hot water (immersion) autoclaves. In these sterilisers, hot distilled water, freshly filled in the stainless steel 'steriliser bath' and heated in a sanitary heat exchanger is pumped around inside the autoclave and is continuously and with high flow sprayed top down over the load to be sterilised. The hot water autoclave contains a mixture of water and air before and during the sterilisation process; no vacuum phase is used (see Fig. 30.5).

During the heating and sterilisation phases the circulating sterilising water is being heated by steam in a heat exchanger and during the cooling phase the circulating water is being cooled by sterilised cooling water in a sanitary heat exchanger.

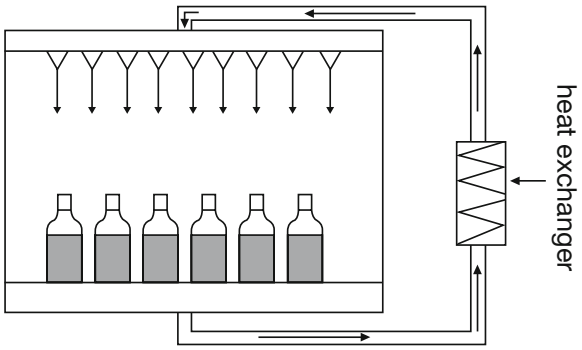

Fig. 30.5 Schematic representation of a hot water steriliser. Source: Recepteerkunde 2009, ©KNMP

During the sterilisation of aqueous solutions by steam or hot water, the temperature within the closed containers (ampoule, vial, bottle or bag) lags behind the temperature within the steriliser chamber, and during cooling the opposite happens. Both effects are shown in Fig. 30.6.

This delayed effect is influenced by the number of sterilisation units (objects) in one batch: the load of the steriliser. It is hard to take all the contributing factors into account for the determination of the correct sterilisation time. Therefore, the temperature sensor that provides the input for the control of the sterilising process is placed inside a container in the coldest spot of the load. The coldest spot is to be identified by validation studies in a standardised batch size and loading scheme.

30.5.1.6 Validation of Steam and Hot Water Sterilisers

To ensure an effective and reproducible sterilisation process, the steriliser should be qualified (see Sect. 34.15) and all sterilisation processes and the empty steriliser have to be validated before first use (see Sect. 34.14). Subsequently all sterilisation processes are revalidated periodically, mostly each year. During process validation, the performance of the combination of steriliser, specific load, and process is assessed. Different kinds of loads all require their own validation protocol. For example, validation of the sterilisation process of aqueous liquids often consists of an empty autoclave, an ampoule program and one or more programs for liquids for infusion in bottles, vials or bags. For medical devices, the load is never homogeneous: multiple types of loads are sterilised at once. Therefore, validation of this process is done by a worst-case approach.

Validation requires specialised knowledge and calibrated expensive equipment and is, therefore, often outsourced to a certified third party. Based on the validation reports, the responsible person (pharmacist, sterile medical devices expert) can judge whether each steriliser functions well and authorises the final validation report.

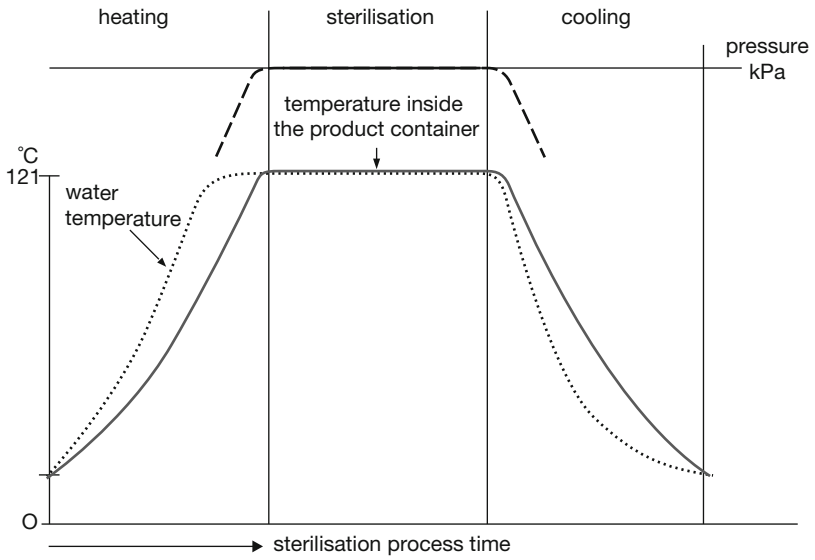

Fig. 30.6 Temperature-time course in the (steam or hot water)-steriliser and in the load during the sterilisation process of aqueous liquids. Source: Recepteerkunde 2009, ©KNMP

Because of the fundamental difference between sterilisation of finished medicinal products and medical devices (temperature-controlled hot water process vs. -pressure-controlled steam process), both processes have their own validation directive. Most countries have their own National legislation and standards on sterilisation and validation. International ISO standards are always useful or are implemented and commented in the own country; for steam sterilisation see [6].

30.5.1.7 Monitoring of Steam and Hot Water Sterilisation Processes

The temperature and pressure in the sterilisation chamber and in the product are saved on the computer and recorded on a digital and/or printed sterilisation report. After sterilisation, release occurs based on a visual inspection of the sterilisation curve in the report, knowledge of the GMP status of the facility, knowledge of the batch load and the validation reports and the absence of critical deviations. Generally, this is a comparison of the record with that of a validated similar process. Critical points are whether the correct temperature and pressure were reached, whether the warming up, cooling down and sterilisation times were normal and sufficient, and whether the desired lethality was obtained. Sometimes biological or chemical sterilisation indicators have been sterilised with the load. The information from these indicators is used as part of the decision for final release. The authorised person signs the report to prove that the final inspection took place and the autoclave load is finally released for further processing.

30.5.2 Dry Heat Sterilisation

Dry heat is used to sterilise materials that are heat-resistant but cannot withstand any contact with water or steam. Examples are powders, glassware, natural or synthetic oils, semisolids such as fats and paraffins. Also parts of pharmaceutical equipment made of stainless steel or glass can be sterilised by dry heat.

In a hot air steriliser, the air is heated by the use of electrical heating elements. For an even temperature distribution in the entire steriliser, a forceful air stream (turbulent or laminar) is essential. For this, a fan and special ventilation sleeves are placed in the sterilisation chamber. The air might be HEPA filtered through dedicated heat-resistant HEPA filters. The stainless steel racks on which the products are loaded must be perforated for a good circulation of the hot air. It is of great importance to check whether the content of all individual elements of the load reach the desired temperature. Therefore some reference temperature probes are placed in the product of containers to be sterilised. The positioning of the items to be sterilised is very important too, each item must have sufficient free surrounding space to allow contact with the hot sterilising air. This check and correction is time-consuming but essential. The heat transfer of dry air is much less efficient compared to steam or hot water sterilisation, thus the integrated process of heating and cooling down of products in a hot air steriliser requires many hours. Because hot air sterilisation is less efficient than steam sterilisation, and the killing mechanism (oxidation) is different, the sterilising temperature is higher and the

sterilisation time longer. The standard conditions described in the Ph. Eur. are minimally 160 °C for at least 2 h [1]. Sometimes higher temperatures and shorter sterilisation times are used. For example 1 h at 170 °C or 30 min at 180 °C for a sterilisation time. Be aware that the Ph. Eur. gives a clear guidance: 2 h 160 °C. It is recommended that dry-heat sterilisation procedures be validated for each individual product with standardised batch size and loading scheme. A new hot air steriliser is initially qualified by acceptance tests (FAT, SAT) and IQ OQ and PQ respectively (see Sect. 34.15).

30.5.3 Ionising Radiation Sterilisation

Ionising radiation contains a lot of energy. Therefore, it can inactivate micro-organisms. Ionising radiation – alpha, beta or gamma radiation – is released when an unstable atom loses energy by decay. Alpha and beta radiation contain particles, gamma radiation consists of electromagnetic radiation only. The penetration power of gamma radiation is therefore much higher than that of alpha and beta radiation. For this reason, usually only gamma radiation is used for radiation sterilisation. By estimation, 40 % of the sterile medical devices are sterilised by gamma sterilisation. Due to the strict safety provisions, gamma sterilisation is restricted to specialised companies. They are controlled by the (inter)national competent radiation authorities and by auditing. Gamma radiation for sterilisation purposes is usually obtained from the radioactive decay of the radio-isotope ^{60}Co into non-radioactive ^{60}Ni, during which gamma radiation is emitted with an energy of 1.33 MeV. The half-life (the time span in which the radioactivity of the source is halved) is 5.27 years. Radioactivity is expressed in Becquerel (Bq): 1 Bq is one disintegration (radioactive decay of one atom) per second. The amount of absorbed radiation is expressed as energy per mass-unit. For this, the unit Gray (Gy) is used: 1 Gy = 1 J/kg. Both the Ph.Eur. and the international standard ISO 11137-1 2006 require that sterilisation is performed with a dose of at least 25 kGy [1, 7].

30.5.3.1 Process Description of Radiation Sterilisation

The product, preferably in the final container, and packaged in dedicated packaging material that withstands radiation and finally packed in for example a closed carton box, is moved around the radiation source in such a way that the content is irradiated homogeneously and receives at the end of the sterilisation a total dose of at least 25 kGy. In practice the products move on a conveyor belt alongside the radioactive source. The dose depends on the intensity of the source, the distance to the source, the residence time in the steriliser, and the density and distribution of the materials.

The quality control checks whether the product has been irradiated homogeneously and received the correct dose. The controllable variables are the source intensity and the exposure time. The process control is performed with a dosimeter, for example plates of polymethylmethacrylate (PMMA) that discolours under the influence of gamma radiation. The extent of discolouration is dependent on the absorbed dose. In one container several dosimeters are placed, which are analysed in the quality control laboratory afterwards in a spectrophotometer.

30.5.4 Gas Sterilisation

Gas sterilisation is performed with ethylene oxide or hydrogen peroxide gas. Sometimes peracetic acid is used, but this method is too specialised to mention here in detail. In the past (from 1940) formaldehyde was used as well, but this method is rarely used anymore. Gas sterilisation is used for sterilisation of medical devices and of surfaces of pharmaceutical containers where the contents are too sensitive to the high temperature of steam sterilisation and/or cannot withstand radiation sterilisation.

30.5.4.1 Ethylene Oxide

Ethylene oxide is a gas under atmospheric conditions. Its boiling point is at 10.4 °C and its vapour density is 1.5 (air = 1). Ethylene oxide is a highly reactive compound that reacts irreversibly with DNA and protein molecules. It is suitable as a sterilising agent because of its strongly alkylating properties. Ethylene oxide can form toxic products (toxic for the operator without shielding) and can polymerise relatively easily into polyethylene glycol.

Ethylene oxide is highly toxic; it irritates the mucous membranes, induces blisters and causes headache. Moreover, ethylene oxide is carcinogenic. The occupational exposure limit (see Sect. 26.7.2) is 0.5 ppm. Furthermore, mixtures of air and ethylene oxide are explosive. For all these reasons, sterilisation with ethylene oxide is now only performed by specialised Units (in hospitals or industrial) that can handle all of these risks.

30.5.4.2 Process Description Ethylene Oxide Sterilisation

The sterilisation process is only described briefly. For more information, reference is made to the literature [8]. The sterilisation process consists of five phases: venting, humidification (preconditioning), sterilisation, degassing, and aeration (see Fig. 30.7).

During preconditioning, the load is brought to the desired temperature and humidity. By applying vacuum, the air is

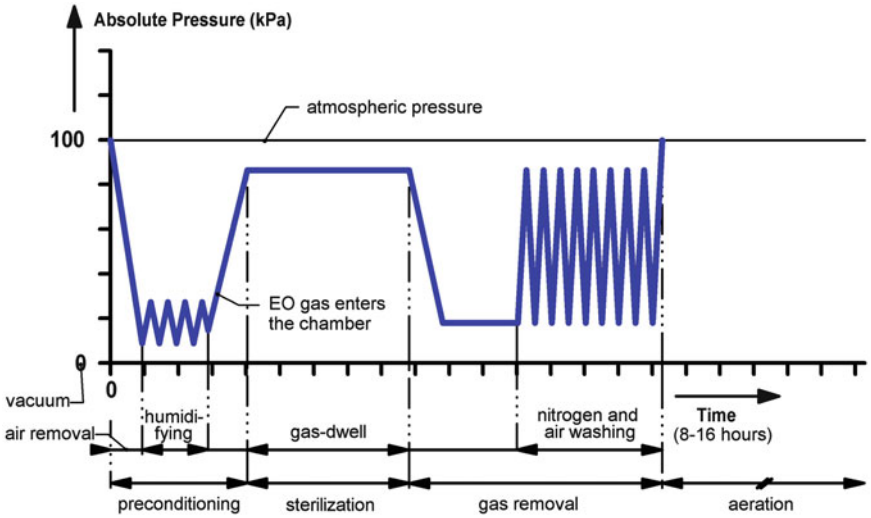

Fig. 30.7 Sterilisation process with ethylene oxide (Reprinted with permission of the publisher [9])

removed from the steriliser, which improves the penetration of the gas into the load. In the second part of the conditioning phase, steam is brought into the chamber to humidify the load as desired. This is important for rehydration of bacterial spores, since strongly dehydrated spores are very resistant to ethylene oxide.

Shortly before the sterilisation phase, the ethylene oxide is brought into the chamber. Sterilisation conditions that are usually applied are: gas concentration 300–1,200 mg/L, temperature 30–55 °C, relative humidity 30–70 %, and sterilisation time 1–4 h [9]. During the degassing phase, the gas is removed from the sterilisation chamber by alternating the application of vacuum and aeration.

Materials such as plastics and rubber adsorb ethylene oxide during the sterilisation phase. For a complete removal of the adsorbed fraction, the chamber is rinsed with clean sterile air for a prolonged period of time (hours to sometimes days). This period is called the aeration phase.

Regarding in-process controls, the Ph. Eur. states: "Whenever possible, the gas concentration, relative humidity, temperature and duration of the process are measured and recorded" [1]. The validation of a gas sterilisation process consists of a physical and microbiological validation [8].

30.5.4.3 Hydrogen Peroxide Gas (Plasma) Sterilisation

Although hydrogen peroxide has been used as a disinfectant for 150 years, the technique to reliably sterilise with this compound is 25–30 years old. The method is applied for sterilisation of medical devices in the hospital.

Hydrogen peroxide is – like ethylene oxide – a highly reactive compound. In contrast to ethylene oxide, hydrogen peroxide does not form toxic products and it is not mutagenic or carcinogenic. The gas is however harmful, it irritates the mucous membranes, induces blisters and causes headache.

The materials that need to be sterilised can be cleaned in the usual way. The packaging materials should be non-adsorbent to hydrogen peroxide. Therefore, plastics such as polyethylene and polypropylene are used instead of paper for wrapping the load.

30.5.4.4 Process Description Hydrogen Peroxide Gas (Plasma) Sterilisation

In a sterilisation chamber, a very large vacuum is created (about 50 Pa). This vacuum is maintained for some time to dry the load and heat it to 40–45 °C. Next, a concentrated hydrogen peroxide solution is injected into the chamber (injection phase). The liquid turns into a gas due to the large vacuum. Next, the pressure is increased to 100 kPa using filtered air, which allows for the hydrogen peroxide to thoroughly penetrate the packaging and in and onto the medical devices (diffusion phase). When the diffusion phase is finished, the gas is exhausted from the chamber and a radio frequency (RF) signal or electrical field is applied to convert the remaining mixture into plasma. Plasma is created when energy is applied to a gas with enough force to strip electrons from atoms. The resulting mixture of free radicals, ultraviolet light, positive and negatively charged particles is known as plasma. In other words: gas plasmas are highly ionised gases, composed of ions, electrons and neutral particles that produce a visible glow. The benefit of low temperature gas plasma is that it has the ability to efficiently eliminate traces of residual hydrogen peroxide from materials and devices. After the RF signal or electrical field is stopped, the plasma converts into water and oxygen, which are not toxic. The critical parameters are: the concentration of hydrogen peroxide gas during the injection phase, the pressure, temperature, and time during the

adsorption phase and, in the case of a plasma phase, the presence and capacity of the RF-signal or electrical field. The process is validated in accordance with ISO [10].

30.6 Filtration

30.6.1 Sterilisation by Membrane Filtration

Certain products that cannot be terminally sterilised may be subjected to an aseptic filtration procedure [11] using a satisfactory sterile membrane filter membrane, tightly fixed in a filter holder. The operator passes the liquid product through a sterile and bacteria retentive membrane, mostly with a nominal pore size of 0.2 μm or smaller. Such membrane filters can capture most bacteria, yeasts and fungi, but not all viruses and mycoplasms. The liquid should be aseptically collected in a sterilised dedicated clean container directly after sterile filtration.

30.6.2 Theory of Membrane Filtration

Filtration processes can be divided into screen filtration and depth filtration. These processes are shown in Fig. 30.8.

The screen filtration principle can be compared to sieving. The particles are retained on the sieve. The capacity of the screen filter to retain particles is determined by the (statistical) pore size distribution. The sieve effect is dependent on the total load, regardless of concentration or filtration rate, and the filter surface. Deformable particles like micro-organisms can form a very compact plaque on the filter surface. With increasing load the filter can therefore clog. Smaller membrane filters, for single use, generally work according to the screen filtration principle.

The depth filtration principle works with a filter that is build up from fibres. Besides the sieve effect that retains larger particles on the surface, smaller particles can be retained within the filter by obstruction between the fibres and by adsorption on to the fibres.

For obstruction, the shape and especially the deformability of the particles are important. Rigid, long fibres have more difficulty travelling a curvy road than spherical or deformable particles, such as micro-organisms. With increasing load, the filter will eventually clog. If this coincides with an increase in pressure, deformation of the filter material may occur, which can lead to the release of particles that were previously retained.

Adsorption applies to even smaller particles. The load is often important in this process. The adsorption process can be compared to adsorption chromatography. Particles migrate through the filter with a rate that is determined by the relative affinity to the stationary phase (the filter material) on the one hand, and the mobile phase (the to be filtered material) on the other. A high flow rate results in a lower interaction probability, and thus decreased absorption. At a higher load, saturation effects and the associated breakthrough occur.

Particles that pass the screen mechanism, can be retained by the depth filtration mechanism. For membrane filters, obstruction and adsorption occur to a certain extent as well. The smaller the pore of the membrane filter is and the larger the particles that should be filtered are, the more important is the screen function.

30.6.3 Retention Capacity

The pore size indicators 0.2 and 0.45 μm are indicative indicators that give an idea of the average of the pore size distribution of the filter, but not of the spread of this

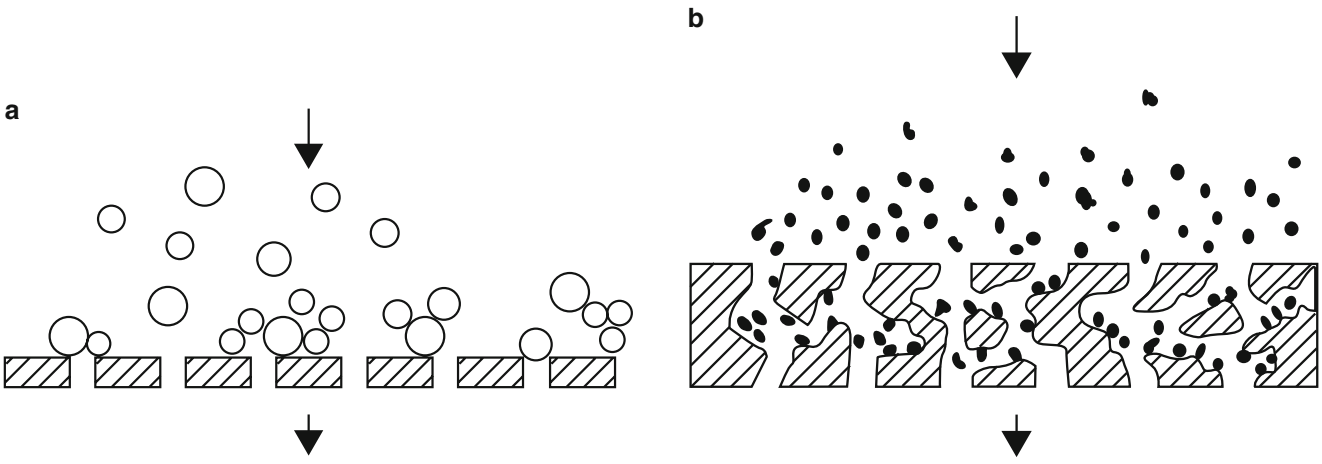

Fig. 30.8 Schematic representation of the screen filtration principle (**a**) and the depth filtration principle. Source: Recepteerkunde 2009, ©KNMP

distribution. The procedure for determination of the pore size may vary per manufacturer. Since pore size does not tell whether the filter can sufficiently retain bacteria, validation of filters is based on the so-called retention capacity instead. This is the capacity of the filter to retain micro-organisms of specified dimensions. The best method to test a membrane filter for germicidal properties, is to load the filter with large numbers of bacteria and subsequently measure the number that passed the filter. For testing of filters with a pore size of 0.2 μm a standardised method is used, in which is tested whether the filter is capable to retain 10^7 colony forming units (CFU) of *Brevundimonas diminuta* (old name: *Pseudomonas diminuta*) per cm^2 [12]. When full-grown this bacterium measures about 0.3 μm. For a positive control, often a 0.45 μm filter is used to show that the bacterium is able to pass this pore size [12].

Membrane filters are available in a large variety of sizes, configurations, and materials. Often used materials are polyvinylidene fluoride (PVDF), polyethersulfone (PES), nylon, cellulose esters, polytetrafluoroethylene (PTFE), polyester and polypropylene. The choice for a material determines, to a large extent:

- The flow properties
- The resistance against the fluid to be filtered
- The possibility to filter a hydrophilic, lipophilic or organic solution
- Whether it is possible to sterilise the filter with steam or with gas

Manufacturers give extensive specifications with their filters which should include these properties. The user should verify that the filter is suitable for the product he wants to filter. In industrial setting, filter properties are usually validated under the conditions in that setting before the filter is allowed for use. Important considerations in such a validation are the adsorption of specific substances to the filter material and the release of unwanted substances from the filter.

30.6.4 Application of Membrane Filters

30.6.4.1 Filter Size and Filtration Rate

The choice of a specific type of membrane filter for the filtration of a solution depends, amongst others, on the volume to be filtered, the type (water or lipophilic/organic solvent), temperature and viscosity and on the available filtration equipment. The larger the surface area of a membrane filter is, the higher is the flow rate at a certain applied pressure. Table 30.3 summarises variables that influence the flow rate through the filter. Filtration of viscous liquids is slow and sometimes difficult. In this case, heating of the liquid, using a larger filter surface area or pre-filtration through a coarse filter may help.

Table 30.3 Factors that influence the flow rate through a membrane filter

High flow rate	Low flow rate
Large pore size	Small pore size
Thin membrane	Thick membrane
Large surface area	Small surface area
High applied pressure	Low applied pressure
Low viscosity	High viscosity
High temperature	Low temperature

Fig. 30.9 Cartridge filter with stainless steel filter case (Picture: Pall). Source: Recepteerkunde 2009, ©KNMP

30.6.4.2 Membrane Filter Types

Membrane filter units for pharmaceutical use are available as disc filter, cartridge filter or capsule filter.

Small disc filters have a filtering surface area of approx. 10 cm^2 (diameter 37 mm) to approx. 50 cm^2 (diameter 80 mm). These filter membranes are fixed in a disposable filter unit or must be placed manually on the supporting plate of a stainless steel filter holder, which always must be done very carefully to prevent damaging of the filter. Wetting of the support screen and the membrane itself with water for injections before handling is essential for the integrity of the membrane after closure of the filter holder and may also ease positioning.

In cartridge filters, also called filter candles, the filter membrane is much larger, folded and fixed into a cartridge (see Fig. 30.9). The filtering surface area of a cartridge of

Fig. 30.10 Capsule filtration unit with folded membrane filter (Picture: Pall). Source: Recepteerkunde 2009, ©KNMP

Fig. 30.11 A disposable ready-to-use membrane filter unit (Picture: Pall). Source: Recepteerkunde 2009, ©KNMP

10 in. length is 0.45 m^2. Many lengths are available. One or more (tightly connected) cartridges are placed in a filter case (see Fig. 30.9). The filter case with the cartridge filter is usually part of the filling line and is sterilised in-line with sterile steam (WFI quality) as such prior to filling. Filter cartridges can be purchased in a sterile disposable form, for single use

In a capsule filter, the filter membrane and filter case of hard plastic are provided as a whole. Also in a capsule filter, the membrane filter is folded, thereby creating a relatively large filtering surface area. In practice, capsule filters have replaced, for a part, the larger disc filters. They have a filtering surface area of approx. 0.015 m^2 to 0.2 m^2. An example of a capsule is shown in Fig. 30.10.

For the filtration of small volumes (up to 100 mL), generally a small disposable ready-to-use sterile membrane filter unit is used. The diameter of these filters is usually 25 mm or more. They are sterile and free of endotoxins, packed individually, have a low dead volume, and are dedicated for single-use (see Fig. 30.11).

In Table 30.4, examples are shown of often used membrane filters of this type (0.2 µm, 25 mm diameter).

The liquid to be sterilised is often pushed through this type of membrane filter by using a plastic syringe. A filter test prior to filtration is commonly not performed in daily pharmacy practice. A successful integrity test, following the filtration, gives assurance of the proper functioning of the filter. Sterilising membrane filtration is not applicable to fluids containing active substances with particles larger than the pore size of a filter (e.g. bacterial whole-cell vaccines).

30.6.5 Integrity Testing of Membrane Filters

Filter tests must be performed by the manufacturer before release to the market and by the individual user also, to ensure that the membrane filter complies with the specifications, is undamaged, and is eventually placed correctly in the filter case by the user. As described before in this chapter, such a test should in fact be performed with *Brevundimonas diminuta*. However, in daily practice this is not possible for the user in the pharmacy, and thus test methods have been derived, which are based on the physical properties of the membrane filter. Such test methods are called filter integrity tests.

Important integrity tests are the bubble point test, the diffusive-flow (forward flow) test, and the pressure hold test [12], which are described separately in the next paragraphs. These three tests are based on the retention of test fluid (usually cooled water for injections) by the filter membrane material by surface tension and capillary forces. When test pressure is applied on the membrane with a test gas, this gas can diffuse through the test liquid, and when more pressure is applied, the fluid will be pushed out of the filter membrane. At this moment, a larger volume of test gas begins to flow through the filter. The pore size of the (intact, undamaged) filter membrane determines how much pressure is required to overcome the capillary action in the filter. In Fig. 30.12 the pressure is plotted against the volume of air passed through the filter.

Table 30.4 Properties of often used disposable ready-to-use membrane filters

Manufacturer:	Pall	Millipore	Sartorius	Millipore
Typ:	DMSO-safe Acrodisc	Millex GS	Minisart NML	Millex FG
Filter material:	Nylon	Cellulose esters	Cellulose acetate	PTFE with polyester
Filter case material:	Polypropylene	PVC	MBS	Polypropylene
Comments:	Resistant to DMSO	Compatible with various aqueous solutions	Compatible with various aqueous solutions	For hydrophobic solutions, alcoholic solutions

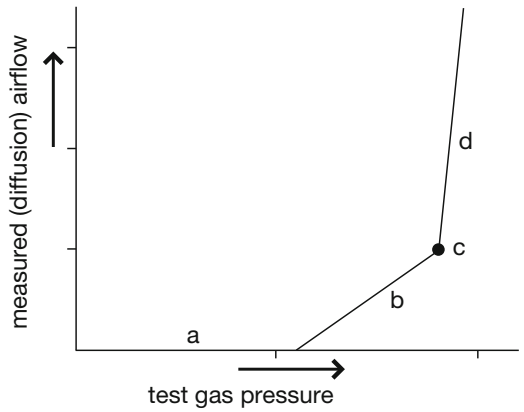

Fig. 30.12 The airflow through a moistened membrane filter plotted against the pressure. The meaning of the phases *a*, *b*, *c*, and *d* are explained in the text. Source: Recepteerkunde 2009, ©KNMP

Figure 30.12 consists of four characteristic phases: (a) a phase of general diffusion of the test gas through the water in the membrane, (b) a phase of critical diffusion, (c) the bubble point, when the water in the first pores is pulled out by the test gas, and (d) a phase of free passage of air through the filter. Especially the phases b and c are suitable for testing a membrane filter.

In practice the filter integrity tests are performed with a dedicated filter test apparatus, suitable for the type and brand of membrane filter holders or filter candles in use. Most of the time all types of filter tests can be executed with this apparatus, and the results are printed or uploaded to a computer file, for control by a qualified operator and release of the tested filter.

30.6.5.1 Bubble Point Test

As described above, a test fluid (usually water) is retained by the filter membrane material by surface tension and capillary forces). This adhesion is, amongst others, dependent on the pore size of the filter. In the bubble point test air pressure is applied to the moistened filter and it is observed at which pressure air bubbles are formed on the sterile side of the filter. The pressure at which the first bubbles are formed is called the bubble point. At this moment, the liquid is pushed out of the largest pores.

When this test is performed after the filling process the filter has to be flushed first with water for injections before the test can take place due to the effect that the filtered product can have on the surface tension.

The relation between required pressure P and the pore size is described in Laplace's law:

$$P = \gamma \cos \theta / 25\ K\ d \qquad (30.7)$$

In which γ is the interfacial tension, θ the contact angle, K a correction factor for the shape of the pores and d the pore diameter. Cos θ is determined by the interfacial tensions between the three components filter membrane material, liquid and air. It is the same angle as in the wetting theory as discussed in (Sect. 18.3.2). The manufacturer supplies the value of the bubble point for hydrophilic filters for a filter moistened with purified water at a specified temperature. A different liquid or product or different temperature in the membrane results in a different interfacial tension and thus a different bubble point.

In most pharmacies a simplified bubble point test is performed. In this test, a moistened 0.2 μm filter should be able to resist the pressure of a syringe filled with air that is compressed down to 15–20 % of its original volume. For a 1.2 μm filter, this value is less: 40–50 %. Therefore cracks in the filter or installation errors, as well as the mix-up of a 0.2 μm and a 0.45 μm or 1.2 μm filter can be easily detected. , The USP [13] doesn't accept this syringe-piston resistance test for pharmaceutical preparation [14] and regards only the bubble point test with a manometer to be sufficiently reliable, see Fig. 30.13.

30.6.5.2 Gas Diffusion Filter Testing

When a test gas (for example ambient air) is applied over a water moistened filter, just below the pressure level of the bubble point, test gas diffusion will occur through the water in the wetted membrane filter. This diffusion happens in all water filled pores, not only in the largest. This principle is the basis for two tests, which use different approaches to measure gas diffusion: the pressure hold test and the diffusive-flow (forward flow) test. Other names for the same principle tests exist. These tests are performed at a pressure of about 80 % of the theoretical bubble point pressure of the filter. It is important that the largest pores are still filled with liquid. In this phase, diffusion occurs more or less linearly with the pressure drop over the

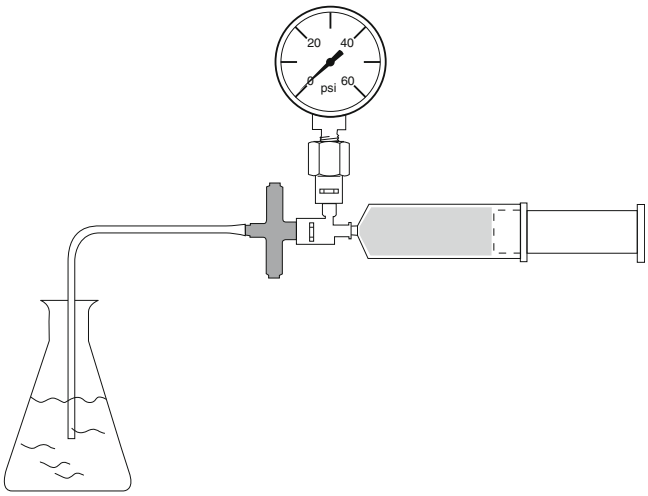

Fig. 30.13 Determination of the bubble point using a simple manometer and disposable syringe. Source: Recepteerkunde 2009, ©KNMP

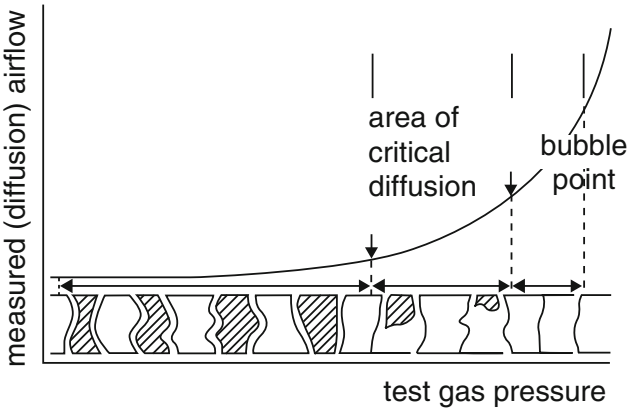

Fig. 30.14 The relation between the applied pressure drop over the membrane filter and the thickness of the liquid film. Source: Recepteerkunde 2009, ©KNMP

membrane filter. Figure 30.14 shows the relation between the applied pressure drop over the membrane filter and the thickness of the liquid film.

The volume of air (test gas) that diffuses through the filter is influenced by the thickness of the liquid film and the fraction of the membrane surface area that is taken up by the pores. When the filter is contaminated, or contains air bubbles by insufficient wetting, diffusion is reduced due to a smaller membrane surface area. Thorough wetting is important.

In the pressure hold-test, the filter membrane or candle in its tightly closed case is set under test gas pressure. Next, the test gas supply to the filter holder is shut. On the side where the pressure was applied (measured in the filter case) the pressure decrease, as a result from gas diffusion through the wetted membrane filter element, is measured. Very sensitive and calibrated manometers in the testing device are required to enable detection of small defective holes in the filter. Another disadvantage is that the pressure decrease depends on the type of membrane filter, the dead volume of the filter case and any supply tubes. Therefore, the maximum allowed pressure decrease should be determined for every combination of filter case and type of filter separately, or the manufacturer should provide these data. Be aware of the influence of temperature on this test.

In the diffusive-flow test, also called the forward flow test, the filter membrane or candle in its tightly closed case is set under continuous test gas pressure. The amount of air that diffuses through the filter membrane per time unit is measured downstream, on the sterile side of the filter. The pressure drop over the membrane should be constant during the test to prevent variations in diffusion rate. Collection and measurement of the air on the sterile side often require actions that may lead to contamination of the setup, and thus these actions should be performed aseptically. Furthermore, for small filter surface areas the volume of air that diffuses through the filter is small and therefore no accurate measurements are possible for these small filters.

30.6.5.3 Water Intrusion Test (for Hydrophobic Filters)

Up to now, only hydrophilic filters have been discussed, which are used for the filtration of aqueous solutions. Filters that are used for gas filtration such as ventilation filters on tanks and boilers are lipophilic filters. Some hydrophobic filter membranes are used to filter oils and other lipophilic solutions. A physical integrity test with water cannot be performed with this type of filter. For moistening, isopropyl alcohol has been used in the past, but the disadvantage of this substance is that it is highly flammable. Therefore, an alternative method has been developed, which is called the water intrusion test [15, 16].

The execution of this test with a 0.2 μm hydrophobic filter membrane is as follows. The entire filter case is filled with water and brought under a pressure of about 200 kPa using pressurised air. This pressure is not sufficient to fill the pores and cause a liquid flow through the filter; this would require around 1,200 kPa. Transport of water due to evaporation does occur. The amount of water that evaporates per time unit is dependent on the pore size. As a result of this evaporation, the pressure in the filter case would decrease. The amount of air that is added to the filter case to maintain the air pressure is measured. This amount should not exceed a value provided by the manufacturer. The method strongly resembles the pressure hold test and can be regarded as the hydrophobic variant of this test.

Figure 30.14: The amount of diffused air flowing through the filter membrane (in millilitres diffused air per minute) and the thickness of the liquid film in the membrane filter, both plotted against the increasing test pressure. The phase

that applies to the diffusion test is to the left of the bubble point pressure.

30.7 Heating at 100 °C over Boiling Water

Heating in a steam autoclave or in a hot water autoclave and also dry heat sterilisation are good sterilisation methods for many products, but pressure and temperature in these autoclaves are high. Some substances in aqueous solutions or in medicinal products formulated as a suspension, or containers do not withstand the high temperatures of 121 °C or the high pressure inside and outside the product container or both in a water or steam autoclave. Active substances or excipients might be unstable at those higher temperatures and suspensions tend to form an undesirable solid precipitate on the bottom of the container during autoclaving at high temperature and pressure.

Membrane filtration is the usual alternative sterilisation method in those cases. However membrane filtration as a sterilisation method is less effective and needs aseptic circumstances. If the product withstands a heat treatment at lower steam temperature (100 °C) for 30 min and no pressure, this treatment contributes to the effectiveness and safety of the membrane filtration process. If the solution contains a preservative, as is often the case with eye drops, the effectiveness of the 100 °C treatment may increase considerably. Heat treatment at 100 °C for 30 min over boiling water as such (without additional measures) is not a reliable sterilisation method and hence not recommended by the Ph. Eur.

As shown in Table 30.1, non-spore forming bacteria do not survive 30 min at 100 °C, and neither do yeasts, fungi, and viruses. Combination of this process with sterilising membrane filtration and aseptic circumstances, gives a higher degree of certainty than aseptic filtration alone as is applied in preparation of eye drops, see Sect. 10.7, notably Tables 10.18 and 10.19.

30.8 Choosing the Best Sterilisation Method for Medicinal Products

What is the best sterilisation method for your product? Is terminal sterilisation better than aseptic processing? See references [17, 18]. The objective of aseptic processing in general is to maintain the sterility of a product that is assembled from components, each of which has been sterilised. Sterile medicinal products should be manufactured using aseptic processing only when terminal sterilisation is not possible. Some types of final packaging and some medicinal products do not withstand the temperatures and/or pressure of a terminal sterilisation process. In such cases a manufacturer can explore the option of adding adjunct processing steps to increase the level of sterility assurance. Modifications to, or combinations of accepted sterilisation methods are accepted by the competent authorities, but proper scientific explanation and justification should be provided in the dossier.

Heating in closed containers in a steam or hot water autoclave is the method of choice for aqueous pharmaceutical products.

For non-aqueous liquids, semisolids and dry powders 2 h sterilisation at 160 °C in dry heat is preferred. Where it is not possible to carry out terminal sterilisation by heat due to formulation instability, a decision should be taken to utilise an alternative method of terminal sterilisation, filtration and/or aseptic processing. It is recognised that new terminal sterilisation processes other than those described in the pharmacopoeia may be developed to provide sterility assurance levels equivalent to present official methods and such processes, when properly validated, may offer alternative approaches. If necessary, a different time-temperature combination may be applied to obtain an SAL of 10^{-6}. If too much degradation occurs in dry heat, ionising radiation or gas sterilisation can be applied. If these methods are not suitable either, sterilising membrane filtration and validated aseptic processing, sometimes robotised or with barrier system technology are considered as a last resort.

30.9 Sterility Testing and Parametric Release

The Ph. Eur. includes a sterility test for the determination of sterility (see Sect. 19.6.1). Due to the limited statistical size of the sample – the sterility test is a destructive test – this test has in theory limited value. This is acknowledged by the authorities. It is recognised that a comprehensive set of in-process tests and controls may provide greater assurance of the finished product meeting sterility than finished sterility testing (see Sect. 34.9.3). The release process without sterility testing before release is called parametric release. Parametric release is only allowed when a number of preconditions are met. Parametric release may be authorised for certain specific parameters as an alternative to routine testing of finished products. Authorisation for parametric release should be given, refused or withdrawn jointly by those responsible for assessing products, together with the GMP inspectors. Parametric release often requires retrospective sterility testing.

In conclusion the essence of parametric release is Good Manufacturing Practice. Furthermore, it is important to have a good understanding of the initial contamination, aseptic conditions and deviations taken place in the manufacturing process.

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Aseptic Handling

31

Frits Boom and Alison Beaney

Contents

Abstract

Aseptic handling is the process to enable sterile products to be made ready to administer, using closed systems. The starting materials are sterile and must be kept sterile during the process. This chapter describes the conditions to do so (sterility assurance). The most important points are trained staff wearing special clothes and sterile gloves, working 'non touch in a Grade A zone (LAF cabinet, safety cabinet or isolator) and using materials and equipment with a low bioburden.

If antineoplastics (cytostatics) are involved requirements are not only to protect the product against contamination of micro-organisms, but also to protect the operator and the environment from these hazardous medicines.

Microbiological checks are carried out firstly to see if staff are sufficiently skilled in aseptic activities, secondly to determine the microbial risk from the environment and thirdly to validate the aseptic procedures.

This chapter does not cover the situation where medicines that cannot be sterilised in their final container are sterilised by aseptic filtration.

Keywords

Aseptic handling • Aseptic processing • GMP Annex 1 • Antineoplastics • Microbiological controls • Monitoring • Validation • Qualification

31.1 Definitions

Aseptic Processing	The process used for products that cannot be sterilised in their final container, i.e. cannot be terminally sterilised.

Based upon the chapter 25 Aseptisch Werken by Frits Boom, Hans van Doorne and Marco Prins in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_31,

Conflicting Definitions for the Term "Aseptic Preparation"
In the EU GMP Annex 1 "aseptic preparation" is used for the preparation of sterile products that cannot be sterilised in their final container [1]. In the UK the term "aseptic preparation" is used for aseptic handling without a manufacturing licence granted by the Competent Authority.

Aseptic Handling	The process to enable sterile products to be made ready to administer, using closed systems.
Closed Procedure	A procedure whereby a sterile pharmaceutical product is prepared by transferring sterile ingredients or solutions to a pre-sterilised container, either directly or using a sterile transfer device, without exposing the solution to the external environment [2].
Bioburden	Total number of viable micro-organisms on or in a health care product prior to sterilisation [3].
Colony Forming Unit (CFU)	One or more micro-organisms that produce a visible, discrete growth entity on a semisolid, agar-based microbiological medium [3].

31.2 Aseptic Processing

Medicines, which cannot be sterilised in their final container, are sterilised by aseptic filtration. The standards required for aseptic processing are laid down in Annex 1 of EU GMP [1]. Aseptic processing is called aseptic preparation in Annex 1 (see Sect. 31.1).

To reduce risks of microbial contamination, aseptic processing is executed in a controlled environment, in which the air supply, facility, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels [3]. Contact between product and environment should be minimised, sterile equipment should be used, and there should be two consecutive filtration processes through sterile 0.2 μm filters. The first filter will minimise the microbial challenge to the second filter, which should be just before the sterile final container. The shelf-life of the product is often restricted and it may be stored in the refrigerator to further reduce the risks of microbial growth.

For more information about membrane filtration see Sect. 30.6.

31.3 Aseptic Handling

Within pharmacy, aseptic handling is carried out in a controlled environment by trained staff. In any hospital, however, aseptic handling also takes place in clinical areas such as wards and operating theatres [4, 5]. This chapter only discusses aseptic handling in pharmacy. Aseptic handling in clinical areas is described in Sect. 13.8.

31.3.1 Guidelines for Aseptic Handling

In 2008 the Pharmaceutical Inspection Convention published the PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments [2]. Although this document is a stand-alone document and should be used for PIC/S related inspections, it is used more and more as a reference for preparation including aseptic handling in pharmacies in Europe.

USP Chapter <797> Pharmaceutical compounding – Sterile preparations describes the conditions and practices for all sterile preparations in compounding pharmacies in the United States [6]. The so-called compounded sterile preparations (CSPs) are divided into low-risk level, medium-risk level and high-risk level. Low- and medium-risk levels use closed systems and cover aseptic handling in controlled environments.

In the United Kingdom "Quality Assurance of Aseptic Preparation Services" are the national NHS standards for aseptic preparation in hospital pharmacies [7].

In 1996, the Dutch Association of Hospital Pharmacists wrote, in close cooperation with the Dutch Healthcare Inspectorate, a GMP guide for hospital pharmacy. The Chapter Aseptic Handling in this guide has been reviewed in 2005 and 2013 and covers aseptic handling in the hospital pharmacy as well as in clinical areas [8]. Different levels of product protection are defined.

In 2012 the German Organisation of Hospital Pharmacy published the ADKA guideline on Aseptic Preparation and Quality Control of ready-to-administer parenterals. All precautions to be taken to keep the products sterile are described systematically [9].

The differences between these guidelines and standards are not huge. They all focus on preventing microbiological contamination and more or less on medication errors, e.g. due to incorrect calculations. This chapter only discusses preventing microbiological contamination.

Levels of Product Protection in the Netherlands [8]
The sterility of the product is maintained by using a controlled environment and trained staff. Depending on how well these can be controlled, three levels of product protection can be distinguished [8]:

- Limited product protection is the lowest of these three levels, and refers to a doctor or nurse carrying out the aseptic activity on a clean worktop.
- Increased product protection is the middle of the three levels. This can be carried out in a clinical area in a separate room within a laminar airflow (LAF) or safety cabinet or isolator by a member of pharmacy staff or by a nurse or doctor.
- Maximum product protection is the highest of the three levels of product protection. In this case the aseptic activity is carried out within a LAF or safety cabinet or isolator sited within at least an EU Grade D of controlled background in the hospital pharmacy.

31.3.2 Complexity

Aseptic handling varies in complexity from drawing up the contents of a vial or ampoule into a syringe, to compounding a parenteral nutrition mixture from several separate starting materials. Complexity of aseptic activity has been defined in several texts [6, 10, 11].

As complexity increases so does risk of microbiological contamination, although there is little evidence to support this. Other risk factors for microbiological contamination include the extent to which the product is a good growth medium, and the time between its preparation and administration to the patient.

Some authors have developed risk assessment tools for injectable medicines [11–13]. These tools can be helpful in determining if a process is simple or complex, and hence a higher risk, see Table 31.1.

31.3.3 Staff and Personal Hygiene

The greatest source of contamination in any clean room is the operator [15]. He or she spreads micro-organisms directly into the surrounding air and either directly or indirectly onto surfaces in the room. This can be minimised by the operator donning suitable clean room clothing such as non-shedding suits or coats (depending on the EU Grade of environment), hair cover, shoe covers or dedicated clean room shoes, gloves, and a mask covering the nose and mouth.

The operator remains a source of microbiological contamination, nonetheless, and so aseptic technique is important to protect the product [16]. The principle is to avoid direct contact between the operator and the product (non-touch technique) and hence it is essential to have suitably trained operators whose competency is regularly assessed and who are appropriately supervised.

Before any aseptic activity, hands should be thoroughly washed and disinfected, usually with an alcohol-based gel. The skin flora is both transient and resident. Resident flora is difficult to remove, so it is recommended to always use gloves within the clean room suite. Whilst carrying out aseptic handling in a Grade A environment, sterile gloves are required.

31.3.4 Working Area

The working area is the immediate environment in which the aseptic handling is performed. It is the working surface (EU Grade A zone) of the LAF or safety cabinet or isolator.

Table 31.1 Examples of simple and complex activities [8]

Simple activities
Drawing an injection liquid from a vial or ampoule* into a syringe
Dissolving a powder for injection and drawing it into a syringe
Injecting a few injections into an infusion liquid
Complex activities
Preparing a medication cassette (several additions, de-aerating, long-term use at room or body temperature)
Preparing parenteral nutrition from components (several additions, mixing large volumes, good growth medium)
Preparing parenteral nutrition starting from a registered all-in-one commercial product with more than two additions (several additions, good growth medium)

*Transferring injection liquid from an ampoule involves more risk of microbiological contamination than from an injection vial as a vial is a truly closed system [14]

The background area is the room in which the LAF or safety cabinet, or isolator is housed. In the case of open-fronted cabinets there is a distinction in background requirements between the different guidelines mentioned before. The PIC/S guide [2] and the German ADKA guideline [9] require at least EU Grade C, the Dutch hospital pharmacy GMP [8] at least EU Grade D and the requirements in the UK are harmonised with Annex 1 of EU GMP, i.e. Grade B. For isolators the requirement for the background in all guidelines is at least Grade D [1].

Reference is made to Sect. 28.3 for more information on clean rooms, LAF cabinets, safety cabinets and isolators.

The precautions for the different kinds of product protection (see Sect. 31.3.1) as used in the Netherlands are summarised in Table 31.2.

Table 31.2 Level of product protection (Example from the Netherlands)

Level of product Protection	Clothing and hand hygiene	Working area	Background area	Air quality in background area
Limited	Clothing, daily cleaned Hands: cleaned and disinfected, single use gloves for each session	Table top, disinfected per session	Quiet	No requirements
Increased	Clothing: overalls, daily cleaned, hair cap, mouth-nose mask Hands: cleaned and disinfected, sterile single use gloves for each session	Horizontal LAF cabinet, safety cabinet or overpressure isolator	Separate, limited access; easy to clean	No requirements
Maximum	Clothing: overalls, daily cleaned, hair cap, mouth-nose mask, special shoes Hands: cleaned and disinfected, sterile single use gloves for each session	Horizontal LAF cabinet, safety cabinet or overpressure (positive pressure) isolator	In accordance with GMP Grade D: smooth surfaces, interlocked changing rooms etc.	Grade D

31.3.5 Aseptic Handling of Antineoplastics

A relevant therapeutic group of active substances, handled aseptically, are parenteral antineoplastics. Many are classified as very toxic for the operator, mainly because of carcinogenicity and reprotoxicity [17], see also Sect. 26.3.3. Therefore, if antineoplastics are involved in aseptic handling, requirements are not only to protect the product against contamination of micro-organisms, but also to protect the operator and the environment from the product. The first measure however is a working procedure to minimise exposure to antineoplastics. This involves

- Working with closed systems (this is good practice for all aseptic handling)
- Using injection vials and needle-free devices, as far as possible, to minimise needle-stick injuries. If sharps cannot be avoided, their use should be minimised [18], see also Sect. 26.10
- Using an aeration spike with a hydrophobic filter to avoid overpressure in vials
- Attaching an infusion system, partly filled with Sodium Chloride 0.9 %, to the infusion bag with antineoplastics to reduce the chance of leakage of antineoplastics when the bag is attached to the patient)

To protect the operator and the environment, the most effective measure is working in a safety cabinet or in an isolator with underpressure (negative pressure). Ideally the exhausts of these cabinets should be connected to the open air. An isolator gives more protection than an open-fronted cabinet. See Sect. 28.3.

The safety cabinet or the isolator should be placed in a well-ventilated and classified background room. To protect surrounding rooms from airborne contamination of antineoplastics the USP advises negative pressure in the background room [6]. However, a study in the Netherlands, carried out by the Netherlands Organisation for Applied Scientific Research (TNO) concluded that airborne contamination from a grade D background (overpressure 15 Pa) to the surrounding environment is not a risk issue.

TNO Study: Risk During Aseptic Handling of Antineoplastics

Risk from airborne contamination of antineoplastics from a background room (with overpressure) to surrounding rooms is only a question of concern in the case of a huge calamity such as a spill or breakage involving a large amount of antineoplastics as a dry powder. Calamities are rare (less than once a year in a Dutch hospital pharmacy) and when it occurs, it is nearly always with a solution in which the antineoplastics are dissolved. The risk of transferring antineoplastic residues to the environment by hands or the outside of vials or finished products is much greater (see also Sect. 26.5.4). Measures to prevent this occurrence and also regular training in emergency procedures are most important to protect people and environment from the risk of antineoplastic residues.

Further protective measures are:

- Personal protection by wearing coveralls and sleeves made of impermeable material and sterile gloves into which antineoplastics do not easily permeate, see Table 26.6
- Working on a sterile preparation pad and removing the pad after each session as antineoplastic-contaminated waste

To prevent contamination with residues it is important to know that cross contamination of antineoplastics from one room to another by direct contact (outside of vials, outside of finished products) is a real risk [19, 20]. This risk can be significantly reduced by a validated cleaning procedure for the safety cabinet or isolator and the background room, and by properly packing the finished products before transport to nursing and treatment centres. Additionally a procedure for removing (potentially) antineoplastic-contaminated waste and a procedure on how to handle spillages or in an emergency are important to prevent contamination with residues. Environmental sampling by wipe tests should demonstrate that all those procedures are effective. In the Netherlands and in Germany a surface contamination limit of less than 0.1 ng/cm^2 is becoming used more and more as a guideline value, see Sect. 26.5.4.

31.3.6 Storage Periods

Wherever possible, aseptic products should be stored at 2–8 °C. The shelf life depends on the chemical stability of the product and the potential for microbial contamination [6, 8]. In the Netherlands, from a microbiological point of view, a shelf life at 2–8 °C for 1 month for simple and 1 week for complex aseptic handling is acceptable. In the UK, aseptic products made in pharmacy can only be given a shelf life of seven days unless the pharmacy is licensed with the MHRA (Medicines and Healthcare products Regulatory Agency) for these activities.

Table 31.3 Shelf life and administration period for aseptic handling [8]

	Shelf life		Administration period*	
Complexity	Time	Condition	Time	Condition
Simple	1 month	2–8 °C	7 days	Room temp.
Complex	7 days	2–8 °C	7 days	Room temp.

*Shelf life and administration period are two separate periods. For example: if the administration with a medication cassette is started 6 days after preparation of that cassette, the administration period still will be 7 days

Medicines produced by aseptic handling are sometimes administered for more than one day (medication cassette, parenteral nutrition etc.). During the administration the product temperature is higher than the storage temperature, which influences the shelf life. Therefore a second period has to be used, the administration period, which is defined as the maximum time from start to the end of the administration. Both, shelf life and administration period for simple and complex aseptic handling at maximum level of product protection as used in the Netherlands are summarised in Table 31.3 [8].

31.4 Cleaning and Disinfection

The emphasis on providing the correct level of cleanliness is to ensure that the properly designed and maintained area is clean and dry. Depending on monitoring results, the use of a disinfectant may need to be considered. However, disinfection is difficult to achieve in an area with even small amounts of dirt [21].

Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

31.4.1 Cleaning of Clean Rooms

A suggested cleaning regime is that floors and work surfaces are cleaned daily and walls, ceilings and storage shelving at least monthly [6]. All cleaning materials, such as swabs and mops, shall be nonshedding and must be disposable or suitably washed after each cleaning session. Mops and swabs used in Grade A or B areas must be sterile.

Swabs and Mops Used in Clean Rooms
Clean rooms have to be wet cleaned with the aid of polyester or microfibre swabs or mops. Polyester is used for light cleaning and disinfecting. The polyester fibres adsorb dirt and if wetted with a disinfectant the disinfectant will be evenly spread out on the surface. Microfibre swabs and mops are used for cleaning only. The microfibres ensure that particles are not only removed from the cleaned surface but are firmly captured within the fibres. Dry polyester swabs or mops are only used for removing wet product or other wet waste.

Some general remarks on cleaning of clean rooms:

- Approved standard operating procedures should state how the various rooms are to be cleaned, what materials have to be used and how adequacy of cleaning is checked.
- Cleaning materials for clean rooms should not be used in other rooms.
- Thorough rubbing is important for the effectiveness of the cleaning process.
- Spilt materials must be removed immediately with a non-shedding absorbing cloth.
- Floors and walls must be cleaned in a fixed order from cleanest to least clean. The air stream and position of the exit determine where to start and where to finish.
- Cleaning of clean rooms requires specially trained staff.
- The same clothing regulations apply for cleaning staff as well as for staff preparing the product.
- The effectiveness of the cleaning should be checked.
- Cleaning must be recorded in a log which gives details of the cleaning agent used in addition to the person who has performed the cleaning.

Regularly (monthly) a general check is advised on the level of cleanliness, paying particular attention to corners and ridges. The cleanliness of the surface is best assessed by floodlight. Specialist ultraviolet lamps are also available for this purpose. If necessary, however, the cleanliness may be checked with a white non-shedding cloth. Contact the person responsible for the cleaning process if the background room or changing rooms are not sufficiently clean.

31.4.2 Cleaning of LAF Cabinets, Safety Cabinets and Isolators

It is advisable to leave LAF cabinets, safety cabinets and isolators running (possibly in standby mode if this can be validated) to avoid dirt and micro-organisms accumulating on the clean side of the HEPA filters, i.e. in the Grade A working zone. Because of the frequent disinfection of these devices, separate cleaning with a detergent is not necessary. Any spills must be cleaned as quickly as possible with a non-shedding cloth and, if necessary, with sterile water.

31.4.3 Disinfection of Clean Rooms

Using good cleaning procedures, the disinfection of a Grade D room should not be necessary. Disinfection of a Grade C room can be a necessity, depending on monitoring results. Grade B rooms need a precise disinfection procedure.

Clean room disinfection should be performed with a broad spectrum (non aggressive) disinfectant. Most commonly used are alcohols, chlorine compounds, hydrogen peroxide, phenolic compounds and quaternary ammonium compounds. Table 31.4 gives an overview of the microbiological inactivation. Alcohols and hydrogen peroxide do not leave residues after evaporation. Sodium hypochlorite is very corrosive towards many materials, including stainless steel. For more information about the disinfectants in Table 31.4 see [6] and [22].

Normally two disinfectants are used alternately to prevent accumulation of resistant micro-organisms, however there is little evidence to support this [23].

Table 31.4 Classes of commonly used disinfectants [6, 22]

Chemical class	Examples	Common activity range
Alcohols	70 % ethanol	Bactericidal, fungicidal (limited range) virucidal (limited range)
	70 % isopropanol	
Chlorine compounds	0.5 % sodium hypochlorite	Bactericidal, fungicidal, mycobactericidal, virucidal, sporicidal
Hydrogen peroxide	0.5 % hydrogen peroxide solution	Bactericidal, fungicidal, mycobactericidal, virucidal, sporicidal
Phenolic compounds	0.4–1.6 % chlorocresol	Bactericidal, fungicidal, mycobactericidal, virucidal
	0.4–1.6 % orthophenyl phenol	
Quaternary ammonium compounds	0.4–1.6 % benzalkonium chloride	Bactericidal (not all gram-negative types), fungicidal, virucidal (limited range)

31.4.3.1 Disinfection of LAF Cabinets, Safety Cabinets and Isolators

Commonly used disinfectants are ethanol 70 % or isopropyl alcohol 70 %. The disinfectant must be sterile and spore-free. This can be achieved by adding 0.125 % hydrogen peroxide, sterilisation by 0.2 µm filtration, or sterilisation by gamma radiation. Neither ethanol nor isopropyl alcohol are sporicidal, i.e. they are not effective against bacterial spores (see Table 31.4). Unless there are validation data from the manufacturer, it is recommended that the maximum in-use period for sterile disinfectants is limited to one week after opening. This should be noted on the container after it is opened. (Often the contents will be used well before then.)

LAF cabinets, safety cabinets and isolators should be disinfected from cleanest to less clean areas, e.g. from back to front for a horizontal LAF, in overlapping strokes. The non-shedding cloth (polyester is advisable due to its low particle load) has to be wetted regularly to make sure there is a constant film of liquid on the surface, and this will dry in the airstream. An extension to hold the cloth may be used to disinfect surfaces that are difficult to reach.

31.4.3.2 Disinfection of Materials and Equipment

The initial microbiological surface contamination (bioburden) of materials and equipment used in LAF cabinets, safety cabinets and isolators (Grade A zone) should be as low as possible. Surfaces of sterile devices (tubes, syringes, needles etc.) are presented sterile. Surfaces of ampoules, vials and bottles however are not presented sterile and must be disinfected before being transferred into the Grade A zone. Although 70 % alcohol is widely used for disinfection, it is non-sporicidal. The most effective method with liquid disinfection is a combination of spraying and wiping [24]. The physical movement of the wipe over the surface will help to remove the organisms. Nevertheless, spore forming bacteria will not be totally eliminated [24, 25]. Beware of excessive spraying, as the maximum allowable concentration of alcohol in the air can easily be exceeded, see Sect. 26.7.2.

There are no formal regulations on how often and where the transfer disinfection has to be carried out. In general, regular microbiological monitoring of gloved hands, materials and equipment has to show that the chosen disinfection procedure is effective (see Sect. 31.6.1). In the pharmaceutical industry, disinfection between each clean room level is common. In the UK, during aseptic handling, materials and equipment undergo at least two separate disinfection steps. In the Netherlands only one step is common.

Just before use, critical spots (vial stoppers, ampoule necks) should be disinfected again.

31.5 Aseptic Work Session

Remove as much secondary packaging as possible before transfer into the background area to minimise dust and bioburden. Transfer materials into clean rooms via interlocking hatches. Minimise storage of starting materials and components in the background area and, if stored, use closed cupboards. Documentation and labels should be generated in outer support areas.

Work with a ‘sterile area’ where materials can be placed after they have been disinfected and before they are put into the grade A zone if the quantity of materials to be processed is too large to have in the grade A zone simultaneously. A ‘sterile area’ may be (part of) a work top or the top of a trolley.

It is recommended that two people perform an aseptic work session [26]. One (the preparer) works in the Grade A zone and the other (the helper) carries out the disinfection and assists the preparer with getting materials to and from the working area.

Staff should be fully trained in good aseptic techniques. Special attention has to be given to ‘non-touch’ manipulation, which means that critical places like syringe tips should never touch non-sterile surfaces. Disinfected surfaces (work top) and hands (even when sterile gloves are worn) must be considered as non-sterile surfaces.

An example of a working procedure step by step:

- Remove secondary packaging as much as possible before materials are placed in the interlocked hatch (in UK the first disinfection stage is at this point).
- Prepare documents and labels outside the background room.
- Wash hands in or adjacent to the changing room.
- Change clothes according to the clothing procedure in the changing room, disinfect hands and put on non-sterile gloves.
- Enter the background room.
- Collect all necessary materials and check these according to the preparation document.
- Hang preparation document in an easy-readable place.
- Disinfect the work top in the grade A zone and if necessary disinfect the ‘sterile area’ outside the grade A zone.
- Disinfect the non-sterile gloves and
  - Disinfect the outside of the materials and place them in the grade A zone or on the ‘sterile area’.
  - Remove the outer layer of the wrapped, sterilised disposable equipment and place them in the grade A zone or on the ‘sterile area’.
- Disinfect hands.
- Put on sterile gloves (this can be done outside the grade A zone).

- Place materials in the correct order in the grade A zone.
- Disinfect critical spots (vial stoppers and ampoule necks).
- Carry out the aseptic handling.
- Label the product.
- Remove the product and waste material from the grade A zone.

Keep Sterile Gloves Sterile!
It is essential to keep the outside of the gloves sterile or at least low bioburden. Thoroughly disinfecting the outer surface of the materials before transferring to the LAF cabinet, safety cabinet or isolator and keeping the gloved hands in the LAF cabinet or safety cabinet are most important. Sterile gloves can be disinfected, but disinfected gloves are slippery. So, don't disinfect too often and dry gloves in the sterile airflow. A disinfection frequency of 30 min is satisfactory in general, however gloves should be disinfected after removal from the work station before returning to the Grade A working zone. Every pharmacy should monitor this process using finger dabs (see monitoring). Check gloves constantly for damage (at least every 30 min as a minimum) and change gloves immediately if they are damaged. Avoid changing gloves during a session unless they are damaged, however.

Sterile filtration is not by definition included in aseptic handling. For aseptic handling, the starting materials and all equipment are sterile and closed procedures are used. When drawing up from glass ampoules (risk of glass particles) a sterile filter straw or filter needle should be used. Replace the filter straw or needle with a fresh needle before adding the solution to another container. In the case of complex aseptic manipulations like filling a medication cassette, sterile filtration (0.2 μm) may be used as an additional precaution, however.

31.6 Microbiological Controls

Although aseptic handling differs significantly from aseptic processing, the principles for microbiological controls, like monitoring and process validation, are the same. As most aseptic work is done manually, the aseptic technique of the operators has to be checked with additional microbiological controls.

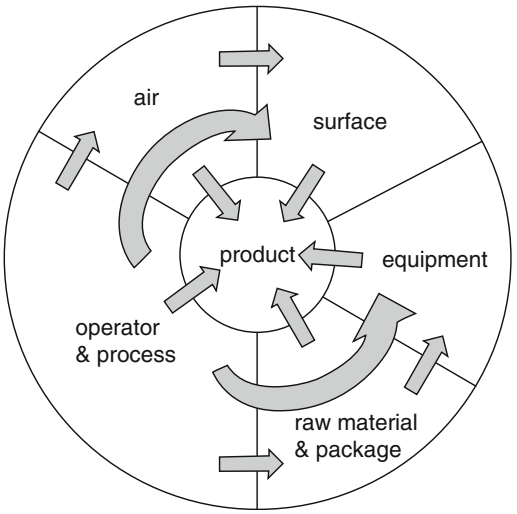

Fig. 31.1 Microbiological threat to the product. Source: Recepteerkunde 2009, © KNMP

31.6.1 Microbiological Monitoring

Microbiological monitoring is applied to determine the extent of environmental contamination. Figure 31.1 states which environmental factors are important: the nearer to the (open) product, the more risk of contamination.

It is most important, therefore, to monitor the areas nearest the product for microbiological contamination. Monitoring generally focuses on counting the numbers of micro-organisms. Where products with a shelf life of several months are concerned, monitoring results have to be considered before product release. In the case of aseptic handling, however, monitoring results are often not available at the point of release of the aseptic product.

31.6.1.1 What has to be Monitored?

For monitoring the air, settle (sedimentation) plates and volumetric air samplers are used. The latter come in various types [27]. Most of them suck up a fixed volume of air and the micro-organisms are deposited on a growth medium. With settle plates, the micro-organisms fall onto an opened 90 mm Petri dish containing an agar medium (see Fig. 31.2).

The opening time has to be 4 h [1]. If the preparation time is shorter (usual in case of aseptic handling) the settle plates have to be closed at the end of the preparation.

Monitoring of flat surfaces is carried out with contact plates of agar medium in a 55 mm dish. The medium has a slightly convex surface which can be gently pressed on the surface to be examined, see Fig. 31.2. These plates are sometimes known as RODAC plates (RODAC is the brand

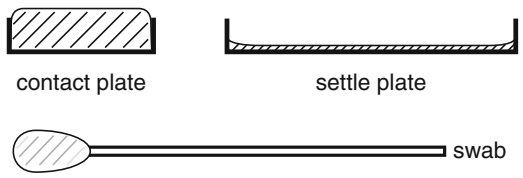

Fig. 31.2 Techniques for monitoring

name meaning Replicate Organism Duplicate Agar Contact). Remnants of the growth medium may stay on the sampling spot so cleaning and disinfection after sampling must be a standard component of the sampling procedure.

If the surface is not flat and or accessible, a swab has to be used. This is a small wad of cotton on the end of a short rod, see Fig. 31.2. First this has to be wetted with sterile water. After that it can be swabbed onto the surface to be examined and finally it has to be wiped across an agar medium in a petri dish. The recovery from a contact plate is 30–50 % and from a swab around 10 % [24].

Monitoring of the gloved hand is done by fingerprints (finger dabs). At the end of each session the tip of the five fingers of the gloved hand should be pressed gently but firmly on an agar surface in a petri dish. Use one plate per hand. In Dutch hospital pharmacies printing is only done with the most used hand [8]. In the UK and USA both gloved hands are monitored [6, 27].

31.6.1.2 Media and Incubation Time

The agar medium in the petri dishes and the contact plates is Tryptone Soy Agar (TSA) on which most micro-organisms that we can expect in the environment grow. Incubation temperature is 30–35 °C and the incubation time is at least 3 days. Especially for yeast and moulds Sabouraud dextrose agar is used. The incubation temperature and time for this medium are 20–25 °C and 5 days. Investigation in Dutch hospital pharmacies has shown that a broad spectrum of bacteria, yeast and moulds grow well on TSA at 30 °C within 3 days [28].

Colonies, which may be counted, grow from the micro-organisms on the agar surface. As it is not known whether the colony has developed from one or several micro-organisms, the expression colony forming units (CFU) is used. The results after incubation are expressed as CFU per plate.

31.6.1.3 Environmental Sampling Plan

An appropriate sampling plan has to be part of the environmental monitoring programme. It consists not only of the sampling locations but also of the sampling frequency. The locations should be based upon a risk analysis to determine the spots most likely to be contaminated during the aseptic activities. For settle plates and contact plates in the Grade A working zone, this is underneath the place where the aseptic activities are carried out.

The sampling frequency during/after aseptic handling in the Netherlands consists of every working day one settle plate and one contact plate in the Grade A working zone and immediately after the session one gloved finger print with the most used hand [8]. The frequency of monitoring the background Grade D room can be lower. A sampling plan of contact plates for the critical spots on the bench top (s) and several settle plates both every month, will give enough information about the contamination levels.

Before starting aseptic handling in a new facility or after a major process change, initial validation should be carried out. Part of this is frequent monitoring of all the locations to determine the average contamination level. After that, monitoring results should be reviewed on a periodic basis as a means of evaluating the overall control of the aseptic process. A graphical representation will help to determine whether there is an upward increase (trend) in the level of contamination present. An example of a graphical representation is shown in Fig. 31.3.

31.6.1.4 Limits, Alert and Action Levels

What are the criteria for monitoring results during aseptic handling? Table 31.5 gives the recommended limits for microbiological monitoring of clean areas during operation from the EU GMP guide [1].

As stated before, the sampling frequency during/after aseptic handling in the LAF cabinet, safety cabinet or isolator in the Netherlands is only one settle plate, one contact plate and one finger print. When there is growth, the average will be 1 CFU or more and that is above the limits for Grade A in Table 31.5. However, when aseptic handling is performed in the right way the frequency of samples with growth is low and the average CFU over a longer period will be far below one [29].

When the average contamination level (in CFU) is known, alert and action levels have to be determined. The alert level is the early warning level; a drift from normal conditions. When this level is exceeded it is recommended that the previous results are checked (is there a trend?) and that the following results are monitored more closely. When the action level is exceeded a thorough investigation should be made into the nature of the contamination, including identification of the isolates, and subsequent corrective actions should be implemented immediately. This may lead to adjusting the procedure and/or retraining the staff. More intensive monitoring will be necessary to be able to quickly assess if the adjustments have been successful. Action may also be required if the trend exceeds 50 % of the base line [30].

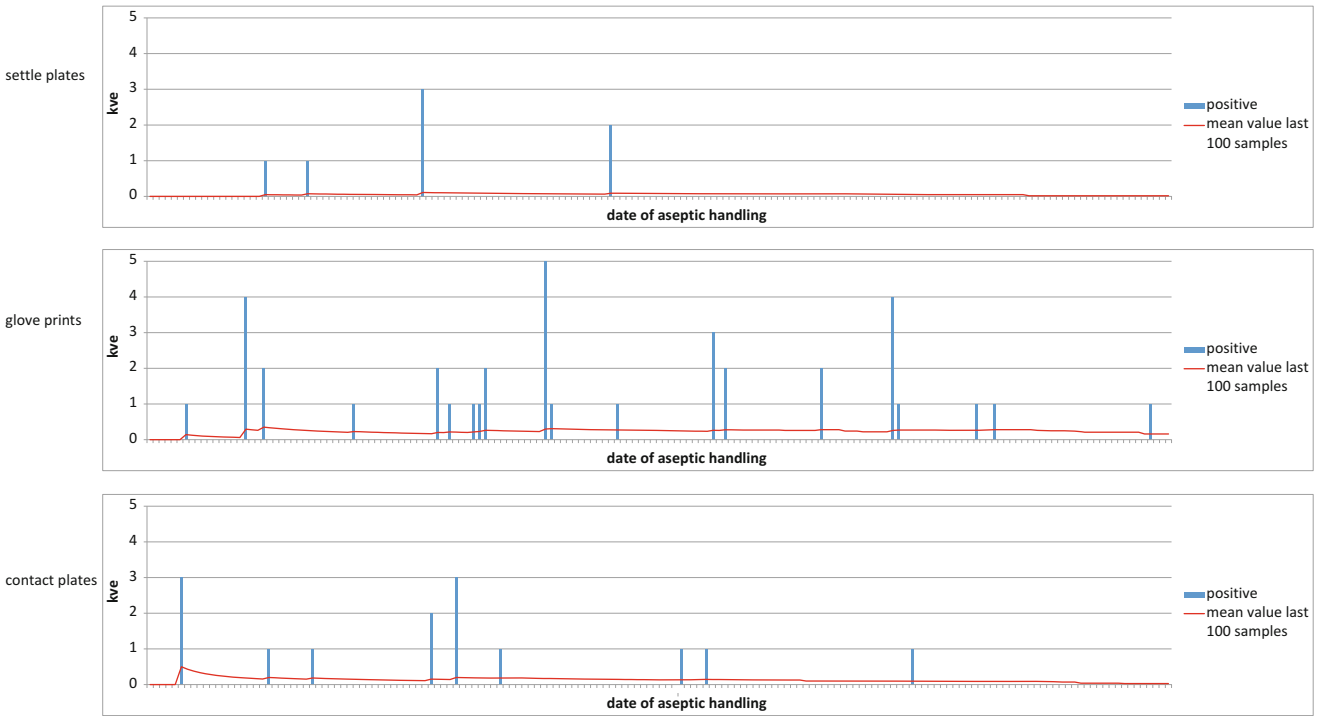

Fig. 31.3 Monitoring results over 1 year during/after aseptic handling in a Dutch hospital pharmacy. Every bar is a positive, the continuous line is the mean values over the last 100 samples

Table 31.5 Limits for microbiological contamination [1]

	Recommended limits for microbiological contamination (a)			
Grade	Air samples CFU/m^3	Settle plates (diameter 90 mm)	Contact plates (diameter 55 mm)	Glove print 5 fingers
		CFU/4 h (b)	CFU/plate	CFU/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes: (a) these are average values; (b) individual settle plates may be exposed for less than 4 h

31.6.2 Microbiological Validation of the Process

The goal of microbiological validation of the process is to demonstrate that the procedures used during aseptic handling and the staff undertaking aseptic processes, are capable of maintaining the sterility of the product [31]. In this validation the aseptic handling is simulated with an appropriate broth solution, typically Tryptone Soya Broth (TSB). The final product is incubated for 7 days at 20–25 °C and 7 days at 30–35 °C successively and should not show any growth (in some countries, such as the Netherlands, 14 days at 30 °C only). The simulation should comprise all critical steps that occur in standard aseptic handling like withdrawing a solution from a vial or an ampoule, dissolving a powder in a vial and adding a solution to an infusion bag or a vial. Working with double or quadruple strength TSB can be helpful to simulate aseptic handling.

The simulation can be carried out daily at the end of a work session or periodically with a number of simulations together. Bringing all the results together, in the long run, provides good information about the overall quality of aseptic handling, however the total number of TSB simulations is limited in comparison to aseptic production in industry.

In judging the results, a validation curve can be drawn [31].

Validation Curve [32]

For judging the results of the microbial validation of aseptic handling by TSB simulation, a validation curve has been developed. The curve rises one unit after a simulation without growth and falls 100 units after a simulation with growth. The maximum is fixed at 299 and the minimum at 0. Three levels of performance are distinguished, see Fig. 31.4.

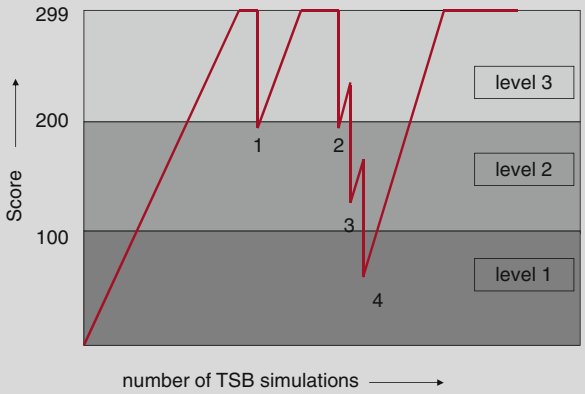

Fig. 31.4 Example of a validation curve

Like the validation of aseptic manufacturing according to GMP Annex 1 [1], corrective measures in the case of growth are made, depending on the total number of simulations without growth. This will be indicated by the level in the validation curve. For example:

- Positive simulation 1 (see Figure above), the curve falls down to 199. The corrective actions belonging to level 2 have to be executed. For example: identification of the micro-organism(s) found in the positive simulation and careful checking of the monitoring results.
- Positive simulations 2 and 3 (see Fig. 31.4), again corrective actions belonging to level 2 have to be executed.
- Positive simulation 4 (see Fig. 31.4), the curve falls down to level 1. The corrective actions belonging to this level have to be executed. For example: as well as the corrective actions for level 2, an audit of aseptic handling has to be performed and TSB simulations should be undertaken more frequently for a specified period.

31.6.3 Individual Qualification

As microbiological validation of the process will not generate sufficient data to give assurance that the aseptic technique of each individual operator is satisfactory, standard assessments for operator technique have been developed. In the Netherlands this assessment is known as "Individual Qualification" and in the UK as "Universal Operator Broth Transfer Validation" [8, 32]. Both tests consists of a repeated number of key techniques such as withdrawing a solution from a bag, vials or ampoules and adding it to empty sterile vials or infusion bags. The solution used is a growth medium (mostly TSB) and the filled vials or bags are incubated for 7 days at 20–25 °C and 7 days at 30–35 °C successively (some countries like the Netherlands, 14 days at 30 °C only) and must not show any growth to pass the test. Qualified operators have to be re-qualified at least every year with the same test.

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Quality Requirements and Analysis

32

Oscar Smeets, Mark Santillo, and Hans van Rooij

Contents

Abstract

For the control of the production of medicines quality requirements are essential. Quality requirements cover the quality of the preparation throughout the whole shelf life, from release until the end of the shelf life. Medicines that are produced by the industry or prepared in a pharmacy have to meet the requirements of the European Pharmacopoeia. Status, type and structure of its monographs are dealt with. This chapter explains what quality requirements are. Also the background to the general quality requirements such as identity and content are discussed.

In this chapter the following quality requirements that are specific to pharmaceutical dosage forms are described: chemical purity, average mass, average volume, average content, uniformity of mass, uniformity of content, uniformity of dosage units, microbiological purity, sterility, endotoxins, disintegration, dissolution, particle size, particulate contamination and physical parameters such as pH, relative density and osmolality.

Based upon the chapter Kwaliteitseisen by Oscar Smeets and Rik Wagenaar in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_32,

An overview of relevant quality requirements of important pharmaceutical dosage forms in practice is given at the end of this chapter. Analysis needs analytical validation; this is generally discussed as well.

Keywords
Pharmacopoeia • Quality requirements • Assay • Identity • Content • Purity • Content uniformity • Disintegration • Dissolution • Particles • FRC • Analytical validation

32.1 Quality Requirements and Regulations

The characteristics of a medicine are that the product is effective, safe and user-friendly, these are the primary requirements of the patient and are also important quality targets for those who formulate and produce medicines.

When a medicine is developed, the requirements of the patient are translated into an actual product (see Chap. 17). The qualitative and quantitative composition are chosen, as well as the pharmaceutical dosage form, the preparation method, the container and the accompanying information for the patient. Pharmacy preparations should have a pharmacotherapeutic as well as technically sound product design. Formulation, preparation method, container and labelling have to meet the relevant requirements.

In the medicine design process the requirements that describe and control the quality are stated, including:

- Identity
- Content
- Chemical purity
- Average of mass of single dose preparations
- Uniformity of mass of single dose preparations
- Uniformity of content of single dose preparations
- Uniformity of dosage units
- Microbiological purity, sterility, pyrogens and bacterial endotoxins
- Disintegration
- Dissolution
- Particles (visible and sub-visible)

Additionally other requirements may be included with regard to certain physico-chemical parameters, for example pH, relative density, viscosity, optical rotation, conductivity and osmolality.

These requirements are from now on referred to as quality requirements. With the exception of the identity, which can only be positive or negative, all mentioned quality requirements can be indicated with a numerical specification, either as range or as a limit e.g.: "less then …". Specifying quality requirements means stating limits or margins for these parameters. The allowed limits should be set such that the product meets the earlier mentioned primary quality requirements, possibly with a certain safety margin. Narrow limits, and hence stricter quality requirements, may not lead to a more clinically effective or acceptable preparation but may possibly lead to higher costs. In practice it is often true that stricter quality requirements are achievable, within acceptable costs, than are strictly necessary from the point of view of effectiveness, safety and user-friendliness. The high level of pharmaceutical sciences and technology available today certainly contributes to this fact.

The limits that medicinal products must comply to are generally specific for each individual product, however, there are some limits that are general valid for dosage forms such as particulate matter in solutions for injections. For industrially prepared licensed products the specification is a part of the marketing authorisation.

Medicines that are produced by the industry or prepared in a pharmacy have to meet the requirements of the European Pharmacopoeia (Ph. Eur.). The monograph Pharmaceutical Preparations in the Ph. Eur. became effective on the first of April 2013. This is a framework monograph regarding the preparation or production of pharmaceutical preparations.

The monograph does not officially cover medicinal products used in clinical studies (Investigational Medicinal Products, IMPs), but authorities may still refer to it. The monograph gives, amongst others, guidelines for the requirements for active substances and excipients that are processed in pharmaceutical preparations and for the requirements for the final dosage form. The pharmaceutical preparations, made in pharmacies, are explicitly covered by the monograph. In the Ph. Eur. pharmacy preparations were not explicitly defined until the appearance of supplement 7.7. Publishing the monograph Pharmaceutical Preparations has changed this and the Ph. Eur. now accepts that pharmacy preparations may be "needed to meet the special needs of the patient". The British Pharmacopoeia [2] has had, for a number of years, a general section on unlicensed medicines and also contains monographs for a variety of unlicensed medicines frequently prepared in the pharmacy.

Medicines that are prepared by the pharmacy have to meet the specific national law. This depends on the country in Europe. As an example the situation in the Netherlands is described here. Regulations about the quality requirements for medicines prepared in the pharmacy are from 2007. It is stated that medicines prepared in a pharmacy, not being investigational medicines, may only be dispensed when they meet the instructions of the European Pharmacopoeia (Ph. Eur.) or, in the absence of a monograph, meet the monographs of an officially used Pharmacopoeia in a member country, or of an officially used Pharmacopoeia in the United States [3] or Japan [4]. Raw materials of good quality must be used.

The Ph. Eur. contains, with exceptions (haemodialysis solution and radiopharmaceuticals), no monographs for finished products. However general monographs for pharmaceutical forms are described. The general monographs for pharmaceutical forms are included in a separate chapter Monographs on dosage forms, separated from the monographs for raw materials. The mentioned quality requirements in there are related to disintegration, dissolution, uniformity of weight, uniformity of content, sterility and more. In the British Pharmacopoeia [2], the United States' [3] and the Japanese [4] Pharmacopoeias monographs for finished products are included. Deviation is only allowed when stated and justified in the product file. This concerns, for example pH, requirements to aqueous solutions or quality requirements to the chemical purity.

The sequence in the mentioned Pharmacopoeias above is not arbitrary, if for a certain product a monograph is included in the British Pharmacopoeia [2], then these quality requirements are valid and not the requirements of a possibly existing monograph in the United States [3] or Japanese Pharmacopoeia [4]. Quality requirements are not cumulative and a product does not have to comply with every Pharmacopoeial monograph available just the first of the above sequence in which it appears.

It is also stated that the amount of a drug substance of a medicine prepared in the pharmacy does not deviate more than 10 % of the amount of that substance that is mentioned on the label of the container. For the average content of the active substance the quality requirements from a foreign Pharmacopoeia are not applicable. It is important to note that all quality requirements are valid in principal until the expiry date of the product.

The Netherlands have not had their own national Pharmacopoeia, since 1993. Various other countries in Europe have retained their own national Pharmacopoeia. Examples are the British Pharmacopoeia (BP) [2] and the Deutsches Arzneibuch (DAB) [5, 6]. In these countries the national Pharmacopoeia is part of the legislative framework of pharmacy preparations. However, throughout Europe, the Ph. Eur. is the accepted standard and legally enforced.

32.2 The European Pharmacopoeia

Before separate quality requirements are discussed, this section is about the status and the importance of the Ph. Eur. A Pharmacopoeia is an official, legally enforceable, published handbook with instructions for the preparation of medicines for human and veterinary use and the requirements which they have to meet.

Almost 40 countries in Europe are party to the convention regarding the composition of the Ph. Eur. The parties that enter into the treaty have agreed to compose a single Pharmacopoeia for all the concerned countries. They also agreed on taking necessary steps to make sure that the monographs that are based on this convention will be accepted and will form the Ph. Eur., and become the official standards in the relevant countries.

The Ph. Eur. has legal force for both human and veterinary medicines. The Ph. Eur. has various monographs. More than half of all the monographs concern raw materials from chemical, herbal or animal origin. Raw materials that are used in the pharmacy for preparing medicines should be of a suitable standard. If medicines meet the quality requirements of the Ph. Eur. then they are of a suitable standard for patient use within any restrictions noted.

For raw materials there is a general monograph available and there are also specific monographs on specific active substances.

Starting materials for the chemical synthesis of active substances are outside the scope of Ph. Eur.

All organic and inorganic pharmaceutical raw materials that are processed in medicines should meet the general monograph Substances for Pharmaceutical Use. This monograph describes how a Pharmacopoeia monograph is composed and is valid for raw materials of which a specific monograph is included in the Ph. Eur. as well as for raw materials of which no specific monograph is available. There are more than 1900 specific monographs for raw materials included in the Ph. Eur. For pharmaceutical raw materials of which no specific monograph is available, the user of the raw material should formulate a specification in the style of a monograph, which minimally meets the requirements of the general monograph Substances for Pharmaceutical Use.

A monograph of a raw material consists in principle of the following parts: name and definition, characteristics, identity, purity, assay, labelling and a list of known impurities. The data mentioned in the section characteristics, such as appearance, odour and solubility are not obligatory. They cannot be considered strict standards. On the other hand one would not expect large deviations from the characteristics listed, for example a substance that is described as white or light yellow, crystalline powder, should not be dark brown.

The sections identity, purity and assay are obligatory, all pharmaceutical grade materials must comply with the standards within them. It may be that certain tests are only applicable when the raw material is meant for a specific use. For purified water for example there is a limit test for aluminium, which is only applicable when the water is meant for use in dialysis solutions.

The section titled labelling describes any specific information that should be included on the label, including any quality relevant parameters, for example a certain viscosity gradient for cellulose derivatives. Those parameters are called functionally related characteristics (FRCs).

Next to monographs for raw materials the Ph. Eur. contains monographs about the various dosage forms such as capsules, suppositories, tablets, creams and ointments. These monographs also have specific sections including definition, production, tests, storage and labelling.

Furthermore the Ph. Eur. contains some general monographs including, for example, vaccines for human use, radiopharmaceutical preparations and homeopathic preparations.

The most important monograph for pharmacy preparations however is the monograph Pharmaceutical Preparations.

This monograph is intended to be the reference source of applicable standards in the Ph. Eur. on active substance, excipients and dosage forms, used in the preparation of pharmaceuticals. Pharmaceutical preparations are medicinal products generally consisting of active substances that may be combined with excipients, formulated into a dosage form suitable for the intended use, where necessary after reconstitution, presented in a suitable and appropriately labelled container. Pharmaceutical preparations may be licensed by the Competent Authority, or unlicensed and made to meet the specific needs of patients according to legislation. There are two categories of unlicensed pharmaceutical preparations: extemporaneous preparations and stock preparations.

Ethical aspects of the preparation of unlicensed medicines are also discussed. The monograph discusses the special position of pharmacy preparations as medicines. Because, contrary to licensed medicines, independent supervision is lacking, attention is asked for the extra responsibilities that professional caregivers have when prescribing and preparing medicines (see further Sect. 35.5.3). A risk analysis is indicated to help guarantee that the preparation keeps an acceptable quality during its shelf life and is suitable for the intended use. The pharmacist gives an interpretation to these definitions by assessing the quality of the design and the practical feasibility of the preparation related to the (therapeutic) value for the patient. See further Sect. 2.2.

In separate sections the importance of choosing and defining relevant quality parameters to guarantee the required quality of the medicine is discussed. It is explicitly mentioned that stock preparations are generally tested more extensively than extemporaneous preparations. It is also mentioned that if it is not practical to perform tests on pharmacy preparations, for example because the batch is too small or because of the delivery time, other suitable methods may be used to guarantee that the required quality level is met. With this, the process validation has obtained an official position next to the end control of products. It should be stressed, however, that when tested at any point during the product shelf life the product must meet the specification in the monograph.

32.3 Identity

The identity of a pharmacy preparation must obviously be correct. Four factors need to be considered when assessing identity:

- What is prescribed
- What is specified on the batch preparation instruction/record
- What is specified on the label
- What is the actual composition of the product

Theoretically these factors match precisely, but in practice for instance a codeine containing cough syrup may contain codeine or codeine phosphate or codeine phosphate hemihydrate. However, the identity must be clear and comply (see also Sect. 23.1)

With the preparation of medicines the pharmacist has some freedom to choose excipients. The active substance should however be identical to those mentioned on the prescription. Sometimes there are pharmaceutical reasons, for example the stability of the product, to change the active substance for a more appropriate clinically equivalent substance.

Generally this will be about the choice of another chemical form, for example theophylline instead of aminophylline or carbasalate calcium instead of acetylsalicylic acid. It is important to pursue a consistent policy on this, for both the stock preparation as well as the extemporaneous preparation and the policy should be clear and consistent. The prescriber should be consulted in order to explain changes to the prescription and in many Countries should be asked consent.

When considering a stock preparation the substances will be described precisely on the batch preparation instruction. This description should also contain quality indications such as water content and particle size. If deviations are made then the original design may not be met. This can lead to unexpected influences on the pharmaceutical quality and possibly even on the primary quality requirements.

See Sect. 37.3 for requirements to the labelling and information for the patient.

32.4 Average Content of Active Substance

In the monograph Pharmaceutical Preparations of the Ph. Eur. there are no requirements for the content of the active substances. In some European countries, such as the Netherlands, it is stated in national law that the amount of an active substance of a preparation prepared in the pharmacy should not deviate more than 10 % of the amount of that substance that is stated on the label.

The limits 90–110 % contain the total variation caused by preparation and analysis. In practice some variation in

average content of active substance in various batches of the same finished product will be inevitable. The size of that variation depends on:

- The variation in the content of the raw materials
- The variation in the preparation process
- The stability of the active substance in the finished product

The sample size and the variation in the analysis of the finished product also play a part. These do not influence the actual content of the product, but do influence the obtained results from a testing laboratory on which a decision on whether or not a product meets its specifications has to be made. See Sect. 20.3 on the statistical background. Every item mentioned will be discussed further below.

32.4.1 Content of the Raw Material and Factorisation

Usually the declared content of the active substance in a final product is based on the chemically pure substance. The chemically pure substance is the substance that is described by the header of the Pharmacopoeia monograph for the specified raw material. The molecular formula and the molecular weight are given. For substances with a varying amount of water this refers to the dried substance. For substances with a sharply defined amount of water of crystallisation the compound including the water of crystallisation is considered the chemically pure substance, provided that this is clear from the declaration.

To obtain the labelled content of the substance as close as possible to the required declared content, factorisation might be used.

Factorisation is correcting the amount of raw material to be taken into production prompted by the content of substance in the specified raw material batch. There are however some problems.

The content of the raw material should be known to be able to factorise. Factorisation however is only useful when it is certain that the content of the raw material does deviate significantly from 100 %. To assess this, insight in the selectivity and uncertainty of the method of analysis used by the raw material supplier or testing laboratory is important.

In practice a deviating value from 100 % for the content on the analysis report often will be only the consequence of the uncertainty in the analysis. This is certainly true when the deviation is smaller than 1–2 %, but may also hold with larger deviations for certain products.

Consequently the Ph. Eur. allows, for certain substances, a margin in the content of 97.0–103.0 % or 96.0–104.0 %. The symmetrical limits around 100 % indicate that these margins are connected to the uncertainty in the chosen assay method. It is principally incorrect to factorise at a preparation based on the outcome of such a determination.

One issue with factorisation is that the quantity of material to be included in each batch needs to be calculated separately and cannot be exactly stated in the master batch preparation instruction (see Sect. 33.4), this is a potential source of preparation error.

Contrary to this there is, in principal, a ‘quality gain’ because the content of the substance lies closer to the declared content. For most of the raw materials only a small percentage of impurities (mostly water) is allowed in the Pharmacopoeia. The quality gain that would follow from the correction for that is not at all relevant to the patient, and is therefore outweighed by the previously mentioned disadvantages. E.g. a cough syrup with codeine is often prescribed by the physician either to a patient weighing 70 kg or 85 kg, being 1.21 times heavier. He will not consider dose adjustment based on body weight.

Considering the above, factorisation should be avoided as much as possible. The requirement of 90–110 % for the content in the finished product, which is official in the most of the European countries, usually offers enough space for that. For countries with tighter limits than 90–110 % for the content of active pharmaceutical substance a different approach may be necessary.

Factorisation is clearly necessary when the amount of impurities is so large that there is significant risk that the content in the final product will be outside of the specification limits. In the Netherlands it is common to factorise if the amount of known impurities in the raw material is more than 4 % .

It is possible to work with the standardised batch preparation instructions by correcting the amount of raw material to be weighed with a constant factor, corresponding with the most probable amount of impurities. So prednisolone sodium phosphate is allowed to contain up to 8 % water according to the Ph. Eur. In practice the water content is generally close to the 8 %. In the batch preparation instructions for Prednisolone Oral solution (see Table 23.23) a surplus of 8 % of the active substance would then be included. However with this approach care should be taken to confirm that the level of impurity is within a specified level before the raw material is approved for use.

Examples of other substances that may contain more than 4 % impurities are dexamethasone sodium phosphate, ergotamine tartrate, erythromycin, codergocrine mesilate, cyanocobalamin, hydroxycobalamin, thiamine hydrochloride and ferrous fumarate.

With factorisation a consistent policy should be pursued, hence when factorisation is done for a raw material with a stock preparation this should also be done for an extemporaneous preparation. In such cases there is an extra danger for calculation errors; after all factorisation has to be combined with all the other necessary calculations.

32.4.2 Preparation Process

As a result of the preparation process content deviations may occur. Process steps including weighing, measuring, heating, mixing, transferring and filling can all introduce deviations.

Weighing and measuring can be done so precisely that they should not significantly contribute to deviations in the content. Loss by evaporation can be prevented usually by making the product up to its final volume as the last step of any process. The other preparation steps usually result in a loss.

Often there is a proportional loss, for example because a proportion of the intermediate or finished product remains on or within the mixing device. A proportional loss of a final product will not have impact on the product quality but may result in a decrease in the yield, for example when filling a batch of suppositories.

Inclusion of air into a product that is filled to volume can lead to an apparent increase in the yield, as occurs for example with a zinc oxide cutaneous suspension (Table 12.21).

When the complete mixture is divided over the number of dosage units to be prepared, for example with the preparation of capsules with a capsule device, then the loss in terms of percentage is related to the decrease in the average content in terms of percentage per dosage unit.

If there is a loss of content of raw materials or intermediate product ahead of the incorporation into the final product then this will be carried over into that final product. If this will lead to a significant deviation then the loss needs to be taken into account when designing the formulation, for example by including an overage for the lost materials.

When the amount of active substance per container unit decreases by air absorption, as for zinc oxide cutaneous suspension, this does not result in a lower content, in the case of suppositories (single dose form) then it does have an impact on the content.

The loss can also be selective, for example by evaporation of one of the components, or by adsorption to the vessel wall. A selective loss of the active substance will usually result in a lower content in the final product, as is the case with the preparation of capsules. With the preparation of small batches of suppositories the selective loss of the melted suppository base may however lead to a higher content (see also Sect. 11.5.2).

Insufficient mixing will usually result in insufficient content uniformity, but with complex processes such as the preparation of suppositories, it may even result in a deviation in the average content, see Sect. 11.8.3.

When the content deviations are too large this will result in an out of specification or at least an out of trend result and the whole preparation process will need to be investigated in a step by step manner to find the causes; an example of such an investigation can be found in [7].

32.4.3 Stability

The instability of an active substance can have significant consequences for the content in the finished product. This usually concerns the chemical stability, however also loss by evaporation and sorption on storage may play a part. Stability issues may arise at any point during processing and storage.

Because the above-mentioned content requirements are valid from the preparation date until the expiry date, any instability has to be taken into account when stating the content limits. For licensed products usually the content on expiry date is allowed to be maximally 5 % or 10 % less than the declared content. This only applies if the toxicity of the degradation products or perceptible cosmetic changes in the external characteristics of the product allow. To extend the shelf life a ‘stability overage’ of, for example, 5 % or 10 % of the declared content may be included in the preparation as long as the levels of degradation products will not be clinically significant. Note that this process is not in line with Committee for Medicinal Products for Human Use (CHMP) guidelines and good formulation practice. The inclusion of an overage to account for loss on storage (i.e. a stability loss) rather than for in process losses is not accepted practice. Products with very short shelf life may only be prepared if a stability overage is allowed. Reformulation into a more stable preparation is however preferred. Another option for pharmacy preparations it is to limit the decrease in the content to maximally 5 % by shortening the shelf life or decreasing the storage temperature (see also Sect. 22.6).

The use of an overage may result in an upper release limit of for example 110 %.

32.4.4 Sample Size

For determination of the average content of pharmacy preparations the sample size has to be sufficiently large for a statistically significant conclusion. With preparations in which the active substance is dissolved, then problems with uniformity of content (see also Sect. 32.7) should be rare and therefore smaller samples will give a suitable level of

assurance. With preparations in which the active substance is suspended in a base, such as with ointments or creams or oral suspensions, the sample size should be sufficiently large to get a representative image of the content. With a sample that is too small very local concentration differences may give an incorrect picture of the real content. This problem is even more important with single dose preparations. Because the contents of the individual units always show a certain degree of variation, this introduces an uncertainty when assessing the average content. As a result of this, more units have to be assessed to get a reliable average.

The Ph. Eur. does not make a recommendation on the minimum number of units to be tested, or the minimum size of the sample. The British Pharmacopoeia (BP) [2] is clearer. The BP describes that the average content of capsules or tablets has to be determined on 20 units. From this a mixed sample is taken, on which the content is assessed. The BP does not describe a general amount for suppositories. In most of the separate monographs for suppositories however a mixed sample of 10 units is taken.

32.4.5 Analytical Error

When assessing the result of an assay method the analytical error has to be taken into account. The result of an assay method does not give the actual content, but only an estimate. In other words, when the result of an assay method is just within the limits, there is a degree of risk (usually taken as 5 %) that the content is outside the limit. The preparer may state release limits within the 10 % content limits in order to avoid the release of products that do not meet the specification. For that purpose the lower as well as the upper release limit has to be 'narrowed' with the unilateral 95 %-confidence interval of the analysis (see Sect. 20.3). In general release specifications that are stated on the basis of analytical error will be 1 % to 2 % from the official limits.

Conversely an independent testing authority (for example an inspector) should only disqualify a product when it is sufficiently sure that the real content is outside the official limit. He also has to take the analytical error into account. It is common practice to state the rejecting limits by extending the official limit with the unilateral 95 %-confidence interval of the analysis. When both parties keep within these rules the chance is small that a batch is released by a producer and consequently rejected by an independent testing authority.

Assays should be conducted in duplicate and ideally the results should be reported individually or as an average and standard deviation where higher replicates are used. With homogeneous preparations, preparations consisting of one phase such as solutions, a duplicate value usually gives sufficient information for a product release decision. When the average content is assayed by analysing several units of a non-homogeneous preparation, a dispersion, not only the standard deviation of the duplicates count but also the standard deviation from the single samples. The standard deviation has to be taken into account when deciding if the average content meets the requirements The separate values will be important in order to make a judgement on extent of variation and on content uniformity in case of separate units.

32.4.6 Interpretation of the Result

The assay method can be carried out following the methods described on the analytical protocol. When the result lies within the release limits, the batch may be released.

It has been found in the Netherlands by proficiency testing that the average content of most pharmacy preparations lie between 95 % and 105 % of the stated content. So when accepting a content limit of 90–110 %, the product will be released without further consideration if an assay result is between 95 % and 105 %. Trends in results (up or down) should be investigated as part of product quality reviews.

When the result lies frequently outside 95 % and 105 % but within the 10 % product specification limits then the cause of such a deviation should be investigated and corrective measures should be taken.

Note that the product shelf life may also be reviewed if the expected level of degradation would predict that the product is out of specification before the end of its usual shelf life.

When the result is outside the product specification limits the batch should not be released and the assignable root cause must be established and fully investigated. Hopefully this will lead to process improvement or elimination of analytical errors.

This general guidance is applicable to homogeneous preparations such as solutions. The interpretation of the result for inhomogeneous preparations is connected to information about the inhomogeneity of the sample. The average content and the content of the individual dosage units will enable a decision on mixing efficiency i.e. homogeneity of the batch. With single dose preparations such as capsules or suppositories the knowledge of the individual contents is essential to get an impression of the uniformity of content and by consequence the correct preparation by the operator. This subject will be discussed further in Sect. 32.7.

32.5 Chemical Purity

When designing quality requirements for a substance a distinction has to be made between impurities that are process contaminants of the synthesis (for example the related compounds in clioquinol) and those present due to

degradation of the substance in the course of time (for example salicylic acid from acetylsalicylic acid).

Although when epimerisation of active substances occurs, it will be during synthesis and during preparation of the finished product as well. The manufacturer will set different specifications for active substance and finished product, but always as low as possible. Unless it appears that epimer formation is a major (more than 10 %) metabolic pathway in the body making an impurity specification of less than 0.4 % rather improper.

Impurities resulting from the synthesis of the raw material that are not degradation products, will not be influenced by the preparation process of the final dosage form. It is therefore reasonable to set an identical requirement for raw material in the Pharmacopoeia and for any final products made from it. Analysis of such impurities will not take place on the finished product, but solely on the raw material and by consequence a specification in the end product has no significance.

When the impurities arise as degradants of the main product, then it is likely that, during the preparation process (dissolving, heating, light influence), the content of such impurities increases. Also during storage the content of these impurities may increase further. The final product specification for such impurities will need wider specification than that specified for the raw material. However, this can only occur provided that the amount of impurities stays within the acceptable criteria from a patient safety perspective which has to be demonstrated, from preclinical studies or literature, on safety. Generally such products will have a clearly defined shelf life and possibly special storage conditions.

Chemical impurities may also be generated as reaction products of components, for example of the active substance and excipients. For example degradation of acetylsalicylic acid may occur in hard fat with a high hydroxyl value. It is obvious that such interactions should be prevented best at the product design phase, by choosing the appropriate excipients.

The percentage of degradation product at the end of the shelf life is generally limited to 5 % of the parent substance. From this percentage generally a requirement for the amount of impurities immediately after preparation can be derived. Obviously other more stringent criteria will be required when the nature of the impurity is such that there can be safety issues for the patient (see also Sect. 22.4.2).

Official limits for impurities in products prepared in pharmacies are not in force in most European countries. In the United Kingdom the limits are stated in the British Pharmacopoeia [2]. In the Netherlands pharmacy prepared products have also to meet the relevant purity requirements as stated in monographs of for example the British Pharmacopoeia or if not available in another international Pharmacopoeia.

32.6 Average Mass, Volume and Content

Medicines clearly need to contain the correct quantity. Therefore requirements are set for deviation from the declared weight, or for the minimal amount in a container that is available for administration. Extractable volume is an example of such a specification. It may also be necessary to set an upper limit to the available amount particularly where the whole content is given as a dose

32.6.1 Average Mass and Theoretical Mass of Single Dose Preparations

A difference between the average mass and the theoretical mass will show deviations in the content in a simple way: a deviating average mass often corresponds with a deviating content. For suppositories this can occur when the wrong molds have been used. With capsules loss during the preparation may be the cause. The Ph. Eur. doesn't set a requirement to the deviation of the average mass from the expected value, probably because the theoretical value is only known to the preparer and not to an independent testing laboratory.

In the Netherlands it is common to use a requirement of 3 % as a limit to the deviation of the average mass towards the calculated mass for capsules and suppositories. For single dose powders this requirement is 5 %. In practice these limits appear to be acceptable and are achievable. When these limits are exceeded, then there are, in principle, two possibilities: reject the preparation or check the average content. When the content complies, the preparation need not be rejected on the basis of the average mass discrepancy. However the cause of the deviation should be investigated and traced and corrective measures should be taken for future batches.

32.6.2 Volume and Content

The Ph. Eur. states requirements to the extractable volume of parenterals: 'The volume of the injection in the container is sufficient to permit the withdrawal and administration of the nominal dose using a normal technique'. In Ph. Eur. chapter 2.9.17 'Test for extractable volume of parenteral preparations' the method of analysis is described.

In some cases it may be necessary to set an upper limit to the amount available per container. A reason may be the risk of overdosing if the entire contents of the container are expected to be given.

For eye ointments and creams the Ph. Eur. determines an upper limit of 10 g per container, in order to reduce the risk of contamination during the period of use. Eye drop containers may contain maximally 10 mL and containers for irrigations for the eye maximally 200 mL.

For drops for oral use it is required that the average weight of 10 units of the size of a usual dose may not deviate more than 15 % of the nominal value. Also, if necessary, the average volume delivered should meet this requirement.

With respect to dosage forms such as oral preparations, rectal preparations and preparations for cutaneous application the Ph. Eur. states that during the development it must be demonstrated that the nominal volume or content can be obtained from the container..

32.7 Uniformity of Mass and Content of Single Dose Preparations

The requirements and assay of average content has been discussed in Sect. 32.4. When a medicine consists of single dosage units, the contents of those separate units (tablets, capsules, suppositories)have to meet content requirements. The separate assay values are used for estimation of the average content but also to estimate the variation between the units (uniformity of content). The separate mass values also have to meet requirements. The mass variation may give some indication of the content variation.

The Ph. Eur. has several monographs on the analysis of single dose preparations:

- 2.9.5 Uniformity of mass of single dose preparations
- 2.9.6 Uniformity of content of single dose preparations
- 2.9.40 Uniformity of dosage units (also including uniformity of mass)

Monograph 2.9.40 will become the only valid monograph in due time. Many licensed medicines have been designed to meet the requirements of 2.9.5 and 2.9.6 and are expected or known not to meet the requirements of 2.9.40. The monographs 2.9.5 and 2.9.6 therefore will be kept for the time being.

32.7.1 Uniformity of Mass

The uniformity of mass is easy to determine and it gives an indication of the uniformity in the content as far as this is caused by mass deviations.

According to Ph. Eur. monograph 2.9.5 the assay and requirements read as follows:

Weigh individually 20 units taken at random or, for single-dose preparations presented in individual containers, the contents of 20 units, and determine the average mass.

For suppositories not more than 2 of the individual masses deviate more than 5 % of the average mass and no suppository may deviate more than 10 % of the average mass. For capsules with a content weight less than 300 mg these percentages are respectively 10 and 20 %, for capsules with a content weight equal to or more than 300 mg respectively 7.5 % and 15 %. For other pharmaceutical forms reference is made to the monograph.

This Ph. Eur. test is clear and unambiguous, but has the disadvantage that the conclusion can only be: 'satisfactory' or 'not satisfactory'. In other words the Ph. Eur. does not set a specific limit. Only when units are deviating too far those deviations may be used to give some insight in the uniformity of mass. A numerical criterion would be useful for comparison of batches or for trend analysis of preparation results. All the tested units should be included in this criterion. The variation coefficient (or relative standard deviation (rsd)) can serve this purpose. It is calculated as follows:

rsd = s/m × 100 %, in which s is the standard deviation and m is the average mass.

Modern balances have a calculator-printer installed, that provide the Ph. Eur. test as well as the calculation of the rsd.

For pharmacy prepared capsules the assessment of the uniformity of mass is a meaningful test. The Ph. Eur. requirements are generally easy to be met. Inappropriate use of the capsule filling device or a badly flowing mixture may lead to deviations. For divided powders that are filled and weighed by hand no uniformity of mass needs to be determined as long as all weights are recorded on the balance print out. It may be prudent however to conduct a random weight determination for monitoring the quality level and enable trend analysis. For divided powders that are prepared with a powder folding machine a uniformity of mass analysis is meaningful; a deviation may occur when a mixture flows badly or when equipment is not used appropriately.

Pharmacy prepared suppositories are required to meet the Ph. Eur. specifications for Uniformity of mass. Batches that do not meet the requirements can often be rejected by visible irregular filling of the molds, air bubbles, etc.

Drops for oral use have to meet the requirement that the separate masses of 10 units equivalent to the normal dose deviate maximally 10 % from the average mass. The total of 10 masses does not differ by more than 15 % from the nominal mass of 10 doses.

The uniformity of mass test does not have to be performed when the test on uniformity of content according to 2.9.6 has been performed for all the active substances included in a preparation. The test on uniformity of content gives much more information about the variation in the

amount of active substance per dose unit in the product than does the uniformity of mass test.

The content uniformity test according to the Ph. Eur. 2.9.40 also regards uniformity of mass.

32.7.2 Uniformity of Content

32.7.2.1 Content Variation

Variation in the content of single dosage units depends on the dispersion type of preparations (see Sects. 18.4 and 29.7): mixtures of two or more solid substances (powders, capsules), dispersions of a solid substance in a semisolid substance (ointments, creams) and dispersions of solid substances in liquids (suppositories, suspensions). Solutions do not show content variation between single dose units, just mass variation may occur. Content variation is caused by poor dispersion, by poor mixing in the bulk or by de mixing at filling, rather than by mass variation due to poor filling/dividing.

The mixing variation is low when the distribution of the active substances in the excipients is as homogeneous as possible and when this homogeneity is maintained during filling.

A measure for content variation is the rsd of the assays of single dosage units. If the mass variation is determined as well, the actual mixing variation can be calculated (see Sect. 29.4). In this way it can be investigated whether poor mixing or poor filling/dividing (or both) is the cause of the content variation. When a poor filling or dividing process is the cause of content variation then the uniformity of mass variation would be expected to be about the same size as the observed content variation. If the mass variation is much smaller then poor dispersion or mixing is the most probable cause.

For monitoring a production process the rsd can be recorded to compare batches in a trend analysis or by control charts (see Sect. 20.4.4).

In order to validate the quality of the mixing process the following may be considered regarding the sample size. When the active substance is dispersed in the vehicle, the content variation depends on the size of the samples that are assayed. Small samples contain smaller particle numbers of active substance, which increases the chance of an irregular distribution. It is logical and practical to take the dose unit as sample size for dispersed systems. For dosage forms for cutaneous application the smallest amount in which the preparation is used by the patient may be used as 'dose unit'.

32.7.2.2 Content Uniformity According to Ph. Eur. 2.9.6

For the specific requirements reference is made to the Ph. Eur. The notable characteristic of this method is that the required limits are normalised towards the average content and not to the declared content.

The requirements apply to single dosage forms with less than 2 mg of active substance per dose or less than 2 % of the total mass.

As with Uniformity of Mass this Pharmacopoeia test for Uniformity of Content is clear and unambiguous, but less suitable to compare batches. For that purpose, as said, the rsd is much more appropriate.

32.7.2.3 Content Uniformity and Mass Variation According to Ph. Eur. 2.9.40 Uniformity of Dosage Units

This test is a requirement of content uniformity but it is actually a requirement for the average content as well. As opposed to the monograph 2.9.6 the requirements for uniformity of content of single-dose units refer to the 'label claim' (declared content) of the batch and not to the average content. This characteristic also makes the test tighter than the 2.9.6 test.

This monograph has been harmonised with the United States Pharmacopoeia (USP) [3] and Japanese Pharmacopoeia (JP) [4].

The monograph defines the application of Content Uniformity (CU) and Mass Variation (MV) on different dosage forms that contain <25 mg active substance per dose unit or where the active substance comprises <25 % of the mass of the dosage unit. A random selection of 30 units is required and the separate units have to be assayed individually.

But the test may be applied as well for the assessment of the MV of dosage forms, e.g. tablets, containing ≥ 25 mg or when the active substance is equal or more than 25 % of the mass of the dosage form.

Unless otherwise stated, the uniformity of dosage units specification is not intended to apply to suspensions, emulsions or gels in single-dose containers intended for cutaneous administration. The test for content uniformity is not required for multivitamin and trace-element preparations.

Variation in unit content based on individual masses ($w_1 \ldots w_n$) is related to label claim by an assay on a representative sample of the batch. This assay must have a relative standard deviation of not more than 2 %, based on validation studies and development data.

The assay result is expressed as percentage (A) of label claim, assuming the concentration in all dosage units to be uniform. The individual contents of a unit then equals $x_i = w_i \times A/W$ in which W is the mean of individual masses.

The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to $L1$ per cent. If the acceptance value is $>L1$ per cent, the next 20 units have to be tested, followed by calculation of the acceptance value.

Table 32.1 Content Uniformity sampling plan for smaller sample sizes (n_i sample size, k_i acceptability constant

Sampling plan	n_1	k_1	n_2[a]	k_2
n = 10/20 (Ph. Eur.)	10	2.4	30	2.0
n = 8/32	8	2.6	20	2.0
n = 7/13	7	2.8	20	2.0
n = 6/14	6	3.0	20	2.0
n = 5/15	5	3.2	20	2.0

[a]n_2 is the sum of the total number of units in the sample

The requirements are met if the final acceptance value of the 30 dosage units is $\leq L1$ percent and no individual content of the dosage unit is less than $[1 - (0.01 \times L2)]$M or more than $[1 + (0.01 \times L2)]$M in the Calculation of Acceptance Value under Content Uniformity or under Mass Variation. Unless otherwise specified, $L1$ is 15.0 and $L2$ is 25.0.

The assessment and calculation of the content uniformity is done by means of the acceptance value (AV).

The number of prescribed assays (10 units at first, probably followed by another 20 units) is rather large in the situation of small-scale preparation. However it appeared to be possible to reformulate the test into a more acceptable set-up with the same statistical confidence. More details on sampling plans are to be found in Sect. 20.4.4. The resulting sampling plan is given in Table 32.1. Statistical background is further given in Sect. 20.4.6 Content uniformity of dosage forms.

As said the 2.9.40 test is more tight than the 2.9.6 test. The current advice is that, from a pharmaceutical quality point of view, the approach taken in the harmonised general chapter on uniformity of dosage units (2.9.40) is considered equivalent to what was previously required in the Ph. Eur. through the general chapters on uniformity of mass of single-dose preparations (2.9.5) and uniformity of content of single-dose preparations (2.9.6). These general chapters, 2.9.5 and 2.9.6, are still included in the current version of the Ph. Eur.

Taking this into account, the decision on what approach to take is left to the applicant (who is submitting a dossier for registration). Application of either the Ph. Eur. harmonised general chapter on uniformity of dosage units (2.9.40) or the Ph. Eur. general chapters on uniformity of mass of single-dose preparations (2.9.5) and uniformity of content of single-dose preparations (2.9.6) are both considered acceptable options to demonstrate compliance with the Ph. Eur. with regard to uniformity of dosage units.

Requirements are in principle valid across the shelf life of the medicine. The monograph 'Pharmaceutical Preparations' however makes an exception for the test on uniformity of dose units, being valid at release only, because homogeneity of active substance in dosage units does not change on storage only the content of active substance.

32.7.2.4 Content Uniformity of Liquid Dispersions

A method for the determination of homogeneity (as well as resuspendability) of oral suspensions is described in the British Pharmacopoeia [2]. At first the suspension should settle, undisturbed, for 24 h. After shaking for 30 s 10 samples should be removed at a depth of 1 cm below the meniscus, while between every sample an additional 10 s shaking is performed. The sample size should match the usual dose unit. The doses are assessed individually according to the method specified in the individual monograph. The preparation complies with the test if each dose is between 85 % and 115 % of the average dose. The preparation fails to comply if more than one dose (out of 10) is outside these limits or if one individual dose is outside the limits of 75–125 % of the average dose.

32.7.2.5 Content Uniformity of Semisolid Dispersions

Although, in practice, when dispersing solid substances with an ointment base several problems can arise (see Sect. 29.3), the Ph. Eur. does not set quality requirements. At the design phase of a semisolid dosage form for cutaneous application in which an active substance is dispersed, the dispersion quality can be validated with, as in 'dose unit', an amount that approximately equals the minimal dose that is applied by the patient. After validation of the preparation method, the dispersion quality is usually monitored with an in-process control: spreading a sample between glass plates and controlling the absence of visible agglomerates.

32.8 Microbiological Purity, Sterility, Pyrogens and Bacterial Endotoxins

The assessment methods and quality requirements for the microbiological purity of the finished products and raw materials have been harmonised worldwide since 2009.

The Ph. Eur. summarises the quality requirements for the microbiological purity of non-sterile preparations in monograph 5.1.4 'Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use'. For raw materials quality requirements are described in individual monographs or in the general monograph 'Substances for Pharmaceutical Use'.

Quality requirements regarding microbial enumeration tests and limit tests for specific microorganisms, see further Sect. 19.6.2.

For the methods of performing enumeration of microorganisms (TAMC and TYMC) see Sect. 19.6.3 and for specified micro-organisms see Sect. 19.6.4.

As part of the quality control of sterilised products the Ph. Eur. requires the performance of the test for sterility. The test for sterility as described in Ph. Eur. chapter 2.6.1 'Sterility' is of relative value only, assuring only the actual units tested, see Sect. 19.6.1. In practice in some countries this can be replaced by validation of the sterilisation process or by validation of the aseptic method of preparation. For products with a short shelf life then it is not practical to obtain sterility testing results prior to product release and in these cases a parametric release process needs to be carried out. This process should consider all of the data available at the time of release, retrospectively obtained sterility testing results should be considered as part of the ongoing process validation. Process validation and end of session media transfer tests may be used in lieu of sterility testing where appropriate, for example where the final products are hazardous Sterile products with an extended shelf life, including those subjected to sterilisation and those made aseptically, should be subjected to a prospective sterility test and/or a batch specific media fill process validation. Parametric release may be carried out on condition that the competent authority has given approval. In the Dutch hospital pharmacy parametric release of sterilised preparations is a generally accepted by the professional group, in the UK it is generally only accepted where the product has a short shelf life. The conditions under which parametric release is carried out need to be well defined and controlled. The starting point for parametric release is the acknowledgement that tests and checks that are performed during the production process may give at least the same level of guarantee that the finished product corresponds to the specifications than when the finished product is tested, see also Sect. 34.14.1.

Quality requirements as to the effectiveness of the preservation are mainly relevant for preparations in dosage forms for multiple use. The Ph. Eur. thereby distinguishes preparations for parenteral and ophthalmic use, locally used preparations and oral preparations. The product has to undergo stress testing with various prescribed strains of micro-organisms. The quality requirements are defined as a decrease (or no increase) in populations at stated points in time. The Ph. Eur. describes in chapter 5.1.3 'Efficacy of antimicrobial preservation' the determination methods of study. For effectiveness of preservation and minimal level of preservation, requirements are given. This differentiation is useful because some preparations are only marginally preserved. In those cases specific requirements are added to decrease the contamination risk, such as restricting the number of doses that can be removed or the in-use shelf life.

For dosage forms for parenteral administration the Ph. Eur. sets limits for bacterial endotoxins and pyrogens. For definition and difference see Sect. 19.3.4. Ph. Eur. chapter 2.6.14 'Bacterial endotoxins' describes six different methods of which the LAL test (gel-clot-method) is the method of reference. On the condition that they are sufficiently validated the other methods may be used as an alternative to the gel-clot-method. See Sect. 19.3.4 for background information on these tests. Ph. Eur. describes an *in-vivo* test for the investigation of pyrogens in Ph. Eur. chapter 2.6.8 'Pyrogens'. This test is based on the measurement of the increase of body temperature of rabbits after intravenous administration of the substance to be analysed. Over the years this test is being replaced by the test for endotoxins, the LAL-test, with the exception of those products which interfere substantially with the LAL test.

An example of calculating the limits for endotoxins

A morphine containing injection solution with the strength of 100 mg/5 mL has been prepared. Because the product will be administered parenterally a bacterial endotoxins test has to be performed. Therefore the administration route has to be known: is this intravenous or intrathecal or epidural. For endotoxins in intravenous administration the requirement is: maximally 5 EU/kg body weight during 1 h. Based on a body weight of 70 kg this means 350 EU/h. Secondly the maximal dose (in volume of the product per hour) will determine the actual limit. This depends on the need of the patient as well. If he needs the full 5 mL, this makes the requirement for the product to be 350 EU/5 mL = 70 EU/mL.

32.9 Disintegration

Only a dissolved active substance can be absorbed in the bloodstream. To be able to dissolve the active substance first has to be released from the pharmaceutical form. The disintegration of oral dosage forms such as capsules and tablets and the disintegration of rectal and vaginal dosage forms such as suppositories are therefore important pharmaceutical parameters for the effectiveness of the medicine.

Ph. Eur. 2.9.1 'Disintegration of tablets and capsules' describes the equipment and the method of analysis. The disintegration medium that has to be used as well as the quality requirements are specific for the dosage form and can be found in the appropriate monographs. The requirement for solid capsules is for example disintegration in water within 30 min.

For disintegration of suppositories the equipment and determination method are described in Ph. Eur. chapter 2.9.2 'Disintegration of suppositories and pessaries'. Fat suppositories have to melt within 30 min, water-soluble suppositories after 60 min.

These quality requirements are mainly tested in the design phase and probably repeated as a release control. Disintegration may however decrease on storage and hence it is recommended to include it in stability testing of the product. The quality requirements of the Ph. Eur. apply up to the expiry date.

Meeting the requirements for disintegration is a minimum condition for the release of the active substance from the dosage form. For solid dosage forms and dispersions (suspensions, most suppositories) the active substance still has to dissolve to be available for absorption (see Sect. 16.1.4).

32.10 Dissolution

The determination of the dissolution rate of the active substance from the dosage form is relevant for solid dosage forms and dispersions, especially when the substance is poorly soluble (see Sect. 16.1.4). Only dissolved substances are available for absorption. Ph. Eur. describes in chapter 2.9.3 'Dissolution test for solid dosage forms' the equipment, the method of analysis and the interpretation of the determination of the dissolution rate of tablets and capsules. For suppositories it is described in Ph. Eur. chapter 2.9.42 'Dissolution test for lipophilic solid dosage forms'.

The general monographs for capsules, tablets and suppositories refer to the dissolution test when relevant. The Ph. Eur. describes for capsules and tablets different equipment, most important variants being the paddle-method and the basket-method. Next to these the flow-through-cell method is described, especially intended for the determination of the dissolution rate of poorly soluble substances.

With the paddle-method the product to be analysed is brought into a vessel with the prescribed dissolution medium, and mixing is performed by a blade attached to a shaft (the 'paddle').

With the basket method the product to be analysed is brought into a cylindrical basket that also provides the stirring.

The choice between both methods is to be made in the product design phase. Ideally these *in vitro* methods are meant to mimic the behaviour in the intestinal environment: *in vivo*. In practice the determination of the dissolution rate is meaningful as a tool in the design phase and as a means to monitor possible changes in (particle size of) raw materials and the production process. If changes are under control (no changes happen) then this test may not be required as part of the batch release specification.

The Ph. Eur. specifies (for information only and so not compulsory) that about the determination of the dissolution of a capsule or tablet the following points should be recorded: type of equipment; composition, volume and temperature of the dissolution medium, rotation speed, sampling times, sample volume and sampling method, method of analysis, acceptance criteria.

Ph. Eur. requires for conventional release preparations that the dissolved amount of active substance from every dosage unit after 45 min should be at least 80 % of the label claim. Other requirements apply to delayed-release and prolonged-release dosage forms.

Ph. Eur. doesn't give requirements for specific medicinal products because it doesn't describe products. The British Pharmacopoeia [2] and the United States Pharmacopoeia [3] describe dissolution rate requirements for almost all capsule and tablet products.

The British Pharmacopoeia [2] gives requirements for the dissolution rate of oral suspensions in the general monograph for 'Unlicensed Medicines'. These quality requirements are similar to the advice of the Ph. Eur. for capsules and tablets. The dissolution rate of an oral suspension, being prepared in pharmacies for instance for patients with swallowing problems or for children, and how it compares to the comparable licensed oral dosage form, is an important consideration when designing such liquid medicines.

32.11 Particle Size

For the significance of the particle size of the raw material reference is made to Sect. 29.2. For terminology and determination methods reference is made to Sect. 23.1.8.

The particle size is determined in the raw material. In the design phase the effective dispersion of agglomerates (see Sect. 29.3) and possible particle growth during storage (see Sect. 18.4.2) have to be validated.

The Ph. Eur. sets quantitative requirements for the size of particles in finished products for suspension eye drops and eye ointments. Per 10 micrograms solid substance maximally 20 particles may be larger than 25 µm, maximally 2 particles larger than 50 µm and no particle larger than 90 µm. These quality requirements are valid until the expiry date.

For semisolid preparations with dispersed particles for dermatological use the Ph. Eur. specifies that care should be taken to control particle size to a suitable level during production. Also for liquid dosage forms with dispersed particles for oral use (oral suspensions) the Ph. Eur. gives an indication of controlled particle size.

32.12 Particulate Contamination

The Ph. Eur. describes methods of analysis for the determination of visible and non-visible particles in parenteral dosage forms. Particles in parenterals, also called particulate contamination, consist of extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions. Because of their small mass and heterogeneous chemical composition they cannot be quantified with a chemical analysis method. Particles in parenterals can cause harm in patients, including phlebitis, emboli and granuloma formation.

Because most parenteral are made particle free by filtration through a membrane filter just before filling, the container has a relatively large influence on the final level of particles in the product. Anecdotally it appears from results of particle counting studies that infusions in glass usually contain more particles than those in plastic packaging materials. Also small units often contain more particles per unit volume than large ones [8–10].

For the determination of visible particles in parenteral dosage forms the Ph. Eur. describes a visual method under standardised conditions in chapter 2.9.20 'Particulate contamination: visible particles'. Here the background, the type and the intensity of the light source of the equipment are stated.

For the determination of sub-visible particles the Ph. Eur. describes two methods of analysis in chapter 2.9.19 'Particulate Contamination'. One method concerns the light obscuration particle count test and the second one the microscopic particle count test. The results of both methods are not always mutually comparable. For quantitative purposes the light block method is mainly used. The microscopic method can be used for viscous products or for those which are problematic in the light obscuration method

The light obscuration method is harmonised between the Ph. Eur., the United States Pharmacopoeia and the Japanese Pharmacopoeia, with regard to the equipment, the determination method, the number of units to be analysed and the quality requirements. For parenterals with a volume larger than 25 mL 10 separate units from a batch have to be counted. Parenterals with a volume smaller than 25 mL have to be combined to a minimal volume of 25 mL that will be counted.

The quality requirements are as follows:

- For units larger than 100 mL: in 10 units an average of not more than 25 particles $\leq$10 μm and 3 particles $\leq$25 μm per millilitre should be present
- For units smaller or equal to 100 mL: in 10 units an average of not more than 6,000 particles $\leq$10 μm and 600 particles $\leq$25 μm per dosage unit should be present

In cases of small batches of product produced in pharmacies a random sample of 10 units can present a large proportion of the produced batch, meaning that quality control becomes very costly. The Ph. Eur. gives some latitude to use a smaller random sample than 10 units under certain conditions. With the aid of statistical analysis it is possible to derive the same level of quality assurance with a smaller sample size. Taking into consideration the uniformity/variability of the quantity of counted particles, the minimum sample size always has to be five units in order to achieve a sufficient level of assurance.

Particles that are unintentionally present are also relevant or ophthalmic preparations.

Only the Japanese Pharmacopoeia [4] and USP [3] set limits for levels of particles in eye drops. The Japanese Pharmacopoeia requires that eye drops after filtration and assessment with a microscope must have a maximum of 1 particle of 300 μm or larger per millilitre. The requirements of the USP are considerably stricter. Chapter 789 (Particulate matter in Ophthalmic Solutions) requires that maximally 50 particles of $\geq$10 μm and maximally 5 particles of $\geq$25 μm per mL eye drop fluid may be present. The method used is the light obscuration method.

The Ph. Eur. has set no specification, firstly because it is difficult to assess the risks posed by particles in eye drops. In general these risks are deemed to be very small to absent as is highlighted by the use of suspension eye drops. In Europe the United States specification is found to be too strict for all eye drops. According to reports the USP rationale is based on the concept that the acceptable particle load of ophthalmic preparations should be related to its use in a damaged eye or by means of an intravitreal or intracameral injection. In the latter case the presence of particles is considered totally unacceptable. However, there is no study that could be the basis of such a judgement.

Conversely the specification should consider what is practically achievable in the pharmaceutical industry with the so-called Blow-Fill-Seal (BFS) production process, cannot necessarily be extrapolated for the quality control of pharmacy made preparations. The USP requirement appears not to be based directly on the control of any apparent clinical risk. The USP standard leads to the monitoring of particle contents in BFS eye drops, performance of trend analysis and to investigate causes that lead to increased particle loads in that type of production process.

32.13 Physical Tests

Physical tests including pH, relative density, optical rotation, refractive index, conductivity, viscosity and osmolality are generally used as in-process controls or as simple laboratory tests for the finished product.

pH requirements may be set for some medicines by the British, United States of Japanese Pharmacopoeia. If not a general rule is that the pH, in the case of a buffered system, is given to one decimal place and the limits for a preparation should be within ± 0.5 unit of the declared value. In practice a requirement immediately after release ± 0.1 unit is often achievable. However the requirement also has to cover the shelf life of the preparation. Values outside these limits could indicate a deviation of the declared composition or to significant product degradation.

Density requirements may also be set by the mentioned Pharmacopoeias, for the relative density of a liquid or solution. For alcoholic solutions such a requirement may be useful to determine whether the correct quality and the correct volume of ethanol have been used in the preparation process. The same is true for other preparations of which the density deviates strongly from water, for example because of the presence of dissolved substances. Preparations that, for example, contain a high percentage of sorbitol or glycerol are well characterised by their density and a determination of the density actually becomes an important identity criterion. The requirements for the relative density are not strictly defined, because the nature and amounts of the excipients may have a significant impact on the density of a product. As guidance a precision of maximally three decimal places may be appropriate, with limits of ± 0.020 unless there is practical information available that requires wider or stricter limits.

Optical rotation requirements may be found for some solution preparations.

This is a measure of the angle of rotation of plane polarised light and is often used as an identity criterion for certain materials, especially sugars. When these substances are present in a significant proportion in the final product and when few other excipients are present, the optical rotation can be used as a characteristic that gives quantitative information to the product concentration.

Refractive index is also generally used as identity criterion for various oils and sugars, but the technique can be used for multicomponent products such as parenteral nutrition solutions as well. In general the absolute scale is used for identification test purposes and the second sugar scale can be used for product analysis for either simple sugar solutions or complex mixtures.

A conductivity measurement is often used as a limit test, for example, when testing water for injection (see Sect. 27.5.2) but can also be used as part of the quality characteristics for other materials. The principle is to measure the resistance of a column of liquid in a conductivity cell. For water testing it is generally an in-process control.

The viscosity may be relevant for some pharmacy preparations, for example for gels or certain cutaneous liquids that have to be applied onto the scalp as well for eye drops especially those used for eye lubrication. A viscosity that is too low or too high may determine the therapeutic usability of a product. Similarly viscosity can be an important parameter for suspensions when viscosity should sufficiently high to reduce settling speed and sufficiently low to enable resuspendability. Hence a requirement for measurement of viscosity may be of added value to the quality or relevant products. For some products for example eye drops containing hypromellose the nominal viscosity should be stated on the label. Often viscosity is studied in the design phase of a formulation but it can also be used as a routine quality control test.

The osmotic value of a solution (see Sect. 18.5) may be an important quality parameter for parenterals, but also for eye or nose drops which should, in principle, be isotonic. Values outside the physiologic limits point to a deviation in the declared composition. The osmolality will be studied in the design phase of the preparation and later often will only be checked as in-process control.

32.14 Herbals

Medicinal plants are either cultured under controlled growing conditions, or collected from the wild under natural growing conditions (wild-crafted herbs).[1] Herbal raw material for herbal medicinal products is not referred to as a herbal active substance by the Ph. Eur. but as a herbal drug. Probably because it is not one ‘substance’ but usually is a mixture of plant material. The quality of herbal drugs as a raw material must be controlled according to pharmacopoeial standards. The Ph. Eur. includes as general monographs on herbals:

- Herbal drugs
- Herbal drug preparations
- Extracts
- Herbal teas
- Essential oils

Quality-related problems are mostly associated with unregulated herbal drugs and include the (deliberate) inclusion of prohibited or restricted substances (e.g. admixture of synthetic actives, adulteration with toxic plants), contamination with toxic substances (e.g. heavy metals, residues) and incorrect declaration of constituents and content on the packaging labels.

The Ph. Eur. describes general methods of analysis to be applied to herbal drug products as well as more specifically dedicated methods (2.8. Methods in pharmacognosy). Identity tests must be specific for a particular herbal drug as

[1] This section was contributed by Herman Woerdenbag, Groningen, The Netherlands

adulterations and falsifications must be excluded. Macroscopic and microscopic evaluation and organoleptic assessment are important for the authentication of the botanical identity. In addition, simple chemical tests (colour reactions, precipitation reactions, chromatographic tests) are carried out. To assure a constant quality of the plant material and to compare different batches, analytical methods yielding a profile of the constituents are often applied. TLC-fingerprints are relatively easy to make and cheap, but GC- and HPLC-fingerprints are used as well.

Purity control of an herbal drug is not only relevant for the quality of a finished herbal medicinal product, but also for its safety. According to the Ph. Eur. herbal drugs are, as far as possible, free from impurities such as soil, dust, dirt and other contaminants such as fungal, insect and other animal contaminants and that they are not subject to decay.

Purity control limits contamination with pathogenic bacteria (*Staphylococcus aureus*, *Escherichia coli*, *Salmonella*-species, *Pseudomonas aeruginosa*, *Clostridium*-species and others), yeasts, moulds, microbial toxins (aflatoxins, endotoxins), toxic heavy metals (lead, cadmium, mercury, arsenic; e.g. from industrial emission), pesticide and herbicide residues, fumigants (ethylene oxide, methyl bromide, phosphine) and radionuclides. Furthermore, impurities with other plants parts ("foreign organic matter") are limited. Moist levels must be below a certain maximum to avoid deterioration by microorganisms. Excreta of animals and dead insects must be absent. The ash value and acid-insoluble ash limits the amount of inorganic impurities (soil, sand).

Assays are carried out specifically, to quantify either single (biologically active) constituent(s) or non-specifically, to quantify a group of closely related compounds (e.g. flavonoids, anthocyanidines, essential oil). Generally, criteria are set for a minimum accepted percentage and sometimes for a maximum as well. If it is unknown which constituents are responsible for an alleged action of the herbal drug, analytical procedures can be used to assay characteristic marker compounds (quality markers, indicators for consistent quality) of the plant. The specificity of a general assay for a group of constituents can be enhanced by combining it with another analytical procedure, which is based on a different principle. An example is a spectrophotometric assay combined with TLC- or HPLC-fingerprinting.

The production process of a typical industrially manufactured herbal medicinal product includes cultivation or collection from the wild followed by harvesting, drying and fragmentation of the plant material, the preparation of a semi-manufactured product (extract) and the preparation of a finished product. Quality assurance and quality control should be part of all of stages in the process. Good quality herbal medicinal plant products are prepared according to GACP, GMP and GLP standards. During the industrial manufacturing of herbal medicinal products not only the raw material is subject to rigid quality control, but also the quality of the semi-manufactured and finished product is monitored (in-process controls) and evaluated (end controls on content, identity, purity). Finally a pharmaceutical dosage form should comply with the applicable pharmacopoeial standards (e.g., crush strength of tablets, disintegration time of tablets and capsules, uniformity of mass and content [11–13]).

32.15 Quality Requirements, overview

Table 32.2 summarises the quality requirements of the most important pharmaceutical dosage forms that occur as pharmacy preparations.

32.16 Analytical Validation

32.16.1 Purpose of Analytical Validation (AV)

Validation is defined as the documentation of evidence of performance properties of a method, procedure or process. A method is valid, when it achieves its expected outcomes in a consistent manner. Many chemical and physical analytical methods are subject to the need for validation. Process validation is discussed in Chap. 34 concerning validation of processes, equipment, procedures, premises.

Analytical validation is essential in pharmaceutical operations as the accurate measurement of a characteristic or quantity in a dosage form is critical to the correct decisions being reached as to its disposition. An accurate and highly precise method will reduce the risk of rejecting batches when, in reality they do comply with the specification and also to reduce the risk of falsely accepting batches which in reality are non-compliant with specifications.

32.16.2 Guidance from EDQM and European Pharmacopeia

EDQM has issued an update of an early ICH document [14] on validation of analytical procedures [15]. EDQM has published a Technical Guide for elaborating monographs [16] that contains essential information for the characteristics of analytical methods. These documents contain definitions of the terminology used (accuracy, precision etcetera) in analytical validation and refer to pharmacopoeial monographs and pharmacopoeial methods.

The documents emphasise that verification of the suitability of the method for its intended use is still needed when

Table 32.2 Quality requirements pharmaceutical dosage forms that occur as pharmacy preparations

	Intravesical	Oral			Rectal		Semisolid preparations	Parenteral
	Irrigations	Fluid	Capsules	Oral powder	Suppositories	Enemas	Various forms	Injections
Identity	+	+	+	+	+	+	+	+
Content active substance	+	+	+	+	+	+	+	+
Content preservative	±	±				±	±	±
Content anti-oxidant		±				±		
Content alcohol		±						
Relative density		±				±		
pH	+	±				±		+
Viscosity		±				±		
Resuspendability		±				±		
Disintegration			+		+			
Dissolution		±	+	±				
Max. volume/content weight								
Particulate matter	±							+
Available volume						+		+
Uniformity of weight			+	+	+	±		
Uniformity of content			+	+	+	±		
Appearance	+	+	±	±	±	±	+	+
Particle size							±	
Chemical purity	±	±	±	±	±	±	±	±
Microbiological purity		+	+	+	+	+	+	
Bacterial endotoxins	+							+
Sterility	+							+

	Cutaneous			E.N.T.			Ocular	
	Semisolid	Liquids	Powders	Nose drops	Ear drops	Various forms[a]	Drops, lotions	Ointment
Identity	+	+	+	+	+	+	+	+
Content active substance	+	+	+	+	+	+	+	+
Content preservative	−	−		±	±	±	±	±
Content anti-oxidant	±	±						
Content alcohol	±	±						
Relative density		±			±	±		
pH	±	±		+	±	±	+	
Viscosity		±		−				
Resuspendability		−						
Disintegration								
Dissolution								
Max. volume/content weight							+	+
Particulate matter							+	
Available volume								
Uniformity of weight								
Uniformity of content								
Appearance	+	+	+	+	+	+	+	+
Particle size	±	±	+					±
Chemical purity	±	±	±	±	±	±	±	±
Microbiological purity	+	+	+	+	+	+		
Bacterial endotoxins								
Sterility					±	±	+	+

[a]Other parameters depending of the dosage form
+always
±if relevant
−not

validation is not required by licensing authorities (usually when pharmacopoeial methods are being used). When used for medicines it must be demonstrated that the outcome of that method is not affected by the presence of excipients and by the formulation (dosage form) itself. The Technical guide provides more detailed information how to design a study method such as how to measure (im)precision. It also provides details on instrumental pitfalls such as the matrix effect in atomic absorption spectrometry.

The Ph. Eur. monograph Pharmaceutical Preparations, applicable to both pharmacy preparation and manufacturing, requires that, unless otherwise justified and authorised, the content of specific excipients such as preservatives need to be determined in pharmaceutical preparations.

32.16.3 Performance Properties of an Analytical Method

Properties of an analytical method including (im)precision, accuracy and repeatability are commonly studied and reported in validation studies and are properly defined in [14–16]. Those definitions are not repeated here. An international vocabulary containing sound scientific definitions from metrological experts [17] is referred to for additional information. For example, the expression analyte is commonly used in chemistry meaning the compound to be measured. However, one measures the quantity of the compound and therefore sound science should call it a "measurand". Here we will continue to use the expression analyte.

When designing an analytical procedure one has to consider the major pharmaceutical objectives in Quality Control, being methods for identity, purity and assay. Those objectives may require different approaches depending on dosage form or depending on how, where and when the method is applied. Examples which require different considerations include, assays used for a product release decision, in-process controls (IPC) stability testing or measuring contamination of surfaces with antineoplastics.

The validation exercises should demonstrate that the method delivers conclusions with a high degree of confidence in relation to the intended use of the finished product. Therefore, each study protocol should have clear aims and relevance. For example, if the method for measurement of surface contamination with antineoplastics is found to have a limit of detection of 5 ng/cm^2, while the intended patient dose is 1,000 mg, one may expect the data generated to meet the purpose of the study. One may question whether a very sensitive and costly HPLC/MS method provides relevant information or that a threshold has to be proposed as part of an AV study.

Recommendations below may provide guidance on how to understand elements of an analytical validation study and avoid any pitfalls.

32.16.3.1 Specificity

Specificity of a method refers to the extent to which it can determine unequivocally analytes under given conditions in mixtures or matrices, simple or complex, without interferences from other components [16].

The term selectivity is similar and a preferred term by IUPAC: while specificity is the ultimate of selectivity, most well designed assays with have a high degree of selectivity without being truly specific, here we will use the term specificity.

An identification test requires a high degree of selectivity especially if similar active substances are used in production where a mix-up may occur. The use of highly selective techniques such as IR will provide a high level of assurance.

Discriminating power (DP) is used to define the capability of the method to discriminate between compounds that strongly resemble each other. An example is the identity testing of quaternary ammonium compounds. When poorly designed TLC systems are used, all compounds may elute in the same way, determined by the same strong interaction of the quaternary nitrogen and the TLC support. The Discriminating Power of the system is then zero and the method is not suitable for purpose.

Therefore, in order to demonstrate selectivity for identity testing or impurity testing one must demonstrate the influence of other components in the sample on the robustness of the method.

32.16.3.2 Linearity and Range

A linear relationship must be demonstrated across the range of an analytical procedure. Where a 10 % deviation from linearity occurs will be the upper limit of the calibrated range of the technique. In general, five concentrations over a relevant range are required. Mathematical transformation of data may be useful. Ideally the range of the method should cover 70–130 % of label claim, to allow for variation within the product to still be measured accurately.

In order to measure within the linear range for a certain method then it may be necessary to include an additional dilution step.

There are many examples of non-linearity in analytical methods including HPLC, refractometry, spectrophotometry and in radiometric devices used for measurement of radiation.

32.16.3.3 Accuracy

Accuracy is a measure of systematic error in the method, and is the ability of the method to give the expected result. This can be compared to precision which is a measure of random

error. A systematic error is defined [17] as a component of measurement error that in replicate measurements remains constant or varies in a predictable manner, in contrast to random errors that vary in an unpredictable manner and are often related to operator performance.

The accuracy of a method is demonstrated on a sample with a known purity or known matrix composition or by comparing the method with a second well-characterised method if the composition is not known. The influence and dependence of other components in the sample on the outcome of the procedure can be shown by preparing differing matrices. For stability indicating methods it is critical to demonstrate that impurities and degradation products will not interfere with the method.

External factors such as the background temperature, variability in reagents etc. may also influence the robustness of the method to produce accurate results.

HPLC data may be influenced by the presence of background matrix components if we consider the presence of compounds in the matrix that have a high retention time then after several runs in which the analyte is determined a major baseline drift (= background) may occur, hindering further quantitation caused by the slowly eluting component. Applying a gradient as wash procedure to clear the column may substantially increase the analysis time. It may be better to develop another method for this analysis.

For the statistical background see Sect. 20.2.3, and for accuracy of weighing and volume measuring see Sect. 29.1.1.

32.16.3.4 Precision/Reproducibility

While the term precision relates to the variation around the mean and hence the random error of the method, in fact, we measure the imprecision of the method by the standard deviation. However as the Ph. Eur. uses 'precision' as term, this is used in this chapter.

In simple terms precision is demonstrated by repeating the analysis multiple times. Reproducibility in its most simple form is repeating the analysis on multiple days or with multiple analysts or both and is more extreme when we incorporate multiple laboratories as well.

Precision should in general be demonstrated with a minimum of 9 determinations (e.g. 3 concentrations /3 replicates) or 6 determinations at 100 % of the test concentration (within- laboratory precision). Include, where possible, an experimental design (matrix) in the study describing typical variations such as days, analysts from another department, equipment. Analysis of variance is usually applied.

When precision is measured in one sample by the same person who injects more than one aliquot into an HPLC machine on one single day, this is referred to as repeatability.

When a method becomes routine, it will still be useful to add limits on imprecision to the written instruction for the method. In daily practice, it is important to document the expected precision value from replicate measurements as a control and check those values against a specification. Such data is important, as it will demonstrate the methods continued ability to perform. Analytical validation data should be available and reviewed when problems are found with a method including if the product gives out of trend or out of specification results

Data treatment, ANOVA and other statistical approaches are not discussed, although of importance in reproducibility studies, where different conditions prevail like different instruments or several technicians.

For the statistical background see Sect. 20.2.3 and for precision of weighing and volume measuring see Sect. 29.1.1.

32.16.3.5 Detection Limit and Sensitivity

The limit of detection is generally important when detecting impurities and degradation products and it is required to demonstrate that such impurities are detectable below their specification limit. This normally involves determination of the signal to noise ratio for the method.. Determination of the detection limit is performed by comparison of measured signals from samples with known low concentrations of analyte with those of blank samples, subsequently establishing the minimum concentration at which the analyte can be reliably detected. Blank samples could be matrix sample or a reagent blank. A signal-to-noise ratio between 3 or 2:1 is generally acceptable. Other methods for establishing detection limits are based on calibration curves [16].

The methods for measuring impurities in samples should be sensitive. In contrast identification tests should be rather insensitive. For example the flame test for sodium ions will give a positive even with trace amounts present hence the use of the precipitation method with zinc uranyl acetate in pharmacopoeias.

32.16.3.6 Quantitation Limit

A quantification or quantitation limit differs from the detection limit. Detection limits are based on the noise of the analytical method or on background from reagents or matrix components that cannot be compensated for and accurate measurement at the detection limit will generally not be possible. Ten times the average noise signal is a commonly used measure for the quantitation limit. Then an observed signal differs statistical significantly from the average noise signal and that signal is considered to be the quantitation limit. The error generated by noise contributes to the signal from the analyte but is negligible at this high signal/noise ratio.

Quantitation and detection limits may be determined by the variability in background conditions or reagents. For

example analytical instruments may be sensitive to variations in room temperature but the impact may not be well understood. This can lead to an uncontrolled systematic error in the method, if this error is small it may be ignored but at extremes of temperature it may have a significant impact and out of trend or specification results may be seen.

Limits of quantification of impurities in dosage forms are often required by licensing authorities depending on actual levels of those impurities and the toxicological impact.

In conclusion, specifications to limit impurities in pharmaceuticals can only be based on proper validated quantitation limits in order to avoid rejecting batches that are maybe of acceptable quality.

32.16.3.7 Robustness

Robustness is evaluated during development of a method and may give information on the critical steps within a procedure. It may provide information to estimate the effect of steps within the measurement procedure on the overall precision.

32.16.3.8 Ruggedness

This is the degree of precision of test results obtained by the analysis of the same samples under a variety of typical test conditions such as different analysts, instruments and reagent lots.

32.16.3.9 System Suitability Test

The system suitability test is carried out to test critical instrument and method related parameters. In HPLC system suitability us determined ahead of running a method and checks that the parameters which can influence the outcome of the analysis are within specification. This normally includes reproducibility, peak shape and tailing and resolution of the ingredients.

32.16.4 European Regulations and Impurities in Active Substances

Requirements from regulatory bodies may generate analytical validation studies of impurities in active substances. If a degradation product has been observed in a new active substance then data regarding this will need to be submitted for a Market Authorisation. Validation data for quantitation limits are useful for industry in dealing with regulatory threshold values, results found in ongoing stability studies and decisions on further qualification of impurities.

The following example refers to a 50 mg daily dose of an active substance showing which analytical validation data are required. The table below refers to raw data such as obtained in chromatographic analysis, meaning peak area is the first raw criterion for a decision upon taking actions. Licensing authorities claim not to be interested in reporting impurities of less than 0.1 % or 0.05 %, based on raw data [18]. The quantitation limit for the analytical procedure should be not more than the reporting threshold, according to regulations. Identification above 0.2 % is required and above a threshold of 0.5 % qualification of the impurity is required. Thresholds for identification and qualification vary depending on Maximum Daily Dose of active substance and Total Daily Intake (TDI) of the degradation product. Higher TDI of degradation product lowers thresholds, see Table 32.3. An example of the application of these guidances is shown in Table 32.4.

In practice, identification ("yes") means: establishment of chemical structure, determination of detection and quantification limit. If the impurity is unusually toxic then it has to be qualified in all above cases, meaning the demonstration of biological safety. An impurity may stay below the threshold, making any action superfluous.

Sometimes it is not possible to identify degradation products and "unidentified impurities" are then reported.

32.16.5 Selection of Test Samples

Validation starts by specifying the intended use and the primary objective of the method. The choice of study material remains important. Normally artificial mixtures with varying composition are prepared on a laboratory scale, including a blank matrix. Samples from production may be

Table 32.3 Quantitation limits

Reporting thresholds	
Maximum daily dose active substance	Threshold
≤1 g	0.1 %
>1 g	0.05 %
Identification thresholds	
Maximum daily dose active substance	Threshold
<1 mg	1.0 % or 5 micrograms TDI, whichever is lower
1 mg − 10 mg	0.5 % or 20 micrograms TDI, whichever is lower
>10 mg − 2 g	0.2 % or 2 mg TDI, whichever is lower
>2 g	0.10 %
Qualification thresholds	
Maximum daily dose active substance	Threshold
<10 mg	1.0 % or 50 micrograms TDI, whichever is lower
10 mg − 100 mg	0.5 % or 200 micrograms TDI, whichever is lower
>100 mg − 2 g	0.2 % or 3 mg TDI, whichever is lower
>2 g	0.15 %

Table 32.4 Application of guidance values for quantitation limits if the maximum daily dose is 50 mg

'Raw' result in %	Result to be reported? (Reporting threshold is 0.1 %)	Total Daily Intake (TDI) of the degradation product in micrograms:	Action? Is identification threshold of 0.2 % exceeded?	Is qualification Threshold of 200 micrograms TDI exceeded?
0.04	Not to be reported	20	No: no action	No: no action
0.2134	0.2	100	No: no action	No: no action
0.349	0.3	150	Yes	No: no action
0.550	0.6	300	Yes	Yes

used during validation of the analytical method but we need to understand that the true assay value of these may not be known. Proposals to change an analytical method can be initiated following multiple failures or problems. In this case it is useful to have samples of both compliant and non-compliant batches when validating this change.

When considering method validation it must be realised that each analytical procedure consists of three distinctive steps: sample pretreatment, purification or separation, and detection. Each step may be of influence or may be critical for each other step. So each step has to be considered separately.

The frequency and extent of validation studies should be sufficient to demonstrate that the validation study provides assurances at a 95 % confidence level. The main conclusion would be that the method is suitable for its intended use.

32.16.6 Reference Standards

32.16.6.1 Physical Quantities

Section 32.13 describes physical quantities that are frequently encountered in Production and in Quality Control. Physical quantities include, pH, relative density, optical rotation, refractive index, light absorption, light emission, conductivity, viscosity and osmolality and mass. Physical quantities can be measured and expressed as a value in numbers greater or smaller than a unit.

Some are considered as in-process controls (IPC), others are for the characterisation of the finished product. HPLC with UV detection is in principle using light absorption as a physical quantity, while retention is inversely proportional to the velocity of the solute in the column.

Reference standards have to be used in those methods for calculating content within samples for example where the procedure asks for a calibration curve that requires weighing of substances on a mass balance (calibrated previously by certified masses). See also Sect. 29.1.

Apart from this approach reference standards referred to a reference materials are used for calibrating or checking physical devices, such as refractometers and thermometers. For example, the melting point is an excellent identification tool, if the thermometer is calibrated or certified by a regulatory body.

32.16.6.2 Chemical Quantities

The primary standard is the reference standard used in other methods and is characterised by its high purity and stability. A primary standard has its purity determined by mass balance and can be used to calibrate secondary standards such as volumetric solutions. These secondary standards are then used in the titrimetric analysis of samples. The titrant may degrade over time so this may need to be checked by titration with another secondary standard

32.16.6.3 Validation of Reference Standards

Reference standards having a declared composition and content are obtained from an official laboratory with a certificate but can be expensive or unavailable. Therefore, secondary standards are preferred and they need to be bought in certified against a primary standard or certified within the laboratory.

Storage of reference standards is critical: they must be stored in well-sealed containers in accordance with instruction (often in a refrigerator) and must not be used beyond their shelf life, at least not without recalibrating them against a new standard.

32.16.7 Technology Transfer

Transfer of products and processes from one laboratory or even one company to another and outsourcing of analytical testing to an independent control laboratory are two examples where transfer of knowledge needs to be robustly organised. General principles of technology transfer are not only applicable to analytical methods but also to production processes, quality control procedures, packaging and cleaning validation.

Technology transfer is well described in the WHO Technical Report Series, Annex 7 WHO guidelines on transfer of technology in pharmaceutical manufacturing [19]. The report describes the management of the transfer between both parties (the sending (or transferring) and the receiving unit) Monograph <1224> from USP 37 on transfer emphasises the need to lay down proper protocols prior to the start [20]. The WHO report lists all responsibilities, Table 1 of that report 'Possible experimental designs and

acceptance criteria for analytical testing', contains proposals for experimental designs and acceptance criteria for analytical testing, such as identity, assay for potency (assay), content uniformity, dissolution, cleaning validation microbiological testing and impurities. Recommendations are given for replication and for set-up of the validation experiments. Statistically derived acceptance criteria are proposed such as two one sided *t*-test with intersite differences or just comparing mean and variability.

Experimental designs in transfer protocols should consider the use of good and bad batches in a comparison test, where criteria are the release specifications and not the intercompany outcomes of the validation, e.g. mean and variability. The USP [20] recommends "that expired, aged, or spiked samples be carefully chosen and evaluated to identify potential problems related to differences in sample preparation equipment and to evaluate the impact of potential aberrant results on marketed products".

Validation studies involving technology transfer from the original industrial party to a smaller party are frequently performed by Validation and R&D personnel and transfer may be considered as cumbersome. Both departments are fully equipped with numerous qualified and highly educated personnel, but the receiving party, the Quality Control department has to perform the routine analyses with a significant less number of personnel, lesser qualified, higher workload, but fortunately often has broader practical experience.

Another useful policy type document is USP 37 monograph <1226> on Verification of compendial procedures [21], if you consider a pharmacopoeia as an analytical control laboratory transferring his methods to laboratories of companies. Documented evidence of suitability should be established under actual conditions of use.

32.16.8 Different Applications Require Different Validation Approaches

Analytical procedures for quantitation of active substances (including preservatives) in finished pharmaceutical products require a conventional validation approach.

Another approach is needed for procedures for the determination of impurities in active substances and excipients or degradation products in finished pharmaceutical products. These procedures may include quantitative assays as well as limit tests. Impurities of interest are various, including metals such as lead and other inorganic substances, catalysts, genotoxic impurities, residual solvents etc. Details can be found in the scientific guidelines on e.g. quality from EMA [22], see also Sect. 22.4.2.

Analytical procedures for the determination of dosage form performance characteristics (e.g. dissolution rate) may be different from the assay of the active substance in the medicinal product as stated above and will also need method validation.

Proper identification methods are important when assessing purchased materials from brokers or suppliers. For example when buying glycerol or propylene glycol as an excipient or solvent a simple identity test such as complexing with Copper (II) in alkaline conditions is not sufficient. In this case high selectivity is required to discriminate from ethylene glycol, a nephrotoxic substance [23] the use of which has resulted in worldwide scandals and accelerated the involvement of licensing authorities in pharmaceutical industry.

Finally microbiological tests and alternative non official tests for e.g. assaying antibiotics are subject to validation, including equivalence testing when there are differences with official methods.

Table 32.5 presents examples of analytical validation objectives in relation to the type of analytical test:

Table 32.5 Examples of objectives in AV (from [16])

	Type of analytical procedure			
		Testing for impurities		Assay
Characteristic	Identification	Quantitative	Limits	Dissolution measurement only Content/potency
Accuracy	–	+	–	+
Precision				
Repeatability		+	–	+
Intermediate precision		+*	–	+*
Specificity**	+	+	+	+
Detection limit	–	–***	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Signifies that this characteristic is not normally evaluated
+ Signifies that this characteristic is normally evaluated
* In cases where reproducibility (inter-laboratory trial) has been performed, intermediate precision is not needed
** Lack of specificity of one analytical procedure, could be compensated by other supporting analytical procedure(s)
*** May be needed in some cases

identification, impurity or assay [16]. The table is created by EDQM and may not have full relevance for analytical methods that are applied by QC in an industrial setting. The comments under the table are from EDQM.

The expression "may be needed in some cases" requires explanation. Competent Authorities may ask for additional information, if they consider a method critical for the product. Industry as well as hospital pharmacists may have their own validation policy.

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Documentation

33

Rik Wagenaar and Mark Santillo

Contents

Abstract

All processes and operations concerning the preparation of a medicine are accompanied by documentation. The documents should promote uniform preparation methods and should demonstrate the achieved quality. This requires not only a detailed description of the process, the preparation and the quality control, but also an accurate recording of processes and operations. In this chapter the most important types of documents within the quality system are discussed, such as procedures, preparation instructions, analytical instructions, preparation records and logbooks. Also the product file is discussed. In the product file all documents relating to a particular pharmacy preparation are brought together, including data on pharmacotherapy, the considerations which led to the choice for a certain formulation, method of preparation and quality requirements of the product. It provides background information on the product and contains an overview of the history of the preparation.

Keywords

Documentation • Standard operation procedures • Work instructions • Preparation instructions • Logbooks • Product file

Based upon the chapter 'Documentatie' by Rik Wagenaar and Mieke de Blois in the 2009 edition of 'Recepteerkunde'.

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33.1 Orientation

Documentation forms an important part of the quality system for the preparation of medicines. The documentation should demonstrate the achieved quality and should promote

Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_33,

uniform preparation methods. For authorised medicines the product documentation should follow the Notes for Guidance for the design and GMP chapter 4 for preparation (see Sect. 35.5.7). This chapter is mainly directed at pharmacy preparation.

Documentation should describe all major stages of the process of pharmacy preparation: the decision to start preparation of a medicine, the drafted formulation, the production method, supporting data for the current preparation, the controls and tests during and after preparation and at release of the product. In this chapter important documents are discussed, including instructions, procedures and records. The focus is on the management of these documents and on the way they are generally used. However, documentation is bound to local rules and preferences. There are a number of ways of achieving the same objective, providing the general principles outlined are followed. However, the system described in this chapter, has proven itself to be useful and feasible in daily practice in pharmacies in the Netherlands and the United Kingdom.

33.2 Documentation Types for Preparation

33.2.1 Documentation and Quality System

Documentation is a part of the pharmaceutical quality system (PQS) of the organisation, see Sect. 35.6.2. Chapter 4 of the GMP guidelines [1] states that proper documentation is an essential part of quality control. Written information is less prone to errors than verbal information. Moreover, the history of a prepared batch can be retrieved based on the recorded information.

The quality manual is a central component of the documentation section of the PQS. It usually refers to the documents needed: descriptive documents, records to be filled in, documents describing particular details, documents explaining their mutual relationship etcetera. To prevent errors and misunderstandings, all these documents should be clear and unambiguous for the user. This requires a simple language, with short, clear sentences. Text should be logical, and operations should be described chronologically. All documents must be dated and authorised by the responsible person, usually the pharmacist. The documentation system should be up to date and the history of documents should be recorded. Past versions should be archived and should remain traceable after they have been superseded. It is important that any decision made in the past remains traceable to provide background to the choices that have been made.

33.2.2 Terminology

Documentation needs a uniform structure and uniform terminology. The terminology for the various types of documents originates from the GMP guidelines [1]: procedures, instructions, records and logbooks can be distinguished. These documents have a hierarchical relationship, see Fig. 33.1.

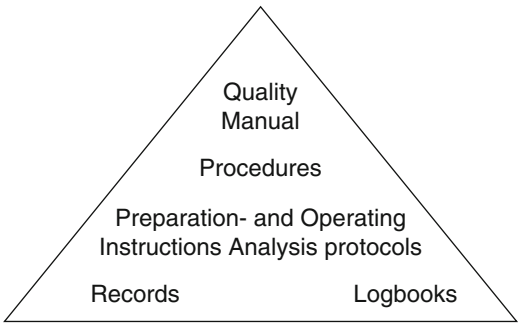

Fig. 33.1 Structure of a documentation system

The purpose of the various documents is as follows:

- Quality manual (see Sect. 35.6.1): the quality manual describes the quality system of the pharmacy. It sets out the structure of the organisation, the responsibilities, the policy and the facilities of the pharmacy, such as rooms and equipment. It contains an overview of all procedures in use. Some procedures may form a part of the quality manual themselves.
- Procedures (see Sect. 33.3): procedures are documents that describe all actions, controls, and other measures related to a particular activity. Procedures have a general structure. Often the term 'standard operating procedures' (SOP) is used, although instructions or work instructions are also commonly used terms. Instructions often provide more detailed descriptions of specific actions. In this chapter, the term Standard Operating Procedures (SOPs) is preferred.
- Records: a record is a paper or electronic copy of a piece of information or series of data, used by the operator to report on the work carried out.
- Logbooks (see Sect. 33.7): a logbook describes chronologically the history of equipment or premises, such as operation during use, maintenance, update, renewal and repair.
- File: collection of information about a specific device or a specific product (see Sect. 33.8), including technical descriptions, supporting literature, research etcetera.

33.2.3 Documentation of the Preparation

Regarding pharmacy preparations, three types of documents can be distinguished:

- Preparation instructions (see Sect. 33.4), describing the formulation, the method of preparation, the batch size, the packaging and labelling of a specific pharmacy preparation. During preparation, all the actions taken are reported in a

preparation record. Preparation instructions for stock preparations and extemporaneous preparations will be distinctive in format, and there will also be differences between standard preparations and non-standard preparations .
- Operating instructions, describing the operation, maintenance and cleaning of a particular device or apparatus. Reporting occurs in a logbook (see Sect. 33.7), in which the user records when the equipment has been used and cleaned.
- Analytical instructions (see Sect. 33.6), concern the examination of a finished product, raw material or packaging. The results of analytical testing are presented in an analytical report or certificate.

When several documents related to the same product are bundled, it is called a product file. The product file is basically a collection of information, instructions, records, investigation results etcetera on a specific product. The product file is further discussed in Sect. 33.8.

33.3 Standard Operating Procedures (SOPs)

Written SOPs are essential documents to ensure a consistent process is followed and provide detailed guidelines for various activities. They serve as guidance documents and contain generic information. SOPs can cover all parts of the quality system, including the establishment and maintenance thereof. Examples of required SOPs include:
- Drafting, authorisation and implementation of SOPs
- Training, assessment and qualification of personnel
- Cleaning and maintenance of premises and equipment
- Preparation methods
- Release of preparations
- Handling of complaints and deviations
- Change management

Sometimes certain actions need to be described in more detail, for example when describing a specific process in a step by step manner. This kind of document is generally called a Work Instruction (WI). Examples are:
- Calibration of balances;
- Preparation of specific dosage forms;
- Sampling for pharmaceutical analysis;
- Microbiological monitoring of preparation areas.

Thus, SOPs and WIs comprise general actions and operations that apply to groups of products or equipment. The preparation of a specific medicine will be described in a Preparation Instruction (PI) (see Sect. 33.4), while maintenance of equipment is laid down in Operating Instructions. SOPs are not suitable for the recording of control data. When the activities described in SOPs or instructions produce results or other data, for example results of audits and investigations or data from calibration of equipment, these results are collected in an audit report, a record or a logbook, which is specific to the equipment being examined Sect. 33.7.

An example of a SOP is shown in Fig. 33.2. The figure gives an impression of the possible lay-out of a SOP, but other choices may be made depending on local preferences or needs. Items that are almost always required in a SOP are mentioned underneath. The numbers correspond to the sections of Fig. 33.2.

Title (1)
A SOP bears a unique title that gives a brief description of the subject. A unique number may be useful. By choosing an indication in letters and numbers a classification and grouping can be made. Furthermore, an SOP number makes it possible to refer to the respective procedure with a short notation, for example in Preparation Instructions.

Date and version number (2)
A SOP bears a date, usually the date of authorisation, in combination with a version number. Whenever changes in a SOP are made, the version number is incremented.

Origin/reference (3)
The source or reason behind the SOP should be recorded and any references included.

Author/responsible person (4)
The source or reason behind the SOP should be recorded and any references included.

Authorisation (5)
The SOP should be authorised and should bear the signature and function of the authorising person

Principle/purpose (6)
It may be helpful to start a SOP with a brief summary, for example when a long or complex process is described. Such a summary is put at the beginning of the text and may contain a brief statement on the purpose of the procedure and its scope.

Responsibilities
The key responsibilities for the tasks outlined in the SOP may be listed, giving clarity as to the level of staff who carry responsibility at each level.

Method (7)
The steps of the procedure preferably should be described as short sentences, with the imperative to create clarity. Where necessary, notes or important background information may be added. It is useful to number each specific point to enable ease of referencing or referral.

SOP F08-4 1	Capsules with low dosage, preparation by solvent method		
date 2	September 2014	drafted by	….
first issue 9	November 1993	revised by 4	….
version number	2.2	authorisation 5	…..
source 3	[1]	authorisation date	19 September 2014

6 Principle

This procedure provides a global way of preparation of capsules with a low dosage of active substance (≤ 5 mg per capsule) by use of the solvent method. For details refer to [1].

8 Related documents

F08-1 Capsules, design composition
F08-2 Capsules, preparation for high dose (> 50 mg)
F08-3 Capsules, preparation for low dose (≤ 50 mg)
[….. ……]

7 Method

Design

Follow the general directions of SOP F08-1 'Capsules, design composition´ if it concerns a new preparation. The solvent method is preferably used for mixtures with very unfavourable mixing ratios (< 5 mg active substance). The method needs careful testing and validation.

- Choice of a suitable organic solvent.
  In a suitable organic solvent the drug should dissolve easily. The solvent must ……
  .

Active substance and dose:	Solvent and amount	Deposition and ratio:	Diluent	Reference
……	…….	…….	……	…….

Determination of amount of diluent

[……]

Dissolving the active substance

[……]

Filling of the capsules

[……]

In process controls

[……]

Control checks

[……]

References

[1]. [……3……]

Fig. 33.2 Example of a Standard Operation Procedure (SOP)

Related SOPs and documents (8)
This section should list other documents that are referenced within the specific SOP including any related Work Instructions.

Document history (9)
Although this may be kept elsewhere in the quality system it is often useful to include a version history of the SOP, summarising the changes made at each version.

33.4 Batch Preparation Instructions and Records

33.4.1 Definition and Use

Stock preparations are performed according to a standardised preparation instruction, an instruction that has been validated prior to use. This is called a Batch Preparation Instruction (BPI). Also for extemporaneous preparations, a standardised preparation instruction – a BPI – is preferred. However, often the operator has to follow a non-standardised preparation instruction that is less extensive, where no prior validations have been performed, see further Sect. 33.5.

A BPI is developed for a given batch size or a range of batch sizes of a standardised preparation. The formulation has been investigated in advance and the method of preparation has been validated. This means that data are collected and reviewed beforehand to ensure that each batch subsequently prepared will possess the required quality. The preparation method as described in the BPI is therefore only valid for the specified minimum and maximum batch size. The selected batch range depends on the equipment and materials used. Automated preparation documentation systems calculate the quantities to be processed when the batch size is adjusted. In the manual mode, for each batch size within the batch range a separate BPI has to be created. Before the preparation of a specific product is started, whether for the first time or after a change, the responsible pharmacist authorises the BPI and subsequently it is released for use.

The BPI forms the basis of any preparation process. Before starting the preparation of a batch, a copy of the BPI may be made to serve as preparation record during the preparation. The operator uses it to record weighings and measurements during preparation, to record the batch details of the starting materials and to record the results of in process controls and release controls. To distinguish between the original BPI and the copy that is actually used for the preparation of the batch, the copy may be referred to as Batch Preparation Record (BPR).

All the sections of the BPR have to be completed. It is very important that all the information recorded is done in real time. Each raw material should have its batch number recorded ahead of it being measured and the preparers should record their initials as soon as the measurement has been completed to maintain the audit trail. The recording activities for a stock preparation and a standardised extemporaneous preparation are not substantially different, but for extemporaneous preparations a careful accounting of the preparation steps is particularly important, because any subsequent analysis of the product is unlikely.

The preparer has to follow all the specified instructions closely and has to give a written justification for any process deviation, either as planned or unplanned deviations. It is important to follow the instructions exactly, and not to make any unauthorised changes. Uncontrolled changes in batch sizes or quantities of material can lead to serious defects in the final product. For any planned deviation from the prescribed process the reason should be known, and an authorisation by a pharmacist should be given beforehand.

A BPI should be clear and should describe a logical sequence of actions and activities (also called unit operations in manufacturing). For a number of issues it may refer to general SOPs or WIs.

- For basic operations, the BPI may refer to a SOP, for example for the process of the filling of capsules.
- For the use and cleaning of specific equipment the BPI may refer to WIs.
- For controls the BPI may refer to a SOP, e.g. for sampling.
- For analytical testing, the BPI may refer to a separate analysis instruction designed to test the preparation or the specific dosage form. When analysis is outsourced, the BPI may mention that a sample should be sent to the approved laboratory.

In the BPI only those quality specifications are included which can be tested during or immediately after preparation. An overview of requirements and analytical tests for pharmacy preparations can be found in Table 32.2.

33.4.2 Drafting a Batch Preparation Instruction

When a BPI is drafted, it is important to present a clear, compact collection of information. The text must be unambiguous, legible and factually correct. Depending on the scale of production, a BPI may consist of only one page for a standardised extemporaneous preparation or may contain multiple pages for stock preparations. The right combination of preparation process, in-process controls and

release controls should guarantee the quality of the preparation.

Obviously, the BPI should be kept clear for proper use and proper control. Therefore, it is important to mention only the issues that are directly related to the preparation of the product. When drafting a BPI some editorial guidance can be given:

Sentence Structures:

- Choose the imperative.
- Use short sentences, with proper punctuation.
- Describe, if possible, one operation (unit operation) per sentence.
- Arrange the operations in chronological order. So for example: 'Dissolve X in Y. Triturate Z with this solution' instead of 'Triturate Z with a solution of X in Y'.

Wording:

- Use familiar words.
- Avoid composed words.
- Avoid 'heavy' expressions, for example, rather 'with' instead of 'with the aid of'.

Sometimes it is possible to use a general exemplary BPI belonging to a standard formulation (such as with FNA or NRF). Such an exemplary BPI will be of a standard template and has to be adapted to the local pharmacy situation. The description of the preparation method may have to be adapted regarding the batch size and the available utensils and equipment in the specific pharmacy situation. For general preparation methods, e.g. for filling of capsules or for the folding of tubes, the general SOP that describes the appropriate preparation method should be referenced.

In larger preparation units, for example the hospital pharmacy, often an automated system for the drafting of BPIs is used. Within such a system, it is usually possible to create one or more standard layouts, adjusted to the needs of the specific organisation and adapted to the type of preparation or the pharmaceutical form.

The sections of the BPI are described in Fig. 33.3, which shows an example of a Batch Preparation Instruction. The items of the BPI are mentioned below. The numbers (if any) correspond to the sections of both Figs. 33.3 and 33.5.

Name, dosage form and strength of the preparation (1)

The name of the preparation is usually the title of the BPI. The name of the preparation normally includes the strength of the active substance. When the preparation contains more than one active substance, it may be decided to assign a specific name to the preparation. It may also be necessary to include the batch size (see below) in this title area where a variety of BPIs exist for a specific product formulation.

Batch Size (2)

Subsequently, usually the batch size or batch range is mentioned. The latter means that the minimum and maximum batch size are defined, resulting in a more flexible BPI. The batch size can be specified as follows:

- Number (for suppositories, capsules);
- Weight (for ointments, creams);
- Volume (for oral solutions, lotions);
- Volume plus weight between brackets (for solutions with a density unequal to 1);
- Volume plus number of containers between brackets (e.g. eye drops).

Origin/reference (3)

Also, it may be useful to refer to the origin of the formulation. This may be a formulary, a scientific publication, information from a manufacturer (e.g. about products that have been withdrawn from the market), or a reference to a proprietary formulation or one from a colleague. It may be useful to mention a version number or date of publication, to give a proper reference.

Authorisation and date of creation (4)

The person responsible for the content and implementation of the BPI, usually the pharmacist, places his signature of approval initials to authorise the document. By authorising it, the BPI is released for use. An unauthorised BPI should never be used. Automated systems are normally equipped with a versioning option. In that case the pharmacist authorises the BPI in the computer. Only when this has been done, can the BPI be used for preparation. When the BPI is modified, the authorisation automatically expires and it cannot be used until the new version is authorised. Together with the authorisation usually the date of creation or modification is mentioned. A version number on the BPI may serve the same purpose. In this way, it will be possible to check if the latest version is used. In automated systems, the system usually records the version number and date of modification automatically.

Batch number and Preparation date (5)

A BPI normally leaves some blank space, where the batch number of the preparation and the date of its preparation can be noted during preparation. For a standard extemporaneous preparation the prescription number can be added for traceability. In order to limit the amount of text, the preparation date and batch number can be combined in one number. For example, when the date is mentioned as YYMMDD, an ascending numbering is obtained, which is simply traceable to the date. For larger scale production, an extended batch number is needed for distinguishing different

1 Tretinoin cream 0.02% FNA **2 400.0g**

Batch size	Source 3	Version nr	Autorisation 4		
400.0 g	FNA 2014	1-2014			
Raw materials 7	**Amount 8**	**Batch nr.**	**Weighed/measured 9**	**Operator 10**	**Check**
TRETINOIN	80.0 mg				
ALCOHOL DENATURATED 95% V/V (LOCAL STANDARD)	20.00 g				
BUTYLHYDROXYTOLUENE	160.0 mg				
CETOMACROGOL CREAM FNA	379.8 g				
ALCOHOL DENATURATED 95% V/V (LOCAL STANDARD)	to 400.0 g				
comments					

Container	Storage condition	Shelf life
Coated aluminium tube 30 g	refrigerated (2-8 °C) 14	12 months 13

Preparation – Avoid dusting of solid substances 11	In-process controls
• Turn off the light.	
• Avoid using metal utensils.	
• Dissolve the butylhydroxytoluene in the denaturated alcohol 95% V/V.	Dissolved?
• Triturate with a glass rod the tretinoin in a glass beaker of at least 100 ml with a few drops of the butylhydroxytoluene solution.	
• Dissolve the tretinoin in this solution, if necessary with gentle warming and stirring.	Temperature: °C Dissolved?
• Cool down unto under 25 °C.	Temperature: °C
• Tare a plastic mortar.	Tare weight: g
• Weigh the Cetomacrogol cream FNA in the mortar.	
• Add the tretinoin solution in portions and mix after each addition until homogeneous.	
• Weigh about 5 g denaturated alcohol 95% V/V in the glass beaker and swirl gently.	
• Add denaturated alcohol 95% V/V to the cream until 400.0 g.	Total weight: g
• Mix until homogeneous.	Homogeneous?
• Fill in the coated aluminium tubes. 12	yield: …tubes
• Take a sample for analysis if necessary.	
Sampling	Analysis
	yes/no

Preparation review (according to Procedure S02-1)		
• Appearance	Consistency	complies/doesn't comply: ….. 17
	Homogeneity	complies/doesn't comply: …..
	No particles	complies/doesn't comply: …..
• Packaging		
• Labelling		
• Analysis	no / yes	results:

Preparation data		Release control	
date of preparation 5		date of analysis	18
batch number		signature analysis	
yield 15			
rejects		release date	19
signature label		final assessment	
signature operator(s) 16		signature for release	

external use		external use
Tretinoin cream 0.02% FNA Date: dd/mm/yyyy Batch nr. Expiry date: mm/yyyy Storage: 2-8 °C		copy of label used

6

Fig. 33.3 Example of a batch preparation instruction

preparations and to obtain a unique batch numbering. It is common to add a number to the date, for example in the form of: 141015-001, 141015-002, 141015-003, etc. Also it is possible to use an alphabetical coding of the months, starting with A for January, B for February and so on. For any system chosen, the important point is that the traceability of each batch is guaranteed.

Reference label (6)
Normally, a BPI is provided with a reference label for the label to be used. On a paper BPI the reference label can be stuck directly, in an automated system the label data may be recorded in the master label template. All the relevant data for the preparation should be included on the master label, only variable data fields such as batch number and expiration date should be left blank. According to [2] the following information should be included on the label:
• Name, dosage form and strength of the preparation
• Full qualitative composition and the quantity of the active substance
• Batch number
• Expiry date
• Special storage conditions or handling precautions
• Directions for use, warnings and precautions
• Route of administration
See Sect. 37.3.2 for additional information on labelling for the patient.
It is useful to leave some space on the BPI where a copy of the label that will be used for the batch concerned can be attached. Ideally this should be next to the sample label.

Raw materials and packaging materials (7)
Subsequently, the BPI provides a list of all active substances and excipients, in a way that defines their identity and quality unambiguously. For example, it should be clear if the free active substance has to be used or the salt form, or, when multiple hydrates exist, which hydrated form is required (see Sect. 23.1).To define the quality of the raw materials it is advisable to use their pharmacopoeial names wherever possible. Preferably, additional specifications (Functional related characteristics, FRCs) which are not mentioned in the monograph that distinguish between different qualities, are added to the name of the raw material. Examples are the particle size of a solid material, the viscosity of a liquid or a cellulose derivative, or the concentration of a solution. Sometimes a brand name reflects the quality better (e.g. Witepsol H15 instead of Adeps solidus). If confusion may still be possible (crystal water, salt forms), addition of the chemical formula might be useful.
It is also important to include a description of the containers, including size and quantity and if necessary other quality characteristics. Raw materials and containers are mentioned in the same order in which the operator will use them. The reason for this is to help the operator record the batch numbers and signatures on the correct line of the BPR. In automated preparation systems, raw materials usually have to be used in the listed order. Their sequence may depend on the equipment used or the batch size.
The BPI should have space where the identity of the raw materials and packaging materials that have actually been used may be recorded, for example by their batch numbers. This may be done either manually or by an automated system with a barcode reader.

Quantity (8)
For each raw material that should be weighed or measured, the needed quantity is listed on the BPI. Excipients which are required on more than one occasion during preparation, may be mentioned separately each time they are needed in the required amount. Also the quantities of the required packaging materials are listed, such as the number of suppository strips.
The quantities listed are given to the accuracy that they need to be measured (see Sect. 29.1).
It is advisable to specify the balance to be used in the BPI. This ensures the use of a balance with sufficient accuracy for the weighing process.
All amounts are mentioned followed by their units, for example grams (g) or milliliters (mL). Weighing is to be preferred (see Sect. 29.1.2) but it may be simpler to work with volumes rather than weights. In that case adequate controls must be in place to ensure that the right volumes have been added. Generally weighing devices can give print-outs of weighings made but volume devices cannot.

Weighed/measured (9)
The list of raw materials on the BPI is usually followed by spaces where the operator records the actual quantities which are weighed or measured, including the units. This may be done manually, but the use of an automated system coupled with an electronic balance provides a better opportunity to capture the weighed quantities. With a manual system there should still be a printed record of any weighings made.

Initials and control (10)
There is generally space where the preparer can place his initials for each measurement or weighing. During preparation, for each raw material the label on the container is compared with the prescribed material on the BPI, then the source and the batch number are recorded, and the material is weighed or measured. The measured quantity is recorded, the raw material is processed and the preparer places his initials. On the BPI model (Fig. 33.2) a column is reserved for the initials of the operator, marked with the letter ‘O’. There may also be space for the initials of a second

employee, who checks during preparation each weighing or volume measurement. In automated system, the weights are controlled and printed automatically. The validation of the system is a prerequisite. Simple weighing systems cannot monitor the volumes measured, which requires a check by a second employee.
Whatever process is used, the measurements and checks must be verifiable. Obviously, a print out of the balance may be sufficient. It can be attached to the preparation record by the preparer, but it should be understood that this print out alone does not prove which material was weighed. It may be that a system such as barcode scanning needs to be used alongside it if the second check at the time of preparation is to be omitted.

Preparation method (11)
The BPI has to provide a clear description of the preparation method, including in process controls and line clearances. All preparation operations are described step-by-step (as unit operations. To improve the readability each step best starts on a new line. If not, all unit operations may be marked separately, to make them easily recognisable. In any case, the essential points of the applied method of preparation, including all in process-controls as well as occupational safety aspects have to be listed.
Also precautions should be stated to prevent any hazards such as fire or damage by corrosive properties of substances.

Packaging process; (12)
A description of the packaging process in a separate part of the preparation instruction may be added.

In-process controls (13)
In process controls that the operator runs during production are mentioned separately on the BPI. In the BPI model a separate section is reserved for these in-process controls. When applicable these controls are described on the same line as the preparation step to which they apply. In that way the operator is instructed to perform the control immediately after this step. In the description of the preparation, the control moments can be emphasised by mentioning them as 'check now . . .' or 'record now . . . ". This should encourage the operator to perform the control at that moment, and not at the end of the preparation. When working in a specific environment, such as laminar air flow (LAF) cabinet, the preparer cannot always interrupt his work to place his initials on a paper record as this would represent poor aseptic practice. In that particular case, a second employee may complete the BPR, and any required signatures can be completed at the end of the process. However, there are also LAF cabinets with built-in display, where the preparer can place his initials electronically.
Automated systems may have obligatory in-process controls, which require that the operator records a result before he is able to proceed to the next step. The nature and extent of the in-process controls are determined in conjunction with the controls on the raw materials before, and in conjunction with the release controls which will follow afterwards. Together these controls ensure the quality of the final product.
If the preparer has to perform a select sampling during preparation, for example to check the content distribution of capsules or suppositories, the sampling method should be described in the preparation text and not under the release controls of the final product. Also the weighings used for a weight control of capsules or suppositories should be mentioned in the preparation text and are part of the preparation process.

Equipment
The required equipment may be listed at the beginning of the BPI, to make sure that all the required equipment is assembled and ready for use. Where applicable, reference should be made to relevant operating instructions, for example for the use of an ointment mill. In the text of the BPI the equipment is described at the place in the process where it is needed. Only if there are compelling reasons, the equipment may be listed separately, for example in an aseptic preparation where the operator should put all equipment in the laminar flow cabinet or isolator before the preparation is started. It may be advisable to leave some space on the preparation instruction for completion of batch numbers and serial numbers of equipment and for signatures of operators at all key stages. Finally, it may be useful to mention the cleaning of the equipment at the end of the description of the preparation method, with referral to the procedure and the logbook where the use and cleaning has to be recorded.

Storage conditions (14)
The BPI may provide information on the storage conditions of the preparation, for example at controlled room temperature (15–25 °C or 15–30 °C) or in the refrigerator (2–8 °C). Also other precautions may be mentioned, such as storage protected from light. The specific location of storage may be mentioned on the BPI.
Storage period
The storage period or shelf life of the preparation is included in the BPI. The shelf-life period of the formulated product has to be determined in advance and standardised. The terms for determining the storage period are described in Sect. 22.7.

Label reconciliation
A separate section is present to cover the label reconciliation to account for the number of labels printed, used and destroyed. The yield of labels is also discussed in Sect. 34.7.

Yield and rejects (15)
A separate section is present to cover the yield of the product. The quantity of deliverable product (= net yield) is often less than the theoretical amount based on the processed quantities of active substances and raw materials. Recording of the gross yield, rejected units and net yield on the preparation record can also provide important information about how the preparation process has been performed. Therefore, the preparer should always fill in the sections ´ Yield and rejects´ on the BPR. Below the notions of 'gross yield´ and 'rejected units' are defined in more detail.

The gross yield is the theoretical yield of the preparation, minus the loss resulting from the preparation process (e.g. residue on the equipment and utensils, rejecting of suppositories, etc.). The gross yield is expressed in a weight, a volume (e.g. oral solutions) or a number (e.g. suppositories). In preparations that are packed in separate containers for the patient, the gross yield can also be expressed as a number of containers. For relatively simple preparations (e.g. oral solutions), normally there is only a small amount of loss during preparation and the gross yield substantially corresponds to the theoretical yield, as listed under "batch size". If there are more preparation steps required (e.g., filtration) or if semi-solid preparations or suppositories are concerned, the gross yield will always be lower than the theoretical yield. In that case the BPI should also specify the expected yield.

In preparations that are filled into containers intended for the patient, immediately after preparation (e.g. eye drops, creams) the gross yield is expressed in number of completely filled containers. The net yield may be even lower due to loss in incompletely filled containers. After preparation of a series of suppositories in molds, there will always be a number which must be rejected. A gross yield which is only a little lower than the batch size may indicate that the units which should have been rejected have not been. For preparations such as capsules or divided powders, the gross yield (number) is always equal to the theoretical amount. The preparation loss that occurs in these pharmaceutical forms, manifests itself in a lower average weight than the theoretical weight. This does not mean that a low fill weight (and therefore a low dose) would be acceptable. For these forms additional specifications are needed to limit the preparation loss.

Rejected products are those which are lost after preparation including: incompletely filled containers, samples for laboratory, breakage, failure from visual inspection et cetera. The gross yield minus the reject number gives the net yield. When the net yield of preparation, the number of packages or the number of dosage units is lower than the expected or required yield, then the reason for the rejected amount should be investigated and recorded (poor appearance, breakage etc.). This may make it possible to take measures to prevent any similar failures in future. Laboratory samples also need to be accounted for although this should be in a separate line to the rejected products.

Theoretical yield (= Batch size) = gross yield + expected preparation loss

Gross yield = net yield + rejects (including laboratory samples)

Net yield = amount deliverable product

Rejects = loss after preparation

Notes Finally, it may be useful that the BPI mentions relevant data and references that were used for designing the formulation and the preparation method (e.g. for suppositories the blank weight of the mold and the displacement factor). Furthermore, for the results of quantitative measurements it may be useful to give standard values for comparison. When performing in process controls, it is important that there are distinct limits within which a measurement result should lie. A section on the BPI is reserved for this.

Deviations A preparation record is intended to record the preparation process in a standardised way, as far as possible. However, there are always unforeseen circumstances which are not provided for in the preparation instruction. All deviations, even if it concerns seemingly unimportant matters, should be recorded on the preparation record. The pharmacist must evaluate any deviation and has to decide on further actions (see Sect. 35.6.13). He should ensure that the deviation is described clearly and precisely and any investigation required is completed ahead of release of the product. For that reason a section on the BPI may be needed where process deviations (either planned or unplanned) can be listed and can be assessed during product release.

Signatures or initials (16)
The person responsible for the preparation process will place a final signature before the product or batch is transferred for final check. The final sign off will be placed by the person responsible for the quality of the product.

Quality Control (17)
A separate part of the BPI may be reserved to indicate which quality control tests are required. These controls may comprise non-destructive tests, which can be performed immediately after preparation, and analytical testing in a laboratory. In the latter case, referral can be made to a separate analysis instruction.

The BPI may indicate a number of criteria that are involved with the assessment of the final product in the case of a stock preparation. Some of these criteria have a general character, while other items are only applicable to a particular dosage form or even to the specific preparation involved. The required procedures may be referenced in the BPI. Standard items are:

- Appearance, such as shape, colour and other external characteristics.
- Non-destructive tests: In addition, depending on the dosage form, specific tests as uniformity of dosage units or deviation between theoretical and average weight may be included.
- Packaging and labelling: it may be necessary to indicate which packaging and labelling aspects should be checked.
- Analysis: here will be listed if samples should be sent to the laboratory for analytical testing, and if so, in what quantity and with what frequency.

How the quality control tests are carried out and to what extent will depend on the type of preparation and on the specific processes in the pharmacy. In extemporaneous preparations or simple stock preparations in a community pharmacy, the operator may perform the non-destructive tests himself, such as a check on the appearance or the weight distribution of capsules. Analytical testing, at least in small community pharmacies, is usually performed by an external pharmaceutical laboratory. In extemporaneous preparations there is usually no possibility for analytical testing prior to release. Therefore, non-destructive final inspections of the preparation are of great importance. Results of the performed tests may be recorded directly on the BPR, thus forming an integral part of the preparation record. However, in large-scale preparation quality control testing will usually be separated from the preparation process, on the basis of an individual analysis instruction. In all cases the results of the investigated parameters should be documented, at least with "conforms" or "does not conform". Laboratory results can be noted on the preparation record, but can also be reported on a separate certificate of analysis record which may be attached to the preparation record.

Review before release (see also Sect. 34.9.1) (18)

The last step before release of the finished preparation is an overall check of the preparation and quality control record of the product. In order to be able to release the preparation, the person responsible for preparation has to check if the BPR has been fully completed. His review should comprise a systematical check on all data, including correct weighings and measurements, in process controls, notes and deviations, if any, and the presence of printed information such as weighing prints or data on a sterilisation process. Also the results of non-destructive and analytical testing are part of the review, if applicable. Furthermore, the review should involve a check on obvious mistakes, for example a yield that shows a large deviation from the theoretical yield or a mean weight that does not correspond to the expected weight, Preferably the review should be performed by a pharmacist, who has not been involved with the production nor the analytical process. As a result of his review, the pharmacist may give a final decision on the preparation: the batch is accepted or rejected. He notes down his conclusion on the BPR.

Release (see also Sect. 34.9) (19)

When the responsible pharmacist accepts the preparation for release to be supplied to the patient, he places the release date and his signature on the preparation record. For a stock preparation, this is the formal way to release the batch so that it may be removed from quarantine and can be supplied to patients. In an industrial GMP environment this is the responsibility of the Qualified Person (QP) (see Sect. 25.3.4).

For an extemporaneous preparation the responsible pharmacist decides whether the preparation is suitable for release. After release, the preparation records are stored systematically for a period determined by local guidelines or national law [1].

33.5 Extemporaneous Preparation Instructions and Records

With extemporaneous preparations a standard BPI is to be preferred. This situation – of a standard extemporaneous preparation – has been described in Sect. 33.4.

But sometimes an extemporaneous preparation is required where no standard formula and hence no BPI is available. In that case the preparation instruction has to be designed just before preparation can start.

The preparation part of a non-standardised preparation instruction (for instance referring to filling of capsules or triturating raw material with an ointment base) will preferably be available as a standard instruction, probably even as a template. Because of the individual character of these kinds of preparations, it is not possible to perform a validation of the specific formulation and preparation method in advance: the preparation instruction has to be drafted on the basis of the prescribed formulation and the prescription assessment which will refer to literature data. This requires additional specialist knowledge and attention to detail in the design of the formulation.

This knowledge is important because, in practice, it is rarely possible to perform an analytical release control on extemporaneous preparations. Hence extra attention needs to be paid to controls during preparation. During the design of the formulation, it should be determined what in process controls and non-destructive release tests have to be

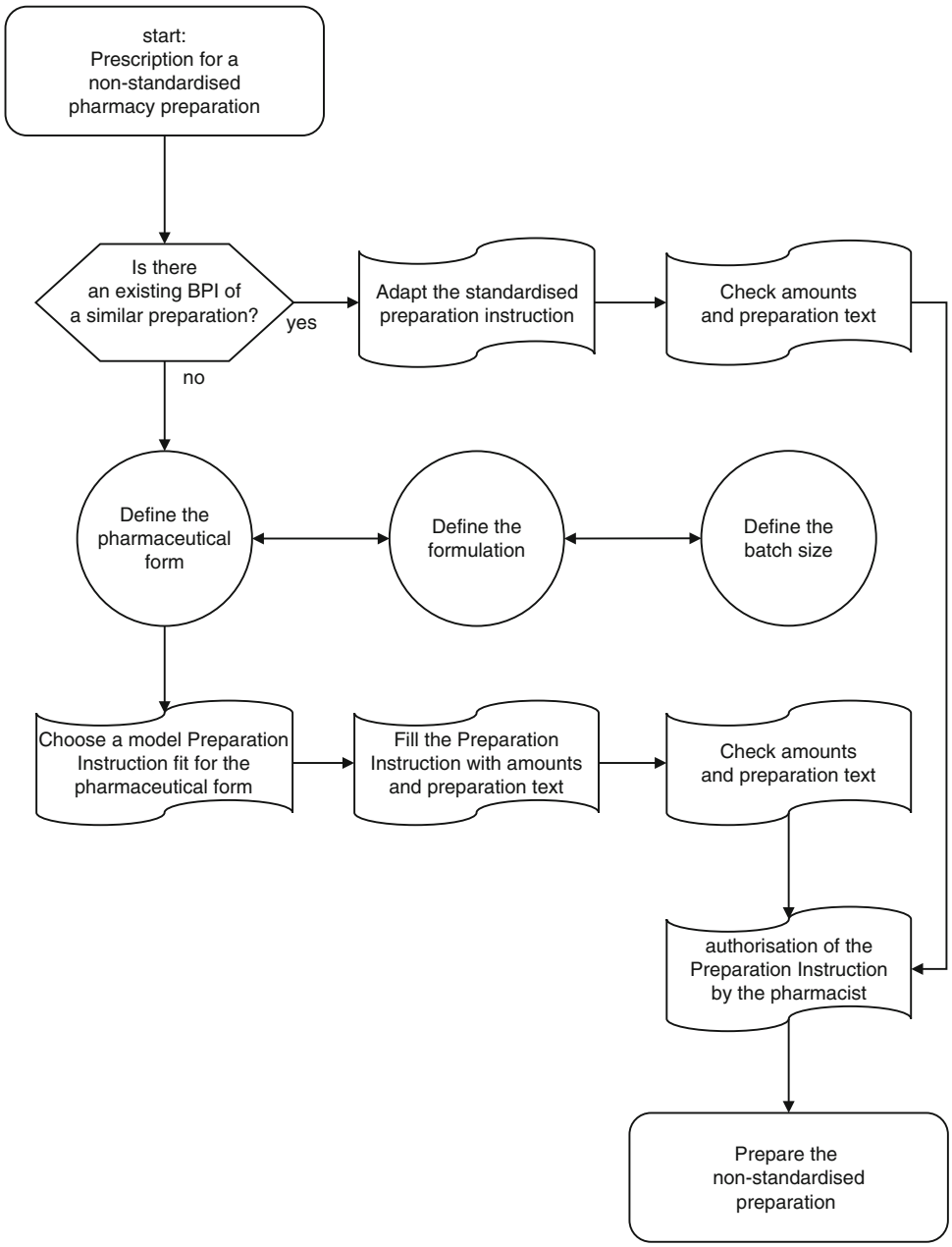

Fig. 33.4 Flowchart design and authorisation of a preparation instruction for non-standardised preparations

performed. The controls and their results should be recorded, to assure the quality of the final product.

For drafting a preparation instruction for a non-standardised formulation, two routes can be followed, see Fig. 33.4. If a BPI is available for a closely related preparation, it may be possible to prepare the non-standardised extemporaneous preparation on this basis. The BPI can be changed for another strength, for example, be modified with respect to a particular excipient, or by a minor change in the applied preparation process. The changes will inevitably turn the standardised preparation instruction into a non-standardised instruction, but working in this way has the advantage that the preparation will largely be in accordance with a standardised formulation, of which the design has been validated. There should be sufficient evidence that the adjustments do not adversely affect the design quality and the alterations must be conducted and approved in a controlled manner before the preparation is carried out.

If no BPI of a related formulation is available, a new preparation instruction has to be designed. When drafting such a preparation instruction, it is advisable to follow broadly the same structure as pointed out in Sect. 33.4.2 for drafting the BPI. A preparation instruction for an

a

..... (Name, dosage, strength) 1

Date: 4	Prescription nr.: 5	Origin/reference: 3	Storage period:	Expiry date:

Amount to be delivered: 8	Batch size: 2	Formulation/ calculations	Operator	Check

Ingredient 7	To weigh/measure	Batch nr.	Weighed/ measured 9	Operator	Check 10
Tare weight:					
Packaging:					

Safety measures:	Preparation method: 11 12

In-process controls: 13

...		...		pH: ....

b

Checks (procedure ...)

Yield: 15 ... Packages of ... ml/g	Rejects and cause:

Creams, Ointments, Suspensions: 17	Appearance:	/n.a.
	Consistency:	/n.a.
	Homogeneity:	/n.a.
	Agglomerates:	/n.a.
	.....:	

Solutions:	Clarity:	/n.a.
	Colour:	/n.a.
	.....:	

Powders :	Fineness:	/n.a.
	Homogeneity:	/n.a.

Packaging:	Labeling: 6	Operator: 16
Final assessment: 18		Pharmacist: 19

Fig. 33.5 Example of a preparation instruction for non-standardised extemporaneous preparations, front (**a**) and backside (**b**). The numbers correspond with the explanations in Sect. 33.4.2

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extemporaneous preparation may differ from a BPI in number and size of the sections, because there is e.g. no time to validate the design of formulation and the method of preparation. It should be kept in mind that the preparation is intended for an individual patient and the risk assessment is paramount (Sect. 2.2).

The composition and preparation method are usually drafted directly on the document shortly before the actual preparation starts. It may be possible to refer to a procedure describing a general preparation method. If available, referral can be made to a relevant procedure for the preparation of a specific pharmaceutical form.

Furthermore, the document has to leave some space for recording the process carried out, any deviations or issues that came to light and for a final product review.

It may be helpful to develop standard models for such preparation instructions, for instance for creams and ointments, for capsules or for suppositories. These models can be used for the drafting the preparation instruction. After authorisation by a pharmacist, it can be used for recording the work during preparation. An example is shown in Fig. 33.5 (numbers corresponding to the sections in Sect. 33.4.2). The model has the following sections:

- The non-shaded sections on the front: these sections have to be filled in before starting preparation (the design).
- The shaded sections on the front: these sections have to be filled in during preparation (preparation phase).
- The back side: here the results of the checks and final evaluation are listed (evaluation phase). There is also a small blank space, for example for calculations or remarks.

33.6 Analytical Instructions

A pharmacy with adequate laboratory facilities will be able to perform analytical quality control tests in-house. In that case the necessary analytical instructions are part of the documentation system. In other cases it may be necessary for a pharmacy to outsource its analytical testing to an external laboratory. Then it is necessary to have a copy of the analytical instructions, including the key acceptance criteria. In this scenario it is paramount that a Service Level Agreement (SLA) or Technical Agreement is in place between the pharmacy and the laboratory (for SLA see Sect. 33.9.1).

Substances and finished products need to be analysed to show that they meet the quality requirements of the pharmaceutical preparation. The analytical instruction indicates which parameters need to be measured and how these tests should be performed. In practice the analytical instruction is often used during analysis as a batch record. The results of analytical controls can be reported in a certificate of analysis, which gives a summary of the release specifications and the results found. The results are an integral part of the documentation of a preparation, and thus should be kept with the BPR. If the analytical testing is conducted in the context of the validation of a new BPI, then the results should be in the validation part of the product file for the product (Sect. 33.8.7).

33.7 Logbooks

For all major premises or equipment instruments and devices which may have critical influence on the preparation or analytical processes, a logbook should be kept. The logbook is the history of a piece of equipment or a facility and it aims at traceability and verification. The investigation of any deviation may use the logbook as a vital source of information to enable the root cause to be traced. In addition, the logbook will include records as to whether equipment is maintained on time, if rooms are cleaned on time etcetera.

It is important to get the balance between too many logbooks, that may lead to a disproportionate amount of administration and too few logbooks, that will lead to a lack of understanding of critical preparation processes.

Logbooks describe in chronological order all the data on the use of a particular device or equipment. All the associated preparations are recorded with date and identity of the operators.

Also data are collected chronologically about maintenance, updates, renovation, repairs and the like. This may actually be recorded on an equipment-maintenance card, as a part of the logbook. On the maintenance card data are noted of when and by whom the unit was cleaned, when and by whom repair or maintenance was done, also when and by whom it was released for use again.

Where equipment is serviced by outside contractors it will be useful to operate a ‘Permit to Work’ (see Sect. 33.9.3) system which controls the access to the equipment, the checking of the engineers report and the steps taken (e.g. cleaning) to put the equipment back into use.

The same goes for cleaning and maintenance of premises, such as the LAF-cabinet or preparation areas. Logbooks must always be present at the place where they are needed, near the device or equipment, or near the workplace, so they can be consulted there during or subsequent to the work.

Logbooks may need to be consulted as part of the product release process in order to confirm the status of critical equipment.

33.8 The Product File

33.8.1 Contents

In the product file all documents relating to a particular pharmacy preparation are brought together, including data on pharmacotherapy, the considerations which led to the choice for a certain formulation, preparation method and quality requirements of the product. It provides background

information on the product and contains an overview of the history of the preparation. Many parts may show similarity with a product dossier of licensed medicines. However, the guidelines for a product dossier of a licensed product are not directly useful for pharmacy preparations. Therefore the pharmacist needs to develop his own procedure to cover the process. A product file should be available for every pharmacy preparation.

The European Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients [2] describes the following list of topics to be covered in a product file, depth and interpretation depending on a risk assessment (see Sect. 21.6.3):

1. Added value and preparation process of the pharmacy preparation
   (a) Description of the final preparation process
   (b) Demonstration of the added value of the pharmacy preparation
2. Composition
   (a) Function
   (b) Demonstration that the active pharmaceutical ingredients, excipients and containers meet relevant requirements, taking into account specific patient needs
   (c) Specifications and traceability of origin of the starting materials
   (d) specifications of the primary packaging material, etc.
3. In-process controls and quality controls of the finished product
   (a) Product specific procedures
   (b) Records of prepared batches
4. In-process controls and quality control of finished product
   (a) Sampling
   (b) Analytical methods
   (c) Acceptance criteria, etc.
5. Results of test batches (namely, information on the development, background and evaluation of the preparation process, including testing)
6. Validation
   (a) Of preparation process
   (b) Of analytical methods
7. Stability considerations
   (a) A plan for own stability studies
   (b) The evaluation of stability data, etc.
8. Use of the product and information for the patient

The list of the European Resolution as mentioned above is a good reference point, but it pays much attention to the technical quality of the product, while it tends to marginalise the information about the therapeutic qualities and the design. However, the prescriber and the patient or his caregiver may need these details: what are the benefits and risks of the product, how should it be administered, which risks may need to be reviewed or evaluated etcetera. In that aspect the product file may be divided into two parts, first information about the product that should be available externally (prescription assessment and user information) and then the details and backgrounds about its design and quality. The way this is done in the Netherlands may serve as an example, leading to the following list of contents for a product file:

- Contents (33.8.1)
- Prescription assessment (33.8.2)
- User information (33.8.3)
- Pharmacotherapy (33.8.4)
- Pharmacovigilance (33.8.5)
- Formulation and Method of preparation (33.8.6)
- Product and Process Validation (33.8.7)
- Stability investigation (33.8.8)
- History (33.8.9)
- Product quality review (33.8.10)

Of course these topics should be discussed in relation to the scale of the preparation and other items that affect the risk assessment. Commonly the product file for a non-standardised extemporaneous preparation, may consist of only a prescription assessment and a preparation record, possibly with a cover sheet for archiving the other sections may remain unfilled. If available, referral can be made to a general file for the appropriate dosage form.

File for the Dosage Form

It might be useful to develop general files for pharmaceutical dosage forms. In such files, all information is gathered about a particular dosage form, linked to the method of preparation. A file for a dosage form has its value in extemporaneous preparations without a standardised preparation instruction. No product validation can be performed but the preparation process of the dosage form can be validated though.

This process validation can be documented for each dosage form in a file in which all the relevant data are collected: preparation data for the model-preparation which was chosen for validation, information on the implementation and results of the validation studies, and the conclusion of the study. In the conclusion the future frequency of analysis of the preparations of the specific dosage form is discussed, generally, in retrospect.

The relevant historical data regarding the dosage form are also collected in this file including any problems encountered and lessons learnt from these. In this way, in the course of time, a clear picture of the quality issues related to a particular type of preparation will come to light, and measures can be put in place to correct for these.

For a standardised preparation the product file may be quite extensive. There is need for a more elaborate evaluation of the topics discussed above, and the product file should also include information on the validation of the preparation and on the stability and shelf life of the preparation. The product file of pharmacy preparations that are distributed on a relatively large scale should be the most extensive. The various topics of the product file in its most extensive form will be discussed in detail in the following subsections. At the end of each section an example of 12.5 mg diclofenac suppositories is used, assuming that diclofenac is not available in this strength as licensed medicine.

33.8.2 Prescription Assessment

Before a prescription with a request for a pharmacy preparation can be approved, it has to be decided whether there is a specific clinical need for it. When defining the place in therapy, part of the assessment is the risk that is presented to the patient or a patient group both from receiving the preparation and from not receiving the preparation because it would not be available [3]. The risk should be estimated on the basis of a documented risk assessment (see Sect. 2.2.3) and the outcome of the assessment is recorded in the product file.

- For a stock preparation of diclofenac sodium suppositories 12.5 mg, for example, the risk assessment should give information why it may be needed for children with a specified indication of their illness, the unavailability of a licensed product in this strength, choice of administration route and dosage form, an estimation of the risk of the use for children and balancing the benefits for the patient group against the risks of a (principally) limited design and preparation quality.
- It is also necessary to list the prescribers and pharmacists who are responsible for this risk assessment and to indicate a frequency of reviewing the assessment for the indication that has been laid down.

33.8.3 User Information

The user information on the product may contain information about its composition and its use, including information needed to perform a medication review.

33.8.3.1 Composition

Patient and prescriber may need a short description of the pharmacy preparation, giving active substance, relevant excipients, strength, dosage form and administration route. See Sect. 37.3 for a comprehensive list.

It is advised to develop a procedure for the way in which the name and strength of a preparation is given. The lists with standard terms of the EDQM for dosage forms, administration routes and containers are recommended. In Chaps. 4–14 these standards have been used.

- The result may be in this case: Diclofenac sodium suppositories 12.5 mg, followed by a list of the excipients, for example hard fat and lactose

33.8.3.2 Information for the Prescriber

The product file should contain the information that the prescriber may need at his decision about the treatment of the patient. This information is related to the more elaborate section Pharmacotherapy (see further) but will generally only include the indication, adverse effects, contra-indications, dosage and way of administration.

- In the case of diclofenac sodium suppositories 12.5 mg the prescriber should know that these suppositories may be given to children up to 12 years of age for pain and inflammations, and what may be the known side-effects and/or contra-indications.

33.8.3.3 Information for the Patient

The product file should also include information for the patient or his caregiver. In many countries national laws prescribe what information should be given about pharmacy preparations. If available, a patient information leaflet on the product is developed and included in the file. See Sects. 37.3 and 37.4 for more information.

In some Countries general leaflets are developed for patients about the particularities of pharmacy made preparations. These may be supplied as well.

- For the diclofenac sodium suppositories 12.5 mg, understandable information for the patient about how to use the product should be available, as well as information about the dosage, the desired effect and the possible side effects of the product etcetera. (However, be aware that this an example. In some countries it is not permitted to claim a therapeutic effect for a pharmacy preparation, this being reserved for licensed products).

33.8.3.4 Information Needed for Medication Reviews

To perform a proper medication review, the pharmacist needs additional therapeutic information such as contraindications, interactions and intolerances, impact on driving, dosing in pregnancy, kinetics (effect of reduced renal function), metabolism, monitoring on polymorphism etcetera.

- For the diclofenac sodium suppositories 12.5 mg information may be obtained from international reference works or national formularies, with additional information on these characteristics.

33.8.4 Pharmacotherapy

As a part of the foundation of the quality of the product, the product file should contain all the relevant pharmacotherapeutic information including biopharmaceutical reasoning and literature, where possible with reference to relevant literature, national guidelines or local agreements.

- Diclofenac sodium is a well-known non-steroidal anti inflammatory active substance, widely described in literature. For the diclofenac sodium suppositories 12.5 mg good references will be available with regard to bioavailability but also what is known from literature about the rectal availability of diclofenac sodium in general and what can be expected from the particular pharmacy preparation.

33.8.5 Pharmacovigilance

Pharmacovigilance is not regulated for pharmacy preparations and not easily performed. Usually there is no possibility to test efficacy and safety before the product is administered to the patient. Therefore, it is advisable to record all the therapeutic considerations in the product file (under Pharmacotherapy) and, if possible, to evaluate the outcomes of the treatment. In this way a minimal form of pharmacovigilance may be accomplished.

The preparation instruction of non-standardised preparations bears the name of the patient, which makes it possible to connect the product to the documented information about the preparation. This is particularly important when standardisation is being considered. Retrospective analysis of the relevant patient records is then recommended. Reporting unexpected effects to a central professional body is desirable.

- Any experience with the use of diclofenac sodium suppositories 12.5 mg will be collected in this part of the file.

33.8.6 Formulation and Method of Preparation

This section of the product file comprises all the details of the formulation and the preparation method and forms the central part of the product file. In general, this section should describe the details and considerations about:

- Formulation
- Packaging
- Labelling
- Preparation method
- Stability and shelf-life
- Storage conditions
- Specifications
- Methods of analysis

According to the paradigm Quality by design (see Sect. 17.2) a solid and scientific documentation of the design process will improve understanding and hence the ability to deal with deviations and changes.

33.8.6.1 Formulation, Packaging and Labelling

The documentation about the formulation should show that the intended formulation will result in a preparation with sufficient technical quality. The choice of a formulation can be based on literature sources or by referring to an existing formulation for a similar preparation. When a new formulation is designed, the chosen formulation is explained here in detail.

The section includes the specifications for the raw materials and containers to be used. Preferably raw materials of a suitable pharmaceutical grade should be used (see Sect. 23.1.2), but this may not always be possible. All the considerations that played a role in the choice of the raw materials are recorded in this section, including the excipients, preservatives, colourants and flavours. Amounts and calculated doses are mentioned, and the need for specific properties (Functionally Related Characteristics) such as purity, fineness or viscosity where this is essential for the final quality.

For the packaging and labelling materials, preferably the functional requirements and specifications are listed. Also recorded is the background about the necessary product information for the patient.

General information about raw materials or packaging components that are used regularly may be collected and recorded centrally in a separate file, to which a reference can be added in the product file.

- For the diclofenac sodium suppositories 12.5 mg not only the choice of the composition (amounts and type of base or any other excipient) is explained, but also the quality requirements for the active substance and the excipients are described in this part. For the quality requirements reference may be made to the European Pharmacopoeia, both for the active substance and for the excipients. Also the size and quality of the suppository molds is described here.

33.8.6.2 Method of Preparation

In addition to the formulation the method of preparation is described in the product file. The process is explained with all the preparation steps (unit operations) in chronological order, including the quantities of active substances and excipients that apply to a particular batch size. Also the safety of the preparation process and the safety of the

operator forms a part of this section. The reason for choices that have been made and in process controls that are required are given here. These topics are discussed in Sect. 21.6.3.

When there is already an existing Preparation Instruction then a referral can be made to this information in the product file. When the preparation is prepared on the basis of in-house decisions and expertise, the considerations which have led to the specific activities are recorded in the file, including the specific work order, the choice of equipment, or the considerations which have led to the inclusion of certain in-process controls. The description of the preparation method must give the pharmacist an overview on the process and should enable him to assess whether a modification might have impact on the quality of the final product. Also it might enable him to trace the critical preparation steps where in-process controls might be in place.

- Here a copy of the batch preparation record of the diclofenac sodium 12.5 mg suppositories could be included in the product file. Additional information may be given to explain the reasons for the choice of the excipients, the melting temperature of the hard fat base, the choice of the preparation method, the determination of overages, and of the number of suppositories that are expected to be rejected during production, etcetera.

33.8.6.3 Stability and Storage Conditions

This section of the product file should give information about the stability of the product and the choices that have led to its shelf life and the storage conditions. In most cases a shelf life for the unopened package is defined, as well as for the container after opening. Also the storage temperature is specified, and if applicable special conditions, for example 'protect from light' or 'in a well closed container'.

If a standardised preparation instruction exists, for example in a formulary, often information about the shelf life and the storage can be found there. In other cases the shelf-life should be supported with data from in-house research. The availability of data from the literature determines how extensively any in-house or commissioned stability research should be carried out.

For infrequently prepared products the analysis of some expired batches may also provide useful support for the shelf-life of a preparation. A more detailed product file should include data from a thorough stability study. Stability testing should ideally be performed prospectively, but it can also be performed concurrently by following the first batches produced, this can be particularly useful if accelerated storage at an elevated temperature is included in the study. The product shelf life can be increased during the study as more data becomes available. The design of a stability study is described in Sect. 22.5.

- Here information from literature about the stability of diclofenac sodium may be included. If any stability data of diclofenac suppositories 12.5 mg are available, these are presented here together with a conclusion about the shelf life and storage conditions.

33.8.6.4 Specifications

The quality requirements are described in a separate section of the product file. These quality requirements include the specifications during preparation (in process controls), immediately after preparation (release specifications) and that at the end of shelf life of the product (shelf-life specifications). The specifications must be relevant to the respective dosage form and should be chosen in a such a way that they characterise the product quality within strict limits, while simultaneously ensuring that sufficient margin is left so that small batch-dependent variations can be accepted.

For products described in a pharmacopoeia, the official specifications can and should be used for the product file, with referral to the official source. The same applies to preparations from standard formulations, in which quality requirements are included. For in-house formulations, the quality requirements have to be set by an appropriately competent person internally. Useful information can be found in the formulation or validation studies. The results of stability studies may be useful when setting the quality requirements for the product, because the premise is that a preparation should comply to the quality requirements throughout the whole shelf life. An overview of the applicable quality requirements, including supporting information, has to be included in the product file. In addition it should be specified how the packaging and labelling are checked, and how and with what analytical method the product quality is controlled. Additionally the validation of the analytical methods is included in this section of the product file.

- For the diclofenac sodium suppositories 12.5 mg the specifications of the product are outlined, together with information about the sources of these specifications. For the specification on the content of active substance may be referred to national laws, for a specification on the uniformity of dosage units referral may be made of the European Pharmacopoeia, but for the appearance own specifications may be used, for example "no holes or cracks".

33.8.6.5 Methods of Analysis

The product file should contain information on how the finished product will be analysed. For a standardised preparation the controls are defined in the file, with reference to the control methods or analytical techniques. If analysis is performed internally, the analytical instruction should be included. When analysis is not performed on every batch, the frequency of testing should be defined with the reasons for the choices that have been made.

- For diclofenac sodium suppositories 12.5 mg it should be clear at least how sampling is performed, e.g. from the start, the middle and the end of preparation, and which parameters should be tested: appearance, identity content, uniformity of dosage units, disintegration. Also the frequency of testing is described, and preferably which analytical techniques are used.

For a non-standardised preparation the control can only take place by checking the outcome of the in-process controls. However, sometimes it is possible to produce an excess of the product for analytical testing afterwards. In that case a discussion regarding the frequency of testing may be given in this section.

33.8.7 Process Validation

This part of the product file contains information about the validation of the preparation process and the method of analysis. It gives the rationale for the method of preparation, with validation data and any changes that have been carried out, and describes, where applicable, the background for the quality specifications of the preparation.

The process validation should show that the chosen formulation, in combination with the chosen method of preparation, will lead to a product with a consistent quality. The results of the validation are recorded on a separate validation record. This record should contain information on the conditions during preparation and on the method of sampling for analysis, together with the date of drawing up the corresponding BPI.

- For diclofenac sodium suppositories 12.5 mg a description may be given of the choices that have been made concerning the production technique, the pouring temperature, the homogeneity, the way of sampling, the ranges for the batch size that have been chosen and how all these have been tested.

33.8.8 Shelf Life Investigation

Normally a separate section of the product dossier discusses the stability of the preparation. All results of stability investigation and data supporting the storage period are described here. Also the preparation data on the batches which have actually been tested for stability are kept here.

- For diclofenac sodium suppositories 12.5 mg all results from stability tests that have been performed are given here, together with the considerations and conclusions that have led to the chosen storage period.

33.8.9 History

Historical data of prepared batches and their analytical results are part of the product file. Although this information can be stored separately and a reference can be made in the product file. The historical data contain all the information relating to the preparation and its production during the past. Here the records are stored regarding the preparation and the analysis of all produced batches

Old versions of BPI's are archived in the product file with a clear annotation that they have been superseded. On the BPI's the changes and corrections which have been made in the course of time are recorded. Also the results of re-validations that have been performed for example after a change in the composition or in the manufacturing process are recorded in the file including the reason for the change. It will give a good picture of how a specific preparation method has changed in the course of time and with what results, and hence will give a full history of the product

It may be practical to collect analytical results on an analysis card or an electronic system, to keep track of them. As more and more analytical results of a given preparation are collected, a clear picture can be gained as to the quality of that product in the course of time. By performing trend analysis on the historic results, intended or unintended deviations in the preparation process can be traced. Also occasional errors can be easily detected. The results of such trend analysis are therefore also part of the product file and form a Product Quality Review.

33.8.10 Product Quality Review

A separate part of the product file includes the aftercare around the preparation regarding an evaluation of all failures or discrepancies. Information on complaints, deviations and recalls is collected in this section, including the details of how these were handled. Based on all the information in this section, it is possible to perform evaluations such as Product Quality Reviews (see also Sect. 35.6.11) to look at the robustness of the preparation and the need for change. Also this information may be useful to determine a frequency for how often the product has to be reviewed.

Complaints, errors and recalls will provide useful information for prioritising the improved design of a product, such as a change in the formulation or the preparation method. Complaints and the resulting corrective actions

should be available in the product file, or be traceable from a central system. If the documentation of non-standardised extemporaneous preparations is kept in files per dosage form, then it is recommended that these data are collected in that file.

The list of complaints, defects and recalls, together with the historical data on the product may lead to a critical evaluation of the file, and -if necessary- a possible adjustment to the product. But even without a direct reason, a product file needs to be updated regularly. The frequency with which this should happen should be recorded in the file.

For evaluation of the file, in response to deviations or by routine review, it always should be considered whether it is necessary to make changes to the product or preparation or analytical methodology. If a decision is reached to make a change, the impact of such a change needs to be fully evaluated and ascertained ('change control, see Sect. 35.6.10). Moreover, it has to be assured that the change leads to the intended quality improvement. The considerations, results of evaluations and support for the change are documented in the product file or in the change control system and cross referenced in the product file.

33.9 Other Documents

33.9.1 Service Level Agreements

Service Level Agreements are documents where a service or part of a service including equipment and facility maintenance or monitoring is outsourced to a third party. They outline the general level of service to be provided including timescales and details of reporting arrangements and often financial information regarding the costs to be incurred.

33.9.2 Technical Agreements

A Technical Agreement is an essential adjunct to the SLA it includes the key responsibilities including the provision of information between the parties for example where there are deviations or planned changes to processes.

33.9.3 Permits to Work

A template permit to work should be produced by the pharmacy and this can be adapted to specific circumstances. The document needs to be raised whenever persons have to enter the pharmacy for maintenance or monitoring of facilities or equipment. At the end of the process the responsible pharmacist needs to check the permit carefully to assure adequate completion and also the equipment or facility before it is signed back into use. Actions that may result from such work may include recalibration of equipment, additional cleaning or revalidation.

33.9.4 Validation Procedures and Reports

All validation exercises should be planned and well documented. Initially a validation master plan should be produced to cover the validation exercise and should set out the details of the system or process to be validated, the validation to be carried out and the acceptance criteria. This is the validation procedure and should be signed off by the key staff ahead of the exercise being carried out. See also Sect. 34.10.

33.9.5 Deviation/ Error/Out of Specification Reports

All process deviations whether planned or unplanned, together with errors and out of specification results should be recorded with a controlled form or electronically onto a database system. Whether a paper system or an electronic system this needs to facilitate the management of the investigation stage, including root cause analysis where necessary, corrective and preventative actions and close out, as well as the data being available for trending (CAPA-system). This is an important part of any Pharmaceutical Quality System, see Sect. 35.6.15.

33.9.6 Training Records

It will be useful to keep training records of all employees concerned with the preparation and analytical processes in the pharmacy, to show their knowledge and experience with the work. This topic is discussed in Sect. 25.5.2.

33.10 Documentation and Automation

Computer automation is an integral part of any pharmacy. For maintaining the documentation system in the pharmacy, there are a large number of systems available, ranging from the publicly available Windows programs such as Word, Excel and Access to specialised quality software for Quality Management Systems. Several programs are available for the control and monitoring of equipment; sometimes

these are already built in into the equipment. An inventory thereof and a weighing of pros and cons is beyond scope of this book.

Computers and automated systems can be used in various ways in the small-scale preparation of medicinal products. Examples include:

- Search and retrieval of information about preparations in professional databases
- Creation, maintenance and management of standardised procedures and instructions
- Processing the results of in-process and final product analysis controls
- Registration and control of identity of raw materials and their weighted amounts
- Management and printing of labels
- Registration of monitoring actions
- Performing trend analysis
- Control and monitoring of equipment (sterilisers, water treatment, refrigerators)
- The management and control of documents

If computer systems are applied to support the small scale preparation in a pharmacy, they have to be validated in the same way as all preparation equipment or preparation processes do, see Sect. 34.15. All forms of automation ultimately may have an impact on the quality of the product. Therefore it is advisable to validate all systems used in advance and to validate any changes ahead of their introduction.

33.11 Management of Documents

A system for the documentation of the pharmacy preparation will only retain its value if it is continuously updated. In addition, the contents of frequently used documents, such as procedures, should be known broadly by all employees involved in the relevant processes. Having read and understood the procedure, the employees should sign or place their initials on a cover sheet or training document to indicate this. In the pharmacy the following should be clearly defined

- Who stores the documents and maintains the archives
- Who assesses and approves changes in documents (including "change control")
- Who is responsible for the correct and timely introduction of new or amended documents
- Who and by when should updated or new documents be read and understood
- Who identifies missing documents, and who is responsible for the drafting thereof
- Who is responsible for correcting document non-conformances raised at audit or through investigative procedures following incidents and errors

The aim is to ensure that all documents controlled within the documentation system are reviewed at least every 3 years, the frequency may need to be increased for certain documents. In order to ensure that all documents are reviewed in time there should be a database or list of documents together with their issue and review by dates, in this way the documentation system can be kept up to date. Automated systems can be a practical tool to help with this.

Besides the periodic review and updating of documents, it may also be necessary to amend documents for the following reasons:

- Inspections and audits (internal or external) or supervision by the pharmacist
- Complaints or errors
- Comments from employees
- Changes in personnel
- Change in the equipment or the batch size
- Change in a formulary or specification
- Modification of a BPI
- External testing results
- Changes in official regulations

Only by continuous maintenance the documentation system can retain its value and play its critical role within the quality system of the pharmacy.

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Production, Quality Control and Validation

34

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Contents

Abstract

The quality of pharmaceutical preparations is the result of the design and the execution of the manufacturing process. The Good Manufacturing Practice (GMP) principles and guidelines are about incorporating quality into all aspects of the manufacturing process. This chapter covers the design, execution, monitoring and validation of the process, as well as the quality control and release of the product.

Preparations differ in size and complexity. The scale can range from a tailor-made preparation for one patient to production for many thousands of patients. The complexity can range from reconstitution to complex preparations from active pharmaceutical substances and excipients. For all kind of preparations it is essential to minimise the risk of mix-up or cross-contamination by applying technical measures and an appropriate working discipline. All preparation steps must be controlled and traceable. A watertight procedure for quarantine, final quality control and release has to be in place. Furthermore, in order to guarantee the quality and safety of a product the preparation and cleaning processes have to be validated, including the qualification of premises and equipment. These validation activities have to be planned and executed in accordance with quality risk management principles.

Based on the chapter Productie by Rogier Lange and Rik Wagenaar in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_34,

Keywords
Production • Quality control • In-process controls • Reconciliation • Validation • Qualification • Cleaning • Quarantine

34.1 Orientation

This chapter is about preparation of medicines and quality control. The text is mainly based on Chaps. 5, 6 and Annex 15 of the GMP [1–3]. We have chosen to clarify a selected number of subjects from these GMP chapters and to give some practical examples. The main topics discussed are briefly introduced below.

Preparations can be divided into stock preparations and extemporaneous preparations. In this chapter the focus is mainly on stock preparations. The principles described are equally applicable to extemporaneous preparations. However, the required extent of quality control and validation might be less in extemporaneous preparations due to the few affected patients and the need to deliver urgently (see also Sect. 21.6.3).

Product quality is the result of the quality of design, documentation and execution of the preparation or manufacturing process. Production operations must follow clearly defined procedures and must comply with the principles of GMP in order to obtain products of the requisite quality. GMP means incorporating quality into all aspects of the process (see Sect. 35.5.7).

First of all, measures to prevent (cross-)contamination and mix-ups must be in place. These measures can be technical or organisational. Other methods to guarantee a safe process comprise adequate documentation including in-process controls and yield and label reconciliation. All processes should be controlled and supervised.

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures, which ensure that materials and products are not released for use, until their quality has been judged satisfactory. Quality Control must be involved in all decisions that may concern the quality of the product. The independence of Quality Control from Production is fundamental.

Batch documentation review and analytical testing are decisive for the release of the products. To ensure a safe release process a watertight quarantine procedure must be used.

An important part of this chapter is dedicated to validation and qualification. It is a GMP requirement that critical aspects of operations are controlled through qualification and validation during the lifecycle of the processes and products. Any planned changes to the facilities, equipment and processes should be formally documented and the impact on the validated status or control strategy assessed. Decisions on the scope and extent of validation and qualification should be based on a justified and documented risk assessment.

Personnel issues, premises and equipment, which may affect the described processes, are discussed elsewhere (Chaps. 25, 27 and 28 respectively), as well as the design of the medicine (Chap. 15) and the documentation of the preparation process (Chap. 33).

34.2 Quality of Production

Preparations differ in size and complexity. The scale may range from a tailor-made preparation for one patient to a (semi-)industrial production for thousands of patients. The complexity may range from the reconstitution of an authorised medicine to complex preparations from active substances and excipients. In this chapter we focus mainly on stock preparations. The principles described are equally applicable to simpler preparations such as extemporaneous preparations and even for reconstitution [4]. However, the extent of quality control and validation should be justified by risk assessment [5, 6 and Chap. 21].

The main elements to guarantee the quality of the preparation process are:

- The use of qualified and validated premises, systems and equipment
- The application of a validated preparation process
- A validated program for cleaning of premises, equipment, utensils and clothing
- Minimisation of the risk of mix-up or cross-contamination
- A clear description of all operations in preparation instructions, operating instructions and procedures (see Chap. 33)
- Continuous education and training of employees (Sect. 25.5.2)
- A clear indication of identity and/or status of materials, premises and equipment in all phases of the production process
- The control and recording of all essential preparation steps, so they are traceable
- The use of deviations, errors, complaints, changes, audit results and periodic evaluation or re-validation of preparation processes for continuous optimisation of the production process or the necessary conditions or both (see also Sect. 35.6)
- A comprehensive procedure for quarantine, final inspection and release

These essential elements are elaborated in the following sections or are cross-referred.

Products that are prescribed sporadically or with a variable composition or with a very limited shelf life are carried out as extemporaneous preparations. Preferably a standardised preparation instruction is used, because this is the best guarantee for a reproducible preparation. Often only the batch size is varied, because the required amount may differ for each patient. For example, the needed amount of a cutaneous preparation depends on the body area to be treated, the nature of the preparation and the duration of treatment.

If no standardised preparation instruction is available, a non-standardised preparation instruction has to be drafted ad hoc. Because hereby the possibility of errors is relatively large, it is preferred to have available a template for each type of preparation in which only the active substances and the amount have to be applied. For instance, templates for preparation instructions for capsules or suppositories could be developed (see Sect. 33.5). Of course, the appropriateness of the templates has to be demonstrated, including the underpinning of the preparation method.

Many preparations for individual patients concern reconstitution of licensed products. Examples are dissolving and diluting a powder for injection or creating an antibiotic suspension. Again, quality is incorporated by standardising the instructions applied.

The quality of preparation and manufacturing processes is based on a combination of technical and organisational measures, instructions, in-process controls, reconciliation, quality control (QC) and documentation. An automated system is recommended for the process support.

34.3 Prevention of Contamination and Cross-contamination

34.3.1 Technical Measures

Contamination is the pollution of raw materials, product or equipment with dust or microorganisms or both. Cross-contamination is pollution with substances from other preparations. Measures to prevent (cross) contamination include the use of dedicated and well-designed facilities and equipment (e.g. closed systems), the use of disposables, maintaining adequate ventilation in rooms and pressure differences between rooms, as well as the partitioning of areas where different activities can take place. The partitioning of rooms, which can be achieved by placing walls or partitions on workbenches, makes the likelihood of mix-ups smaller as well. Other technical measures, such as the installation of barriers, the use of different colours in the floor covering, mainly support the maintaining of a proper work discipline. Performing a valid cleaning process of areas, equipment and utensils (Sect. 34.16) is also intended to prevent cross-contamination.

34.3.2 Organisational Measures

It cannot be stressed enough that humans are a key risk factor for contamination and cross-contamination. The work discipline should aim to avoid mix-up of materials at each stage of the preparation process. The golden rule is: never work on different products in the same room simultaneously or subsequently, unless any risk of confusion is excluded. An example of achieving this is the practice of performing only one preparation per workplace and that this workplace is released before starting a new preparation; this is also called line clearance. It is advisable to organise the work in such a way that once started, preparations can be completed undisturbed and uninterrupted.

A logical method is needed to avoid mix-ups. An example is the weighing process of different ingredients, where all steps (putting out, identification, opening container, weighing and replacing of the container) always take place in the same logical order. The weighed ingredients must preferably be processed immediately. If this is not possible, encode them and keep them together so that it is clear for which preparation they are intended (see Sect. 34.4).

Another example is the implementation of a line clearance of a labelling process. At the end of the process all printed labels not attached to the product, must carefully be removed and destroyed. Before a new product is labelled, the correct line clearance must be verified.

A good working discipline is essential to prevent cross contamination. This requires careful planning, but a system for identification as well. In stock preparations the identity of the product in operation must be fixed to premises, equipment and vessels. For this purpose labels can be used, or a form that is part of the preparation record. Logbooks can also play an important role in the securing of the history of use of rooms and equipment (see Sect. 33.7). If a room or equipment has been cleaned according to the applicable procedure, the status indication “clean” has to be applied.

In extemporaneous preparation, the identification of premises, equipment and vessels is not necessary because of the very short processing time. A clean workspace and clean materials are satisfactory.

The working methods need attention. During weighing and processing of ingredients, dusting has to be prevented. Manufacturing processes and cleaning operations must be run so that no remnants of preparations can end up elsewhere. If this happens even so, for example in a calamity, a proper cleaning procedure has to be followed before the room or equipment or both can be released for the next preparation. See also Sect. 26.9.1.

34.3.2.1 Supervision

Despite the presence of well-trained staff and clear documents, deviation from the procedures and agreements may occur inadvertently. This requires supervision of working behaviour (see Sect. 25.5). The immediate superior, such as a team leader, may perform this. Also a stepwise supervision system can be considered, in which both experienced pharmacy technicians, the team leader and pharmacists play a role. In all cases it is helpful to make checklists to record all control operations that are part of the supervision carried out. Examples of items on such a checklist are the control of completing logbooks and cleaning verification.

34.4 Material Handling

In connection with the traceability of all materials used, it is important to have clear procedures about the routing and encoding of these materials. Herein should be specified that all materials are put into quarantine upon entry, then be sampled, tested and finally released. In all these steps, the status of the article must be clear. Until release the status is "in quarantine". It is worthwhile to mark containers with "sampled" on the packing of raw materials upon sampling and to note the date of sampling for ingredients with a short shelf life after opening. Upon release a label is placed on the package with identifying items, an analysis number and the expiry date. The analysis number may be printed in the form of a barcode as well. This makes identification when weighing or measuring the ingredients easy, because in the analysis number the identity, status and expiry date of the article are incorporated. Only released ingredients shall be used for preparation. Packaging materials and labels are processed the same way as all pharmaceutical ingredients.

Also during the preparation process, it is important that materials have been identified and that the status of the process phase is unambiguous. If ingredients are not directly further processed after weighing or volume measurement, the preparation for which they are intended has to be indicated unambiguously.

The storage conditions and allowed storage period of bulk and intermediate product should be mentioned in the product dossier and, if needed, the product should be stored under security control. At relevant points in the process the quarantine status is marked and monitored. An example is an intermediate or bulk product that is not directly processed further. Unambiguous procedures for dealing with surplus and discarded materials must be in place. Surplus materials may be kept in storage again only if these procedures are met.

For example, how to deal with germ-free packaging materials when the overpouch is removed has to be defined.

If it is not yet clear whether materials can be used in the future, the material has to be marked clearly with "quarantine" and stored separately.

The way rejected materials and products should be removed safely has to be described in a procedure. In addition a procedure on the permissibility of reprocessing (when an intermediate or bulk product does not meet the requirements) has to be in place. Reprocessing should be minimised and performed only in close collaboration with the quality control laboratory and documented carefully. Reprocessing of previously delivered and returned products must be excluded.

34.5 Batch Documentation

The documentation that guides a preparation, called batch preparation instruction and batch preparation record, has two functions: the documentation of all operations to be carried out during the entire process (from weighing of ingredients to the release) and the traceability of all used materials, premises and equipment (see Sect. 33.4). It is possible to refer to the instructions and procedures available for the preparation concerned. Due to the potential impact on the quality of the product and the consequences for the quality control all deviations from the intended process and the conclusion must be recorded. As part of the continuous quality improvement, it is also useful to record suggestions for improving the preparation instructions on the preparation record (see Sect. 33.4).

The weight or volume measurement or both of ingredients must be verified independently, both the weighing/measurement as well as the control have to be recorded. If an automated system is used for these recordings, it has to be validated (see Sect. 33.10).

34.6 In-process Controls

In-process controls, also called IPC's, are important parts of the preparation instruction (Sect. 33.4.2). These are controls in the preparation process, which are incorporated in order to ensure that critical process steps (unit operations) have been performed correctly (see also Sect. 15.7). There are quantitative or numerical IPC's, where results are logged (e.g. pH value) and qualitative or alphanumeric IPC's, where an observation is described (e.g. colour) or ticked off (with initials) (e.g. if a solution is clear). Some IPC's relate to the product (e.g. homogeneity), some to the process (e.g. a mixing time) – but all IPC's can be related to the initial risk assessment and the determined critical control points.

As unnecessary IPC's may reduce the awareness and discipline of the personnel it is important to consider carefully whether IPC's are really necessary in order to control the quality of the product. An example is the preparation of an all-in-one parenteral nutrition admixture wherein the aqueous part has to be checked for clarity, because precipitates or particulate matter cannot be seen after the fat emulsion is added. Another reason for the use of an IPC is to control critical process steps when no final quality control of the product is possible. An example of this is the control of the application of nitrogen for making ampoules oxygen-free after the filling process, because the laboratory is unable to measure the oxygen content in each ampoule. This IPC is based upon the conclusions from the validation of the oxygen replacement process.

The results of the IPC's are useful data for performing trend analysis and the validation of preparation and manufacturing processes.

34.7 Label and Yield Reconciliation

Labelling and packaging operations are an essential part of the process. These operations can be recorded in a separate packaging instruction. However, in pharmacies, given the limited batch sizes and the short process time, it is common to include these operations in the batch preparation instruction (Sect. 33.4.2).

In general, roll-feed labels are preferable to cut-labels in order to prevent mix-ups. With the label accountability, also called reconciliation, justification of the processing of all printed labels takes place, including the throwing away of the remaining labels. The reconciliation has to include all labels used or destroyed including any labels used for the quality control samples and for documentation in the batch record or the logbook or both. The number of rejected labels (for example, due to poor printing quality) has to be recorded and justified as well.

The yield must be recorded in an unambiguous manner. It should be clear how many units have been produced, but also how many are not used (e.g. due to fracture) or rejected (e.g. at visual inspection) in various stages of the process. If the final net yield deviates significantly from the theoretical yield according to predefined limits, the reason has to be clarified. See example in Table 34.1.

Table 34.1 shows that the ampoules are packed in boxes of 12 ampoules. At first glance the reconciliation seems to fit. On closer inspection, there are some deviations: it seems that 10 ampoules are not labeled and there are two boxes labeled too much (4,116 ampoules correspond to 343 boxes). There is nothing else than to check whether the line clearance has been performed, to inspect the produced batch (are all boxes filled?) and to count the ampoules and boxes again. A non-conclusive reconciliation can be based on counting and/or writing errors. The relatively low yield may be explained satisfactorily. However, verification of sufficient inspection of the ampoules (glass particles present?) is needed. Also additional particle counts can be considered because of the reported trouble in the sealing of the ampoules.

Table 34.1 Label and yield reconciliation of a batch of ampoules

	On product		**On secondary packaging**		**Initials**
Label reconciliation	Used	Printed	Used	Printed	
Created labels		4,200		365	
Labels on product/box	4,116		345		
Labels on lab samples	10		1		
Labels on quarantine forms	2		2		
Labels on batch record	1		1		
Labels rejected	2				
Labels unused	69		16		
Total	4,200	4,200	365	365	
Yield reconciliation		**Loss**	**Yield**		**Initials**
Theoretical yield			4,750		
Yield after preparation			4,165*		
Loss during inspection		27			
Loss during labelling		2			
Laboratory samples		10			
Final yield		4,126			
Total		4,165	4,165		

*Cause of additional loss: failure of ampoule filling machine at sealing ampoules

34.8 Quarantine Management

To prevent the delivery of unapproved products a watertight quarantine policy is very important. Materials with a quarantine status must be separated from released materials in a totally safe way.

The following items must have the quarantine status:

- Unreleased starting materials
- Intermediate and bulk products which are not directly further processed
- Filled units that have not yet been labelled
- Products not yet analysed or released or both
- Starting materials or products where doubt about quality is raised after release of the batch in question

It is preferable that these items are placed in a lockable quarantine location. An alternative is storing in lockable cabinets or quarantine-carts. The access to the quarantine locations should be limited to a small number of people.

If storage in a closed quarantine location is not possible, for example a bulk product in a production vessel that is not directly filled and labelled, the quarantine status is stated with a striking and well attached plate or label.

The quarantine status is indicated and also recorded on the batch documentation, including the number of items placed in quarantine and the additional number of samples that may be taken.

34.9 Quality Control and Release

34.9.1 Batch Documentation Review

Final inspection is an essential element in controlling the quality of pharmaceutical preparations. In the first place, the final control comprises of the control of the batch documentation. In a larger organisation, such as a hospital, this is often the task of the production pharmacist.

The final inspection of the batch preparation record should comprise of the following checks:

- Are all raw and packaging materials properly identified and is the correct amount of each substance processed?
- Are all items of the preparation record completed correctly?
- Are all initials put?
- Are all IPC's within limits and are any discrepancies handled correctly?
- Is the necessary documentary evidence, such as print-out of pH meter, packaging of used filter, print-out of filter testing device, sterilisation indicator and sterilisation report, attached?
- Are raw data for critical processes within specifications?
- Are the correct labels used and are the printed data correct and complete?
- Is the label and yield reconciliation, including line-clearance, performed correctly?
- Are deviations, if any, adequately documented and concluded?

If there are deviations from the desired process that need extra attention during quality control, this is noted on the protocol. An example is a too long sterilisation process, in which case special attention must be paid during analysis to the presence of possibly formed degradation products.

34.9.2 Quality Control

The Quality Control (QC) department has to operate according to Good Quality Control Laboratory Practice (GQCLP) standards [2]. All QC methods have to be validated and verified before application. The instruments used for QC are qualified and calibrated before QC testing is performed. There is a procedure in place for the investigation of Out Of Specification (OOS) and Out Of Trend (OOT) results. The reference standards used should be certified, qualified and verified. Documentation and traceability are important such as in production. All raw data should be retained.

During quality control the laboratory checks whether the product meets all specifications. The control of the end product includes a number of non-destructive tests, such as checking the yield or the weight distribution or a visual control of packaging and labelling. Subsequently the required analytical and microbiological tests are carried out. The assessment of the finished product includes production conditions, the results of IPC testing, the documentation review and compliance of the final product with the specifications.

An important part of the quality control is the sampling policy (number of samples, method of sampling, select or random samples or both see Sect. 20.4). The selected samples must be taken in those places where the risk of deviations is greatest (worst case procedure, see for instance 11.5 for sampling suspension-type suppositories after serial filling). In addition, samples are taken for stability testing (reference and retention samples) and validation.

QC is not restricted to laboratory operations, but should be involved in all decisions related to product quality (see Sect. 35.6). As an example, QC participates in the investigation of complaints about product quality. QC is involved in the assessment and the monitoring of the stability of the products as well. The QC department has to approve the IPC methods used in production. In all situations, the independency of QC from the production department is fundamental.

When the pharmacy doesn´t have own facilities for conducting pharmaceutical analysis, these QC activities can be outsourced [4].

34.9.3 Release Policy

The final release of products comprises a major responsibility, which must be independent of production. In pharmaceutical industry release is performed by a qualified person (QP), in pharmacies often by a pharmacist. Investigational medicinal products (IMPs) always have to be released by a notified QP (Sect. 25.3.4).

The extent of the final inspection and release policy depends on the type of preparation. Thus, for extemporaneous preparations an independent control of the preparation record and a few non-destructive inspections of the product will suffice. If no abnormalities are observed, an authorised pharmacist can perform the product release. In some countries a delegated person may release the extemporaneous product conditionally; afterwards, within a defined time frame, the authorised pharmacist releases the product formally.

In some situations, for example with very short-lived radiopharmaceuticals, conditional release before all QC tests are performed is necessary. As a consequence, process validation is important. An immediate recall procedure must take place, when product quality is found to be insufficient.

Stock preparations usually undergo an extensive analytical control (see Sect. 34.9.2) and remain in quarantine until the QC is fully completed (see Sect. 34.9). The release is based on the assessment of the document control in combination with the analytical quality controls. During release, final reconciliation takes place. For certain preparations (e.g. aseptic preparations) also the results of monitoring of production conditions are included.

Parametric Release

Parametric release is a system of release that gives the assurance that the product is of the intended quality based on information collected during the preparation process and on the compliance with specific GMP requirements related to parametric release [7]. The principle is based on the recognition that a comprehensive set of in-process tests and controls may provide greater quality assurance that the finished product meets the specifications than finished product testing. Parametric release might be applicable for the routine release of finished products without carrying out a sterility test and can be authorised if the data demonstrating correct processing of the batch provides sufficient assurance, on its own, that the process designed and validated to ensure the sterility of the product has been performed. At present parametric release may only be applied for products terminally sterilised in their final container.

Parametric release of products with a market authorisation has to be authorised by the competent authorities. Authorisation is based on a strict set of requirements described in annex 17 of the EU GMP [7]. The principle of parametric release is also used in the release of terminally sterilised products in hospital pharmacy (see Sect. 30.9). The requirements mentioned in GMP annex 17 have to be described in a procedure. One of the requirements is a risk assessment of the process (see box in Sect. 34.14.1).

34.10 Validation: General Principles and Terminology

34.10.1 Validation and Qualification

The GMP (Annex 15) requires that the producer controls the critical properties of the product and of the critical steps in the process [3]. This means that the quality of the design of the product, the preparation or manufacturing process, the equipment and automated systems used have to be assured. The organisation must demonstrate that processes, equipment, systems, installations and analysis perform reliably and reproducibly under all possible conditions. This is usually called validation.

According to GMP, validation is the action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results. Qualification is the action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

Because of these somewhat vague and overlapping definitions, in this chapter the term qualification is used in the case of equipment and persons and the term validation when assessing processes or methods.

34.10.2 Prospective, Concurrent and Retrospective Validation

As a rule, qualification of equipment and building-related installations takes place before putting into operation (= prospective). Validation of preparation and manufacturing processes is done preferably prospective as well, when designing a new process. However, in some situations qualification or validation has to be performed simultaneously with the application of the equipment or process; this is called concurrent qualification or validation. Concurrent qualification or validation should only be applied to simple equipment or processes, where there is very little chance that the outcome would be negative and products would have to be destroyed.

It is also possible to perform a qualification of equipment or validation of a production process that is already operational, but has not been previously validated. This so-called retrospective validation consists of collecting, evaluating and assessing data from the past. Retrospective validation is only possible if no significant changes in the method of preparation or equipment have occurred during the measuring period, and if sufficient, reliable data are available. If that is not the case, additional prospective validations have to be performed.

When changes occur, it has to be ascertained that the product still meets the specifications and whether re-validation is necessary to prove this. Therefore, an effective change control procedure has to be in place.

34.10.3 Re-validation and Requalification

A one-time validation or qualification does not exist whether regarding equipment or process. The minimum requirement is that the status of validation and qualification has to be evaluated on a regularly basis. The evaluation frequency has to be pre-defined in accordance with a risk-based approach. The evaluation has to include a systematic going through any changes, deviations or trends in performance e.g. as indicated from test results. If the evaluation leads to the conclusion that the "validated state" is changed a targeted re-validation has to be done. If there is no indication or need for re-validation the evaluation is documented in a report, which has to be approved by the same functions as the initial validation or qualification. For sterilisation processes re-validation is mandatory every year. Beyond the regular re-validation an important reason for re-validation is an essential change in the equipment, the process or the product range.

All proposed changes must go through the change control procedure (see Sect. 35.6.10) to determine the impact of the proposed change on all related equipment, systems and processes. A standardised risk assessment procedure may be helpful to determine the extent of re-validation activities. It is usually not necessary to entirely repeat the initial validation. Guided by the quality requirements of the product and the nature of the changes a decision is made which parts of the initial validation have to be repeated.

34.10.4 Organisation

In general, the head of the production department and the head of the QC department have management responsibility for the validation program. Quality staff may play a significant supporting role in supporting validation activities. The final responsibility for validation is described in the validation master plan (see Sect. 34.11). Validation activities should only be performed by suitably trained personnel who follow approved validation procedures.

Despite its complexity, validation provides benefits. Besides the increased control of processes, validation provides more insight into the critical factors, which can result in increased patient safety, fewer errors and less rejections. The PIC/S has published a recommendation regarding validation, which may be used as reference material [5]. However, the latest version is from 2007 and recent developments are not included.

In the following sections the principles and different forms of validation and qualification are elaborated.

34.11 Validation Master Plan

Validation has to be planned, implemented and maintained in the total life cycle of products, premises, equipment and systems. A systematic approach targeted at local conditions is mandatory and it is recommended to document this approach in a so-called validation master plan (VMP) [3, 8]. According to Annex 15 of the GMP validation master plan contains the following subjects:

- Validation policy
- Organisational structure of validation activities
- Summary of facilities, systems, equipment and processes to be validated
- Documentation format: templates for protocols and reports
- Planning and scheduling
- Change control
- Reference to existing documents

The validation policy indicates the necessity of the validation work and the responsibility of the management, so that the preconditions for implementation can be met.

In the VMP the organisation of the validation and the tasks of the members of the validation team (see below) are laid down. What to validate and to what extent is decided after the execution of a risk assessment. The most frequently used methods for risk assessment are described in ICH Q9 [9] (see also Chap. 21).

Through prioritisation, the sequence of the qualification and validation activities is formulated. For each device or process acceptance criteria have to be set based on a risk assessment including critical aspects for the total product range. Tests in relation to acceptance criteria are described in test plans. Tests have to be reported and the approved report might be the base for future change control. Ideally, protocols and reports with a fixed layout are used.

Qualification and validation can be outsourced. However, the responsibility remains in-house so the contract-taker has to be approved according to current GMP requirements for outsourced activities [10]. For example, the following qualification and validation items can be outsourced: LAF cabinets, safety cabinets, HVAC-systems, sterilisers, rinsing machines and devices for performing filter integrity testing. When tasks of qualification and validation are outsourced, internal approval of protocols, raw data and reports have to take place according to internal procedures.

Activities should be planned in a logical way for efficiently achieving a validated state. After listing and prioritising the activities a validation plan (including costs and need for resources) and a timetable are formulated and presented to the management. A logical planning begins with the validation of the analytical methods because they underpin the conclusions of the process validation. Also before initiation of process validation of production processes the qualification of the relevant equipment has to be finalised. For example, before validating aseptic processes, qualification of the HVAC-installation has to be finished.

34.12 Validation Documentation

Documentation is an important part of validation. Prior to the validation protocols need to be set up, in which the execution is described. The person responsible for the validation checks and authorises the protocols together with other disciplines; then they can be used.

Validation protocols and reports may include the following sections:

- Introduction
- Functions and tasks (for executing activities, for evaluation the results and for release)
- Execution
- Acceptance criteria
- Results
- Conclusion
- Conditions for and contents of re-validation
- Test plans

The results of the validation are archived in a validation file. A validation file of equipment may consist of the following chapters: URS, functional/technical specification, DQ, IQ, OQ, PQ, re-validation(s) (see Sect. 34.15).

34.13 Validation Team

For successful validation a multidisciplinary approach, involving production, quality control, quality assurance and technical service, is mandatory. The GMP places the responsibility for validation at the head of production and the head of quality control.

Extensive and complex validations can be addressed by establishing a validation team. The validation team may consist of the pharmacists who are responsible for production, quality control and quality management, and a pharmacy technician, an analyst, a quality manager and an employee of the technical department. If necessary, an additional person can be added to the team for specific expertise. In larger projects, the validation team can act more decisively by working with a steering committee (e.g. pharmacists and quality manager) and dedicated working groups per validation topic. In the formation of a validation team it is important to incorporate thorough knowledge of the process to ensure the best possible assessment of quality risks and to set the right priorities.

34.14 Process Validation

34.14.1 General Aspects

Process validation aims to show that the producer controls (the critical steps of) the process so the preparation method consistently leads to the intended result [11]. The structure and the critical steps of the process have to be determined using process analysis and risk assessment (see Chap. 21). The effects of small or large deviations in the preparation process have to be determined in order to define the necessary limits during routine production, the so-called design space (see Sect. 17.6).

In most cases, a preparation process is not designed from scratch. Typically, the process, whether or not after acquisition from the literature or from a colleague, is developed further and recorded in procedures and instructions. A useful tool in the development and validation of the preparation process is process analysis. Hereto, the entire process is divided into small steps (unit operations, see Sect. 17.6), which are performed after each other. It must be clear how

Table 34.2 Process analysis: preparation of injections in ampoules

Process step	Conditions/Requirements
1. Machine set	Proper settings
	Correct mounting of the filling pump
2. Weighing ingredients	Controlled conditions
	Qualified balances
3. Preparation of solution	Qualified room
	Clothing/hygiene according to procedure
	Production vessel clean
	WFI from qualified installation
	Proper mixing time
	pH adjustment is correct
	Adequate oxygen removal
	Analysis of sample meets requirements
4. Filtration	Right filter and correct placement
	Filter integrity test passed using qualified device
5. Pump and filter rinsing	Method/time according instruction
6. Placing filling needle and nitrogen needle (if needed)	According to instruction
7. Filling/closing ampoules	Qualified filling and closing machine
8. Volume control	Correctly adjusted
9. Visual inspection	Absence of particles determined by qualified employees
10. Cleaning	According to validated cleaning procedure

each step has to be performed and which conditions has to be met. See example in Table 34.2 The correctness of each process step has to be checked, for example by means of in-process controls. Also, the influence of external circumstances or factors on the different process steps has to be verified.

A useful tool in the further development of a process is a risk assessment [9, see also Chap. 21]. On the basis of the severity of certain errors in the process steps, the probability of occurrence and the timely detectability of a mistake, the preparation process can be provided with appropriate instructions and in process controls (see example below).

A detailed evaluation of a process is not only necessary for the optimisation of a preparation process, but also for the validation.

A risk assessment is the basis for parametric release of sterilisation processes, replacing the sterility test. One of the requirements of GMP Annex 17 for applying parametric release is the implementation of a risk-analysis of the sterility assurance system [7]. All process steps in which errors can occur are listed (see Sect. 21.4). Then the severity of any possible error, the probability of occurrence and how likely it is that the error is not detected in time is assessed. Each of these three factors is scored, for example between 1 and 5, and the product of the outcomes is calculated. The resulting number is called the Risk Priority Number (RPN). The RPN is a relative number. It is a way to identify the principal risks of the process and the focus items of validation.

An example of a process step with a relatively low risk is the used water for injections (WFI). As a possible error WFI with a too high bioburden is considered. The severity is 2 (bacterial filtration and terminal sterilisation of the finished product), the probability of occurrence is 1 (WFI is continuously kept at a temperature of above 80 °C and circulated), and the risk of non-detection is 3 (continuous monitoring of temperature and conductivity, regular determination of the bioburden), and. $RPN = 2 \times 1 \times 3 = 6$.

An example of a process step with a relatively high risk is the incorrect loading of the steriliser. Here the severity is 5 (insufficient heat penetration in certain units by incorrect loading), the probability of occurrence is 2 (a load instruction is in place) and the risk of non-detection 3 (only one person is loading and unloading and controls the load), so, $RPN = 2 \times 3 \times 5 = 30$. This process step needs more attention than the other example.

34.14.2 Process Validation in Practice

Process validation is basically a facility-based activity specific for each product or group of products [11]. The base for validation of a preparation process consists of the qualification or validation of the components of that process:

- Building-related installations
- Equipment
- Utilities
- Automated systems
- Process validation of unit-operations
- Cleaning methods
- Analytical methods

Furthermore it must be assured that relevant documentation is up to date and available. If data from Product Quality Review (PQR, see Sect. 35.6.11) and stability testing are available they should be evaluated in order to identify any critical aspect of the processes. If not available related quality indicators, such as test results, deviations and complaints should be evaluated.

It is very important to keep the correct order when validating (see Sect. 34.11). This shows that process validation is a complicated experience. Later in this section the validation of the process 'preparing injectables' is elaborated.

When all components of a preparation process are qualified and validated separately, the largest part of the validation process is complete. The prerequisites are described in a protocol and test plans for the final validation are enclosed. In general process validation includes preparation of three consecutive batches with extended sampling. Acceptance criteria typically include: no OOS, no OOT and critical IPC within specified limits. Samples may be collected from critical control points during the manufacture. However, when unit operations have been validated, often only samples of the finished product (after packaging and labelling) are tested. A conclusion about the preparation process as a whole is reported in a Validation report, which has to be approved by the heads of Production, QC and QA and afterwards will be a base for change control in relation to the process.

Due to the large amount of products in a (hospital) pharmacy validating the preparation process separately for each product, is not feasible. The preparation of a group of products can be validated if the used production process is standardised. An example is performing media fills to simulate and validate aseptic handling (see Sect. 31.6.2). Another example is the validation of a mixing process by using an ingredient with poor mixing properties. This is called a worst-case scenario. It is necessary to argue for each product whether the general process validation is applicable and to record this in the product dossier.

In the validation master plan is laid down which processes have to be validated and which priorities have been set (see Sect. 34.11).

Processes with a high degree of reproducibility, for example filling injection liquids in ampoules with a machine, are generally easier to validate than processes with many manual steps or stages, such as mixing a semisolid dermatological preparation manually in a mortar, or the small-scale preparation of capsules. For processes with many manual steps the knowledge and skills of the preparer plays a crucial role, and the emphasis is on the qualification of the employee and the execution of in-process controls. These give essential information about the correctness of that step or the process up to that point.

Preferably, process validation is carried out prospectively. The process is performed an agreed number of times (often three) and is taken into use only after a positive evaluation.

As an example, the process of the preparation of parenteral solutions in ampoules and its validation are elaborated. In Table 34.2, the process from weighing the ingredients to sterilisation of the ampoules is displayed stepwise. During the validation of this process there is referral to the following "external" factors that need to be qualified or calibrated:

- Premises (air control, microbiological monitoring)
- Water production
- Balances
- pH meter
- Oxygen meter
- Filter integrity testing equipment

Usually, existing processes are validated retrospectively. Here a representative period is considered in which the process took place without adjustments, e.g. 3 years.

An important part of the retrospective validation is the collection of all batch preparation and analysis records of the preparations in the period examined. This is done in a systematic way by ascertaining that all preparations are performed in accordance with the applicable procedures and instructions, all in-process controls met the requirements and all discrepancies (e.g. less yield than normal) are adequately explained. All preliminary and final analytical results are taken from the analysis records. To support the data collected the analytical validation is used.

If any product is properly prepared and if all in-process controls and final quality controls meet the requirements, the retrospective process validation may yield no surprises. Nonetheless, the evaluation of processes often provides useful information. The process is reviewed in the same way and by the same person. This allows trends to be discovered which are not noticed in the assessment of individual products. It may also become clear that certain aspects of the process are still too little known. This is a motivation for additional research.

The conclusion of a process validation is based on the measured quality of all process components studied.

In the validation report a recommendation is entered at what time the process must be re-validated. Re-validation is indicated if significant changes in the process are introduced. The change control procedure (see Sect. 35.6.10) provides for this. It is also necessary to define a maximum period within which re-validation should be performed, so that the influence of small or creeping changes on the quality of the process is visible in the course of time. An example of a creeping change is a decrease in the working discipline that can occur with changes in the personnel. During re-validation it is checked whether there have been changes in (the performance of) one of the process steps, for example in response to recommendations in the initial validation report. Also handling of deviations and reported complaints about products have to be addressed.

The design of the re-validation largely follows that of the initial process validation. However, if no significant changes have occurred and evaluation of data does not indicate the presence of OOT, re-validation may be limited to paperwork.

34.14.3 Extemporaneous Preparations

The preparation instruction of standardised individual preparations is validated beforehand. For non-standardised preparations this is not the case, and therefore it is advisable to validate the preparation template of the relevant dosage forms. By choosing a model preparation for each combination of dosage form and method of preparation the validation can be performed. It is not necessary to prepare the model preparation in daily practice. An example is the validation of the manual preparation of suspension suppositories. Suppositories with acetylsalicylic acid 100 mg can serve as a model preparation, because the equal distribution of the active ingredient in this product is difficult (see Sect. 11.5.2). By scheduling the model preparations in a periodic cycle, this validation can be coupled to the permanent qualification of personnel.

Additionally it is useful to analyse individual preparations from the daily practice at a fixed frequency, for example by the preparation of an excess.

A practical approach for the validation of non-standardised extemporaneous preparations may be:

- List all non-standardised extemporaneous preparations performed in a sufficiently long period.
- Group them according to their dosage form.
- Per dosage form: list all applied methods of preparation (such as capsule filling after dry mixing or using the solvent method).
- Specify all utensils used.
- Determine important factors for risk analysis: high frequency of preparation, critical preparation method (e.g. dispersing), critical quality requirement (e.g. content uniformity).
- Based on the combination of dosage form/preparation methods/utensils and on risk analysis, decide on way and frequency of validation.
- Decide which validations have to be performed generally and which have to be operator-specific.

Parameters to be analysed (this list is meant as a guidance):

- Capsules: content, uniformity of weight, content uniformity, appearance, disintegration time, dissolution rate.
- Cutaneous preparations: content, homogeneity, appearance, particle size, chemical purity, microbial purity.
- Solutions: content, appearance, homogeneity (especially with viscous solvents), chemical purity, microbial purity.
- Suppositories: content, mean weight, content uniformity, appearance, microbial purity.
- Suspensions: content, resuspendability, homogeneity, appearance, particle size.

How to choose model preparations:

- Active substance should be rather troublesome to process but doesn't need to be practically relevant (for instance acetylsalicylic acid in suppositories; hydrocortisone acetate to be dispersed in a cream base; salicylic acid to be dispersed in white soft paraffin).
- Analysis should be feasible and if possible easy to perform.

How to sample:

- Define the sample size. Generally 1 sample is sufficient for homogeneous preparations and 6 for divided dosage forms.
- Define the sampling method, for instance:
  - Capsules: per filled portion 3 from the corners and 3 from the center
  - Cutaneous preparations: 6 spread across the batch
  - Solutions: 1 or 2 random samples
  - Suppositories poured in series: first and last one plus 4 in between
  - Suspensions: take 2-3 samples after shaking, spread across the batch

34.15 Qualification of Premises, Installations, Equipment and Automated Systems

See also Chap. 27. Building-related installations (including utilities), preparation equipment and automated systems have to be qualified for use according to predetermined specifications based on specific user requirements (URS). For the qualification of equipment and installations specific guidelines are given in annex 15 of the GMP. Annex 11 of the GMP states that computerised systems should be validated [12, 13]. Detailed instructions for the validation of computer systems can be found in the document Good Automated Manufacturing Practice Guide for Validation of Automated Systems in Pharmaceutical Manufacture (GAMP) [14]. This guidance has been designed by the International Society for Pharmaceutical Engineering.

When, for example, a new machine is purchased, the following order of the qualification process might be used although other terminology may also be used:

- Determine user and regulatory requirements for the intended use of the machine (User Requirement Specification, URS).
- Draft functional and technical requirements (Functional Requirement Specification, FRS and Technical Requirement Specification, TRS).

- Usually the previous two steps are accompanied by a risk assessment to determine which requirements are mandatory and which are nice to have.
- Qualify the design (custom-made) or justify the purchase (Design Qualification, DQ).
- Carry out a factory acceptance test (FAT) and a site acceptance test (SAT), if applicable.
- Perform the installation qualification (IQ).
- Perform the operational qualification (OQ).
- Perform the performance qualification (PQ).

Depending on the associated risk, some of the above mentioned steps may be skipped or combined or extended.

The user enters the (legislative) requirements and his wishes concerning the equipment in the URS (see Sect. 21.5.2 for a URS based on risk assessment). Then he tries to find a supplier who can supply a machine or installation that meets the URS. After the URS the FRS has to be drafted. The FRS results from the translation of the wishes of the user (what should it be able to do?) to the functionality and design of a device or installation (how are the requirements met?). The functional requirements describe what the equipment should be able to do and how it should look, such as the size or the materials to be used. Sometimes technical requirements are laid down in a separate document, the TRS. On the basis of these specifications a vendor may then, if necessary, design the machine or installation. The more carefully the user prepares the URS and FRS, the better the quality of next steps are.

The next step is the Design Qualification (DQ), in which the purchase is justified and the design (when it is custom-made) of the equipment is approved, including drawings and documentation. It is important to prepare the first edition of the URS before agreement with the supplier and to finalise it in connection with the DQ at the latest.

For very large and expensive projects it is worthwhile to include FAT. If possible staff from the pharmacy should participate in FAT tests in order to become familiar with the equipment and in order to detect failures as soon as possible – this can save a lot of time and money. Usually, after delivery SAT is performed to check the correction of the deviations identified at the FAT and to detect any damage caused during delivery. Conclusion of SAT tests may have major legal and economical impact as handover of the equipment may be linked to finalisation of this step.

After delivery of the equipment the IQ is performed. In fact, this is a check to see whether the equipment is delivered and installed according to the specifications. Also, a check on the completeness of the documentation, such as operating, maintenance and cleaning instructions, calibration requirements and reports of critical meters, is carried out. It should also include technical drawings ('as-built' drawings) and diagrams (Piping & Instrumentations Diagrams (P & IDs)).

During the OQ the operation of the equipment is tested and measured effectively. The aim is to show that the system works as shown in the functional specification, according to pre-established acceptance criteria. The OQ includes tests for the system operation, calibration, operation of alarms and the simulation of emergency situations. Also a SOP and a maintenance plan have to be drafted in this stage.

The IQ- and OQ-tests may be performed by, or in cooperation with the supplier; the formal qualification is the responsibility of the user.

The final step in the validation process is the PQ, which is the verification of the suitability of the installation for the intended purpose in the production process. Often quality control of the finished product is involved in carrying out the PQ. An example is the measurement of the homogeneity of a mixture that is produced by a mixing machine. The PQ is performed by the user. When all the above-mentioned steps are completed, the equipment is qualified and can be used in a preparation process.

The different phases of the validation process can be shown in a V-model (Fig. 34.1), which shows the mutual relationships. Each step in the validation process reverts to a step prior to the purchase. This model was developed with a view to software validation, but may well be applied to equipment and installations.

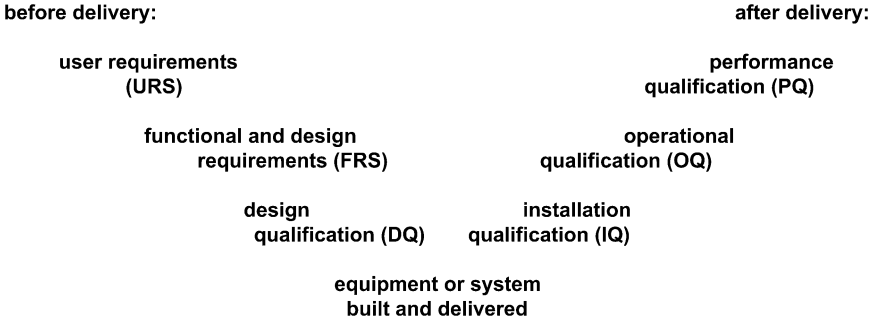

Fig. 34.1 V-model for qualification and validation

34.16 Cleaning

34.16.1 Good Cleaning Practice and Cleaning Validation

Proper cleaning of premises, equipment and utensils is essential to prevent microbiological and cross contamination (see Sect. 34.3). The purpose of cleaning validation is to demonstrate that the correct cleaning processes are applied, that the frequency is adequate and that cleaning leads to the desired result, namely the prevention of cross-contamination during preparation [8, 15]. In general, cleaning validation is necessary before use of new or changed facilities or equipment, in the context of corrective and preventive actions (CAPA, see Sect. 35.6.15) after non-conformities or monitoring trends and if cleaning procedures or materials are changed.

Cleaning validation begins by describing all cleaning activities and to standardise these when possible. The influence of the human factor in cleaning processes cannot be overestimated. Cleaning activities can be divided into cleaning of premises, equipment and utensils.

34.16.2 Premises, Workbenches and Worktops

Own staff may clean the premises, workbenches and worktops, but outsourcing is possible. In both cases, it is important to record what is being cleaned, with which tools and products and in what frequency. Supervision and control forms and logbooks are useful to determine whether these activities are performed in accordance with the agreements. In the case of outsourcing, it is necessary to agree on a service level agreement (see Sects. 36.4 and 32.9.1). It is also important that only people with proven background knowledge on hygiene perform cleaning.

Cleaning and disinfection of qualified areas such as clean rooms (see Sect. 31.4), require intensive training, a special attitude and a thoughtful system. This is necessary to ensure that the persons performing the cleaning do not cause the opposite.

Wet cleaning can constitute a problem with the moisture regulation. As the walls, floors and ceilings of clean rooms are basically airtight, introduced moisture has to be removed through condensation in the Heating Ventilation Air Conditioning (HVAC) system (see Sect. 27.5.1). This is not only energetically unfavourable, but it takes too long. This is a risk, because a too damp room promotes the growth of microorganisms.

Cleaning with a clean room vacuum cleaner (vacuum cleaner fitted with a HEPA filter) is preferred to remove dust. Dust from prior activities that is not removed through the HVAC system is accumulated, mainly, on the floor. To remove non-dusty dirt (e.g. spilled and dried liquids) damp cleaning is suitable, preferably with disposable mops on wipers. The required frequency of cleaning can be different for floors, walls, counter tops and ceilings. Affected places such as door handles, push buttons and switches should be explicitly addressed. For the cleaning of small surfaces disposable low-dust wipes may be used. Microfibre towels are suitable as well; they can be re-used after washing at minimal 70 °C and centrifuging at 1,000 rpm. The advantage is cleaning without moisture and detergents. The disadvantage is that they have to be used within a day after they are washed and centrifuged because of microbiological reasons.

Cleaning materials should not be moved from a less clean environment to a clean room. The use of dedicated cleaning materials for each manufacturing area is preferred.

There is an important difference between cleaning and disinfection. Cleaning is removing dirt and other unwanted substances. Disinfection is aimed at reducing germs on surfaces (e.g. worktops) and is effective only when the surfaces are cleaned beforehand (see also Sect. 31.4). In practice, the right order is: first cleaning and then, where necessary (for example, the work surface of a laminar flow cabinet), disinfection.

Monitoring of the cleaning is performed by visual inspection (note this in the logbook), but also by microbiological monitoring and wipe tests. Microbiological monitoring provides insight into the microbiological contamination of critical points in rooms. Since microorganisms are often attached to dust particles, microbiological monitoring also gives an indication of the particle contamination. By sampling before and after cleaning the quality of the cleaning can be measured. At high risk processes, e.g. preparation of antineoplastics or radiopharmaceuticals, periodic surface sampling (wipe tests) is performed to check the cleaning (see Sect. 26.5.4). These wipe tests have to ensure the safety of employees, but the results of the wipe tests also provide an insight into the quality of the cleaning.

The validation of the cleaning of rooms is required for surfaces that may come into contact with the product. It can be executed retrospectively by checking whether all scheduled cleaning activities are performed in accordance with the agreements and whether correct actions have been taken with any deviations. Furthermore, the results of the microbiological monitoring, wipe testing and validation of air quality gives quantitative information on the quality of the cleaning processes. By setting limits, conclusions can be drawn about the effectiveness of cleaning activities.

34.16.3 Equipment

The operating instructions of equipment provide information as to how it is cleaned. After cleaning, each apparatus must be visually checked for residues of the product or detergent (if applicable). The spots of the equipment to be visually checked must be well defined, based upon experiments with, for instance, contamination with riboflavin (see further). However, this is not sufficient, because not all residues are visible and some equipment cannot be inspected entirely.

Cleaning validation is required only for surfaces of multipurpose equipment that come in direct contact with the product. When using dedicated equipment only verification of the cleaning process is necessary. Attention should be paid to so-called hot spots: difficult-to-clean locations, which if improperly cleaned would lead to contamination.

Sampling should be performed through wipe tests and by collecting flushing liquid. Hot spots can be detected by UV light when a model substance such as riboflavine is used in the test procedure. The suitability of the sampling procedure has to be proven. In the analysis of rinse water, it is important that the cleaning has been carried out in the correct manner. When cleaning a production vessel, the rinsing of the inside of the lid could be forgotten. If the rinse water is clean nothing can be concluded about the cleanliness of the production vessel. As an example, in a kitchen one will not decide upon the cleanliness of a pan only from the clarity of the rinse water. Because a wipe test is conclusive about local cleaning, both methods should be carried out [8, 16].

For many devices, the microbiological purity is of importance for the quality of the products prepared with it. This equipment must be designed and constructed 'sanitary'. This means that all parts that may come into contact with the product must be cleanable and that after cleaning, no moisture remains. A chemical cleaning (often an alkaline detergent, followed by an acid agent for neutralising) combined with rinsing leads to a strong bacterial reduction. Microbiological controls, including the determination of total bacterial count in a subsequent preparation, provide information about the cleaning procedure.

For the validation of the cleaning of equipment existing products or model substances can be used. When validating a solution a model substance is chosen of which the solubility is similar to the worst-soluble substance in the preparation, since this is the most difficult to remove (worst-case approach). Per device or preparation method the nature of the model substance(s) (organic, inorganic, or both) is substantiated. Because the pH may affect the solubility of active substances and excipients this must be taken into account in the design of the flushing procedure and the choice of the model substance.

Furthermore, the analytical methods to assess the rinse and wipe samples have to be validated. Also, the recovery of the test substance during sampling has to be established.

The amount of an active substance that may be present in the next product must meet established criteria, such as the strictest of the following three conditions [8]:

- Up to 0.1 % of the normal dose of each product may be detectable in the maximum dose of the next product.
- Up to 10 ppm of each product may be detectable in the next product.
- No residual should be visually perceptible.

To assess acceptance criteria for cleaning validation, limits for the maximum allowable carryover of product residues must be calculated, based on the pharmacological or toxicological properties of the substances studied and their permitted daily exposure (see Sect. 26.7.2). A risk assessment may be useful to support choices and decisions.

If allergens, steroids or antineoplastics are prepared, these must not be detectable above the detection limit of the analytical method used [8], but see also Sects. 26.5.4 and 26.8.

The detection limit of model substances should be low enough to meet the established requirements.

Finally, the dirty hold time and the clean hold time have to be established [17]. When a vessel is not cleaned immediately after use, the remnants may dry in so the vessel may not be cleanable using the normal procedure. The dirty hold time is the time for the cleaning to be completed to be sure that the validated cleaning procedure is still effective. The clean hold time is the time that the equipment may be considered clean after performing cleaning and sanitisation (if applicable) and can be safely used for the next production.

34.16.4 Utensils and Clothing

Tools or utensils used for manufacturing include glassware, mortars and spoons. Because the cleanliness of these items and of clothing and clogs directly or indirectly may influence the quality of the product, the cleaning of tools and clothing has to be validated.

Utensils and clogs can be cleaned and disinfected manually or mechanically. A manual cleaning is difficult to validate. Only the end result can be assessed by visual inspection and by analysing random wipe and rinse samples. To avoid unnecessary validation activities, the use of disposables can be considered.

Mechanical cleaning is more reproducible and therefore better to validate. A disinfection step can be introduced by increasing the temperature to above 80 °C by the end of the cleaning phase, so the cleaned articles are germ-free after the procedure. The process can be monitored by measuring the temperature, the use of detergents and the conductivity of the

process water. In addition, tools are available that can demonstrate the cleaning effect of the process (e.g. Tosi® test). Random sampling for visual, analytical and microbiological checks of the final result may yield additional substantiation of the quality of the cleaning and disinfection process. Separate attention must be paid to the drying and storage of utensils, because recontamination must be avoided.

> The Tosi® test is a validated cleaning indicator, which is made up of a grooved stainless steel plate on which a strong adhesive red colored substance has been applied. This plate is mounted at a very narrow angle in a transparent plastic container. At the end of the cleaning process, the plate must be fully free of the red test substance. If not, the cleaning process has been insufficient.

Garments can be thrown away after use (disposable clean room overalls), or reused after cleaning. If clothes are used that are cleaned in house, validation of this process will not be easy. Therefore, the use of clothing cleaned and packaged by specialised and, preferably, certified companies is preferred.

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Pharmaceutical Quality Systems

35

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Contents

Abstract

A quality management system (QMS) is an important tool for process control and continual improvement. After a brief section about development of the quality principle in the preparation of medicines over the years, this chapter lists the processes in preparation and in the manufacture of medicines that have to be controlled. A medicine, whether developed in a pharmacy or in industry, starts with defining the needs of the patient. Then the formulation and the method of preparation are designed to meet product specifications. The next step of the product life cycle is the production, including quality control and release.

In practice pharmaceutical quality management systems (PQSs) may follow the structure of quality standards for medicines, mainly GMP, PIC/S-GPP, and Q10 to which GMP is referring. These standards are described as well as standards that are more applicable to preparation in the pharmacy i.e. the Ph. Eur. monograph Pharmaceutical Preparations, the Council of Europe (CoE) Resolution and USP Compounding Standards. If a PQS has to cover the complete life cycle of the product, preparation in pharmacies or even all pharmacy activities then a more universal structure such

Based upon the chapter Kwaliteitszorg by Mieke de Blois en Yvonne Bouwman-Boer in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_35, © KNMP and Springer International Publishing Switzerland 2015

as 7 Pillars or ISO 9001 may be used, more precisely the EN 15224 as it applies to health care.

Any of these structures or models contains similar elements. These are dealt with including: Quality Manual, Management review, Change management, Complaints, Deviations and Recall.

Keywords
QMS • Quality • PQS • GMP • Q10 • ISO 9001 • EN 15224 • Regulation • 7 pillars • Standard

35.1 The Purpose of a Quality Management System

The processes of design and preparation of medicines need to be controlled, monitored and continually improved in order to deliver products with the intended quality now and into the future. This may be accomplished in a controlled and structured way: using a quality management system (QMS), which for pharmaceutical preparations is more commonly called a Pharmaceutical Quality System (PQS). The implementation of a PQS supports the operations in the highly regulated field of medicinal products. This field is characterised by high-level professional standards and comprehensive requirements to transparency and documentation.

A QMS is common to all types of organisations and products and generally intends to achieve:

- A system, that allows the delivery of products or services of the right quality
- A state of control through shared standards and effective monitoring and control systems
- Facilitation of development and continual improvements

All QMSs circle around the query: how does everything that happens within an organisation affect the final quality?

The concept of managing the processes – maintaining them and continually improving them as well – is visualised by Deming's quality circle, also called the PDCA-cycle: Plan, Do, Check, Act (see Fig. 35.1).

The Deming cycle entails: make a plan for an improvement, do it, check whether the desired result is obtained, and act from now on in this way. Continuous monitoring of the result, if necessary followed by (further) adjustment, allows for a structured quality improvement. In the pharmaceutical area a QMS (PQS) is also necessary for the demonstration of compliance with regulatory requirements and professional standards. Thus, the Ph. Eur. monograph Pharmaceutical Preparations (see Sect. 35.5.3) states: "Manufacture/preparation must take place within the framework of a suitable quality system and be compliant with the standards relevant to the type of product being made."

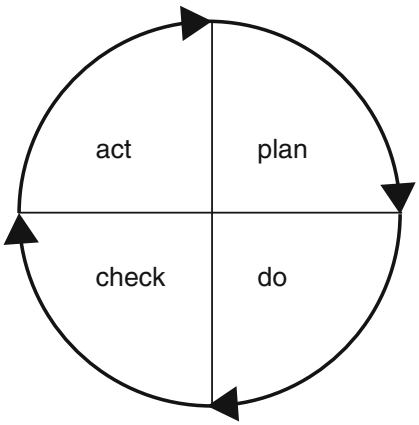

Fig. 35.1 Deming's circle or PDCA-cycle for quality improvement

Definitions of some frequently used quality terms are as follows:

Quality	The degree to which a set of inherent characteristics of a product or service fulfils requirements. Requirements may be prescribed by law, but may also reflect needs and expectations of organisations, customers and other stakeholders, in short: of society.
Quality management	All activities of the management of an organisation meant to achieve and demonstrate the intended quality level as well as further improvement. These activities require a joint contribution from all concerned.
Quality management system	A set of interrelated or interacting elements that organisations use to direct and control how quality policies are implemented and quality objectives are achieved.
Quality control (QC)	The operational measures that are taken to meet the specified requirements. This includes the activities for maintaining the quality management system, such as analysis of the product, procedures for change control, deviations and complaints, internal and external auditing.

35.2 Structure of the Chapter

For pharmaceutical manufacturing it is quite common to refer immediately to GMP guidelines (see Sect. 35.5.7) if considering a PQS. Section 35.3 accounts for the historical background of that approach. There are a few reasons however for this chapter to put the PQS in a broader perspective, such as that of the International Standards Organisation (ISO, see Sect. 35.7.2):

- The general ISO approach of quality is more conceptual and applies, thus connects, to all other enterprises in society.
- GMP is absorbing by and by the ISO concepts.
- Pharmacies, as opposed to manufacturers of medical products, are part of health care organisations, which have clinical processes as their principal activity.

Pharmacy preparation is essentially a clinical process if it is meant (see Sect. 3.2) to provide patients with the medicines they need and which are not available as licensed medicines. ISO, especially its particularisation to health care EN 15224, can be applied to healthcare organisations. So it can be applied to pharmacies as well. The EN 15224 consideration that 'pharmaceuticals to be regulated elsewhere' applies to licensed medicines but not to pharmacy preparations.

GMP is principally directed at and very specialised in the manufacturing of licensed medicinal products. GMP lacks therefore some principles that are necessary for a PQS for pharmacies.

Section 35.3 gives the development of pharmaceutical quality thinking. Section 35.4 describes the Product Life Cycle for pharmacy preparations as well as for licensed medicines. A PQS has to cover the life cycle of a medicine.

Section 35.5 is about Legislation and Quality Standards, for pharmacy preparation and for manufacturing. These give the quality objectives as well as some guidance how to create a PQS.

Section 35.6 describes a large series of PQS elements, each of them with examples from pharmaceutical preparations. The extent of their use in the manufacturing situation or in pharmacies depends on the outcome of risk assessments. As elements they should principally be adhered to in both situations.

Section 35.7 tries to put all elements of a PQS into a structure, a visualisation that helps to keep an overview.

In many hospital pharmacies the structure of a PQS for the production department will probably be found in its Quality Manual that contains all SOPs, well structured in chapters, presumably those of GMP. If however characteristics such as benefit/risk ratio, timeliness, availability or patient empowerment have to be added, a hospital pharmacy may be better off with a structure that uses the ISO 9001–EN 15224. Such a structure may be useful as well if the PQS for production has to be merged with the PQS for the whole pharmacy.

35.3 Pharmaceutical Quality Development

This section shows how ideas about guaranteeing pharmaceutical product quality have developed over time.

In the early days of the 1960s through to the late 1970s, quality activities in relation to the production of medicines, as of other products, mainly focussed on product control: on detection and subsequent restoration or elimination of flawed products. Organoleptical controls were utilised as a pharmaceutical key competence and laboratory testing played a key role. The quality management of products was based on professional standards, knowledge and experience. However, even though the professionalism was high, quality varied. Documentation of decisions and production data was poor and knowledge management challenging. As shortcomings in processes do not always become apparent and as not all shortcomings in the product quality are detectable, it was understood that end product testing was not sufficient. Quality had to be built into the products.

Building quality into the product has always been an important process for pharmacy preparations in order to obtain confidence about the finished product. The analytical quality control of the product may be limited because of the limited access to analytical resources (or even lack thereof) or because of the immediate need for the product, and often the 'batch' only comprises of one preparation. The entire process from the request by the doctor, design of formulation and preparation was for a long time in the hands of one expert: the pharmacist that worked *secundum artem* (literally: following artisanal rules). Due to the involvement with all stages of the process this pharmacist encountered no barriers to implement necessary processes immediately. Later the *secundum artem* concept developed more and more into quality thinking. Pharmacy preparation still puts great emphasis on in-process controls and the individual pharmacist being acquainted with all stages of the process.

For industrial production, in addition to product control, process control was introduced. This occurred mainly with the introduction of Good Manufacturing Practices (GMP) regulation but also with pharmacopoeial requirements.

> The GMP directives were composed in the 1960s in the United States and a GMP guide was issued as the Orange Guide in the UK in 1971. In 1989 the GMP directives were introduced in Europe. They can be considered as a collection of instructions, warnings and recommendations that intends to minimise all risks for the product and thereby guaranteeing constant yield and quality. It serves patient and manufacturer.

(continued)

Worldwide the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, see also Sect. 35.5.9) is involved in further development of GMPs. The ICH is a collaboration of the pharmaceutical industry and registration authorities from Europe, the United States, and Japan. The initial objective of this organisation in the 1990s was harmonisation of the technical regulations and requirements for the registration of medicinal products, to accomplish that registration in different countries could be obtained as fast, efficiently, and cost-effectively as possible. Since the beginning of the twenty-first century, the objective has shifted more towards international harmonisation in general.

The concept of the Qualified Person (QP, see also Sect. 25.3.4), giving the final responsibility for release to an appointed individual with a required set of skills, was introduced in manufacturing through the EU GMP. The QP responsibility includes all aspects in relation to quality of the released products as well as conformance with regulatory requirements as appropriate. Even today the QP concept is a keystone in EU GMP, and to be seen as a significant difference in GMP understanding compared with other regions.

Process control is defined as taking measures to monitor and, if necessary, adjust processes that lead to the end product. Quality of products can still not be guaranteed but a production based on professional standards aims to build quality into every step of the preparation process.

Subsequently, system control was introduced, through defining preconditions for the prime processes, such as well-trained personnel, adequate premises and equipment. Continuous improvement was going to be supported by, among others, Root Case Analyses and Systems for Corrective and Preventive Actions (CAPA). The need was recognised of structured decisions based on Quality Risk Management (see Chap. 21).

The concept of Supply chain management was subsequently developed. All parties in the supply chain cooperate on quality for the end user.

Ultimately, all processes, including all personnel, determine the quality of the product and associated services. For everything that happens within an organisation, the senior management asks the question: "How does this affect the final quality?" This approach is called total quality management, and quality improvement is pivotal in maintaining a quality system. Ideally, a learning organisation is created, founded on the rationale that continuous quality improvement and innovation are required to meet the ever-increasing demands of customers and the achievements of competitors.

From about 2000 especially the pharmaceutical industry pays more attention to the importance of the quality of design of the formulation and preparation method. The concept of Quality by design was introduced. With small-scale preparation in pharmacies, the design phase has always been part of preparation as design and preparation of a medicine were, together, including the prescription assessment.

In recent years focus is on Quality Leadership: the need of commitment from senior management to quality.

Besides quality, also the costs of a product are of importance for an organisation. Manufacturing industry utilises the terminology Lean Management to promote an approach that leads to a both qualitatively sound and cost-effective product. Some key elements in Lean Management are:

- Constant and persisting focus on the needs of the customer
- A systematic elimination of any waste (in relation to value for the customer)
- A standard approach to elimination of variations and continuous improvements

35.4 Product Life Cycle

With the development ICH Q10 (see Sects. 35.5.9 and 35.7.4) as a standard for a pharmaceutical quality system, the process approach (maintenance as well as improvement) was emphasised. Q10 states as well that a PQS should cover the whole product life cycle. This section describes the product life cycle of medicines, for preparation in pharmacies as well as for industrial production. A medicine whether developed in a pharmacy or in industry is designed to meet the needs of the patient and starts with clarifying that need. The product life cycle consists of a series of processes that need to be controlled and continually improved in order to deliver products with the intended quality.

35.4.1 Product Life Cycle Approach

Generally the product life cycle consists of four main processes:

- Pharmacotherapeutics
- Formulation
- Preparation process
- Storage & Distribution

This description will usually do for pharmacy preparations. Pharmacy preparation sees that the patient's need is combined with a knowledge of pharmacotherapy with a known

active substance. The assumption of a positive benefit/risk ratio regarding this pharmacotherapy leads to a request, commonly a physician's prescription, for the active substance in a suitable dosage form. Next a formulation, a way of preparation and packaging have to be designed, specifications set and assays developed. The actual preparation has to be started. If more patients need this medicine, the preparation has to become predictable and reliable to deliver more preparations or even batches with a constant quality and yield. Quality control has to be defined, as well as release, storage, distribution and transport. The actual use of the preparation by the patient should lead to any form of feedback about effectiveness and safety, patient friendliness and fitness for the healthcare process that it serves. The life cycle of a pharmacy preparation will end with a discontinuation, usually because of a new licensed medicine with a better benefit/risk ratio. Sometimes its life cycle ends due to e.g. unavailability of substances or packaging materials or to stability problems.

The life cycle of a licensed medicine follows this sequence as well, although it is much more regulated and with formally separated processes, due to larger batches and widespread use.

For industrial production the Product Life Cycle for new and existing products is characteristically defined by ICH Q10 as a sequence of four groups of technical activities, with subgroups:

Pharmaceutical Development
- Active substance development
- Formulation development (including container/closure system)
- Manufacture of investigational products
- Delivery system development (where relevant)
- Manufacturing process development and scale-up
- Analytical method development

Technology transfer
- New product transfers during development through manufacturing
- Transfers within or between manufacturing and testing sites for marketed products

Commercial manufacturing
- Acquisition and control of materials
- Provision of facilities, utilities, and equipment
- Production (including packaging and labelling)
- Quality control and assurance
- Release
- Storage
- Distribution (excluding wholesaler activities)

Product discontinuation
- Retention of documentation
- Sample retention
- Continued product assessment and reporting

The following sections discuss the Product Life Cycle in more detail, mainly based on the four main processes for preparation in pharmacies.

35.4.2 Pharmacotherapeutics

Pharmacotherapeutics for pharmacy preparation is about prescription assessment, information of physician and patient, and pharmacovigilance. The therapeutic quality of the product is the outcome of a benefit/risk balance. It accounts for efficacy and effectiveness, patient friendliness and the contribution to the safety of healthcare processes (see Sect. 2.2). The benefit risk balance at the start of the life cycle is assumed to be positive, which has to be proven to a reasonable extent before the patient gets the medicine. For pharmacy preparation a review of literature, medical opinion and sound thinking usually provides the start. The benefit risk assessment is the duty of care of all health professionals involved, as it is put in the Ethical guidance and considerations of the Ph Eur monograph Pharmaceutical Preparations (see Sect. 35.5.3). The CoE Resolution on Pharmacy Preparation (Sect. 35.5.4) also mentions this duty: the pharmacist has to prove the 'added value' compared to licensed medicines. Documentation of these professional decisions is essential for building up knowledge, communication between healthcare professionals and from a liability point of view. Forms for this type of documentation are given in Sect. 2.2.

For the application for a marketing authorisation clinical trials have to be performed. An official European body, the European Medicines Agency (EMA), assesses the therapeutic benefit risk ratio.

An EMA project on benefit-risk methodology is being performed. Some approaches of the assessment method have been published [1].

If the medicine is used for other indications its benefit risk balance will be different and should be assessed again. If not the medicine is used 'off-label'.

After the introduction or start of use of any medicine, the benefit risk ratio may be changed, because of:
- Unknown adverse reactions
- Unexpected problems with product stability e.g. the detection of toxic degradation products
- New indications
- Development of better therapeutic alternatives
- Unexpected differences between groups of patients

These possible changes necessitate monitoring: pharmacovigilance. Pharmacovigilance has been defined by the

World Health Organisation as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem [2]. For the monitoring of the pharmacotherapy of licensed medicines, the qualified person for pharmacovigilance (QPPV see also Sect. 25.4.4) has to handle complaints and reports of suspected adverse events. Monitoring occurs by a regulated system of pharmacovigilance. Patients, caregivers and health care personnel may be questioned, and regular product reviews are created, including the analysis of complaints and of literature. This monitoring may lead to a conclusion that the active substance is not beneficial any more, the dosage form should be changed, indications added, volume or packaging improved etcetera.

Pharmacovigilance for pharmacy preparations has not yet been developed very well. However in some countries the competent authority expects pharmacies to have pharmacovigilance procedures.

The information about the therapeutic qualities of licensed medicines is part of the product dossier to obtain and keep a marketing authorisation. For pharmacy preparations information about therapeutic quality and about its monitoring can be part of the product file (see Sect. 33.8).

35.4.3 Design of Formulation and Method of Preparation

The formulation has to meet the needs of the patient with active substances, excipients, dosage form and package, it has to meet (regulatory or professionally set) product specifications and it should support a sound production process (see Chap. 17 Product design). The preparation's stability plays a large role, its shelf life has to be predicted and analysed (see Chap. 22 Stability) and instructions for use have to be developed (see Chap. 37 Instructions for use).

A good and well-organised documentation of the design process can be very supportive and time-saving on many moments in the product's life cycle. It will help when process deviations need to be explained or changes need to be made.

For the design of pharmacy preparations the pharmacist refers to knowledge sources, such as this textbook. Chaps. 4–14 describe the essentials of the design processes for most dosage forms.

For the specifications of the active substances, excipients and dosage forms the pharmacist can refer to the Ph. Eur. If it is necessary to deviate from these requirements to meet the needs of the patient, the pharmacist should document the rationale for that decision in the product file (see Sect. 33.8). For the documentation of the decisions about the design and the risk assessment, some checklists and forms are available, see Sect. 2.2. The process of formulation design may be laid down in SOPs for different dosage forms.

For licensed medicines the description of the design has to be given by the manufacturer in the registration dossier. Notices to applicants contain instructions for a registration dossier, which can be used in consultation with national professionals and the EMA. Furthermore, scientific recommendations from the Committee for Medicinal Products for human use (CHMP), Reflection papers, and Scientific guidelines (see Sect. 35.5.1: Volume 3 of the Rules) are available. So-called European Assessment Reports (EPARs) of specific licensed medicines can be quite informative about design backgrounds. They are published at the EMA website. The national registration authority or the EMA (pan-European) have to approve the quality of the design.

35.4.4 Preparation or Manufacturing Process

The production process is the most visible and most extensive part of the Product Life Cycle. Several pharmaceutical quality systems in use support 'just' the preparation process. These PQSs may extend from the involvement of senior management, handling complaints, change management, maintenance of facilities and documentation, self-inspection to analysis and knowledge management. These elements are elaborated in Sect. 35.6. Structures to group these elements in a logical way are discussed in Sect. 35.7.

35.4.5 Distribution

A PQS usually covers the distribution process as well. GMP (see Sect. 35.5.7) specifies the distribution being part of the PQS in Chap. 1 Pharmaceutical Quality System:

- Records of manufacture including distribution which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.
- The distribution of the products minimises any risk to their quality and takes account of Good Distribution Practice.
- A system is available to recall any batch of product, from sale or supply.

Information on storage of medicines, transport and distribution is dealt with in Chap. 36 Logistics.

35.5 Pharmaceutical Legislation and Guidelines

35.5.1 PQS, Legislation and Guidelines

The quality characteristics of medicinal products and quality objectives of a preparing pharmacy or manufacturer are generally and sometimes in detail covered by European and national legislation and guidelines. A quality system for medicinal products will therefore have to connect with the appropriate legislation and professional guidelines that are meant to support their quality.

Legislation is aimed at the protection of the citizen, and are nowadays often supranational. The professionals, for instance the national pharmaceutical society, may have defined standards for the implementation of or complementing the regulations.

This section deals at first with the basic European legislation on medicines. Then follows the monograph Pharmaceutical Preparations of the Ph. Eur. This is legally binding for preparation in pharmacies as well as for industrial manufacturing and it covers three parts of the product life cycle: pharmacotherapeutics, product design and preparation process. It states the need for a PQS by: "Manufacture/preparation must take place within the framework of a suitable quality system and be compliant with the standards relevant to the type of product being made."

With regard to preparation in pharmacies three other guidelines are relevant: the Council of Europe (CoE) Resolution on Pharmacy Preparation, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) – Good Preparation Practice (GPP) Guide, and the professional guideline USP Compounding standards. Some other European professional guidelines are mentioned as well, which however are not easily accessible due to their language.

For licensed medicines the GMP guidelines are legally binding, insofar that other practices are allowed on the condition that the same principles are fulfilled. They give many details on production and a PQS. The EU GMP (see Sect. 35.5.7) states that a manufacturer should establish, document and implement a "comprehensively designed and correctly implemented QMS incorporating Good Manufacturing Practice and Quality Risk Management". The GMP principles apply as well to preparation in pharmacies. The global International Conference on Harmonisation (ICH) guidelines Q8, Q9 and Q10 are mainly in use in industrial production. The regulatory function of the Qualified Person, with functional connections to a PQS, is dealt with in Sect. 35.5.7 and Chap. 25 Human Resources. Regulations about Investigational Medicines are shortly dealt with in Sect. 35.5.10 with focus on the tasks of hospital pharmacists.

35.5.2 European Directives, Regulations and Guidelines

European legislation on medicines for human use consists of several directives and regulations, further referred to as 'Rules'. They are clustered in Volumes, to be found at [3]. The main series that are relevant for the production of medicines are in Volume 1 and 4.

In Volume 1, EU pharmaceutical legislation for medicinal products for human use, the main directive is Directive 2001/83/EC on the Community Code relating to medicinal products for human use. It is directed at licensed medicines. Pharmacy preparations are however mentioned in Article 40:

> However, such authorisation shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally licensed in the Member States to carry out such processes.

Directive 2001/83/EC points with Article 47 2nd paragraph at the Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice (see Sect. 35.5.7) in respect of medicinal products for human use and investigational medicinal products for human use. In the introduction on GMP it is stated that

> The principles of GMP and the detailed guidelines are applicable to all operations which require the authorisations (..). They are also relevant for pharmaceutical manufacturing processes, such as that undertaken in hospitals.

The definition of pharmaceutical manufacturing processes is however not given.

Articles 48 49, 51 are about the Qualified Person that has to be at disposal of any Manufacturer's Authorisation Holder (see further Sect. 25.3.4).

This basic legislation is supported by a series of guidelines:

- Volume 2 – Notice to applicants and regulatory guidelines for medicinal products for human use and specific rules for medicinal products for paediatric use, orphan, herbal medicinal products and advanced therapies (mentioned in Sect. 35.4.3)
- Volume 3 – Scientific guidelines for medicinal products for human use (mentioned in Sect. 35.4.3)
- Volume 4 – Guidelines for good manufacturing practices for medicinal products for human and veterinary use (see Sect. 35.5.7)
- Volume 8 – Maximum residue limits (mentioned in Sect. 22.4.2)

- Volume 9 – Guidelines for pharmacovigilance for medicinal products for human and veterinary use (mentioned in Sect. 35.4.2)
- Volume 10 – Guidelines for clinical trials (see Sect. 35.5.10)

Guidelines are meant to guide the implementation of legislation, as it is stated for instance: "Volume 4 contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively."

35.5.3 Pharmaceutical Preparations Ph. Eur.

This monograph [4] had its first edition in 2011. It applies to all pharmaceutical preparations: licensed medicines as well as pharmacy preparations; or in other words: to licensed as well as unlicensed medicines.

Pharmaceutical Preparations Ph. Eur. monograph contains the sections:

- Introduction
- Definition
- Ethical considerations and guidance in the preparation of unlicensed pharmaceutical preparations
- Production
  - Formulation
  - Active substances and excipients
  - Microbiological quality
  - Containers
  - Stability
- Tests
  - Appearance
  - Identity and purity tests
  - Uniformity
  - Reference standards
- Assay
- Labelling and storage
- Glossary
  - Formulation
  - Licensed pharmaceutical preparation
  - Manufacture
  - Preparation (of an unlicensed pharmaceutical preparation)
  - Reconstitution
  - Risk assessment
  - Unlicensed pharmaceutical preparation

Especially the Ethical considerations are important for a PQS for pharmacy preparation:

> The underlying principle of legislation for pharmaceutical preparations is that, subject to specific exemptions, no pharmaceutical preparation may be placed on the market without an appropriate marketing authorisation.
>
> The exemptions from the formal licensing requirement allow the supply of unlicensed products to meet the special needs of individual patients. However, when deciding to use an unlicensed preparation all health professionals involved (e.g. the prescribing practitioners or the preparing pharmacists or both) have, within their area of responsibilities, a duty of care to the patient receiving the pharmaceutical preparation.
>
> In considering the preparation of an unlicensed pharmaceutical preparation, a suitable level of risk assessment is undertaken.
>
> The risk assessment identifies:
> - the criticality of different parameters (e.g. quality of active substances, excipients and containers; design of the preparation process; extent and significance of testing; stability of the preparation) to the quality of the preparation; and
> - the risk that the preparation may present to a particular patient group.
>
> Based on the risk assessment, the person responsible for the preparation must ensure, with a suitable level of assurance, that the pharmaceutical preparation is, throughout its shelf life, of an appropriate quality and suitable and fit for its purpose. For stock preparations, storage conditions and shelf life have to be justified on the basis of, for example, analytical data or professional judgement, which may be based on literature references.

These guidance points at three processes that are part of pharmacy preparation's life cycle: pharmacotherapeutics, product design and preparation process. Therefore to be in accordance with this Ph. Eur. monograph, the corresponding quality system should cover all three processes, including responsibilities, to be most useful. The monograph gives further guidance to the process of formulation design.

The ethical considerations of the monograph may, for instance, be specified by the following paragraph, to be included in the PQS of a specific hospital pharmacy (see Sect. 35.7.6):

The duty of care for the pharmacist implies that he considers the consequences for his patient(s) of not preparing a preparation that is required by the physician and the patient. He may consider the availability of a specific medicine to be more important than the degree of quality assured by a licensed preparation. The pharmacist should balance the safety of the product (therapeutic qualities including toxicity and adverse events, design quality and product quality) and the unavailability of the medicine. This balancing (see Sect. 2.2) refers to an individual patient in case of an individual preparation or to a defined indication or patient groups in case of a stock preparation.

35.5.4 Resolution on Pharmacy Preparation (Council of Europe)

The full title of this resolution is: Resolution CM/ResAP (2011)1 on quality and safety assurance requirements for

medicinal products prepared in pharmacies for the special needs of patients [5]. The aim of this resolution is "to set a standard for national requirements for quality and safety assurance for pharmacy preparation in community and hospital pharmacies." It mentions many levels of pharmacy preparation: from industrial manufacturing of unlicensed medicines to extemporaneous preparation for a single patient and reconstitution on the wards.

For the quality management system of the preparation process, reference is made to the GMP and the PIC/s GPP, the PIC/S seen as 'GMP light' (see Sect. 35.5.5). The choice between these should be determined by a risk assessment that has to include the scale of preparation.

The Resolution states: "All pharmacy-prepared medicinal products should be prepared using an appropriate quality assurance system. Before preparation, a risk assessment should always be carried out in order to define the level of the quality assurance system which should be applied to the preparation of the medicinal product. It is recommended that the PIC/S GPP Guide be used for an appropriate quality system for "low-risk preparations" and that the GMP Guide be used as a reference for "high-risk preparations". The application of other guidelines with an equivalent quality level is possible, depending on the national legislation or guidance."

If the pharmacist however has to assess which products are 'less critical' he may as well use the GMP principles as starting point. These principles are valid for any sort of preparation; they just have to be detailed and specified (by a risk assessment, see Sect. 21.6.3) for any pharmacy preparation situation.

For the quality management of therapeutic assessment of the physician's request and formulation design (two other processes of pharmacy preparation's life cycle), no reference is made other than to professional responsibility and education. In this way, the Resolution (and thus its example model for a risk assessment) is rather unbalanced, because too much is focussed on the preparation process itself.

The Resolution seems valuable as a starting point for further standards, and will play its role in complicated legal discussions about how to regulate large-scale preparation of unlicensed medicines. However because its risk assessment procedure is not covering therapeutic qualities and formulation design, it may not lead to the best way to assure the quality of patient medication. The Ph. Eur. monograph (Sect. 35.5.3) puts the different aspects in better balance.

35.5.5 PIC/S GPP Guide

The Guide to good practices for the preparation of medicinal products in healthcare establishments (PIC/S-GPP Guide) [6] was published in 2008. It states: "the basic requirements presented in this Guide apply to the preparation of medicinal products normally performed by healthcare establishments for direct supply to patients."

The PIC/S is a global organisation that is committed to harmonisation and mutual recognition of the inspections of various countries. It publishes inspection guides, which can serve as guidance to inspections by National Authorities. One of these guides is the GMP guide:

PE 009-10 Guide to good manufacturing practice for medicinal products – Part I (2013); – Part II (2013); – Annexes (2013). The content of this guide resembles, more or less, European GMP, except for a few definitions.

Furthermore, PIC/S publishes recommendations regarding various GMP topics. Examples are

- Recommendations on general aspects of validation (PI 006-3)
- Recommendations on the validation of aseptic processes (PI 007-4).

It is considered as a GMP for pharmacy preparation, has a GMP-like structure and starts from the same principles. It is easier to read than the GMP because details not referring to pharmacy preparation are left out. Deviations from GMP (for instance in Annex 1 on Sterile Preparation) are however not explained. It was developed before the CoE Resolution (Sect. 35.5.4), which refers to it, or the Ph. Eur. monograph (Sect. 35.5.3). The Resolution limits the use of PIC/S GPP to 'less critical products'.

The PIC/S GPP Guide approaches pharmacy preparation from an industrial production process perspective, only marginally acknowledging specific qualities of the preparation process in pharmacies. Only a differentiation based on scale is made: between extemporaneous and stock production.

GPP touches upon the processes: assessment of the physician's prescription or formulation design in the Documentation paragraph: "a pharmaceutical assessment of therapeutic rationale, safety data, toxicity, biopharmaceutical aspects, stability and product design should be carried out, before preparation takes place." No further details are established however.

So from a quality system viewpoint the PIC/S GPP can only be used for quality of the preparation process, not for prescription assessment or design of formulation.

35.5.6 Professional Guidelines

35.5.6.1 European Professional Guidelines

The results of an enquiry in 2009 by EDQM [7] highlight that most European countries have professional guidelines for pharmacy preparation. Most of them only give a global description. Only some of them include the therapeutic rationale and pharmacovigilance. This situation might have been improved in the meantime.

Professional guidelines to be mentioned:

- Referenzsystem Qualität für Spitalapotheken (in German and French) [8], a Swiss PQS for hospital pharmacies. It is compatible with the ISO 9001 methodology, see also Sect. 35.7.6.
- ADKA guidelines from the German Society of German Hospital Pharmacists (ADKA) (in German):
  - Preparation and quality control in hospital pharmacy (2005) [9].
  - Aseptic preparation and quality control of ready-to-administer parenterals (2012) [10].
- GMP-H(ospital pharmacy) from the Dutch Society of Hospital Pharmacists NVZA, The Netherlands (in Dutch), contains the interpretation of GMP guidelines and Addenda on Formulation and Preparation method design, Extemporaneous preparation, Aseptic handling and Occupational Health and Safety [11].
- UK Guideline on the Quality Assurance of Aseptic Preparation Services by the Regional Quality Control Pharmacist's Committee [12].

The accessibility of these professional guidelines for the international reader may be limited because of the language.

As none of the European regulations or models yet cover the complete process of pharmacy preparation, European professional guidelines may still be very welcome as an elaboration of the Ph. Eur. monograph. Such guidelines should cover as said all main processes and pay attention to specific preparation processes in pharmacies such as:

- Adapting licensed medicines (see Sect. 5.5.1)
- Aseptic handling (see Chap. 31)
- Extemporaneous preparation from raw materials (see Sect. 33.5)
- Preparation in non-dedicated rooms (see chapter Premises)
- Conditional release (see Sect. 34.9.3)
- Validation of small batches (see Sect. 34.14.3)

35.5.6.2 USP Compounding Standards

USP being a private company, USP standards can be considered as professional guidelines. Their 'compounding standards' [13] consist of the following chapters:

<797> Pharmaceutical Compounding—Sterile Preparations

<795> Pharmaceutical Compounding—Non sterile Preparations

<1160> Pharmaceutical Calculations in Prescription Compounding

<1163> Quality Assurance in Pharmaceutical Compounding

<1176> Prescription Balances & Volumetric Apparatus

The General Chapter <1163> Quality Assurance in Pharmaceutical Compounding [14] describes a quality assurance program as "a system of steps and actions that must be taken to ensure the maintenance of proper standards in compounded preparations". It consists of following sections:

- Training
- Standard operating procedures
- Documentation
- Verification
- Testing
- Cleaning, disinfecting and safety
- Containers, packaging, repackaging, labelling and storage
- Outsourcing
- Responsible personnel

Through the section Standard operating procedures several processes are mentioned, though not further detailed, such as:

- Compounding methods
- Environmental quality and maintenance
- Equipment maintenance, calibration and operation
- Formulation development
- Quality assurance and continuous quality monitoring etcetera

Through chapters <795> and <797>, many of these sections and SOPs can be detailed. For instance chapter 795 [15] has among others the following sections:

- Categories of Compounding, giving criteria for classifying preparations into simple, moderate or complex, or in other words to enable risk assessment for whether or not to compound a specific medicine
- Responsibilities of the compounder, also containing ten general principles of compounding
- Compounding process, giving all steps from the prescription assessment until instruction of the patient or caregiver
- Compounding facilities

- Compounding equipment
- Component selection, handling, and storage
- Stability criteria and beyond-use dating
- Packaging and drug preparation containers
- Compounding documentation
- Quality control
- Patient counselling
- Training

This Standard has no clear relation to EU GMP but gives attention to three processes of pharmacy preparation: prescription assessment, design of formulation and preparation process. It might be useful for structuring a quality system for pharmacy preparation (see Sect. 35.7.6).

35.5.7 Good Manufacturing Practice (GMP)

35.5.7.1 EU GMP

EU GMP guidelines are located in Volume 4 of the Rules [16]. This Volume is also called the current GMP (c-GMP). Compliance with c-GMP is a prerequisite for a manufacturing authorisation. Compliance is assessed by the Competent Authority.

Volume 4 consists mainly of the basic legislation, three Parts and Annexes:

- Part I – Basic Requirements for Medicinal Products – discusses the requirements with which the production of a licensed medicinal product should comply.
- Part II – Basic Requirements for Active Substances used as Starting Materials – deals with the requirements for active substances that are used as starting materials in medicinal products. These substances are referred to as active pharmaceutical ingredients (APIs).
- Part III – GMP related documents – contains documents such as Site Master File (Sect. 35.5.8) and ICH Q10 (Sect. 35.5.9). The aim of Part III is "to clarify regulatory expectations and it should be viewed as a source of information on current best practices."
- Annexes, elaborating on topics mentioned in the chapters of Part I.

GMP contains instructions on the setup of the quality management system (Chap. 1), on preconditions such as the premises, and on the actual production process at a detailed level, as seen in Chap. 5 Production, and Annex 1 Manufacture of Sterile Medicinal Products. Table 35.1 depicts the detailed contents of Parts and Annexes of EU c-GMP. The chapters and annexes of the GMP are regularly revised and complemented.

The chapters of part I of the GMP are headed by the main principle for the part of the production process with which the chapter deals. The body of the chapters describes the aspects a manufacturer should take into account when implementing the principle.

Some detailed GMP guidelines may only be applicable to specific (industrial) production processes. GMP principles are however generally valid, also for pharmacy preparation [17].

EU GMP contains no guidelines about the design phase, because that part of development of medicines belongs to the authorisation process. Volume 3 of the Rules gives some directions for the design (see also Sect. 35.4.3).

35.5.7.2 Other GMPs

Other GMPs that may be relevant for European pharmacists are the US-GMP created by the FDA [18] and the WHO-GMP [19]. The latter may act as a basis for countries that lack own GMP legislation. There is a global harmonisation activity of GMPs through the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme [20].

35.5.8 Site Master File

A Site Master File (SMF) gives a concise overview of the current manufacturer's situation and is required as a public document for the Inspectorate to give to other Agencies, when requested. It is mentioned in Part III of EU-GMP (see Sect. 35.5.7). It includes some identical elements as the Quality manual (Sect. 35.6.1). Table 35.2 shows the abbreviated contents.

The site master file describes both practical aspects, such as the address and the location of buildings, and quality aspects. For elaborate contents reference is made to the relevant PIC/S inspection guide [21]. The sequence of aspects is the same as in the GMP and also matches the form that a manufacturer should fill to obtain a manufacturing licence.

35.5.9 ICH Guidelines Q8, Q9 and Q10

ICH Guidelines are the result of global harmonisation in medicines manufacturing. Q8, Q9 and Q10 are getting internalised in regional or national regulations and quality standards. Although created for the production of licensed medicines, they can be helpful for structuring PQS for pharmacy preparation as well.

35.5.9.1 ICH Q8

ICH guideline Q8 (Pharmaceutical development) is also called Quality by Design (QbD) and it guides how to build

Table 35.1 Contents of c-GMP in force at July 2014

Introduction	
Commission Directive 2003/94/EC, of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use	
Chapters part I	
1	Pharmaceutical quality system
2	Personnel
3	Premises and equipment
4	Documentation
5	Production
6	Quality control
7	Outsourced activities
8	Complaints and product recall
9	Self inspection
Chapters part II	
1	Basic requirements for active substances used as starting materials
Chapters part III	
	Site master file
	Q9 quality risk management
	Q10 note for guidance on pharmaceutical quality system
	MRA batch certificate
	Template for the 'written confirmation' for active substances exported to the European Union for medicinal products for human use
Annexes	
1	Manufacture of sterile medicinal products
2	Manufacture of biological active substances and medicinal products for human use
3	Manufacture of radiopharmaceuticals
4	Manufacture of veterinary medicinal products other than immunological veterinary medicinal products
5	Manufacture of immunological veterinary medicinal products
6	Manufacture of medicinal gases
7	Manufacture of herbal medicinal products
8	Sampling of starting and packaging materials
9	Manufacture of liquids, creams and ointments
10	Manufacture of pressurised metered dose aerosol preparations for inhalation
11	Computerised systems
12	Use of ionising radiation in the manufacture of medicinal products
13	Manufacture of investigational medicinal products
14	Manufacture of products derived from human blood or human plasma
15	Qualification and validation
16	Certification by a qualified person and batch release
17	Parametric release
19	Reference and retention samples
Glossary	

Table 35.2 Abbreviated Site Master File Structure

Site master file – content	
1	General information on the manufacturer
	Contact information
	Authorised pharmaceutical manufacturing activities of the site
	Any other manufacturing activities carried out on the site
2	Quality management system of the manufacturer
	The quality management system of the manufacturer
	Release procedure of finished products
	Management of suppliers and contractors
	Quality Risk Management (QRM)
	Product quality reviews
3	Personnel
	Organisation chart showing the arrangements for quality management, production and quality control including senior management and Qualified Person(s)
	Number of employees and their functions
4	Premises and equipment
	Premises (site, buildings, lay outs and flow charts of production areas, warehouses and storage areas)
	Equipment (for production and laboratory, cleaning and sanitation, GMP critical computer systems)
5	Documentation
6	Production
	Type of products
	Process validation
	Material management and warehousing
7	Quality control (in terms of physical, chemical, and microbiological and biological testing)
8	Distribution, complaints, product defects and recalls
	Distribution
	Complaints, product defects and recalls
9	Self Inspections (self inspection system, criteria used for selection of the areas to be covered)
Appendices with lists, charts and schemes	

quality into the design of the formulation and the preparation process. QbD starts when the need for a therapeutic product emerges, for example, due to a particular clinical problem ('target product quality profile') and thereby stresses the importance of meeting patient requirements. A control strategy needs to be defined and in-process controls planned correspondingly in connection with the design of the preparation. Quality by design is further dealt with in Chap. 17 Product design.

Q8 may contribute to a structure for the PQS part on the design of pharmacy preparations (see Sect. 35.7.6), for its contents are grouped as:

- Components of the drug product (active substance, excipients)
- Medicinal product (formulation development, overages, physico-chemical and biological properties)
- Manufacturing process development
- Container closure system
- Microbiological attributes
- Compatibility

Q8 is adopted as a Note for Guidance, so for creating an application for authorisation, by the EMA/CHMP [22].

35.5.9.2 ICH Q9

ICH Q9 Quality Risk Management provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality, most of them directed to complex manufacturing situations. It is included in Part III of current GMP (see Sect. 35.5.7). It is further dealt with in Chap. 21 Quality Risk Management.

35.5.9.3 ICH Q10

Although the ICH guideline Q10 strictly speaking only aims to serve as a model for a PQS, in practice it serves as a standard for it as well, by mentioning many elements that are considered necessary. Q10 is included in part III of current GMP (see Sect. 35.5.7).

The ICH Q10 guideline is developed as a PQS model for the whole life cycle of an industrially made product. It therefore starts with the design phase of the product and ends with product discontinuation. It does not include however the very first step: the therapeutic issues (prescription assessment, benefit/risk balance) which are relevant for pharmacy preparations.

35.5.10 Investigational Medicines

Investigational Medicinal Products (IMPs) are not medicines and the subjects are not patients. The purpose of IMPs is not to treat a disease but to experiment with a product to discover if it would treat a disease.

The legislation on Investigational Medicinal Products (IMPs) is described in Volume 10 of the Rules [23]. It consists of six chapters, each containing several documents that are regularly updated:

1. Application and Application Form
2. Safety Reporting
3. Quality of the Investigational Medicinal Product
4. Inspections
5. Additional Information
6. Legislation

GMP annex 13 Investigational Medicinal Products applies GMP to the manufacture of IMPs. Separate legislation for IMPs as compared with medicines warrant their specific position. The formulation of the product may change during the trial. Blinding is often required which introduces the risk of mix-up. The preparation or reconstitution process is not routine yet. Extra securities on the preparation are necessary not only to protect the subject, but also to prevent differences between batches or improperly documented batches.

Production of Investigational Medicinal Products needs a manufacturing license. This brings about compliance with GMP, for the dosage forms involved and the availability of a Qualified Person. So a hospital pharmacy needs a QP (see Sect. 25.3.4) for this functionality.

Every IMP has to be accompanied by an Investigational Medicinal Product Dossier (IMPD). Drafting an IMPD is less laborious than a full dossier but requires pharmaceutical expertise and knowledge of the mentioned elaborated regulations. In hospitals, medical researchers are generally not trained in drafting an IMPD independently, but pharmacists are. A hastily drafted research may prove useless when the quality characteristics and controls of the product have not been thoroughly investigated or documented. Pharmacists are also faced with judgement of IMPDs and the extent of GMP compliance of a trial preparation.

Most hospital pharmacists don't produce IMPs but have to supervise the clinical investigations with IMPs in the hospital.

35.6 Elements of a PQS

This section is about common elements of a PQS, with focus on pharmacy preparation as a process and community and hospital pharmacies as the organisations. For industrial production the same principles are valid but more elaborate literature exists. Most elements are common to any Quality Management System and are for instance described and structured in ISO 9001 (see Sect. 35.7.2). Some elements are closely related and are therefore seen as pharmaceutical quality subsystems. They are combined in one subsection, for instance internal audits, inspection and external audits

35.6.1 Quality Manual

A quality manual is a written representation of the quality management system. The making of a quality manual in the pharmacy usually starts with the establishment of work instructions and operating procedures, such as preparation protocols, analysis protocols and clothing instructions. The description of more general activities, such as the assessment of a request for a preparation, installing new equipment, or handling of a complaint is usually done in a later phase. However, especially those descriptions contribute to the structure of the manual and are the starting point for improvements and risk assessments.

A quality manual contains at least a description of:

- The quality policy.
- The scope of the PQS.
- The PQS processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools for clarifying pharmaceutical quality system processes in a visual manner.

- The organisation (organisational chart, management responsibilities).
- The facilities, such as premises and equipment.
- Furthermore, procedures and work instructions can be a part of the manual.

The establishment of a quality manual can cover:

- A part of or a department of the organisation
- A standard that should be adhered to
- The entire organisation

A disadvantage of a manual for each department is, when multiple departments of the same (pharmacy) organisation are described in this way, this usually leads to double descriptions and indistinctness about relationships between departments.

Establishment of a quality manual according to the requirements of a standard has the disadvantage that the manual usually does not complies when the organisation should also adhere with another standard. Actually, a PQS, and thus a quality manual, including the preparation activities as well as the clinical processes of a pharmacy is not easy to structure. See further Sect. 35.7 for possible solutions and Sect. 35.7.5 for a practice advice when working with the 7 Pillars model.

The descriptions in the quality manual should be concise to keep the manual manageable. When the descriptions are too extensive and detailed, it is difficult to obtain a uniform document in the available time. Moreover, its maintenance requires much more time.

35.6.2 Documentation and Knowledge Management

35.6.2.1 Documentation

Documentation is the total of written quality manual, procedures, instructions, dossiers, records, etcetera. Documentation provides knowledge and work agreements, which thereby becomes transferable between employees. It supports uniformity of procedures, which reduces the chance on deviations in processes and thus in the end product. For documentation, and especially for its maintenance, agreements should be made to prevent the current practice from deviating from the documented system before revision. See also Chap. 33 Documentation.

Many documents, often dossiers or files, will contain knowledge and explanation about backgrounds of the design of the formulation and the preparation method, or of procedures. As soon as a PQS has been created all changes in the system should be documented: through change-logs. These will contain knowledge that can be very useful for future actions and decisions. It serves one of the principal purposes of a QMS: the support of development and improvement, and of QbD by supporting the understanding.

35.6.2.2 Knowledge Management

Knowledge management is seen by ICH Q10 (see Sect. 35.7.4) as an "enabler" of a QMS. The description by Q10 includes much of what is defined under documentation (see above), such as: "(. . ..) of development activities using scientific approaches provide knowledge for product and process understanding. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product life cycle; manufacturing experience; innovation; continual improvement; and change management activities."

For pharmacy preparation external sources are very important, such as formularies, standards and reference works. Keeping up with updates of those sources is essential and needs its own procedures. Some sources or institutions, such as EDQM, already offer the possibility of getting notices by mail, but this is not yet the case with, for instance, GMP guidelines.

35.6.3 Management Responsibility and Commitment

GMP defines in Chap. 1 the responsibilities of Senior Management in a Quality System. It states that "Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System."

These responsibilities are further elaborated on in Q10 by stating that Senior management has the ultimate responsibility to achieve the quality objectives. Management should participate in the design, implementation, monitoring and maintenance of an effective pharmaceutical quality system, define individual and collective roles, responsibilities, authorities and inter-relationships of all organisational units related to the pharmaceutical quality system.

In terms of an industry whose sole purpose is the manufacture of pharmaceuticals it is obvious that Senior Management is at Board level of the organisation. This is not so obvious in the case of hospitals where the focus of top

management may be concentrated elsewhere. Nevertheless the Board is where decisions on finances, staff numbers and premises will be made. The Board will also hold a 'Corporate liability' for everything that happens in the organisation. There will be a delegation of some roles and responsibilities to Department level. Nevertheless the Board must be informed of the principals of the QMS implemented in the pharmacy to fulfil their responsibilities. Contacts for recalls etc. are often delegated to the Pharmacy Department. The involvement of the Board in the Pharmacy systems will ensure a commitment and understanding necessary for the future improvement of the pharmacy.

The EU Directive [3] introduced the concept of an individual taking responsibility for releasing a batch of product to market. This position, unique to Europe, is defined by the Qualified Person. This individual has to take decisions independent from the Board. The role is further elaborated on in the Guide to GMP (see also Sect. 25.3.4). This role is only defined for products with a Marketing Authorisation and Investigational Medical Products. However the function is equally applicable to preparations made by the pharmacist. Pharmacies should nominate a person, independent of the preparation function, to be responsible for the release of the preparation.

35.6.4 Management Review

A management review reflects the governance of the senior management and it reports on suitability and effectiveness of the QMS. It also shows how senior management has dealt with reviews of the performances of processes. Management reviews should provide assurance that process performance and product quality are managed over the life cycle.

Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review [24]. They are very valuable especially when looking at trends for several ongoing years. Some persistent problems or slowly developing negative trends may require senior management actions.

An example of items to be discussed when having a Quality Management Review (QMR):

- Status regarding actions from last Management Review
- Presentation and discussion of key performance indicators in relation to product quality, such as recalls, complaints and adverse events, non-conformities, out of specifications (OOSs), any conclusions from product quality reviews, rejections
- Evaluation of the state of facilities, equipment and systems
- Review of the (local) PQS: inspections from authorities, internal audits, needs for corrective actions in relation to documents in the PQS systems, issues related to outsourced activities
- Quality related projects and changes

In a hospital pharmacy QMR meetings may be held 1–2 times a year. Participants may be Senior management together with management representatives from Production, Laboratories and other relevant departments. If a QP is part of the organisation this person may host the meetings. Minutes from the meetings are available for participants and also for inspectors on request.

35.6.5 Quality Policy, Quality Plans, Quality Objectives

Quality policy is the choice of an organisation regarding quality management, usually described in terms of concrete, measurable and time-dependent objectives. The quality policy, which the senior management drafts in general terms and for a prolonged period of time, should always be accompanied with a quality plan and quality objectives. These are valid for a limited period of time, for example for a year. When this period ends, the management should perform an evaluation, which results in new quality plans and quality objectives. To be able to perform an evaluation, the quality objectives should be Specific, Measurable, Acceptable, Realistic and Time bound (SMART).

> For pharmacy preparation quality policy may be formulated such as: "in the next five years, both the quality and the efficacy of the preparations will be improved."
>
> The accompanying quality year plan could then state: "this year, non-standardised dermatological preparations will be reduced by 20 %, either by standardisation or by providing alternatives."

35.6.6 Resources

In a quality management system 'resources' apply to human resources, financial resources, materials, premises and equipment.

The description of organisation, processes, premises and equipment is necessary to get an overview and is usually the first that is done when a quality management system is

drafted. New employees can be informed this way and are trained to work according to the same procedures.

A hierarchic overview of departments and functionaries (organisational chart, see Sect. 25.2.4) is the basis for the description of human resources of an organisation. Tasks, responsibilities, competences and required qualifications are specified in a function description. An employee description entails the true competences and qualifications of an employee, including the development of the employee by training and other activities. (see Sect. 25.5.1).

Premises, equipment and systems most often are described in a Validation Master Plan (VMP, see Sect. 34.11) part of the PQS and are consequently subject to change control. The VMP has to include a summary of the facilities, systems, equipment, processes on site and the current validation status. A Site Master File (see Sect. 35.5.8) includes more detailed description of facilities, equipment and systems. If a Site Master File is available the VMP may simply refer hereto and only add policy and instructions related to the validation activities.

35.6.7 Product Realisation, Product Design

The design of a new medicine (or health care service) has to be planned and controlled. It is reasonable to lay down the elements of that process in the PQS.

The element Product Realisation of ISO 9001/EN 15224 (see Sect. 35.7.2) specifies:

- Design and development stages
- Approaches for risk assessment in each stage
- Review, verification and validation that are appropriate to each design and development stage
- Responsibilities and authorities for design and development

In pharmacy preparation the very first step of Product realisation is the prescription assessment for an individual patient or the benefit/risk assessment (and definition of indications) for a stock preparation. See Sect. 2.2 for the performance of this step and for the assignment of responsibilities.

ISO 9001/EN 15224 further points to sub-elements such as:

- Quality characteristics (for setting specifications) (see Sect. 35.6.9)
- Change management (see Sect. 35.6.10)
- Product quality review (see Sect. 35.6.11)

The design of a product does not end as soon as the first batch has been produced or the first version of a service has been provided. It continues during the whole life cycle, thus includes the discontinuation of the product or the healthcare service. More about that process in Chap. 17 Product design.

35.6.8 Quality Risk Management

Quality Risk Management (QRM) is seen as a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. Risk management is, whether explicitly or not, used in almost all phases of quality management processes. It is dealt with in a separate chapter in this book (Chap. 21). ICH Q10 sees QRM as an 'enabler' for the PQS.

35.6.9 Quality Characteristics and Quality Requirements

The intended quality level is determined by quality standards, see Sect. 35.5. Those are point of departure and will be supplemented continuously by results from the handling of non-conformities (see Sect. 35.6.13) and from validation (see Sect. 34.10) as well as from the change management process (Sect. 35.6.10).

For pharmaceutical preparations the Ph. Eur. (see Sect. 35.5.3) considers the following quality characteristics required to obtain a product that has "an appropriate product quality, is suitable and fit for its purpose":

- Efficiency, effectiveness, safety
- Quality of active substances, excipients and containers
- Good design of the preparation process
- Significant testing
- Stability of the preparation

From the viewpoint of health care by pharmacies some additional quality characteristics may be taken into account: availability, continuity of care, timeliness. Those characteristics are mentioned by ISO 9001/EN 15224 (see Sect. 35.7.2) and identified as 'inherent characteristics' for the quality of healthcare services. They may however conflict with the usual characteristics for product quality. Conflicts are easy to be imagined between for instance:

- Timeliness and significant testing, or
- Availability and good design of the preparation process

Which characteristics are most important in particular situations has to be the professional decision of the pharmacist who performs a risk assessment (see Sect. 2.2). Keeping a record of those decisions is essential.

Quality requirements can be seen as elaborations of quality characteristics. They are dealt with in Chap. 32.

35.6.10 Change Management, Change Control

Change management includes the evaluation of proposed changes, the attendance of the implementation and the evaluation of it. The importance of change control for the PQS is reflected in GMP Chap. 1 (see Sect. 35.7.3) and also in other

GMP sections such as Annex 15, as well as in ICH Q10 Sect. 3.1.3.

GMP 1 states: "A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: (. . ...) (xiii) After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality".

Change management with pharmacy preparation also includes any change of therapeutic risk/benefit ratio (see Sect. 35.4.2), of formulation or of specifications.

The basic understanding is that every change potentially increases the risk for errors and unexpected consequences, so an increased risk for patients. If the handling of changes is structured (Change control) the risks of changes will be diminished. Change management also supports the involvement of the right professionals.

It should not be forgotten that also changes in the PQS have to be subject for change control.

35.6.11 Product Quality Review

The quality of the design has to be monitored, with help of a regular review of results of analysis, complaints, recalls etcetera. In order to frame that activity into the PQS, the term 'Product quality review' is used. GMP Chap. 1 emphasises the importance of product evaluation: an annual evaluation of product quality for every product, and a risk analysis as well. A Product Quality Review has "the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements".

Well-known elements of a Product quality review are (see also GMP Chap. 1):

- Trend analyses
- Stability monitoring
- Retrospective validation
- Supply chain traceability of active substances
- Critical in-process controls and finished product results
- Deviations or non-conformities and the effectiveness of the subsequent corrective and preventive actions
- Quality-related returns, complaints and recalls
- Qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

Product quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified. This is an appropriate approach for a quality review of non-standardised pharmacy preparations, see also Sect. 34.14.3.

35.6.12 Internal Audits, Inspection, External Audits

This combination of elements is seen as a pharmaceutical quality subsystem. Auditing gives the opportunity for feedback, adjustment, and thereby optimisation. Auditing is the 'check' phase in the PDCA-cycle (see Fig. 35.1); it contributes to the cyclic character of quality management: a situation of continuous improvement. The relevant types of auditing are: the internal audit, management review and certification/accreditation. Management review has been discussed in Sect. 35.6.4. Inspection is dealt with as a type of external auditing.

35.6.12.1 Internal Audit

During an internal audit or self-inspection, trained employees of the organisation check the functioning of the quality system. They may use structured questions and checklists with which they compare the information in the quality manual and connected procedures with the actual situation. An experienced auditor will also use a more intuitive approach for instance getting information about (lack of) cooperation between sections or departments, exploring peculiarities or interviewing staff. When discrepancies are found, they will usually be classified as critical, important or minor. Subsequently corrective or preventive measures (see Sect. 35.6.15) should be taken to adapt the actual methods or the documentation in order to make them match again.

Internal audits can be performed according GMP Chap. 9 Self Inspection. This chapter points at examination of personnel matters, premises, equipment, documentation, production, quality control, distribution of the products, arrangements for dealing with complaints and recalls, and . . ... self-inspection.

Common elements of the production processes that are eligible for internal audits may be:

- Involvement of the senior management
- Training of staff
- Facilities (gases, water, air, premises, maintenance, cleaning)
- Reporting within the organisation
- Organisation of decision-making
- Corporate culture to recognise commitment of employees
- Design of procedures and demonstrability of following them correctly
- Progress in handling of deviations
- Consistency of computer systems
- Follow-up of improvements, which in the case of prior audits have been required

Internal audits are usually conducted according to a prearranged programme, which should leave room for

ad-hoc audits due to complaints or due to the implementation of a large change.

The frequency of internal audits should be the highest for the most critical processes. A risk assessment, focussed on the risk for the patient, can be used to put processes in an order of criticality. In hospital pharmacies the preparation of parenterals is generally seen as having the highest risk. For a large medicines preparation department in a hospital pharmacy, frequencies may be set at:

Once a year:

- Aseptic handling and preparation
- Processes with doubtful track records (non-conformities in internal audits or related to inspections)

Every 2 years:

- Quality Control
- Production of parenterals
- Quality Management
- Other production processes

Every 3 years:

- Other departments, entities and processes

Plans for internal audits are revised regularly, for instance biannually. Quality management reviews will include monitoring of audit outcomes and may consider whether audit frequencies are appropriate.

Some additional suggestions for the performance of the internal audit are:

- The audit is preferably performed by persons not directly involved in the subject.
- Results of the self-inspection must be justified through a protocol and reported to the senior management or the head of Quality Management.
- If corrections of the subject of the audit prove to be necessary, the corrective action must be documented along with a deadline and the name of the department or person who is responsible for corrective or preventive action.
- The self-inspection is completed only after the auditor has reviewed and approved the corrective or preventive action.

35.6.12.2 Inspection

Any institution or company that is preparing medicines will be inspected by the relevant regulatory Competent Authority.

In the Netherlands, for instance, the Healthcare Inspectorate monitors the organisation and the quality and safety of all provided care. It uses general monitoring, but apart from that, phased monitoring becomes more prominent.

General monitoring entails inspections without a specific cause. They are performed to gain insight into the general quality level and quality control of pharmacies, including the preparation unit. For general inspections a set of performance indicators is used. A performance indicator is defined as a measuring point that gives a good indication about the functioning of a process. Examples of performance indicators are:

- The time that a complaint is open
- The time that is taken up by adjusting the process
- Number of recall procedures.

And specifically for preparation in pharmacies:

- The number of preparations produced without an approved preparation protocol
- The number of stock preparation without a product file
- The ratio between non-standardised and standard preparations

Performance indicators can help management or external auditors to roughly get an insight into the functioning of the quality system.

Phased monitoring is inspection focussed on locations with the highest risks for irresponsible care. The latter methodology consists of three phases:

- Gathering quality data, analysis, and reporting from all institutions
- Further investigation at specific institutions, assessment, and decision on measures
- Administrative sanctions, tracing, and prosecution

Within the context of phased monitoring, the inspectors request annual information on the quality of care from healthcare providers. For application of phased monitoring it is important that the professionals have knowledge of the extent in which they adhere to regulatory and professional standards.

For the preparation of licensed medicines and preparations for clinical trials, an inspection is always performed because the provision of a manufacturing license requires it.

When after one or more audits the inspected organisation does not comply with the standards and shows insufficient improvement, the Inspection Team may advice to put the organisation under “increased monitoring”. This is a severe type of monitoring that often precedes enforcement measures such as imposing an administrative fine, requesting the Minister for an instruction, or imposing a sanction. In the

(continued)

Netherlands the Inspectorate publishes cases of increased monitoring on its website, including the inspection reports.

The frequency and scope of audits of production sites by the Inspectorate may be determined by taking into account, according to one of the illustrations at ICH Q9 [25]:

- Existing legal requirements
- Overall compliance status and history of the company
- Robustness of a company's quality risk management activities
- Complexity of the site, manufacturing process, product and its therapeutic significance
- Compliance status and history
- Results of previous audits/inspections
- Number and significance of quality defects (e.g. recall)
- Major changes of building, equipment, processes, key personnel
- Experience with manufacturing of a product (e.g. frequency, volume, number of batches)
- Test results of official control laboratories

35.6.12.3 External Audits and Certification

In some countries community and hospital pharmacies may opt for external audits by independent quality institutions which may lead to certification. Such an external audit may be required by stakeholders, such as their patients or health insurance companies, or in some situations pharmacies to which their pharmacy preparations are supplied.

Certification is about confirmation of certain characteristics of the organisation to a standard. When external auditing institutions audit a pharmacy as an organisation, they usually audit according to ISO 9001 or ISO 9001/EN 15224 (see Sect. 35.7.2).

Manufacturers are, in addition to the Inspection's audits, legally subjected to (external) audits from companies that have outsourced their activities to them. Auditing of suppliers of starting materials by companies, pharmacies or associations of pharmacists is also possible.

In the Swiss 'quality reference system' RQS [8] (see also Sect. 35.7.6) audits are performed by a certification expert together with a professional expert: a hospital pharmacist who has received extra audits training. The certification amounts to RQS as well as ISO.

In Germany, as in several other European countries, all pharmacies must or are supposed to have a PQS. Certification is optional and can be performed by a professional pharmaceutical body or a certification organisation.

35.6.13 Non-conformities (Deviations and Complaints)

Non-conformity means that a requirement is not fulfilled. Non-conformities can occur related to any of the quality characteristics and its related quality objectives. Non-conformities may refer to defects, mistakes and errors in processes, violations and deviations of regulations or procedures, problems with equipment, customer complaints, etcetera. Near misses, incidents and adverse events in clinical or occupational health context can be treated as non-conformities concerning patient or employee safety.

In a pharmaceutical production environment non-conformities are usually called 'deviations'. In production of pharmaceutical preparations planned deviations are commonly distinguished from unplanned deviations.

Planned deviations are a foreseen result of a planned and documented temporarily event such as using the appropriate type of filter while the batch preparation instruction mentions an alternative one. An unplanned deviation, such as a content of 115 %, is unexpected and requires investigation of the root cause, next to an assessment of the quality consequences.

Complaints are non-conformities as well. Complaints may originate from patients but may also be brought by one department to another. The pharmacy or company will also bring complaints to suppliers or starting materials, for instance.

Deviations may be noticed within the organisation without leading to a defective product or service. In a less strictly organised situation such as a pharmacy, deviations may be expected to be less noticed. In contrast patient's complaints will, in pharmacies, come through quite quickly. Patients are the end users and in fact 'test' each element of the batch, but a patient complaint about a slightly deviating content is quite unlikely.

Deviations and complaints can be classified into minor, major and critical. An example of a minor deviation in preparation is a raw material for which one test for identity fails, while another test undoubtedly determines the identity of the active substance. A major deviation may be that the amount of active substance exceeds internal limits, is Out of Specification (OOS), for instance outside 95–105 %, while not exceeding the legal limits of 90–110 %. Moreover stability testing of this medicine has demonstrated that within the shelf life the content remains constant. A critical

deviation means that the patient may be immediately at risk for example due to the presence of unexpected degradation products.

The handling of non-conformities and the actual content are to be included in product quality reviews and management reviews.

35.6.14 Recalls

When a pharmacy is faced with a recall it is usually related to a defective licensed medicine. According to ISO 9001, a recall is considered to be a complaint and should be dealt with according the general complaint procedure. This also applies to complaints due to medicines prepared in the pharmacy.

GMP Chap. 8 Complaints and Product Recall refers, for licensed medicines, to legislation as the principle of a procedure to be followed in case of a potential defective product: "All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. In order to provide for all contingencies, and in accordance with Article 117 of Directive 2001/83/EC and Article 84 of Directive 2001/82/EC, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market." GMP is listing in Chap. 8 all actions that have to be part of a recall procedure.

If a decision is made to recall, this must be executed after discussion with other staff, quality control laboratory, experts, board of directors and competent authority (this must be laid down in the complaints procedure), regarding the impact of the decision.

35.6.15 Root Cause Analysis and Corrective and Preventive Action System

The way in which Root Cause Analysis (RCA) and a Corrective and preventive action system (CAPA) can be used to improve quality is given by the statement from GMP Chap. 1 Pharmaceutical quality system:

> An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. This can be determined using Quality Risk Management principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventative actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles.

Root-cause analysis (RCA) is meant to identify the root-cause of an important incident, in order to be able to take measures to prevent recurrence of the incident.

A standard method and a standard form is used to determine which incidents are severe enough to analyse. Three questions are to be put:

- What happened? (reconstruction)
- How did this happen? (evaluation)
- What measures can be taken to prevent recurrence? (prevention)

RCA has proven most effective when used for severe incidents that occur relatively often of which the cause is rather obvious.

For the structured over-all analysis of deviations the Corrective And Preventive Action system (CAPA system) can be used. This system means to document, analyse, solve, and if possible prevent all problems and deviations. It uses data from other quality assurance systems, such as: complaints, deviations, recalls, out of trend (OOT) and out of specifications (OOS) data, notices from internal and external audits. By combining all these data in one system, a better overview of confounding factors is obtained, which enables an organisation to address problems structurally and prevent recurrence.

Either corrective actions can be taken: actions that restore an actually occurred deviation, or preventive actions: actions that prevent a potential deviation.

A CAPA system does not only lead to quality improvement, but also to fewer (product) errors and thus to cost reduction. For the implementation of a CAPA system, forms, a (excel) database, or even especially developed software systems can be used.

An appointed person controls the CAPA system and takes care of timely determination and execution of actions, and thereby closing of pending problems. System actions that lead to structural changes should be evaluated following the change procedure, to establish the effects of the modification on other parts of the quality management system.

A CAPA system only works properly when the system is carefully drafted. It should be clear what information should and should not be put into the system, to prevent soiling it with irrelevant problems. Furthermore, it should be known who enters the data into the system, who is responsible for solving pending deviations, and who checks the efficacy of the system: if problems are solved within a predetermined period of time, if recurrence of incidents is really prevented etc.

35.7 Structuring a PQS

35.7.1 Desire for Structuring

As said, in many pharmacies and even industries a pharmaceutical quality system may have started with a list of technical SOPs. As a next step GMP (or PIC/S GPP) may have been used to group SOPs in chapters and to add SOPs for general quality activities. With a PQS developing, the number of PQS elements can become considerable and the overview may get lost. Clustering of the elements in sections and a visual structure (diagram) may help. Using a diagram may stimulate the perception of quality management as a process, such as reflected by the Deming circle (Fig. 35.1) in its simplest way.

This section discusses four possible structures for PQSs: ISO 9001/EN 15224, GMP Chap. 1, ICH Q10 and 7 Pillars; the latter two using diagrams. Which structure is considered useful depends on the extent of the processes or organisation that has to be covered. Should the PQS indeed cover the complete product life cycle of a medicine or just the preparation/manufacturing process. Is the PQS meant for the production department of a pharmaceutical manufacturer or of a hospital pharmacy or for the complete clinical services of a community pharmacy.

The experiences about failures of PQSs in practice stimulated the development of the 7 Pillars visualisation [26]:

- Key processes (such as validation, pharmacovigilance, purchasing) were not included in the PQS.
- Silo management: separate systems had evolved within different departments or functions, which leads to lack of communication and harmonisation.
- Gaps between the GxPs, especially performing clinical trials within a proper PQS.
- Design faults within individual elements of a QMS, such as an extremely complex documentation system.

ISO 9001/EN15224 and 7 Pillars, although very different, offer a structure that can be used for a PQS that covers the clinical aspects of preparation in pharmacies as well.

35.7.2 ISO 9001/EN 15224

ISO 9001 is the global standard for quality management systems. It has been specified for healthcare by EN 15224 [27].

ISO 9001 is based on eight management principles: customer focus, leadership, involvement of personnel, process approach, system approach to management, continual improvement, factual approach to decision making, mutually beneficial supplier relationships.

The current ISO 9001 standard applies to quality management systems for products and services, all kinds and in a universal sense; ISO 9001 is considered useful for services in health care as well.

Specifying ISO 9001 for healthcare into ISO 9001/EN 15224 has adjusted and specified the requirements for healthcare as well as the product concept and customer perspectives. Products in health care are always trying to value the interactions between patients ('customers'), health care personnel, suppliers, insurers, industry and governmental bodies.

ISO 9001 states that a quality policy for products and services in general:

- Is appropriate to the purpose of the organisation
- Includes a commitment to comply with requirements and continually improve the effectiveness of the quality management system
- Provides a framework for establishing and reviewing quality objectives
- Is communicated and understood within the organisation
- Is reviewed for continuing suitability

EN 15224 adds that a quality policy of health care organisations:

- Is based on ethical values and the specific quality requirements and characteristics
- Includes a commitment to clinical process management including clinical risk management

Table 35.3 gives the chapter titles of ISO 9001 with some subchapters that may be relevant for preparation of medicines as well as those health care elements added from EN 15224. The last column tries to connect the ISO structure to quality system elements common to pharmaceutical quality systems, including specific items for pharmacies.

Would pharmaceutical preparations be within the focus of EN 15224 or not? To put it differently: are pharmaceutical preparations to be considered products or clinical services?

EN 15224 states that 'material products such as (. . .. .) pharmaceuticals (. . ...) and medical devices have not been focused in the scope as they are regulated elsewhere'. Extensive regulations exist for licensed medicines indeed (see Sect. 35.5.2). These regulations allow pharmacists to prepare medicines for individual patients on the base of their needs. The assessment of the patient's need for a pharmacy preparation is definitely a clinical process. Quality characteristics used in such an assessment (see Sect. 2.2) are included in the EN15224, for instance availability, continuity of care,

Table 35.3 Connections between ISO 9001, EN 15224 and elements common to Pharmaceutical Quality Systems

ISO 9001 Chapter titles	Some ISO subchapters	Additional elements for health care systems (ISO 9001/EN15224)	Elements common to pharmaceutical quality systems
General quality principles/process approach		Quality in healthcare	Patient focus, clinical need, benefit/risk ratio
		Clinical risk	
Quality management systems			Quality manual
			Documentation
			Knowledge management
Management responsibility	Management commitment	Patient focus	Management responsibility
	Quality policy	Quality objectives such as availability, continuity of care, effectiveness, efficiency, timeliness etcetera	Management review
	Customer focus		Quality policy, plans, objectives
	Planning		Management of outsourced activities and purchased materials
	Quality objectives		
	Responsibility, authority and communication		Quality risk management
Resource management	Provision of resources		Personnel
	Human resources		Organisational chart
	Infrastructure		Training
Product realisation	Customer-related processes	Clinical risk assessment	Prescription assessment
	Design and development		Product design
	Purchasing		Quality characteristics, quality requirements
	Production and service provision		Change management, change control, quality control
	Control of monitoring and measuring equipment		Product quality review
			Outsourcing
			Procurement
			Supplier management
Measurement, analysis and improvement	Monitoring and measurement	Clinical process management	Audits, inspection, certification/accreditation, management review
	Analysis of data		
	Improvement (CAPA)		Non-conformities (deviations, complaints)
			Recalls
			Pharmacovigilance
			Analysis of deviations (RCA, CAPA)
			Quality risk management

effectiveness, efficiency, timeliness. These may help to frame decisions into the PQS of the organisation about situations such as:

- A recall of an industrially produced medicine leads to unavailability of an essential medicine and pharmacy preparation could provide a solution, but with limitations as to quality control.
- To improve patient's adherence to his medication, a pharmacy preparation that combines licensed medicines or adapt them, would really make a difference.
- A pharmacy prepared medicine would improve the safety of the health care process on wards or at home care.
- A medicine is available when imported from another country, but will not be reimbursed in that situation. A pharmacy preparation may (temporarily) solve the problem.

The quality policy could define the position of pharmacy preparation in relation to licensed medicines in line with EN 15224 as follows:
Unavailability of licensed medicines:
Unavailability of licensed medicines is the situation in which a medicinal product is not available as a licensed preparation, or temporarily not available, or if no licensed medicine suits the patient well enough to comply with his therapy, or if a pharmacy preparation will improve the safety of the healthcare process or diminish the health risk of healthcare providers.

In such situations the attending pharmacist examines, in consultation with the prescriber and patient or health care providers, the possibilities for

(continued)

import or a pharmacy preparation. The decision whether or not to choose a pharmacy preparation is based on a risk assessment that is documented. The clinical benefits and risks are weighed against the risks of design failure and of preparation failure and take feasibility into account. The documented considerations are the transparent testimony of the pharmacist about his legal responsibility for the preparation including the pharmacotherapy.

The only accessible PQS for pharmacies that has been published to our knowledge, the Swiss PQS for hospital pharmacies, is based on the ISO 9001 methodology as well as on the EFQM quality model [28].

The Swiss PQS was developed before the EN 15224 was created. It applies to the hospital pharmacy as a whole.

This PQS contains elements for pharmacy preparation:

- For legislation for extemporaneous or small-scale preparation reference is made to the Swiss Pharmacopoeia (which is for that part almost identical to PIC/S GPP, see Sect. 35.5.5) and for stock preparations to EU-GMP (this Swiss PQS was developed before the Ph. Eur. monograph Pharmaceutical Preparations, see Sect. 35.5.3 and the Council of Europe Resolution, see Sect. 35.5.).
- For the hygiene concept and quality control reference is made to those standards as well.
- For specific preparation activities reference is made to national guidelines.
- A yearly list of stock preparations including the amount produced should be available.
- Every preparation is evaluated at least every 2 years as to efficacy and efficiency.
- Prescriptions for extemporaneous preparations are assessed for formulation, dose, clinical and economic benefit.
- Attention is paid to the relation between stress and quality of aseptic handling.
- Maintenance of equipment for preparation and quality control.
- Outsourced preparation activities.
- Licences for handling narcotics, for pharmacy preparation as such.

35.7.3 Pharmaceutical Quality System of GMP Chapter 1

Chapter 1 of EU GMP gives guidance for a Pharmaceutical Quality System. It starts with a Principle emphasising the responsibility of senior management, participation and commitment of all staff and suppliers, full documentation, sufficient resources, and the relationship between quality management, GMP and QRM.

It consists of guidelines on five issues:

- Pharmaceutical Quality System
- GMP for medicinal products (including a reference to Good Distribution Practice)
- Quality Control
- Product Quality Review
- Quality Risk Management

The guidelines on the Pharmaceutical Quality System may be used as a structure for a PQS, however GMP Chap. 1 already points at ICH Q10 as being more suitable for that purpose. ICH Q10 provides structure for the design processes and for skills such as knowledge and quality risk management, review of trends and patient satisfaction. These skills 'enable' effective quality management.

35.7.4 ICH Q10 as a Structure

As said (Sect. 35.5.9) the ICH Q10 guideline [24] is developed as a PQS model for the whole life cycle of a licensed medicine. It starts with the design phase of the product and ends with product discontinuation. ICH Q10 is included in part III of current GMP (see Sect. 35.5.7).

ICH Q10 clusters PQS elements in four subsystems:

1. Process performance and product quality monitoring system
2. Corrective action and preventive action (CAPA) system
3. Change management system
4. Management review of process performance and product quality

These subsystems can be applied to each of the stages of the product lifecycle (see Sect. 35.3). Many parts of ICH Q10 are relatively easy connectable with ISO 9001. However some are not, such as Enablers, Management responsibilities etcetera. The relationship between all parts of ICH Q10 is visualised in the diagram of Q10 Annex 2, see Fig. 35.2.

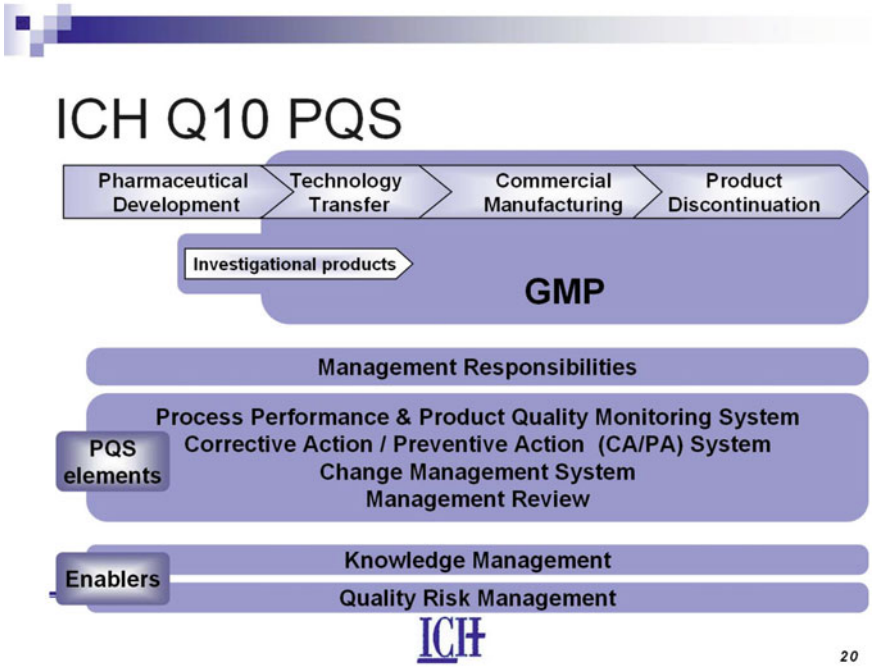

Fig. 35.2 Diagram of the Q10 PQS model (Copyright © 2014 ICH (ich.org))

The relationship between the parts of the diagram is explained as follows:

> This diagram illustrates the major features of the ICH Q10 Pharmaceutical Quality System (PQS) model. The PQS covers the entire life cycle of a product including pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation as illustrated by the upper portion of the diagram. The PQS augments regional GMPs as illustrated in the diagram. The diagram also illustrates that regional GMPs apply to the manufacture of investigational products.
>
> The next horizontal bar illustrates the importance of management responsibilities (. . ..) to all stages of the product life cycle. The following horizontal bar lists the PQS elements which serve as the major pillars under the PQS model. These elements should be applied appropriately and proportionally to each life cycle stage recognising opportunities to identify areas for continual improvement.
>
> The bottom set of horizontal bars illustrates the enablers: knowledge management and quality risk management, which are applicable throughout the life cycle stages. These enablers support the PQS goals of achieving product realisation, establishing and maintaining a state of control, and facilitating continual improvement.

35.7.5 Seven Pillars Model

Another visualisation of a PQS (described in the model as a Quality Management System QMS) is the 7 Pillars model [26], see Fig. 35.3, developed by Dr. Tom Duffy of Lowden International to help getting involved in quality management in a proper and understandable way, using the pharmaceutical vocabulary.

The model is first described when applied to the preparation of a medicinal product. Subsequently its wider pharmaceutical use across the whole product life cycle is explained and illustrated.

35.7.5.1 Description of the Model[1]

Principles

The 7-Pillars model is a ‘patient benefit model’ and applies only to the pharmaceutical environment. It was not intended to have the general applicability of the ISO standards. Indeed it was developed in the 1990s because the ISO standards were not then considered as appropriate for the production of medicinal products. The model was aimed originally at the industrial and hospital preparation of medicines only and the GMP environment. It has since been extended to cover the whole product lifecycle, all the GXPs and all functions involved in the preparation and production of pharmaceutical products, including QC, Regulatory Affairs, Development etcetera. This has been done by developing the concept of ‘the product’: thus, for example, test results might be considered to be the product of a QC department; a registration dossier could be the product of a Regulatory Affairs department. Once the concept of product is accepted, the Quality Attributes necessary for patient benefit can then be defined and the 7-Pillars Model adapted and applied.

The primary principle for the 7-Pillars Model is that patient wellbeing is secured by supplying a medicine (‘product’) with the correct Quality Attributes and by compliance with regulatory requirements. Regulatory requirements do

[1] As described by Dr. Tom Duffy.

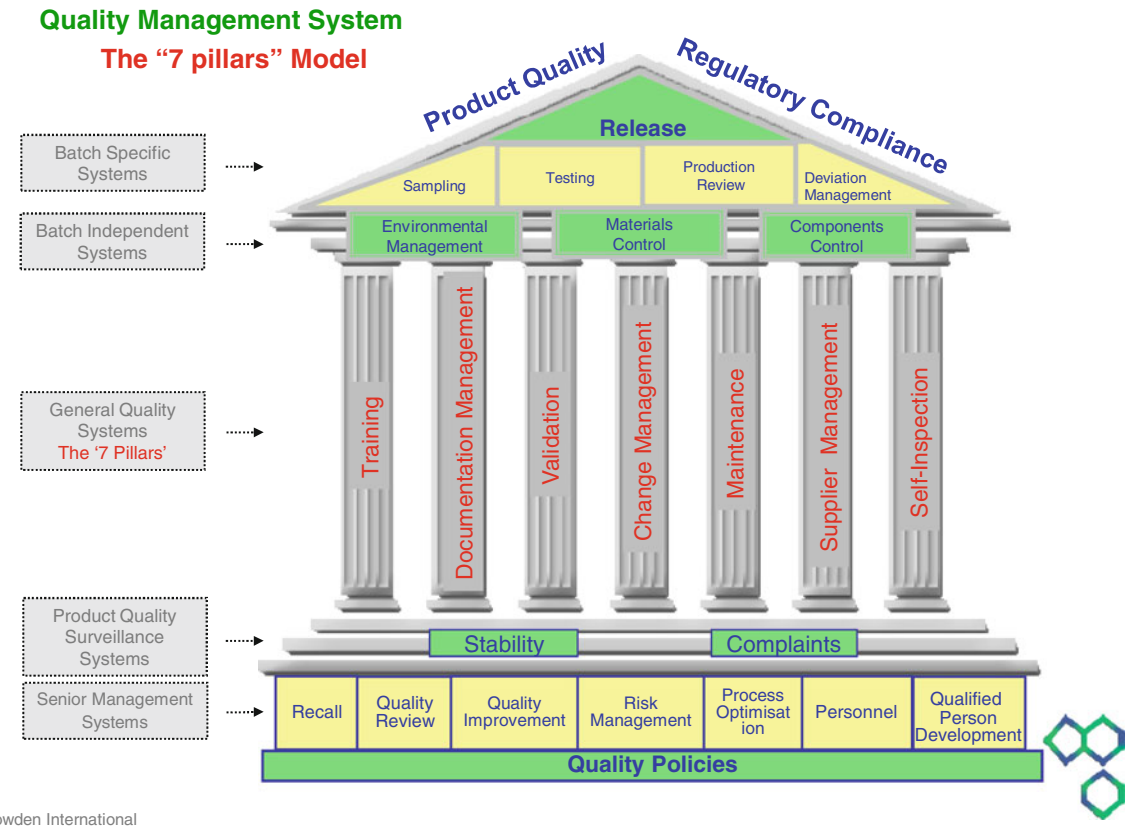

Fig. 35.3 7 Pillars model (Copyright © Lowden International, with permission)

not just mean regulations in the sense of legal requirements; they include codes of practice, ethics and professional standards. They have also existed ever since the practice of Pharmacy began and the apothecary of old had to have a 'Release System' which was in effect a primitive Quality Management System. Hence the Release System sits on the top of the model (which is an ancient temple) and all the other 24 elements in the model (the pillars and building blocks in the temple) exist to support the Release System, thereby safeguarding patient benefit by assuring appropriate quality and regulatory compliance.

The second principle for the model is that no QMS can be effective unless it is supported by the senior management of the organisation. Management support must be exercised through a system of senior management processes and policies. These therefore sit at the base of the model forming the foundations of the temple.

The third principle is that all of the 25 elements in the QMS are defined as processes which are documented in 25 formal procedures. A Quality manual contains 25 separate policy statements formally endorsed by senior management.

Explanation of the Model

Batch Specific Systems. The first level of system elements which support the Release process are referred to as Batch Specific because they are operated during the preparation of every batch or lot and generate data specific to that lot. These are Sampling, Testing, Review of Production Documents and Deviation Management.

Batch Independent Systems. Monitoring what happens during an individual batch is not enough since other factors can affect product quality and hence must also be managed by QMS elements. These are the systems for controlling and monitoring Environment, Materials and Components which have major impact on quality but are not associated with any one specific lot. These are represented as the second level of systems supporting Release.

General Quality Systems. There are seven of these and they give the QMS model its name since they are represented as seven supporting Pillars which are the third level of systems supporting the Release process. They are the systems used to manage Training, Documentation Control, Validation (including Qualification), Change Control, Maintenance (including Cleaning), Supplier Control and Self-inspection.

Product Surveillance Systems. The presence of these acknowledges that the QMS must still operate after Release. Thus Complaints must be investigated and there must be on-going assessment of the 'product' to assure that it continues to meet its Quality Attributes throughout its life

(Stability). These represent the fourth level systems supporting Release.

Senior Management Systems. The fifth level supporting the Release process are the foundation stones, the senior management systems (see the third principle above). These are the systems for managing Recalls, Quality Performance Review, Quality Improvement (including CAPA), Risk, Process Optimisation, Personnel and QP Development (or QP equivalent in non-production functions). Quality Policies are the final base layer (a concrete raft) and are also part of the Senior Management Systems. In this QMS they are statements of *what* is done for each of the 25 elements. The process based procedures for each of the individual elements define *how* the element operates.

A major advantage of the 7-Pillars QMS Model is that, owing to its pictorial nature, it enables personnel at all levels in the organisation to accurately explain their QMS and how it works. Indeed a picture of the model can be inserted into the Quality Manual and used to give an overview to inspectors.

35.7.5.2 Wider Pharmaceutical Use of the Model

The model seems to be focused on the release of medicinal products. However it is also applicable to the 'release' or quality management of other pharmaceutical 'products', such as a product dossier, a patient dispensing operation or a laboratory analysis. Many efforts to control the quality are similar and the model can be used for the integration of the quality management of all 'products'.

For the wider use, at first the product has to be defined with its quality attributes. Subsequently each element of the 7 Pillars model is worked through and checked whether each element applies to the product in view. Two elements may be merged into one or renamed in order to best suit the organisation.

A validation report or the therapeutic assessment of a pharmacy stock preparation exists and needs to be accessed and up to date as soon as related activities are performed. Providing availability and readability has to be an element of the quality system. It would mean for instance that a file system has to be developed whether physically or digitally. In case of digital storage care has to be taken that the documents remain accessible when programs are updated.

Keeping procedures up to date is notoriously difficult organising. If up to date procedures are seen as a product, it may be well organised in the quality system.

35.7.6 Suitability of Structures for PQS in Pharmacies

The preceding Sects. (35.3, 35.4 and 35.5) have shown that a PQS for pharmacy preparation may need at least the same elements (including the design phase) as the industrial manufacturing, but will differ in several ways:

1. A PQS for pharmacy preparation moreover needs the element of controlling and documenting the therapeutic aspects, as well as the prescription assessment in case of extemporaneous preparation; for licensed medicines this part is separately regulated in the registration process.
2. It should contain a system (and procedure) on how to handle medical-ethical issues for instance in cases of non-availability or non-compliance to quality standards.
3. It preferably has to be integrated with the PQS of the pharmacy or even of the hospital, so with their clinical and logistic activities, as well as with human resourcing and accounting.
4. It has to implement different legislation.
5. The smaller the scale, the easier it will be to have all elements connected and in concise overview, especially when many elements will be executed by the same person.

The first three conclusions require an extension of the PQSs described until now. The fourth will have some influence on the level of detail. The fifth conclusion suggests that for pharmacies the PQS will be much easier to be surveyed than for industries.

With a PQS modelled according to ISO 9001/EN 15224 the clinical phase can be included. This may also be possible with the 7 Pillars model but not with GMP Chap. 1 or Q10.

As to standards, a distinction can be made as well, being relevant because a PQS structure may be directed to them.

Table 35.4 shows the coverage of the pharmacy preparation life cycle by the different models and standards. The life cycle phase Distribution is included for completeness. The standard GDP is discussed in Chap. 36.

The general model for a Quality Management System for healthcare establishments: ISO 9001/EN 15224 is applicable to the pharmacy as a whole, including pharmacy preparation. All pharmaceutical specificities have to be created, for which the Swiss system [8] may be useful if updated to EN 15224. The 7 Pillars model is applicable to the whole pharmacy as well. If used to preparation terminology, this system offers the advantage of using familiar terminology.

Table 35.4 shows which standards (discussed in Sect. 35.5) may be useful for details of the several phases of the life cycle.

If a complete PQS for the whole pharmacy is not aimed at, Q10 can be used as a model or a model based on a relevant Standard.

Table 35.4 Suitability of models and standards upon which a quality systems for pharmacy preparation may be based

Life cycle phases to be covered by the PQS →	Easy connection with the other pharmacy processes?	Coverage of pharmacy preparation life cycle			
		Pharmacotherapy	Product design	Production process	Distribution
Models ↓					
ISO 9001/EN 15224	+			[a]	
7 Pillars	+				
Q10	–				
and Standards ↓					
Pharmaceutical preparations Ph. Eur.	+				
PIC/S GPP	–				
USP Compounding standards	–				
CoE resolution on pharm preparation	–				
GMP chap. 1	–				
GMP other chapters	–				
Q8					
GDP	–				

[a]ISO however does not address the position and responsibilities of a QP

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Logistics

36

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Contents

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Abstract

Medicines are not normal commodities of commerce, due to their special nature and the need to protect the health and safety of the public. Legislation has made the pharmacist the custodian of the Nations medicines. The pharmacist has the duty to ensure the availability of the appropriate medicine at the time of need. This objective is achieved by an expert knowledge of medicines backed by a robust system of procurement logistics. The outline of which is described in this chapter where logistics is about procurement, distribution and storage. Storage and distribution is controlled through Good Distribution Practices (GDP). The range of products handled by hospital pharmacies across Europe varies but medicines are usually the prime focus for the hospital pharmacist and the preparing pharmacist in particular. Where other commodities are included such as medical devices, nutrition supplements etc. other legislation may apply. However when the pharmacy has the responsibility the controls outlined in this chapter will apply to all the commodities handled.

Keywords

Stock control • Procurement • Suppliers • Goods receipt • Storage • Distribution • Recalls • GDP

Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_36,

36.1 Scope

Where items or products are referred to in this chapter the terms will mean all the products for which pharmacy is responsible. Depending on the local policies these may include healthcare services, other healthcare products such as dressings and other medical and surgical products. The chapter covers all aspects of procurement in a pharmacy but is focused on the needs of the preparing department which may have its own independent procurement section or may be part of the main (hospital) pharmacy procurement function. Whatever is the arrangement the preparing section must take responsibility for the products that it uses and makes.

36.2 Quality Requirements

36.2.1 General

As with all functions in the pharmacy the logistics function will be controlled by a Quality System. This is described in Chap. 35.

General guidelines that will be applied are known as:
Good Procurement practice [1–3]
Good Distribution practice (GDP) [4] (See Sect. 36.2.4)

36.2.2 Competent Authority and Inspectorate

The setting of the standards for the conditions under which stock is stored and distributed from manufacturers and wholesalers is the responsibility of the Competent Authority and is enforced by it's Inspectorate. The controls placed on hospital pharmacy and community pharmacy is Country dependent. There will be a system of accreditation but again, with whom, and the extent to which this is applied, will be different in each Country.

36.2.3 Traceability

The prime purposes of medicines legislation is to ensure the quality, efficacy and traceability of products throughout the supply chain. The manufacturer, wholesaler and pharmacies are pivotal in ensuring those objectives remain with the product when received by the patient. Falsified medicines (see Sect. 36.13) enter the supply chain when parts of this chain do not adhere to the agreed rules. The quality and efficacy of the medicine will be compromised by poor storage and distribution.

36.2.4 Good Distribution Practice (GDP)

Pharmacies are exempt from the legislation covering GDP for medicines, unless they are wholesaling or importing/exporting medicines, however the principals outlined in the legislation should be considered when drawing up the Quality System of the pharmacy.

Distribution of medicines by licensed Wholesalers is controlled by the European Commission Guidelines of 5th November 2013 on Good Distribution Practice of medicinal products for human use (2013/C 343/01).

Under these Guidelines The Distributor is required to have in place a suitable

1. Quality System (see Chap. 35), which includes:
   - Documentation system which has the prime objective of preventing errors arising from spoken communication and to permit the tracking of relevant operations during the distribution of medicinal products.
   - Management of outsourced activities such that the principal is that there should be a written contract between the Contract giver and the Contract acceptor such that there will be no confusion over the duties of either party
   - Management review and monitoring
   - Quality risk management
   - Qualification of Suppliers
   - Qualification of customers
   - Receipt of medicinal products
   - Storage
   - Handling of Complaints
   - Product recalls
2. Sufficient competent personnel with an understanding of their role and suitably trained in GDP. The guideline also introduces the role of the 'Responsible person' (RP). This person should meet the qualifications and conditions provided for by the legislation of the Member State. The Guidelines state that a degree in Pharmacy is desirable and that the person should have appropriate competence as well as knowledge of and training in GDP.
   The role of the RP is analogous to that of the QP in manufacturing (see Sect. 25.3.4).
3. Suitable premises and equipment. The premises should be so designed to allow for separate storage and monitoring of the different categories of stock e.g. stock for distribution, cold storage, returns etc. The equipment should suit

its intended purpose and be qualified, validated and maintained appropriately (see Sects. 28.2 and 34.15).

36.3 Stock Control

36.3.1 Overview

Stock Control is about the ability to have medicines for patients when needed, i.e. to avoid out of stock situations and not to have wastage through out of date stock, usually caused by over stocking. Stock Control is also about the best use of resources in terms of costs of storage and staff time. Stock movements are used to predict future requirements.

Good stock control relies on the principal of first to expire, first out which means that, with manual storage of articles, the one with the shortest expiry date have to be placed so that they will be picked first. Robotic systems rely on the computer program to select the product with the shortest expiry date.

The stock of pharmaceutical products must be regularly checked for products nearing their expiry date, accounting for a reasonable usage period for the user e.g. patient, stock hold on wards etc. Expired products must be removed from the shelves immediately (see also GDP [4] Sect. 5.5).

36.3.2 Shortages

Shortages of Medicines is a growing concern throughout Europe and elsewhere in the World. How such shortages should be handled is dealt with in Sect. 3.2.2.

36.3.3 Stock Turn

Procurement of items must be at the most appropriate level in order to obtain the best value for money while ensuring the quality of the product and the supply chain. This level will vary according to local/national policies. It will include consideration of the most appropriate Stock Turn for the individual items. A Stock Turn is the rate at which a company's goods are sold and replaced. With main line stock there should be a turnover of around five or six times a year. However in pharmacies there are a number of medicines which require different considerations when applying stock control principals. The medicines in these categories may never be used but it is essential to have them available if needed. Therefore, for these medicines the concept of a 'Stock Turn' will not apply. However, if possible, the pharmacist should endeavour to rotate some of the stock through the normal hospital stock e.g. antibiotics. The following is a description of some of those categories.

36.3.3.1 Emergency Medicines

The public health role of pharmacists becomes specialised in situations of pandemics and emergencies where 'Emergency Medicines' will be required. The list of such medicines is Country specific and are to cover such situations as pandemics, air disasters, explosions involving large sections of the public etc. Pharmacists must have a knowledge of national legal and organisational requirements and of the national organisation who will be active in those situations. The national government generally takes the lead in distribution.

36.3.3.2 Essential Medicines

"Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness.

Essential medicines are intended to be available within the context of a functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford" [5].

The term is more relevant to Countries who have difficulty in obtaining any medicines and for such areas the list will usually be defined by the World Health Organisation (WHO). However in times of National disaster individual Countries may specify their own list. This is a separate list to the Emergency Medicines described above which are to cover single, specified incidents.

36.3.3.3 Seasonal Medicines

Some medicines may be considered seasonal and require special attention with regards to stock control at different times of the year for example, flu vaccinations. The concept of a 'stock turn' for these materials has to relate to the period in which they will be required and not to the usual yearly considerations.

36.3.3.4 Raw Materials for Preparations

Many raw materials used in preparations will not be packed in containers suitable to comply with a normal Stock Turn and therefore should be considered to be outside such rules. For example they may only be available in 500 g when the needs of the preparation unit is for 10 g per year. Nevertheless care should be taken to minimise stock loss through out of date materials on the shelves.

36.4 Procurement

36.4.1 Procurement Process

The section or person in pharmacy responsible for procurement shall evaluate and select suppliers based on their ability to supply product in accordance with the pharmacy's specified requirements. Information on the quality attributes of each item or service will be maintained by the pharmacy procurement system and this information will be used in the procurement function

Those requirements should include:

- The required legal status of the supplier of the product, i.e. is the supplier appropriately licensed to supply the goods required
- Quality criteria both of the product (e.g. if purchasing an eye drop is an integral dropper required or a separate dropper) and the required method of delivery (e.g. is there a need for validated cold chain etc.)
- Criteria for specified timeliness of delivery
- Criteria defining the acceptable shelf life remaining on a delivered product
- Availability of technical support and product information (e.g. if the product is a device, can the Company give technical assistance in setting it up or, especially for medicines, has the supplier an acceptable Medicines Information Department)

The procurement process may also be applied when using internal or external services, for example in-house support services, services provided by one department to another, clinical laboratory and imaging services. Where services are being procured a service level agreements (SLA, see Sect. 33.9.1) will be required

The criteria for selection, evaluation and re-evaluation shall be established, see also Sect. 21.5.1. Records of the results of evaluations and any necessary actions arising from the evaluation shall be maintained.

The purchasing information shall describe the requirements for the approval for each product to be purchased, including, where appropriate:

- Full description of the product with the procedures to be followed to assess compliance which will include the necessary equipment and processes needed
- Requirements for risk assessment
- Requirements for compatibility with existing procedures, equipment, devices, infrastructure and software
- Quality management system requirements
- Purchase history

The pharmacy shall ensure the adequacy of specified purchase requirements prior to placing the order with the supplier.

Orders will be placed in accordance with the required stock turnover of the specific item required.

36.4.2 Tendering

Technically all purchasing, whether it be for one item or thousands, will be by contract. This involves defining the product required, the quantity, the quality, delivery times and the price and agreeing these with the supplier. In order to reach this contract a tendering process is required. This may be a simple process such as agreeing to purchase off a price list for a small number of items purchased locally to a complex tendering process, for example e-procurement [6] controlled by the EU legislation [7] on tendering for supplies to a public body.

The Basic Principals of the EU Legislation are:

1. Contracting authorities shall treat economic operators equally and non-discriminatorily and shall act in a transparent way.
2. Contracts whose value exceeds the specified amount (excluding VAT) over the period of the proposed contract (EUR 134,000 in 2013 (EU 1336/2013) which is updated every two years) must be advertised in a standard format in the Official Journal of the European Union (OJEU).
3. Specifications which are non discriminatory and which refer to EU or other recognised standards must be used where ever possible.
4. Objective criteria must be used when selecting suppliers and awarding contracts.

36.4.3 Types of Contracts

- *rolling contracts* which does not have a specific end date but does have an agreed review date, usually one year, and an agreed cancellation period
- *fixed term contracts*, which last for a fixed length of time which is set in advance or can end when a specific task has been completed or when a specific event has taken place
- *one off contracts* as the title infers this type of contract is for a single purchase with no on going agreement.

36.4.4 Suppliers

Products can be sourced from a variety of different suppliers. The main ones are discussed below.

36.4.4.1 Manufacturers

Companies licensed by the Competent Authority to manufacture are also licensed to supply those items for which they have been granted a Marketing Authorisation. They can sell directly to pharmacies and elsewhere in the medicines supply chain e.g. to licensed wholesalers and registered pharmacies. A number of bulk items such as intravenous fluids are often supplied directly to pharmacies.

36.4.4.2 Wholesalers

Wholesale distribution covers all activities consisting of procuring, holding, supplying, exporting or importing medicinal products, it does not include supplying medicinal products to the public [8]. There are special categories of the Wholesaler Dealers licence for some of these activities e.g. importing.

A wholesale distributor has to hold a wholesale distribution authorisation and must comply with Good distribution Practice (GDP). The Company has to maintain the quality and integrity of the delivered product, to keep it in the legal supply chain during storage and transportation.

A wholesaler has to qualify his customers and monitor his transactions. The Company delivers either to persons with wholesale distribution authorisation or someone authorised or entitled to store and supply medicinal products to the public, usually pharmacists, medical practitioners, dentists, or veterinarians.

Wholesale dealers must have a GDP Responsible Person (RP) nominated on their license and it is this contact that the pharmacist should use if they have any queries as to the legitimacy of any product supplied though a Wholesale Dealer.

Most pharmacies have contracts with a number of Wholesalers and the choice will depend on the normal procurement criteria; speed of delivery, availability etc. Delivery times can vary from a couple of hours to 24 h depending whether the pharmacy is in a city or a town and whether the item is a stock item.

36.4.4.3 Central Stores (Centralised Pharmacies)

Some Countries will have centralised pharmacies which are specialised pharmacies that pick, package and label medicines to be dispensed by the pharmacy. This category would also include those preparative units which will prepare specialised medicines according to a supplied prescription. These centralised facilities may be part of the pharmacy or they may be a different legal entity (see Homecare, Sect. 36.4.4.4).

Whatever the commercial status of the facilities, it is the purchasing pharmacist who is responsible for ensuring that the appropriate quality systems are in place including registration with the appropriate licensing authority, in the facility from which the purchase is made.

Specialised pharmacies pack medicines for each dose (semi-automated medicine distribution system). Normally they unpack medicines from their original package, store the unpacked medicines and repack them for a specific patient. This activity has been designed to increase medication compliance and to support patients, on difficult dose regimes, to stay at home. These pharmacies will be responsible for:

- Assessing the suitability of medicines for repackaging in distribution packages
- Implementing suitable controls over
  - The process of unpacking from the original package the process of repacking in the chosen distribution package (including apparatus and software) and all relevant validation (see also Sect. 22.6.2)
  - And the possibility of mix-up and cross contamination
- Converting shelf lives from original package to the shelf life in containers for storage and then to the shelf life in the distribution package
- Light protection where relevant
- Ensuring that sufficient occupational health and safety precautions have been taken (see also Sect. 26.7.3)

36.4.4.4 Homecare

There is now a growing market, in the UK for example, for supplies to be made directly to patients at home from private companies in order to continue their medication after leaving hospital. These are known as 'HomeCare' companies. This can also involve nurses to administer cytotoxic products, TPN and some psychiatric medicines. The purpose is to remove patients from hospitals to save money, and make them more comfortable, but the hidden costs maybe huge and therefore needs careful assessment. The quality and responsibilities of the various professionals involved in the process also needs defining and monitoring. Whoever is responsible for approving the contract with such Companies they must specify, in writing, where the relevant professional responsibilities lie. For example what doctor is responsible for managing the patient, what pharmacist is responsible for the final dispensing of the product and who is to approve the costs.

36.4.4.5 Importation

Some products are not available within the Country but are available elsewhere in the World. In that case the pharmacist has to apply to a specialised wholesaler or manufacturer for importation. Hospital pharmacies can also hold Wholesale (Import) licenses.

Import is relatively easy between countries within the EEA (see Sect. 3.7), because quality requirements and GMP [9] are the same. However when importing from outside the EEA different quality requirements may apply. A full risk assessment is required before considering importing the medicine. Some medicines may have previously been licensed in Europe but then withdrawn due to health concerns, however they may remain licensed in other parts of the World. In such cases a full risk assessment would be required before contemplating importation.

The attending pharmacist has to deliver the patient information in a language and style that a patient will understand.

36.4.4.6 Suppliers for Products Other Than Medicinal Products

Raw materials and packaging will usually be purchased from wholesalers. Wholesalers for raw materials and packaging do not usually need a wholesalers licence. However some countries have specific regulations requiring such wholesaler to hold a license.

Clinical trial materials [8] (see also Sect. 35.5.10) are usually supplied directly by the initiating Company. In those cases where the clinical trial is a non commercial, internal trial, then the hospital pharmacist will have to obtain supplied from any of the above mentioned sources. The comparator product usually has a Marketing Authorisation and is therefore obtained from either a Manufacturer or a Wholesaler. It should be checked to see if the Trial requires a single batch of comparator and if so a special purchase of sufficient product of the same batch number to cover the trial is often required.

36.5 Medical Gasses

These are usually medicines with a Marketing Authorisation and are usually obtained from the specialist gas manufacturer due to their bulk and handling hazards. Some of the liquid gasses (see also Sect. 23.13) may be on an automatic top up agreement. The responsibility for the ordering receipt, storage and distribution of medical gasses can become confused between pharmacy and other departments e.g. engineering. Written protocols should exist specifying those responsibilities with due reference to the Licensed nature of the gas. In some Countries e.g. the UK and The Netherlands, the pharmacist is responsible for the quality of the gasses in the pipelines in the hospital.

36.6 Goods Receipt

The pharmacy shall establish and implement an inspection procedure or other activities necessary for ensuring that a purchased product meets the specified purchase requirements. The verification shall be in proportion to the risks involved in the use of product or delivery of a service.

Where the pharmacy or its customer intends to perform the verification at the supplier's premises, the pharmacy shall state the intended verification arrangements and method of product release in the purchasing information.

Verification may vary from simple checks on expiration dates of pharmaceutical products, visual inspection of items, e.g. surgical instruments, to acceptance testing of equipment, e.g. an infusion pump, a linear accelerator or software (see also Sect. 34.15).

The pharmacy must have written procedures for receiving, handling and dealing with any returns of supplied medicinal products. Those procedures must include:

- Check if the received goods match the ordered ones.
- Putting aside any which were not ordered.
- Note and complain about items not received.
- Check if the beyond use date allows a reasonable usage period for the patient.
- Register if necessary medicines into a beyond-use system/database.
- Check on the legal status of the medicine and record as necessary any controlled medicines.
- Check for damage and contamination. If necessary cleaning of the outer package.
- Ensure that non-accepted medicines cannot be used or dispensed.
- Identify those pharmaceutical products that require special storage conditions.
- Check for certificates of conformance where required such as for Raw Materials.

36.7 Returned Medicines

The pharmacist must provide a safe storage for pharmaceuticals marked for return to a supplier, prior to return or destruction. There must be procedures in place which will prevent the use of such medicines. See also Sect. 38.5.2 for handling medicines brought back by the patient.

36.8 Controlled Substances

Medicines legislation of the European Union has the objective of "preventing and combating crime, organised or otherwise, in particular terrorism, trafficking in persons and offences against children, illicit drug trafficking and illicit arms trafficking, corruption and fraud" [10].

The EU legislation, which follows on from the 1961 and 1971 UN Conventions, treats an international control system to monitor the production of narcotic drugs and psychotropic substances by prohibiting any use of substances not previously permitted by the national authorities. Under these

Conventions, any use, possession, production and so on of scheduled substances is forbidden, except when exclusively intended for 'medical and scientific purposes'.

The preamble to the 1961 Single Convention recognises:

That the medical use of narcotic drugs continues to be indispensable for the relief of pain and suffering and that adequate provision must be made to ensure the availability of narcotic drugs for such purposes.

Narcotic and psychotropic substances (see also Sect. 2.3.5) are listed in the four Schedules to the 1961 Convention and the four Schedules to the 1971 Convention according to their therapeutic value, risk of abuse and health dangers. In all Countries the ordering, recording of receipts and issues and the storage of items listed in the schedules are subjected to strict rules.

Patients may be in possession of these items provided that there is a legitimate prescription in existence. This also relates to patients crossing borders while in possession of such items. Some Countries may require the authenticity of the prescription to be verified by some government agency in the issuing Country.

Other substances (see also Sect. 2.4.7) will be identified by individual Countries as requiring controls on their purchasing, record keeping and storage and use e.g. diazepam, codeine ergotamine and ephedrine. There are also substances which may be hazardous in another way i.e. the explosive nature of potassium permanganate. Pharmacies must be aware of these requirements and comply with all local legislation.

Many controlled substances are used in preparation areas and it is the responsibility of the preparing pharmacist to comply with the relevant record keeping and storage requirements. Particular attention should be paid to the reconciliation of the powders in this category.

36.9 Storage

36.9.1 Pharmacy

The layout in pharmacies should provide easy cleaning, sufficient lighting, separated product flows and dedicated areas (products to be dispensed, products to be delivered, products to be returned, products suspected of falsification and damaged products). Also dedicated areas for hazardous products such as medicinal gases, combustibles, flammable liquids and solids. The storage of hazardous products above a certain limit have specific requirements for the premises e.g. Facilities with 'blow off' roofs.

Items should be stored as to prevent spillage, breakage, contamination and mix-ups. They should not be stored directly on the floor except for single gas cylinders.

The layout should support the prevention of abuse and theft. The pharmacist must always be aware that medicinal products in the pharmacy provide a risk of abuse. This is not only with regard to the criminal aspect of theft, but also to the risk to public health from improper use. The criminal risk is greatest for narcotics. But also certain chemicals that are innocent in itself can be as precursors for synthesis of drugs of abuse. The pharmacist shall take measures to prevent abuse as much as possible. Access to the stored medicines by anyone other than the employees of the pharmacy is limited and must be organised physically or electronically.

In some Countries, e.g. the UK, Controlled substances are required to be stored in a secure room or vault, protected by alarms that can be monitored 24 h a day. However in some Countries the pharmacist is responsible for deciding on the most appropriate storage conditions to ensure that controlled substances are stored in such a way that the risk of abuse is low

The Pharmacy must have procedures for the entrance of third parties to the pharmacy.

Premises and cupboards must be maintained, clean and germ free.

The pharmacy personnel must know how to operate when an emergency occurs and how to handle it, and know where to find the relevant materials and safety equipment such as gloves face masks, buckets and mops etc. (see Sect. 26.9). Emergencies cover a wide range of accidents that disrupt the normal pharmacy process. This is about relatively limited accidents, such as the breakage of packaging liberating the content to disasters like fire, flood and pandemic. A pandemic could cause the illness of nearly all the pharmacy staff, thereby rendering the reliable dispensing of medicines from the pharmacy almost impossible.

36.9.1.1 Spilled Substances

Hazardous substance may be spilled at preparation, but also during transport, unpacking of incoming goods, delivery and dispensing. All employees of the pharmacy, and if applicable, the employees of the institution where the pharmacy belongs, therefore should be aware how they should act., thus they should be trained. This applies also to logisticians, delivery personnel and nurses (see also Sect. 26.9).

36.9.2 Wards

Storage requirements and responsibility for stock on the wards may differ between countries. In general the pharmacist, if not directly responsible, is responsible for the training of ward staff on how to store and handle pharmacy supplied stock.

36.9.3 Other Areas

Medicines, including specially prepared medicines, will often be stored under conditions which are not controllable with respect to the temperature e.g. Doctors emergency bags, cardiac arrest boxes in wards, ambulances etc. In such cases the pharmacist should advise on the adjustment of expiry dates (see Sect. 22.6.1)

36.9.4 Temperature and Humidity

The temperature of the storage room for medicines should not exceed 25 °C. This requirement may bring about the need of climate control, for example air conditioning. There must be provisions for refrigerated and deep-freeze storage, both at 2–8 °C and at up to −18 °C (see also Sect. 28.9). Now there is a growing requirement for storage at −40 °C, for some clinical trial materials.

The temporary storage space for overnight delivery must provide a means for storage at 2–8 °C. Frozen products are typically delivered in a special packaging making a short storage period outside the freezer possible.

The temperature of these storage areas must be monitored and are equipped with an alarm if the temperature exceeds specified limits. If the storage temperature, is exceeded for instance because of a power failure, the pharmacist shall assess the measures to be taken. The capacity of the cold storage to withstand power outs should be known i.e. measure the rate at which the storage warms when power is switched off. Some fridge products can stand temporary storage at higher temperatures for short periods. The product information from the manufacturer (SPC and Scientific Discussion in the European Public Assessment Reports [11]) may contain such data.

The ICH stability testing guideline defines mean kinetic temperature (MKT) as 'a single derived temperature which, if maintained over a defined period, would afford the same thermal challenge to a drug substance or drug product as would have been experienced over a range of both higher and lower temperatures for an equivalent defined period' This Mean Average Temperature calculation has been used, for short excursions from the required storage temperature, to calculate the likelihood of damage to stored products [12].

If medicines are kept in their original packaging it should be sufficient if the humidity at storage does not exceed approximately 60 % RH. Medicines with a desiccating cartridge in their packaging must not be repackaged, unless it is known by how much the shelf life will be decreased.

36.9.5 Waste

Pharmaceutical waste must be separated from other waste, properly and safely packed and appropriately labelled for removal to destruction. For the removal the pharmacy will need to have a contract with a specialised company. For industrial waste, other rules apply. See also Sect. 38.4.6.

36.10 Distribution

36.10.1 Overview

The principals of GDP ensures that the right product reaches the intended destination under appropriate conditions in a timely manner. In order to achieve this strict attention must be paid to:

- Temperature sensitive products: cold chain (but also prevention from freezing e.g. of vaccines)
- Hazardous products and radioactive materials
- Medicines with a potential for abuse
- Other specific requirements of individual medicines e.g. those containing proteins that must not be shaken

GDP not only applies to goods supplied to pharmacies but to the distribution of goods from pharmacies to areas such as: Wards, Clinics, Theatres, and Off site purchasers

The pharmacist should use a validated cold chain distributor for pharmaceutical products that require fridge or freezer conditions. This also applies to the overnight delivery and for the delivery to the patient's home (see also Sect. 36.10.3). Any delivery exceeding the recommended temperature, for example as a result of a power failure, has to be investigated.

36.10.2 For Goods Received into the Pharmacy

The pharmacist should understand the method by which the supplier maintains the cold chain for example in the case of delivery to the pharmacy the refrigerator or cool box with ice packs, in the transporter must have been validated

- If medicines are to be kept in the freezer then they must be transported in coolers with freezer cooling elements.
- The temperature must be monitored during transport. If the medicines have to be kept frozen it must be offered personally and unpacked by the pharmacy staff for immediate, appropriate storage. Such items cannot be delivered out of hours. Items requiring refrigeration only may be delivered out of hours provided a fridge is available for temporary storage.

36.10.3 For the Delivery to the Patient's Home of Fridge and Freezer Products

The following should be part of the protocol for delivering to a patient's home:

- The person delivering the medicines must be trained in the important aspects of transporting and handling medicines.
- The products must be stored in the freezer or refrigerator until the delivery occurs.
- The delivery person should be informed of freezer and fridge products so that priority is given to the delivery of those items.
- Provide a cool box, a cooler bag, a refrigerator or airco (in the delivery car) during transport of:
  - Vulnerable fridge medicinal products.
  - For frozen products.
  - On days when the average (outside) temperature is above 25–30 °C.
  - If delivery takes more than 2 h.
  - Ice packs should be used where necessary must not be allowed to come into contact with the medicinal product due to the danger of freezing. Bubble wrap may be used as insulation.
  - If the delivery is to institutions such as nursing homes then arrangements should be made such that the articles are placed in a refrigerator immediately after arrival.

For the instruction for the patient who is taking his medicines home see Sect. 35.7.

36.11 Recalls

36.11.1 Overview

The preparing pharmacist must have procedures in place to handle drug recalls from two different perspectives. Firstly as a 'manufacturer' the preparing pharmacist may have to initiate a recall on a product that has been prepared in the pharmacy. Secondly there must be a procedure to handle recalls initiated from outside the pharmacy. This latter procedure is usually the responsibility of the main pharmacy. However the preparing pharmacist must be part of the team which acts on recalls if the recalled product is associated with a prepared medicine because of the legal responsibilities held by the individuals in the preparing section. This may initiate a recall as a 'manufacturer'

36.11.2 Recall (as a Manufacturer/Preparer)

For Recall as a part of the Pharmaceutical Quality System, see also Sect. 35.6.14.

A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation. If this person is not the Qualified Person (QP) or equivalent in hospital, the QP or equivalent should be made aware of any recall operation.

- There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.
- Recall operations should be capable of being initiated promptly and at any time.
- All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.
- The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.
- Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- The progress of the recall process should be recorded and a final report issued, including a reconciliation between the prepared, delivered and recovered quantities of the products.
- The effectiveness of the arrangements for recalls should be evaluated regularly.

36.11.3 Recall (as a Receiver)

In the case of a recall arising from a defect in a product manufactured or prepared outside the pharmacy, in some Countries, a Direct Healthcare Professional Communication (DHPC) will be received. In most cases it is the EMA or the national Competent Authority who initiate a DHPC but it is sent under the responsibility of the manufacturer itself.

The responsibility of the pharmacy is to verify that internal action is needed. If so,

- Remove packs of the appropriate batch(s) from the stock, mark them as blocked and place them in quarantine.
- Check to see if external action is needed (i.e. recall from patients). Replace the recalled batch(s) by unaffected batches.
- If supplying an unaffected batches is not possible, consider therapeutic substitution. The recall letter may

suggest a therapeutic alternative, but this should always with the prescriber's approval.
- Prioritise patients who are already using the product.
- Inform the users about the backgrounds and risks.
- Maintain a recall balance and use it to support the risk assessment for the patients of the pharmacy.
- Send the affected batches back to the supplier according to the instructions in the recall letter.
- Make a risk assessment and decide if a pharmacy preparation must be destroyed or recalled (see Sect. 36.11.2).
- Adjust the stock in the pharmacy.
- Evaluate causes and take corrective measures if necessary. Record all actions, even if there were no packs of the recalled batch in the pharmacy.

36.12 Education, Experience, Training

All staff involved in procurement require the appropriate initial training and to participate in continuous professional development.

The categories of staff usually involved in these procedures are:
- Pharmacists
- Technicians
- Store Keepers
- Secretarial and administrative Staff

They should receive training on the requirements of GDP relevant to their role. The training should be based on written procedures and in accordance with written training programme. They should receive specific training in identification and avoidance of medicines entering the supply chain.

Those personnel dealing with specialised products which require more stringent handling should receive specific training. The senior pharmacists should also receive specialist training in, for example, Contract Law, negotiating with suppliers, and obtaining best value for money through good procurement. Some Countries have specific degree courses in the subject [13].

A record of all training should be part of the documentation system in the pharmacy and the effectiveness of the training should be regularly tested.

36.13 Falsified Medicines

Falsified medicines (the term 'falsified' is used to distinguish the issue from patent violations, so-called 'counterfeits') are a major threat to public health and safety [14].

EU legislation tries to decrease this phenomenon by the Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products [15].

The pharmacist must be alert to the occurrence of falsified medicinal products (counterfeit) and is aware of his role in preventing falsified medicines reaching the patient. Patients should be informed of the dangers of ordering medicinal products through internet sites which have not been validated.

Safety features, initiated by the Pharmaceutical Industry, should assist in the verification of the authenticity and identification of individual packs, and provide evidence of tampering.

The pharmacist can contribute to a safe supply chain as to falsified medicines by:
- Validating their supply chain and being aware that falsified medicines can also enter the legal supply chain
- Being alert about those medicines that are susceptible to falsification
- Have a decision tree for action when suspicion are raised regarding a product
- Taking seriously complaints by the patient about medicines that look unfamiliar or have a different or no effect
- If in doubt contact the Competent Authority and the Supplier immediately

A suspicious product may be compared with the original. Pay attention to the following aspects:
- The packaging and sealing system. Tablets that normally are blistered, may be in a different packaging. The colour of a pack might be pale, seals may be missing and any holograms may be more vague than on the original.
- The labelling. Text and prints may contain spelling errors or batch numbers may be constructed differently. Also the name of a medicine may be spelled different: Vi@gra or V!agra).
- The product information. This may contain spelling mistakes. Different fonts may be used or different kind of paper may be used.
- Regarding the external features of the product. Compare if possible with an original product that has been obtained through a reliable supplier. Tablets should look uniform, break lines, inscriptions or coatings may be missing.

Any product suspected of being a falsified medicine should be immediately segregated and stored in a dedicated area and the Competent Authority should be informed at once.

See also Toolkit by World Health Professions Alliance (WHPA) [16].

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Instructions for the Use of Medicines

37

Suzy Dreijer - van der Glas and Anthony Sinclair

Contents

Abstract

One of the aims of pharmacy practice is to help patients to make the best use of their medicines. This means that patients should not only get therapeutic information by counselling but also the practical instructions and advice that they need in the actual use of their medicines.

Generally this is covered by the product information related to a particular medicine. Directions for use, storage and expiration date are part of the label and the package leaflet, owing to legal requirements. For some patients or their caregivers however, the instructions on the label or in the package insert are not enough to enable them to handle a medicine correctly. This may be due to the type of medicine, or the needs of a particular patient. Some medicines need reconstitution before they can be used (e.g. antibiotics in oral liquids, injections). Patients with swallowing problems for instance may need manipulations with tablets or capsules before they can take them.

This chapter deals not only with the legal requirements on labelling and patient information leaflet, but also with reconstitution and other manipulation needed prior to use or administration as well as instructing the patient about it, with the focus on the needs of the patient.

Keywords

Patient instructions • Use of medicines • Caregiver • Labelling • Storage • Feeding tube

Based upon the chapter Gebruiksadviezen by Suzy Dreijer and Yuen Yee Li in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_37,

37.1 Introduction

The FIP/WHO Guidelines on Good Pharmacy Practice defines the aim of pharmacy practice as "contribute to health improvement and to help patients with health problems to make the best use of their medicines". The idea that patient counselling mainly deals with pharmacotherapeutic issues is not true. It cannot be taken for granted that patients will use all the dosage forms defined in the chapters of this book in the correct manner. Thus when dispensing medicines, patients should not only receive information but also instructions and counselling that they need to make the best use of their medicines.

First of all this means product information related to a particular medicine. Directions for use, storage and expiration date are normally part of the label and the package leaflet, as a legal requirement. This chapter describes how to deal with these requirements.

Helping the patient goes further than the legally required instructions. It is focused on the needs of a particular patient in the use of the medicine. Some medicines for instance need reconstitution before they can be used (antibiotics in oral liquids, injections). For some patients or their caregivers, instructions on use are not enough to enable them to handle a medicine correctly. They may need help in manipulations required to use the product. To what extent the pharmacist should help will depend on the type of medicine and the type of patient. Instructing the caregivers may sometimes be the best option. Therefore this chapter not only deals with dispensing, but also with reconstitution and other manipulation needed prior to use or administration.

37.2 Knowledge and Skills

In order to be able to give appropriate advice on the use of a medicine a pharmacist will need to draw on their underlying knowledge in three broad areas:

1. Knowledge of the product characteristics
2. Information and directions for use and administration, for patient and caregiver
3. Reconstitution and other manipulation to be carried out on the product

Product knowledge implies an understanding of how the product is produced and the consequences for use and storage. In other words the physico-chemical properties such as storage temperature and compatibility with bulk parenterals and infusion tubing. It may also mean awareness of possibly unwanted excipients, e.g. ethanol. Product knowledge and instructions for the patient are always needed, reconstitution and manipulation prior to use or administration only for particular (groups of) patients or particular medicines.

Examples of manipulation include not only the reconstitution of powders for suspension by adding water, but also measuring the right amount of liquid using a syringe, either for oral use or injection. Whether the patient or caregiver actually needs help in manipulation or just instruction depends on their skills and the type of manipulations. The pharmacist has to take care that it is done properly, whether this is done in the pharmacy or at home by patient or caregiver. This demands not only knowledge of the product, but also empathy with the patient or caregiver. Special attention is needed for the instructions of hospital personnel on the reconstitution and admixing of parenterals and manipulation of solid dosage forms.

37.3 Label and Patient Information Leaflet

37.3.1 Legal Requirements

In the Product-information templates of the European Medicines Agency (EMA) the requirements for the labelling and package leaflet for licensed medicines are published [1].

Particulars to appear on the outer package and the immediate package:

- Name and strength of the medicinal product *
- Statement of active substance(s), qualitatively* and quantitatively, per dosage unit or for a given volume or weight
- Excipients known to have a recognised action or effect (in some dosage forms all excipients)
- Pharmaceutical form and content of the package*
- Method and route(s) of administration*
- Instructions on use
- Special warning: "Keep out of the sight and reach of children"
- Expiry date, stating month and year*
- Storage conditions
- Instructions on use
- Special warnings e.g. for disposal, if appropriate
- Name and address of the marketing authorisation holder
- Marketing authorisation number
- Batch number*
- Information in braille (if possible)

The items marked * are the minimum to appear on small primary packages.

In licensed medicines this information can be printed on the outer package when there is not enough space on the actual label on the primary container. In many countries it is permitted to include part of the information in a patient information leaflet, as it will often not fit within the label. A reference to such a leaflet should be made in that case. Since 2013 the European Pharmacopoeia (Ph. Eur.) monograph on Pharmaceutical Preparations have made most of

these regulations apply to the labelling of unlicensed pharmaceutical preparations with the exception of the data on market authorisation [2]. Relevant requirements given in the general dosage forms monographs are also required in unlicensed products. In addition, "relevant EU or other applicable regulations apply".

The Ph. Eur. monograph Pharmaceutical Preparations does not clearly mention a package leaflet, although it says under the heading Labelling that "relevant European Union or other applicable regulations apply". Most national regulations do not require a package leaflet either. A short overview of the requirements of the EMA for package leaflets is shown below.

Items to appear in the package leaflet of licensed medicines:

- Name, active substance and therapeutic indications
- Contra-indications, special warnings and precautions
- Interaction with other medicines, food and drink
- Possible side effects
- Instructions on use
- What to do in case an overdose has been taken or a dose was missed
- Storage
- Contents of the pack and other information

Many of these items are important for the users of (unlicensed) pharmaceutical preparations as well. From a strictly legal point of view therapeutic benefits and side effects cannot be claimed, not being agreed by any licensing authority. But in many countries the needs of the patient will prevail and patient information leaflets for unlicensed pharmaceutical preparations have been developed. These may be specific for a preparation included in a formulary, e.g. the Formularium der Nederlandse Apothekers (FNA) [3] see Sect. 39.4.5, the Neues Rezeptur Formularium (see Sect. 39.4.2)] or the Formulário Galénico Português [4] or just for an active substance. Much of this type of information can also be found on websites published by pharmacy organisations, or by (groups of) pharmacies or hospitals.

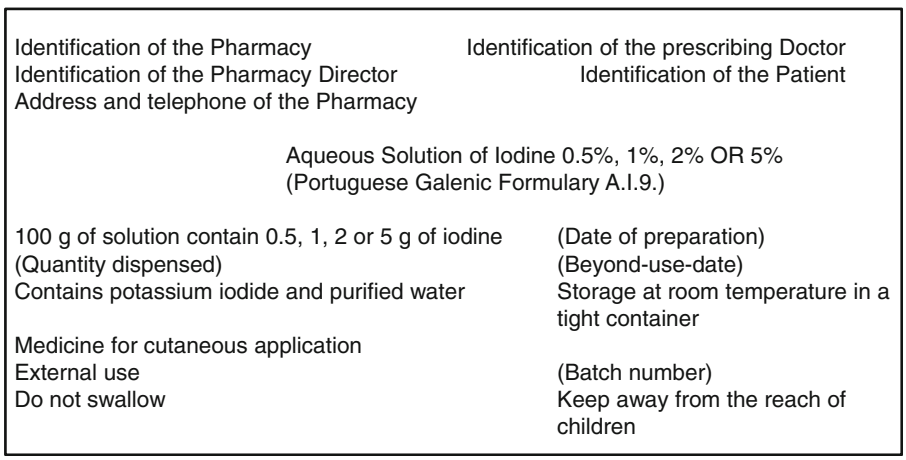
> The medicines for children organisation in the UK has a set of information leaflets [5] that parents can download free of charge for individual medicines. These leaflets are designed for paediatric use advice and don't have warnings for example that would worry a parent giving a medicine to a child, off-label.

The EMA templates on labelling state: "on the printed outer packaging material an empty space should be provided for the prescribed dose". When a medicine is dispensed on prescription in a pharmacy, often a (additional) label is attached, intended for a specific patient. In many countries this is compulsory, but when no (national) legislation exists, dose and frequency are sometimes written on the package. Legislation may vary between countries, but the label on a (licensed) medicine that is delivered on a prescription to an ambulant patient should contain at least the following information:

- Name of the patient
- Name (and address) of the pharmacist (or pharmacy)
- Directions for use (dose and frequency)
- Date of dispensing

According to the existing national rules for the labelling of pharmacy preparations, the labelling often is a combination of the requirements for a specific patient and the general requirements for licensed medicines. A good example is the standardised label of the Formulário Galénico Português (FGP) [4] (Fig. 37.1).

The legal rules for specific labelling for ambulant patients in most countries do not apply to hospitalised patients. But


Identification of the Pharmacy
Identification of the Pharmacy Director
Address and telephone of the Pharmacy

Identification of the prescribing Doctor
Identification of the Patient

Aqueous Solution of Iodine 0.5%, 1%, 2% OR 5%
(Portuguese Galenic Formulary A.I.9.)

100 g of solution contain 0.5, 1, 2 or 5 g of iodine
(Quantity dispensed)
Contains potassium iodide and purified water

Medicine for cutaneous application
External use
Do not swallow

(Date of preparation)
(Beyond-use-date)
Storage at room temperature in a tight container

(Batch number)
Keep away from the reach of children

Fig. 37.1 Standardised label for Lugol's Solution FGP (From Formulário Galénico Português with permission)

many hospital pharmacies will have their own guidelines, normally including the following minimum requirements for labelling for an individual patient:

- Name of active substance, form and strength and quantity issued
- Essential warnings i.e. do not crush or chew; shake the bottle
- Patient's name (and sometimes a hospital identification number)
- Date
- Ward that the patient is on

In some countries professional standards are in force. In these countries guidelines for the labelling of medicines in the hospital have been published.

In other countries working groups of hospital pharmacists are preparing such guidelines for special groups of medicines, i.e. antineoplastics or paediatric medicines.

37.3.2 Labelling and Package Leaflet in More Detail

Labelling should fulfil the legal requirements, preferably in a way that helps the patient. In some countries, organisations of, for example, hospital pharmacists may have developed their own guidelines on labelling. This section comments on how to deal with the legal requirements, more or less in the order they appear on the label. It is important to note that legislation at this point varies from one country to another. As a consequence this chapter can only give general recommendations.

37.3.2.1 Route of Administration

The uppermost zone of the label shows the route of administration, if this not the oral one. Officially the Standard Terms of the European Directorate for the Quality of Medicines and Health Care (EDQM) [6] should be used, but in some countries all non-oral routes may be indicated as 'Not to be taken'. A more specific term such as Eye drops, Ear drops or 'For rectal use' is to be preferred. Some patients may not know the meaning of the term 'rectal use'. Also the words 'Not to be taken' sometimes need explanation, for instance in the case of a mouth rinse.

The use of colours, either for the complete label or for a strip at the top to emphasise non-oral use is widespread, and in some countries compulsory. The colour may differ per country. A blue strip is often used, but a red label is common in other countries, e.g. Croatia and the Czech Republic. Also other colours on the label may be used as a signal for certain groups of medicines, e.g. in hospitals.

37.3.2.2 Name of the Pharmacist or Pharmacy

Although legislation will vary, name, and address or telephone number of the dispensing pharmacy should always be clearly indicated. Sometimes the legislation specifies that the name of the owner or the pharmacist should be on the label, or other ways of identification of the pharmacy are used.

The Pharmacy Practice Order (Apothekenbetriebsordnung) in Germany demands, besides the name of the owner, the initials of the person who has dispensed the medicine on the label, or the name of the supervising pharmacist [7]. In Croatia and the Czech Republic this applies for the label of pharmacy preparations. In the UK it is good practice to write the initials of the pharmacist and those of the dispenser if they are different, but this is not law.

37.3.2.3 Date

Usually the date the medicine is dispensed will appear on the label. It is important to notice that this date may be different from the date it is actually delivered to the patient. The date can be used as an instrument for tracing a dispensed medicine, but in most of the national legislation a batch number is required for pharmacy preparations

37.3.2.4 Name of the Patient

Just the name is usually not enough to identify a patient. Date of birth, first name(s) and address give additional information. Hospitals may use a unique identification number. In delivering a medicine to someone else than the patient in person, the pharmacist assumes responsibility. When in doubt, inquiries from the patient himself, or a proof of identity may be asked.

37.3.2.5 Name and Strength of the Medicine

For the indication of the active substance in the name of pharmacy preparations the generic or International Non Proprietary Name (INN) is to be preferred. The purpose of the strength in the name is to indicate the quantity of the active substance, which is relevant for the correct use and identification of the product, and its distinction from similar presentations. The strength in the name should, therefore, be based on user/prescription criteria rather than analytical

criteria according to the Recommendations on the expression of strength in the name of centrally licensed human medicines from the Quality Review of Documents group (QRD) [8].

At the same time it should be clear which form of the active substance is meant in the indication of the strength. This can for instance be the hydrate of a salt, or just the active moiety, without the salt or hydrate water (see Sect. 23.1).

For instance, in morphine preparations normally morphine hydrochloride trihydrate or morphine sulphate pentahydrate will be used as raw material. These salt hydrates are included in the Ph.Eur. and BP (British Pharmacopoeia) respectively [9]. Then if the name would say just morphine, the strength should refer to the morphine base moiety. But as usual doses refer to the salts, the salts should be indicated in the name. Examples are:

- Morphine sulphate injection 10 mg/ml BP
- Morfinehydrochloridedrank (Morphine Hydrochloride Oral Solution) 20 mg/mL FNA

The same applies to many generic medicines, e.g. Metformin hydrochloride 1000 mg tablets. These could also be called: Metformin 780 mg tablets (as hydrochloride), but this would be very confusing, as dosing regimens always use the hydrochloride.

For inorganic compounds both cation and anion are always mentioned. Abbreviations for the elements are allowed. The EMA now recommends that name and strength of licensed medicines should refer to the active substance or moiety [1]. Therefore in preparations that were licensed by EMA recently, the name and dosing schemes usually refer to the active substance only, even if it is present in a salt form. For instance Pradaxa® 75 mg capsules contain dabigatran etexilate mesilate, equivalent to 75 mg dabigatran etexilate.

Sometimes the strength is indicated in two ways. For instance in Sifrol® 0.7 mg each tablet contains 1.0 mg pramipexole dihydrochloride monohydrate equivalent to 0.7 mg pramipexole. Because doses, as published in the literature, refer to the salt form, the name on the package is Sifrol® 1 mg (0.7 mg base).

37.3.2.6 Ingredients of the Medicine

In some countries it is permitted to use, for preparations included in a national formulary, the product name mentioned in that formulary, provided the formulation corresponds exactly with the one in the formulary (e.g. Hydrocortisonacetaatcrème FNA in the Netherlands). Adding the name of the formulary is necessary in that case to identify the formulation. Additional information about the ingredients should be in the package leaflet. For cutaneous preparations in particular it is important that prescribers can obtain this type of information. Special editions of a national formulary, intended for prescribers, exist in some countries.

If the product is not a standard formula, the names of all the active ingredients have to appear on the label, and preferably of all the excipients as well. At least preservatives and antioxidants should be mentioned. The EMA requires excipients known to have a recognised action or effect to be mentioned [1]. A list of such excipients is available on the EMA website [10]. Examples are ethanol and propylene glycol, and benzyl alcohol, especially in medicines for children. See also Sect. 5.4.5.

In naming pharmacy preparations with more than one active substance, it will in practice not always be possible to follow the rules about the name and the strength. If for instance 0.1 % triamcinolone acetonide is added to ketoconazole cream, the name on the label for the patient would probably be: 0.1 % triamcinolone in ketoconazole cream, simply because the full name would not fit.

Therefore it is important to list the full formula on a separate label.

Names of substances should be written in full, including water of hydration, if appropriate. For substances of pharmacopoeia quality the name as mentioned in the Ph. Eur. may be used, followed by the initials, Ph. Eur. In this notation it is usually not necessary to state the amount of water of hydration, as this will be defined in the Ph. Eur. monograph. Using the Latin name of the Ph. Eur. for the substance may be an alternative way to indicate their quality.

37.3.2.7 Content of Active Substance in Pharmaceutical Preparations

The amount of active substance should be declared as ‘pure substance’. This means the content that would be determined in a chemical assay. For example, in the preparation a calculated excess of active substance is processed, because the material may contain water of hydration. This excess should not appear on the label (i.e. the label claim), as the assay refers to the active substance without water.

However, when the quantity of active substance refers to a hydrate, this should appear on the label. The content of the hydrate should then be determined.

For preparations presented in single-dose-units it is important to indicate the composition per dosage unit, as well as the number of units supplied. As a consequence it will sometimes be necessary to calculate the quantity of excipients per unit from the amount used for the whole batch (i.e. fillers in capsules). When only the quantities of ingredients for the whole batch are indicated in the label, there is the risk that other caregivers will interpret the composition falsely. For the same reason, according to the EMA

the concentration of oral liquids and other multidose forms should be indicated per millilitre or per dose, so not as a percentage [8]. For semisolid preparations like creams and ointments, the concentration or strength should be indicated as amount per unit weight (e.g. mg/g).

37.3.2.8 Units

For the indication of strength or amounts of active substances and excipients the following physical parameters are used: volume, mass and or quantity, with units according to the international system (SI). The following units and derived units are used:

- Volume: litre (l), millilitre (ml); however according to the Ph. Eur. the litre is written with a capital L: litre (L) and millilitre (mL); mass: kilogram (kg), gram (g), milligram (mg) and microgram (microgram rather than µ, µg and mcg)
- Quantity: gram molecule (mol), milligram molecule (mmol), microgram molecule (micromol, rather than µmol or mcmol)

Despite of the fact that µg is the SI unit, the use of this abbreviation should be discouraged. Some fatal errors have occurred in the past, as a result of false readings of drug doses in the microgram range. Although modern printers reduce the risk of reading errors, they may never be completely excluded. There is also the risk of false interpretation of this kind of symbols, when changing from one data carrier to another.

Dimensionless notations like percentages are only used in preparations for external application, and, by exception, in traditional combinations (normal saline 0.9 %, dextrose 5 %). If possible, a percentage should be indicated as m/m, m/v or v/v. According to the EMA the use of percentages should be discouraged, and the indication in mg per unit weight or per unit volume is to be preferred [8].

For substances that are standardised biologically, biological units are allowed. According to the international system (SI) only the International Unit may be abbreviated (IU). All other units should be written in full. In the UK the National Patient Safety Agency has recommended that even IU is not used but should be written out in full [11]. This was due to a number of deaths that have occurred owing to errors with abbreviations of (international) units. Also in other countries errors in dosing were discovered, due to lack of clarity in the necessary calculations from mg to USP units [12].

When labelling infusions or injections concentrations can be indicated in different ways, as in the following examples:

Potassium chloride 10 mmol = 10 ml (1 mmol/mL) or
Potassium chloride 10 mmol in 10 ml (1 mmol/mL) or
Potassium chloride 745 mg = 10 ml (74.5 mg/mL) or
Potassium chloride, K 1 mmol/mL, Cl 1 mmol/mL
Theophylline 200 mg = 1 ml
Heparin 5,000 IU = 1 ml

The EMA has developed recommendations for the expression of the strength of liquids [8], including parenteral medicines, where the way of expression also depends on the way of use, see Table 37.1.

This means that for injections usually both the total amount of active substance and the concentration should be indicated, whereas for infusions the concentration and the total volume would be enough.

Note that in these recommendations only milligram is used, not mole. In practice for electrolytes the amount in moles is usually given as well. Doctors prescribe dosages of electrolytes based on blood concentrations that are given in mmoles.

37.3.2.9 Dose

Dose and frequency are indicated, if necessary at what times of the day. In case of variable doses ('on demand') the maximum use per 24 h and sometimes a maximum per week should be stated. Additional instructions may be needed, i.e. 'Shake well before use', or 'Take with meals', depending on the type of medicine. Of particular importance are warnings for staining or bleaching of clothes, or 'highly flammable'. Lack of information of this kind may result in damage to the user or his property.

In some countries, e.g. Switzerland, a warning that the preparation contains ethanol is compulsory for oral mixtures with >0.7 %.

According to the European Regulation on Classification, Labelling and Packaging of Substances and Mixtures (CLP Regulation) [13] (see Sect. 26.6.3) hazard symbols are not compulsory in the labelling of medicines; for patients safety however, symbols referring to the risk of flammability and explosion are needed. For flammable substances the need depends mainly on their flashpoint.

As already mentioned, it is not always possible to fit all the information within the label. Examples are a dosage schedule for different times of the day, or a reduction scheme for corticosteroid treatment. In these situations additional oral and sometimes written explanation will be needed.

Table 37.1 Recommendations for the expression of the strength of liquids [8]

Parenteral preparation	Preferred strength in name	Format
Single dose (in case of total use of ampoule)	Total amount in container	z mg = z mL (1 mg/mL)
Single dose (in case of partial use)	Amount per unit volume	X mg/mL (z mg = y mL)
Multidose	Amount per unit volume	X mg/mL

In the UK patients on steroid treatment receive a Steroid Treatment Card [14] so that they carry a warning against suddenly stopping therapy (and other information) in addition to the dosage schedule.

Dose administration aids, also called compliance aids, may help the patient to keep the overview. These weekly pill boxes are reusable boxes that allow medicines to be housed in grid like compartments, in preparation for sequential dosing according to a prescribed regime. Most boxes cater for up to 4 doses per day for 7 days. See also Sect. 37.7.4

37.3.2.10 Expiry Date and Beyond-Use Date

Expiry date and storage instructions are legally required on the label of all medicines. After the expiry date the manufacturer cannot guarantee the quality and safety of the product, no matter whether the package has been opened or not. For most patients however it is more important to know the expiration period after opening. This is the usage period, or period until the beyond-use date. Therefore the beyond-use date should be on the patient label, rather than the expiry date. In some countries pharmacists are required to affix beyond-use dates, supposing that the package will be opened shortly after dispensing. In licensed medicines, a beyond-use date is legally required only for special categories, such as parenteral medicines, ear drops and eye preparations.

For pharmacy preparations, usage periods per dosage form are given in Table 22.7. These general suggestions are mostly based on microbiological factors, and sometimes on physical properties. Often they may also be used for licensed medicines. See Sect. 22.7. for details.

The general advice for the maximum usage period only apply when there are no limits due to (chemical) instability of the active substance. For nationally standardised formulations, both shelf life and usage period usually have been determined. Examples are formulations in the German NRF (see Sect. 39.4.2), the Portuguese Galenic Formulary (PGF) [4] and the Dutch FNA [3], see Sect. 39.4.5.

The expiry date of pharmacy preparations depends on the date of preparation, the conditions under which the preparation is made, the type of container and the storage conditions. It should always be part of the label of stock preparations. In practice, it will not always be necessary for the patient to know this expiry date, as long as the beyond-use date lies *before* the expiry date, and the container is opened shortly after dispensing. Most important for the patient is that the label is clear and unambiguous on the maximum period of storage.

In treatments that should have a limited duration for pharmacotherapeutic reasons, the duration should be stated with the dosing scheme. Examples are strong topical steroids, or nose drops with decongestants.

37.3.2.11 Storage

Storage instructions that are important for the usage period should be on the label (e.g. Keep refrigerated, or Store at room temperature). Sometimes only the pharmacy stock needs to be kept in the refrigerator, while this is not necessary for the short period the patient uses the medicine. Examples are Acetic acid Ear drops and Atimos® or Foradil® aerosol. Both ear drops and preparations for inhalation should be at least at room temperature when used, because low temperatures can be unpleasant for the patient.

37.3.2.12 Where to Attach the Patient Label

In pharmacy preparations usually the primary container is labelled. The label on tubes should be near the cap, in order to keep it visible as long as possible during use of the product. A transparent film can be stuck on top of/over the label to protect it from the ointment in the tube. Cartridges that are filled for use in insulin pumps should not be labelled, as a label may interfere with the fitting of the cartridge into the pump. In such cases the label should be placed on the secondary packaging instead. Very small containers, such as eye ointment tubes or ampoules, can be labelled with a flag label with the minimal information that is required legally on the patient label. The remaining information should then appear on the label of a secondary package, or in a patient information leaflet (see Sect. 37.3.1).

For licensed medicines the patient label is often attached to the secondary packaging. This has the disadvantage that the label with the dosing information becomes lost if the patient discards the secondary package. But many primary packages, such as blisters or small vials, are unsuitable for labelling or it may simply not be allowed to open the package before dispensing. In such cases patient labels can only be attached to the secondary package; preferably a label on each single container of medicine when more than one is delivered.

37.4 Instructions on Use

37.4.1 Oral and Written Instructions

When dispensing medicines, oral instructions on use should be given in the pharmacy together with additional written information as appropriate. The way patients (or caregivers) receive instructions is one of the factors determining the

quality of their manipulations with the medicine. Also it is important to try to understand a patient's capabilities, language skills and situation. Research has shown that demonstrating, followed by copying by the patient, and additional written instructions all lead to better results, compared to just oral instructions [15]. This study focused on measuring liquid medicines with a measuring device, but the same applies to eye drops or inhalers.

Many countries have websites where patients can find instructions, or let them reproduce the instructions. Drug manufacturers give information on their websites and instruction videos for specific medicines. This product information is often not appropriate for drugs used in off-label situations, so in those cases the pharmacist's advice is even more important. Information for specific patient groups can often be found on websites specialising in their disease (e.g. cancer or diabetes patients). But not all people have access to internet to access that information.

37.4.2 Packaging

Opening a package in the right way may require explanation (e.g. eye drop bottles, suppository strips, orally disintegrating tablets). Sometimes a user may prefer a specific container, for instance a jar instead of a tube for ointments.

37.4.3 Way of Use

37.4.3.1 Tablet Types

Solid oral dosage forms need explanation on the type. An effervescent tablet has to be dissolved before use, but small dispersible tablets could also be swallowed as a whole, with a glass of water. Taking the medicine with water is allowed, but not necessary in orally disintegrating tablets, which are designed to disintegrate on the tongue. Enteric coated tablets and dosage forms with controlled release usually must be swallowed whole. In Sects. 4.9 and 4.10 an overview is given of tablet types.

37.4.3.2 Dividing Tablets

Dividing or breaking tablets is another point of interest, and not only when it is mentioned in the prescription, or as a means of obtaining the prescribed dose. In many cases patients divide tablets on their own initiative, to ease swallowing or because they want to take a lower dose [16, 17]. Such actions are not always successful (Fig. 37.2).

The package leaflet does not always indicate whether a tablet may be divided, and the presence of a score line does not guarantee that splitting is possible or even allowed [18]. When in doubt, the pharmacist can refer to the product information for details of the formula. Enteric coatings, for instance, have characteristic components, see also Sect. 4.10.

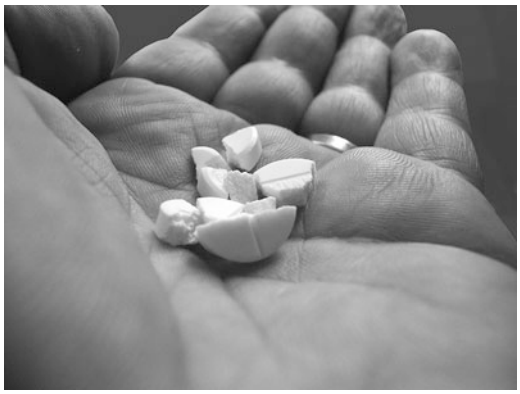


Fig. 37.2 A tablet in bits and pieces (Photo Marcel Terlouw, Argos. Source: Recepteerkunde 2009, ©KNMP)

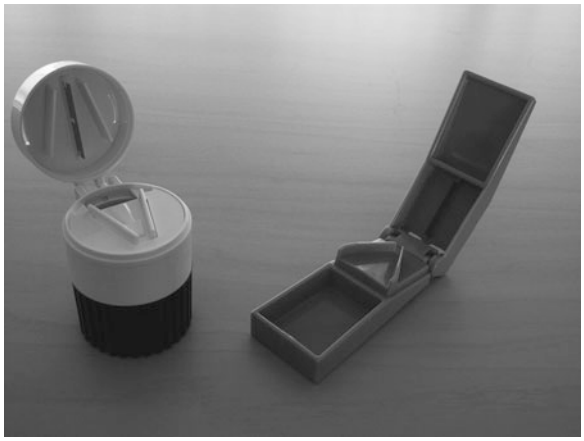


Fig. 37.3 Tablet splitters (Photo Luuk Dreijer. Source: Recepteerkunde 2009, ©KNMP)

When tablets may be subdivided and they have a break-mark, the halves have to comply with the requirements on the uniformity of mass of the Ph. Eur. under S*ubdivision of tablets* [2]. Up till now these requirements only apply for scored tablets where subdivision is necessary to meet all the doses that are mentioned in the product information, not for break-marks intended to ease swallowing. There are also requirements proposed on the loss of mass by subdivision and the ease of breaking. In a Dutch study on a representative selection of tablets with a market authorisation only 24 % complied with the requirements on the uniformity of mass of the halves, and 34 % with the proposed standards on ease of subdivision [19]. These results were comparable to those of other studies on patient experiences with the performance of score lines [16, 17]. A so called tablet splitter can be useful (Fig. 37.3), although it does not always give better results than a kitchen knife or breaking by hand.

That tablets break into unequal halves may not be clinically relevant, but patients tend to think it is important.

Therefore it would be better if the requirements on uniformity of mass of the Ph. Eur. would apply to all tablets with a break-mark, whether this is needed for authorised doses or not.

In the meantime the pharmacist can try to reassure patients on this point, by using pharmacological knowledge.

37.4.3.3 Measuring Liquids

In pharmacy preparations packaging and measuring devices are part of the design of a product. In other words, attention should be paid to the feasibility of measuring the expected quantities with the supplied device from the container chosen.

For licensed medicines however, it is not uncommon that the dosing device in the package is unsuitable to measure the prescribed quantity to particular patients. In that case the pharmacist should supply a better measuring device. In young children administration of liquids with an oral syringe is often easier than with a measuring spoon. Cleaning instructions for oral syringes and pipettes are important when oily liquids are dispensed. A problem can be that the markings of the oral syringe may begin to wear off with normal use in a very short time. To measure the right dose of liquids for use in nebulisers, sometimes sterile syringes and needles are needed Fig. 37.4.

The devices supplied and the way the manipulations are carried out can greatly influence the dosing accuracy.

In a study from the USA, 14 % of the participants could measure 5 ml of an oral liquid within an acceptable range with a measuring cup, whereas 67 % could do this with a syringe. This percentage rose to nearly 100 % when the participants were given instruction and a demonstration with the syringe [20]. In 2005 EMA has published a guideline on the suitability of the graduation on measuring devices. Points of attention are the possibility to measure the minimal and the maximum dose, the dosing steps in relation to the advised dose, and the readability of the graduation [21]. In general it is recommended that a measuring cup or syringe should be filled to at least 40 % to obtain dosing with adequate accuracy (see Sect. 29.1.7). For very small volumes this will not always be possible.

37.4.3.4 Homogenising

When the label of a medicine bears the warning ‘Shake well before use’, some explanation to the patient may be needed to avoid mistakes. For nose sprays, which are suspensions for instance, the patient should first shake well and then start pumping, to prevent clogging of the tube.

However suspensions of insulin or other proteins should not be shaken, but gently rolled to homogeneity. So this kind of preparations should definitely not be labelled with: ‘Shake well before use’ but ‘Roll gently until well mixed’ instead (See also this chapter Sect. 37.7.3).

37.4.3.5 Special Devices

Preparations for inhalation are supplied with special devices, see Sect. 6.5. Inhaling the proper way is essential in order to

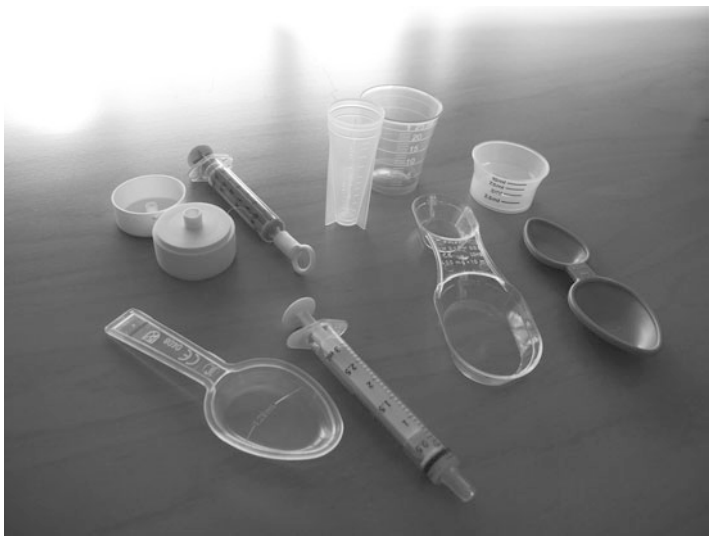


Fig. 37.4 Measuring spoons, cups and syringes (Photo Luuk Dreijer. Source: Recepteerkunde 2009, ©KNMP)

get a sufficient amount of the medicine on the right place, i.e. the lungs. Young children and many elderly people have to use a spacer to be able to inhale the right way. Spacers exist in different models, depending on the manufacturer of the medicine. Often a spacer can only be used with the products of the supplier. In these situations counselling starts with the choice of the right devices, in accordance with the medicine and the age of the patient. After that, (repeated) instruction will be needed, and control of the patients way of inhaling. Section 24.4.19 deals with dosage delivery devices in general. In the chapters on dosage forms, information on special devices is included.

37.5 Storage

An example of storage instructions for the patient is "Store below 25 °C". "Keep refrigerated" means: store between 2 °C and 8 °C. The instruction "Keep cool" means between 8 °C and 15 °C. This advice is often difficult, as not many households will have that possibility. Some explanation may be needed in the instruction "Keep refrigerated, do not freeze". Depending on the season and the climate, the patient has to be warned to put the medicine in the refrigerator as soon as possible, to avoid either warming or freezing.

The following is an example of a patient information leaflet about storage of medicines.

Keeping Medicines

Store medicines in such a way that they do not deteriorate. For most medicines this is quite simple. When in doubt, check with your pharmacist. For certain categories of medicines your pharmacist will give special advice.

Cupboard:

A good place to store most medicines is a dry cupboard, where the temperature will not exceed 25 °C. Even during periods of extreme warm weather your medicine is safe there. Such a cupboard is acceptable if the label does not mention any special storage instruction. The bathroom is not a good place to store medicines: it is too damp there.

Refrigerator:

- Do you have to store medicines in the fridge when it is hot? Not necessarily. Look at the storage instruction on the label or the package leaflet. Ask your pharmacist when in doubt.
- Suppositories may melt with heat. But perhaps they do not have to be stored in the refrigerator. Look at the storage instructions.
- Liquids such as oral mixtures or ampoules with injection fluids should not be refrigerated as a rule, because the cold may affect them in an unwanted manner. For instance, crystals may appear in a mixture. Look at the storage instructions.
- Eye drops, ear drops and enema's should maybe not in the refrigerator. Look at the storage instruction. If these preparations are stored in the fridge, it is a good idea to warm them in your hands for about 5 min before use. Otherwise they will be very unpleasant to use.
- Always, but especially for medicines in the refrigerator, remember: keep medicines away from children. Put the medicines in a box that cannot easily be opened.

Carrying your medicines home:

It can be hot when you are on your way home, coming from the pharmacy.

- Take care that your medicines are in the warmth for a period as short as possible. So, if you need to do more shopping, visit the pharmacy at the end and go home straight from there. For some medicines a cool box may be useful.
- Do not leave medicines in a hot car.
- When you are carrying your medicines going on holiday: do not store your medicines on your body (in your trousers for instance). Keep them in a bag.
- Ask your pharmacist if you expect problems in keeping your medicines refrigerated when travelling or on holiday.

Typical patient questions on this subject have to do with storage during holidays and temporary storage at temperatures higher than they should be. Information on this subject is not always clear from the information leaflet, but often medicine manufacturers will have additional data on request. A large amount of such data has recently been compiled [22]. That booklet covers storage of a broad range of medical products. Especially the sections on insulins, vaccines and medical devices give much information.

For the application of the theoretical background of stability at different temperatures in daily practice see Sect. 22.6. More detailed information about storage and transport in general can be found in Sects. 36.9 and 36.10.

37.6 Special Patient Groups

The need for (extra) help and counselling by the pharmacy depends not only on the type of medicine, but also on the cultural, educational, linguistic and medical condition(s) of the patient.

37.6.1 Disabilities or Ergonomic Problems

For patients with rheumatism several assistive devices exist, such as easy to open tablet containers and devices for opening blister packaged medication [23]. Tablet splitters have already been mentioned (Sect. 37.4.3). A variety of assistive devices are available for the administration of eye drops. See Sect. 24.4.19.8.

According to the EMA templates the name of a licensed medicine should be on the package in Braille, for blind or short-sighted patients. If this is not possible, the manufacturer has to provide justification for such exclusion and the relevant national authorities must agree with it [1]. The Braille is only readable if the label of the pharmacy is not put on top of it. Patients with impaired hearing may have problems in hearing the 'click' of an insulin pen or an autoinhaler.

When the patient is not able to carry out the manipulations that are needed, the pharmacy can offer to help. Examples of this are:

- Opening a package or a seal
- Supplying ready to use mixtures for nebulisers, provided of course that the mixture has sufficient stability; see Sect. 6.6.5
- Breaking tablets (in amounts for a limited period, as the package and therefore the storage conditions are changed)

37.6.2 Swallowing Problems

Swallowing problems often make patients ask for a liquid dosage form of (licensed) medicines that are on the market only as a tablet or capsule. Or worse, they may crush tablets that are to be taken as a whole. The careful choice of active substance and dosage form is an important step in pharmaceutical care for this kind of patients. Instruction about easier swallowing may be worthwhile. But even then some adaptation of the medicine may be necessary. Any alteration of the dosage form should be done in cooperation with the physician.

37.6.2.1 Easing Swallowing

The taking of medicines which need to be swallowed is not easy for every patient. Severe swallowing problems are called dysphagia and require treatment. But every patient can benefit of knowing how to swallow most easily. When taking medicines, people often automatically tilt their head back but this interferes with the swallowing action. If tilting the head slightly forward while swallowing, the throat adopts the natural curve and widens. As a result, the oral solid medicine slips easily inside and does not stick in the throat. A sip of water before and after swallowing also helps the medicine to go down.

As an alternative dosage form to ease swallowing, not only are oral liquids an option but also chewable tablets, granules, disintegrating tablets. oromucosal or orodispersible tablets.

Being unable to swallow tablets and capsules is not uncommon and occurs in any age group, most common however in young children and the elderly.

Children under 2 years cannot swallow oral solids. Only from the age of 7–8 the swallowing of tablets generally gives no problems [24, 25] although a throat infection may bring the problems back again.

In the elderly, a stroke, neurological problems such as Alzheimer's disease or Parkinson's disease may give rise to dysphagia as well as specific medication.

Some people may have an aversion to swallowing medicines because they imagine the medicine getting stuck in the throat or they fear retching. Patients who have had a feeding tube may also experience swallowing difficulties. Pharmacists may advice patients to consult a speech or swallowing therapist for the assessment and eventual treatment of dysphagia. In severe cases of dysphagia, the patient may need a feeding tube to bypass the part of the swallowing mechanism that is not working normally.

A patient, who got crushed medicines because of swallowing difficulties, was referred to a speech therapist at the request of a new nursing home doctor. The speech therapist investigated the patient's swallowing and noticed that the swallowing function was all right but that the patient was afraid of tablets getting stuck in the throat. The fear was overcome by exercises and the medicines did not needed to be crushed anymore.

37.6.2.2 Suspension from Tablets is not that Simple

The preparation of a suspension by crushing a number of tablets will lead to a mixture of uncertain quality. Therefore this is not the method of choice to change a solid oral dosage form into a liquid one that can be used for some period. Badly formulated suspensions create too great a risk for a patient to be acceptable. The suspended part consists of the excipients and possibly (part of) the active substance. The various components that are needed to make a tablet may affect the physical stability of the formulation, once in solution. The physical form of the active substance is not always clear and cannot be found out by visual control. The quality of such a suspension depends on the suspension base, the tablet formula and the way of preparation. To know the stability and storage period of a suspension, physico-chemical data are needed. For many suspensions made by crushing tablets data of this kind may have been published, but often only the chemical stability of the active substance was investigated. Although this is useful information, it does not say much about the physical stability of the suspension. Besides, the physical stability of the suspension may be different when tablets of a different brand are used as raw material. See also Sect. 5.5.1.

It is the physical stability that determines the dosing accuracy of a suspension. To assure the quality of the final product, it is best to process just one dosage unit shortly before administration.

37.6.2.3 Methods of Processing Tablets for Ingestion

Two ways exist of processing a tablet to obtain a dosage form suitable for patients with swallowing difficulties: crushing the tablet first, or letting it disintegrate in water by shaking in a capped syringe. In most cases lukewarm water (35 °C) will do for processing a tablet in a syringe. For some dosage forms (coated tablets, soft capsules) it may be necessary to use warm water (60–70 °C). But crushing tablets, followed by mixing with food, is normal practice. Crushing in a mortar causes more loss of material than shaking in a syringe. There are however automated tablet crushers on the market that minimise the loss of material. Cleaning of this type of apparatus is important, because of the risk of cross contamination when different tablets are crushed one after another.

A so-called crushing syringe is another possibility for crushing tablets. It includes a barrel and a plunger with abraded surfaces on each. The plunger is meant to work as a pestle and after crushing liquid can be sucked up in the syringe. A variation of this method is obtained with the PillDrink [26], see Fig. 37.5.

Fig. 37.5 PillDrink device for crushing tablets in case of swallowing problems (Photo Inresa, France, with permission)

For reasons of unintended exposure to medicines the syringe method is preferred, especially when it is not the patient who carries out the preparation. The disadvantage of shaking in a syringe is that it can be time-consuming. When a number of tablets have to be processed, time is often important. For all of these methods it is best to process one solid dosage unit at the time.

Only regular (coated) tablets should be crushed to powder. Enteric coated tablets and tablets with controlled release will lose their pharmaceutical properties when they are crushed. The active substance will be released on the wrong site, or all at once, leading to an unacceptable overdose [27].

When crushing and mixing with food care must be taken due to physico-chemical or pharmacokinetic interactions with food. Because dairy products show many interactions, a product such as apple sauce is generally preferred (see Sect. 16.1.6)

37.6.2.4 Capsules

Most licensed hard capsules can be opened. After opening the capsule, powder content can be handled in the same

manner as crushed tablets. Granules often may be mixed with food, provided they are not crushed. The pharmacy can prepare capsules, if a dose is needed that does not correspond with one tablet or half a tablet, and no liquid form is available. The methods of processing a tablet are not suitable when only part of the dose is needed. Lactose is preferred as filler for capsules, because it is soluble in water and artificial feeding.

37.6.3 Feeding Tubes

Some patients with a feeding tube are still able to swallow. In those cases they can take their medicines orally, along the feeding tube. For enterally tube-fed patients not able to swallow alternative routes of administration may be a possibility. If no other routes are available, medicines will have to be administered through the enteral feeding tube, although this has limitations (see also Sect. 5.4.3). Apart from interactions of medicines with enteral feeding, there may be the risk of blockage of the tube, or interactions between medicine and tube material Solvents other than water in particular are at risk of interactions. The emulsifier acetem, for instance, cannot be used in PVC tubes. PVC contains plasticisers that can migrate to the acetem. When crushed solid dosage forms are given, too coarse particles may block the tube. Especially the narrow tubes for children are prone to this kind of problems.

For gastro-enteral administration the following dosage forms are possible, each with their own points of attention in the manipulations before passing down the tube:

- Liquid oral medicines
- Injections
- Solid oral dosage forms (after processing)

37.6.3.1 Liquid Oral Medicines

Liquid licensed medicines or standard pharmacy formulations should be diluted when they are too viscous.

37.6.3.2 Injections

The gastro-enteral administration of an injection is a possibility; provided the active substance will tolerate the acid environment of the stomach, and the pH of the solution is not too high to be tolerated. Especially in young children attention should be paid to unwanted excipients, e.g. ethanol or benzyl alcohol. Good instructions and clear labelling will help in preventing administration errors by the patient or caregiver. The solution for injection can, for instance, be transferred to a bottle in the pharmacy and provided with an oral syringe before dispensing. For Percutaneous Endoscopic Gastrostomic (PEG) ports special adaptors for oral syringes exist. Oral syringes and syringes for feeding tubes differ from injection syringes in such a way that needles cannot be attached.

Especially on a hospital ward it may be quite normal for injection solutions to be held as stock. This brings the risk that a request for the nurse to administer is misinterpreted, and the injection solution is administered parenterally in error. For that reason the oral use of injection solutions in hospital wards is in general not recommended, although in paediatrics it is often unavoidable.

37.6.3.3 Solid Oral Dosage Forms

The methods that were mentioned under the heading ‘swallowing problems’ can also be used when making medicines ready for gastro-enteral administration. The particles that are obtained after crushing or disintegrating must be small enough, so that they will not block the feeding tube. After crushing the powder is brought into a cup with the aid of water, and sucked up with a syringe. Crushing tablets followed by moving the powder will lead to loss of material, thus to lower dosing. This can be avoided by rinsing with water and taking care that nothing is left. This applies especially to medicines with a small therapeutic window, such as acenocoumarol [28].

Using extra water for rinsing may be a problem in patients with fluid restriction. Letting the tablet disintegrate directly in the syringe reduces loss of material without using extra water, but the disintegration time may be a practical hindrance.

37.6.4 Compliance Aids and Individualised Dispensing

Many types of compliance aids exist, all with the aim that patients take their medicine at the correct time and do not omit them. There are several systems of individualised dispensing of medication by a pharmacy besides the boxes for arranging weekly medicines that can be filled by the patient himself. This means that the medication is packed in an organised way, according to a time schedule, for a specific patient. These systems are mainly used in nursing homes and residential homes, but also for individual ambulant patients they are becoming more popular in many countries. Particularly elderly patients taking many different medicines and psychiatric patients may benefit of this service. Patients receive their medication every week (or every 2 weeks) in a week tray (so called blister pack) or in small bags, one for each day and each time of the day.

Besides advantages these systems may have drawbacks: opening of the package can be a problem for the patient and the manufacturer’s package leaflet is lacking. The labelling needs extra care, and should preferably enable identification of each tablet in the package. It is perhaps even more

important that the pharmacy should provide the right information to the patient or caregiver. In nursing homes or hospital wards the distribution or administration of medication often has to be ticked off on a list that is produced by the pharmacy. Especially for patients with swallowing problems, it is of great help to the caregivers to give information on this list what manipulations are allowed for the solid dosage forms.

Repacking solid dosage forms for individualised dispensing results in changed storage conditions. This implies that the date of expiry on the label of the original package is not valid anymore. This has to be kept in mind in those situations when the patient needs medication for a period longer than 1 or 2 weeks, i.e. for a holiday.

37.7 Special Types of Medicine

37.7.1 Suspensions

The chemical stability of some active substances, typically antibiotics, makes it impossible to bring them on the market in a liquid dosage form. In these cases the licensed medicine is a powder for suspension that has to be mixed with water before use. In some countries this mixing is done in the pharmacy, shortly before dispensing, as patients usually do not have a graduated cylinder to measure the prescribed amount of water. Sometimes the manufacturer has put a grade mark on the bottle, but this does not guarantee that the patient can produce an adequate suspension. The powder contains viscosity enhancers that may produce insoluble lumps with water. Shaking the bottle first, to loosen the powder, is an important step. The second problem can be that surface active substances in the powder will cause foam, which makes it difficult to see if the grade mark has been reached already. Section 5.4.6 gives detailed information on the formulation and preparation of oral suspensions.

Suspending a powder for injection in a solvent before use is another common procedure. In these dosage forms homogeneity is important in order to get the complete dose out of the vial. Too coarse particles or too high a viscosity may cause problems by blocking the needle.

Oral suspensions should best be prepared in the pharmacy just before dispensing, but in situations where this is not possible, e.g. on holidays, it will have to be done by the patient. In such cases the pharmacy could supply a bottle with a grade mark, to measure the right amount of water.

Some suspensions have such a limited stability, that they have to be prepared just before use. An example is an enema with budesonide, where the active substance is incorporated in a dispersible tablet, that has to be added to a solution for rectal suspension. Here again, correct instruction of the user or caregiver is important.

37.7.2 Antineoplastics

Dispensing most antineoplastics or other medicines with carcinogenic substances, requires specific warning and information and possibly supply of the materials needed for safe handling (e.g. needle containers, gloves or disposable mats). The effects of these medicines on other people than the patient who has to use them can be seriously harmful. The patient and his or her caregiver(s) have to handle preparations with carcinogenic substances in such a way that the risk of exposure to caregivers and house mates is minimal (see also Sect. 26.5.4). Patient information on handling this type of medicine at home should contain at least the following topics:

- Storage
- Instructions on use for that particular dosage form
- What to do if medicine is spilt
- Disposal of waste and excretion products

Store antineoplastics in a separate box when they have to be kept refrigerated, to avoid contact with food. Tablets should not be broken and capsules not opened. Reconstitution of powders for suspension should be done only if suitable precautions have been taken to protect the persons who carry out this kind of preparations.

The use of disposable, absorbant mats are recommended in handling liquid preparations, to absorb any spilt material. Patients should wash their hands after use to prevent contamination of the eyes or other objects. For caregivers wearing disposable gloves is recommended. The more so in the administration of cutaneous medicines like coal tar preparations. After unprotected exposure during clinical coal tar treatment a small rise of the amount of PAH's (Polycyclic Aromatic Hydrocarbons) in the urine was found in 70 % of the nursing personnel [29].

If this type of medicine gets accidentally on the skin, it must be washed off immediately. Spilt antineoplastics must be absorbed in disposable material before any further cleaning. The disposable material, waste material of wound care and empty packages should be disposed of in a double waste bag that can be closed securely. Needles and syringes can be put in a needle container. Because the medicine and its degradation products will also get into urine and faeces, special precautions are required in going to the toilet and in the handling of bedpans or urinals. This means that the toilet should only be used in sitting position (for gentlemen also), and flushed twice with the lid closed. Aprons and gloves are needed in the handling of bedpans and urinals.

From a medication safety point of view, the exact number of tablets for one course of treatment should be dispensed to the patient, not less and not more. In practice, this may be a risk for pharmacy personnel, especially in the dispensing of non-blistered tablets. If for this reason a larger number of tablets have to be delivered, it is important to inform the

patient, for instance on intermittent use and the return of leftovers to the pharmacy. From case reports is known that even the combination of oral and written information is no guarantee that the patient will understand how the medication should be used, in particular for complicated dosing schemes [30]. A safer way would perhaps be to call the patient by telephone at the end of the foreseen course of treatment, to make sure that the information was understood properly.

37.7.3 Protein Medicines

Many new active substances are proteins or peptides, which can only be administered parenterally. Proteins and peptides are often unstable, and therefore need extra care in reconstitution, storage and transport. Most protein medicines have to be kept refrigerated (2–8 °C). Storage at too high temperatures will soon cause loss in biological activity. Temperatures below zero give even more risk of breaking up the protein structure. See also Sects. 22.2.5 and 18.4.1.

Any form of shear stress applied to proteins will have an adverse influence on their stability. Peristaltic pumps are best avoided, and solutions should not be shaken, as shaking may also cause foaming. The material of primary containers and of devices for reconstitution and administration may affect the activity of the protein. Not only adsorption is possible, but also interaction with plasticisers or other components of the packaging material. When proteins come into contact with hydrophobic surfaces, aggregation may occur. Protein aggregates are undesirable, not only because of loss of activity. Aggregates are thought to cause immunogenicity [31].

The solubility of (freeze dried) proteins in powder form may diminish when moisture is attracted.

Many proteins are not on the market as a ready-to-use solution. The licensed product consists of a vial with freeze dried powder, and sometimes an ampoule of the solvent. This kind of products should be reconstituted just before use. Gently swirling, not shaking, is the way to get such powders into solution. Protein suspensions for example long-acting insulins, should be resuspended by rolling the ampoules between palms instead of shaking.

37.7.4 Sterile Products

Sterile medicines, and parenterals in particular, often require reconstitution (sometimes in excess of the SmPC) to make them ready to administer. Reconstitution of parenteral products requires aseptic handling (see Sect. 31.1). This handling can be simple (drawing up of a solution in a syringe for direct injection) or complex (preparation of a cassette reservoir with a number of substances for continuous infusion). The manipulations may be done in a (hospital) pharmacy in a Laminar Airflow (LAF) cabinet (cross or down flow) or isolator, or by nurses on the ward, or by the patient at home. If aseptic handling is carried out under quite different conditions, it may lead to a difference in the risk of contamination of the sterile product. Or the other way round: the risk of contamination of the product defines the conditions for reconstitution of parenterals (aseptic handling). See Sect. 31.3.1 for more information. The degree of product protection and the complexity of the handling are the two factors that determine whether the preparation may take place some time prior to the administration. The greater the complexity of the handling, the more often the preparation will be done in the (hospital) pharmacy, rather than on the ward or at home. It is only in a purpose-built aseptic unit, in or outside the (hospital) pharmacy, that aseptic handling can be carried out with the degree of product protection needed (see Sect. 37.8.2). Chapter 31 deals with the details of aseptic handling and processing.

37.7.4.1 Simple Reconstitution (Often by the Patient)

In order to make reconstitution of sterile products simpler for the patient, new types of packaging have been developed. After instructions most patients can manage the more simple types, for example pre-filled syringes and auto-injectors. This type of packaging is usually intended for once-only administration of a fixed amount of liquid. Some pre-filled syringes however are intended to administer different doses. The patient first has to measure the correct amount. From a medication safety point of view this is not the preferred method, because it requires special instructions to remove part of the content of the syringe in a safe way. Injection pens, that contain a cartridge filled with injection solution, are intended for multiple use when needed in different doses. This type of medicine requires to be made ready to administer. It may also need to be brought to room temperature and in addition homogenising, setting the right dose and inserting a new needle. These pens require carefully worded instructions and some skills from the patient. The best known examples are the insulin pens, which appear in new, improved types rather frequently. Besides instructions, supplying patients with a container for used needles and syringes (so called sharps bin) should be part of the counselling. Patients should handle this waste in the same manner as unused medicines, that is as hazardous waste. The options to dispose of it will vary in different countries, or even per area within a country, but a secure package for the needles is the first condition. See also Sect. 38.5.2.

37.7.4.2 Complex Reconstitution (in the Hospital)

For reconstitution in excess of the information in the SPC (meaning in ways not indicated in the SPC), product knowledge is one of the main conditions (see Sect. 22.6). This

means information on reconstitution, possible dilutions, chemical stability and incompatibilities. Instructions for the nurses should describe, for each medicine, the reconstitution or preparation process (including diluents and incompatibilities), the route of administration (route, site and rate) and, if relevant, storage of the ready-to-administer product and the necessary in-process controls . In the description of the reconstitution the necessary care should be given to the accuracy that is required to obtain the correct dose. The pharmacist though needs background information about the active substance, such as solubility, pK_a and stability in relation to pH. This information enables him to answer questions, or to write instructions where these are lacking. Physico-chemical knowledge is the indispensable basis upon which to predict incompatibilities.

On occasion parenteral therapies are given at home instead of in the hospital. Some patients can learn to administer the medicine (to) themselves. When this isn't appropriate, support from home care organisations can be arranged. In these situations community pharmacies can play a role, in giving advice as well as in the actual reconstitution.

Dosing accuracy in parenterals depends on the accuracy of the syringes used, the dead volume in the syringe (see Sect. 29.1.7) and what stays behind in the needle. This is important in the following manipulations:

- Minimal volume measurable with a given syringe
- Measuring reconstituted solutions
- Diluting solutions by mixing in a (large) syringe

In a Canadian study on morphine infusions, diluted for syringe pumps, the measured concentration of 65 % of the solutions varied >10 % from the ordered concentration. The concentration of 6 % of infusions showed deviations of >20 % [32]. In a second study, a difference of >10 % of the intended content was found in 25 % of methotrexate products for intravenous use [33]. In this study the differences in content turned out not to be clinically relevant, which will often be the case. Working routines however should aim for the reduction of avoidable faults to acceptable values. What faults are avoidable and what values are acceptable will depend on the situation. Generally a difference of 5–10 % of the intended dose is tolerated, but there are exceptions. Exceptions may have to do with the formulation and availability of licensed products, or with the required speed of working in emergencies. An example is the drawing up of 0.1 mL of a suspension in a syringe. It is impossible to measure this amount within the standard limits of accuracy. As diluting will not be an option for a suspension, there is no other choice, other than a less concentrated product.

In emergency situations drawing up 0.1 mL might also be chosen, because diluting first would take too much time.

37.8 Instructions for Professional Caregivers

37.8.1 Reconstitution and Manipulation Outside the Pharmacy

In nursing homes, residential homes and hospitals reconstitution and other manipulation, and often administration as well, are tasks carried out by the caregiving personnel. So they are the ones that instructions and coaching should be focused on. In many cases their level of education will not be sufficient for a reliable handling of medicines for their patients. From Dutch studies it is known, that personnel in nursing homes and residential homes do not consider themselves sufficiently competent enough to carry out reconstitution or other manipulation prior to administration in the proper way [34, 35]. This is particularly true for manipulating oral solid forms, for patients with swallowing problems or a feeding tube, and for reconstitution of parenteral medicines. In the Dutch Medication Error Report Program in 2012 5 % of the reports had to do with reconstitution. Twenty four percent of the errors were 'wrong dose' errors, probably as a result of miscalculations [36]. Five years before a study on the mathematical skills of nurses in four Dutch hospitals concluded that their level was insufficient for the 'pharmaceutical' calculations required [37]. In the meantime various measures have been taken to improve this situation. However, in a multinational study of 2009 (27 countries on five continents) on errors in administration of parenteral drugs in Intensive Care units, 75 errors per 100 patient days were found. Nearly 15 % of them were wrong dose errors, ca. 5 % wrong medicine and ca. 5 % wrong route [38].

37.8.2 Parenteral Medicines

Whoever will actually carry out the reconstitution and other manipulations to make parenteral medicines ready to administer, instructions will be needed. In many hospitals pharmacists have written a 'Parenteral guide' or 'Parenteral Manual' including standard operating procedures to guide the personnel and compiled monographs on specific products. It has been shown that working according to a protocol can improve the quality of reconstitution and administration of parenteral medicines [39]. Information on the general procedures can be found in Sect. 31.3.

In several countries governmental organisations or associations of professionals have developed detailed guidelines on this matter [40, 41].

37.8.3 Oral Solids

It is more often than not the case that in nursing homes, the percentage of tablets that are crushed before administration is often higher than what one would expect as a pharmacist [34]. Sometimes enteric coated tablets or slow-release formulations that should be swallowed as a whole are being crushed. National organisations of nurses or pharmacists, and also hospitals have published general guidelines on this subject and also an 'Oral Guide' or 'Oral Manual" with monographs on specific products [35, 42], see also Sect. 39.2.1.

According to some guidelines, prescribers are to indicate on the prescription if a tablet should be crushed before administration, preferably after consulting a pharmacist. As this does not always happen, it would be more practical if not only the prescriber but also the pharmacist would know when a patient has swallowing problems, or an enteral feeding tube. In that case, he or she can take into consideration if manipulations with the dosage form are allowed for each new prescription.

By analogy with monographs on specific products for parenteral use, such data are also wanted and in some countries already compiled for oral solid medicines. The pharmacist can consult the manufacturer about crushing tablets. However, if this information about crushing is not in the SPC, crushing means using the medicine in an unlicensed way. Therefore it may be useful to record the reasoning of decisions made (for instance by one of the forms in Sect. 2.2).

When a number of tablets have to be administered, they should preferably be crushed one by one. As this is time-consuming, in settings such as nursing or residential homes different tablets may be crushed together. Usually the risk of unwanted chemical reactions by this method will be negligible, so it can be acceptable. But there are exceptions, where the pharmacist should warn the patient or caregiver to keep the tablets separated. Examples are combinations of acid and basic substances, i.e. ascorbic acid and sodium hydrogen carbonate.

37.8.4 Occupational Health and Safety

When reconstitution and other manipulation to make medicines ready for administration is carried out in health care institutions, working conditions have to be considered. Frequent crushing of tablets may cause wrist problems and exposure to hazardous substances. Normally the management of the institution will be responsible for health and safety at work, but the pharmacist is the person who can give advice on safe handling of possibly hazardous medicines. The handling of antineoplastics is dealt with in Sects. 37.7.2 and 26.8. Within health care institutions, transport needs special attention. Hazardous preparations should be clearly marked so as to make them easy to identify, and transport personnel should be aware of the risks, and trained to appropriate action in case of spillage accidents.

The administration of antineoplastics in hospitals usually follows special rules. These rules ensure that the risk of exposure to hazardous substances or contaminated material by hospital personnel is reduced to a minimum.

37.9 Special Categories of (Medicinal) Products

37.9.1 Veterinary Medicines

The EMA has published guidelines on the labelling and packaging of veterinary medicines [43]. In addition to these guidelines many countries have specific requirements for the labelling of veterinary medicines that are available on prescription only. In some countries it is normal practice for veterinary medicines to be supplied by pharmacists (see Sect. 2.4.4), but often this is done by veterinarians. When dispensing veterinary medicines, the pharmacist should be able to give the correct instructions on use to the owner of the animal. The administration of liquids, for instance, will be simpler with a syringe than with a spoon. Whether crushing of tablets is allowed may be important, although in general it is easier to hide a whole tablet in a piece of meat than a powder.

In short, the same principles apply as in counselling special groups of human patients: focus on the needs of the particular animal species (and its owner) to help them make the best use of the medicine.

37.9.2 Medical Devices

For the definition and legislation of medical devices see Sect. 2.4.5. Examples range from a simple sticking plaster to a pacemaker or surgical instruments.

The manufacturer should have drawn up a file with technical information on the product, but this is not made public. Therefore it is often difficult for the pharmacist to get the information needed for instruction and counselling of patients or users. The manufacturer has to provide instructions on use of his product, but these are not always clear. Besides, specific knowledge may be required to make

the best use of the product, e.g. for wound dressings. If a pharmacist has to give instructions about a medical device being used in a way that is not included in the instructions for use, he has to contact the manufacturer.

37.9.3 Chemicals

Sometimes chemicals may be sold in pharmacies (see also Sect. 2.4.7). When supplying chemicals it is important to provide the user with the appropriate safety information, e.g. about inflammability. Solvents such as denaturated ethanol, or dilute solutions of hydrogen peroxide are usually supplied in small packages, that are labelled in the right way. Should a chemical substance be supplied from the pharmacy's own stock of materials, the pharmacist as supplier is responsible for ensuring that it is supplied using appropriate packaging, that has been correctly labelled together with relevant safety information. For hazardous substances a safety data sheet (SDS, see Sect. 26.3.4) may be compulsory. In general, it is recommended to get information about the intended use before selling chemicals.

According to national and international laws it is not permitted to sell narcotics, also called controlled drugs or substances. Legislation of the Council of Europe forbids selling of substances that may be used in the manufacture of illicit drugs, also known as precursors (see Sect. 2.4.7).

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Impact on Environment

38

Bengt Mattson and Tessa Brandsema

Contents

Abstract

It is probably clear to everyone that pharmaceutical products have increased the quality of life tremendously for billions of people around the globe over the years. During the last decade it has also become more and more evident that manufacturing and use of medicinal products may impact negatively on the environment.

The impact on environment may occur throughout the life cycle, from manufacturing and preparation, through distribution and dispensing, to patient excretion and final disposal of unused medicines and waste.

The impacts include the potential emissions and discharges of medicinal substances, so called active substances, as well as other chemicals and solvents used. Active substances are biologically active, and hence it is likely that they will potentially affect organisms, e.g. water living organisms, if released into the environment. Eventually they could also negatively affect humans if concentrations in the environment increase high enough.

This chapter gives a general introduction, with references to the regulatory framework and briefly discusses environmental impacts from manufacturing of medicines, from patient excretion and from unused medicines. Although releases from manufacturing operations have received increased interest during previous years it should be realised that the major cause of the presence of active substances in the environment is the excretion of substances by humans and animals that subsequently find their way into surface waters through municipal waste water treatment systems.

Impacts from pharmacy operations are described and discussed in more detail and the chapter provides proposals for actions to be taken to minimise the environmental burden.

Based upon Chapter Milieu by Yvonne Bouwman-Boer en Mirjam Crul in the 2009 edition of Recepteerkunde.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_38,

Keywords
Medicines • Environment • Pharmacy operations • Waste • Packaging materials • Energy • Excretion • Unused medicines

38.1 Environmental Hazards and Risks

The inherent environmental hazard of a pharmaceutical substance is taken to mean it's toxicity, it's potential to safely degrade and it's potential for deposition in fat tissue in, for example, fish. An active substance that is considered highly potent and toxic for humans and posing occupational hazards as well to operators and healthcare staff will not automatically be the one posing the greatest environmental risk. For example an antineoplastic, which is very toxic, may be easy degradable or only given to few patients. In both cases it may result in a negligible environmental risk. Of course, it is crucial to use and handle such substances correctly and with the utmost care, but less potent and less toxic substances used in greater quantities may result in higher environmental risks. Thus it is important to distinguish between the hazard of an active substance when given to patients, when used by operators and when disposed in the environment. Subsequently there is a difference between the environmental hazard and the environmental risk in which the quantity is taken into account:

$$\text{Risk} = \text{hazard} \times \text{quantity}.$$

To assess whether a pharmaceutical substance poses an environmental risk or not, first the highest concentration of that specific substance has to be discovered which will *not* cause negative effects in animals and plants. The tests for this level are tests standardised by e.g. the Organisation for Economic Co-operation and Development (OECD), International Standards Organisation (ISO), Food and Drug Administration (FDA). Since the classification focuses on possible adverse aquatic environmental effects, the data usually apply to algae, daphnia and fish. From these data the ratio between predicted no-effect concentration (PNEC) and the anticipated concentration (PEC, predicted environmental concentration) is calculated: PEC/PNEC gives a number between 0 and infinity, and as long as it is below 1 the risk is regarded insignificant or low and to be under control.

There are several ways in which substances naturally degrade. Biological degradation takes place in soil or water by means of microorganisms. Non-biological degradation is based on chemical reactions or reactions to UV rays in sunlight. Substances are classified regarding biodegradation according to standard laboratory tests. If substances degrade slowly or not at all, it is likely that the concentrations in the environment increase over time, and hence the environmental risk (i.e. PEC/PNEC increases).

Highly lipid-soluble active pharmaceutical substances may have the ability to bioaccumulate in the fat tissue of animals. Animals higher in the food chain are most susceptible. They eat animals that in turn have eaten other organisms that may have accumulated the substance. A top predator may hence be exposed to higher concentrations of the substance once again the risk has increased. Active pharmaceutical substances are classified in regard to bioaccumulation based on standard laboratory tests.

38.2 Regulatory Framework

The environmental impact from pharmaceutical manufacturing operations and use of medicinal products is regulated on the European level by the environmental legislation and the pharmaceutical legislation respectively. Generally: pharmaceutical substances as chemicals are covered by legislation on chemicals, unless specific legislation exists for medicines, which will prevail over the general legislation on environmental matters.

38.2.1 Environmental Legislation

Environmental regulations that are fully or partly applicable to pharmaceuticals include, but are not limited to:

38.2.1.1 IED (Industrial Emissions Directive: 2010/75/EU) [1]

Industrial production processes account for a considerable share of the overall pollution in Europe: emissions of greenhouse gases and acidifying substances, waste water emissions and waste. In order to take further steps to reduce emissions from such installations, the European Commission adopted the Directive on industrial emissions on 21 December 2007. The IED entered into force on 6 January 2011. The IED is, in essence, about minimizing pollution from various industrial sources, e.g. manufacturing of pharmaceuticals, throughout the European Union.

38.2.1.2 REACH – EC 1907/2006 [2]

REACH is the European Community Regulation on chemicals and their safe use (see Sect. 26.6.2). It deals with the **R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emical substances. The law entered into force on 1 June 2007. Medicinal Products on the EU market are exempted since they are regulated by the pharmaceutical

legislation (see Sect. 35.5.2). Manufacturing and handling of active substances as raw materials, as well as Quality Control activities are however covered by the REACH legislation.

38.2.1.3 Packaging and Packaging Waste Directive: 94/62/EC [3]

The directive provides for measures aimed at limiting the production of packaging waste and promoting recycling, re-use and other forms of waste recovery. Their final disposal should be considered as a last resort solution. The directive covers all packaging placed on the European market and all packaging waste, whether it is used or released at industrial, commercial, office, shop, service, household or any other level, regardless of the material used.

38.2.1.4 WFD (Water Framework Directive [4])

On 23 October 2000, the Directive 2000/60/EC of the European Parliament and of the Council establishing a framework for the Community action in the field of water policy or, in short, the EU Water Framework Directive (or even shorter the WFD) was adopted. There is a list of so-called priority substances within WFD. For substances on the list of priority substances an Environmental Quality Standard (EQS) have to be developed. The EQS sets the limit on the concentrations allowed in EU water bodies. Three active substances (ethinylestradiol, estradiol, and diclofenac) were included on the so-called Watch List in 2013 to be further evaluated for a potential future inclusion on the List of Priority Substances.

38.2.2 Pharmaceutical Legislation

Pharmaceutical legislation contains requirements on unused medicines and on an environmental risk assessment of active substances:

38.2.2.1 Unused Medicines

Under Article 127b of EU Directive 2001/83/ (Community code relating to medicinal products for human use), as amended, all EU Member States "shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired".

38.2.2.2 Environmental Risk assessments (ERA), Directive 2001/83/EC — Community code relating to medicinal products for human use and Guideline on the ERA of medicinal products for human use (EMEA/CHMP/SWP/4447/00)

Environmental risk-assessment of medicinal products for human and veterinary use is the process through which the European Medicines Agency ensures that the potential effects of pharmaceuticals on the environment are studied and adequate precautions taken in case specific risks are identified. The environmental risk-assessment (ERA) of medicinal products is to be performed by companies during the development of new medicines. The results are submitted to the European Medicines Agency for evaluation in conjunction with the scientific data on quality, safety and efficacy required to support the request for marketing authorisation of medicinal products intended for human or veterinary use via the centralised procedure.

38.3 Manufacturing of Medicines

Industrial manufacturing of active substances as well as medicinal products, like the manufacturing of all other chemicals, is regulated by e.g. the Industrial Emissions Directive as described briefly in Sect. 38.2.1.1. During the last 5 years, special interest has been given to releases of active substances from manufacturing facilities. Releases regarding large quantities of active substances reaching the environment have been described e.g. by Joakim Larsson et al [5] and by US Geological Survey [6]. Releases from manufacturing facilities could result in environmental concentrations at the point of discharge from a factory or a waste water treatment plant that are larger than the relevant PNEC and hence will present an environmental risk (see Sect. 38.2.2).

38.4 Pharmacy Operations

38.4.1 Preparation of Medicines in Pharmacies

The International Pharmaceutical Federation (FIP) and WHO have developed guidelines on good pharmacy practice. Those guidelines state [7]:

- Good Pharmacy Practice requires that an integral part of the pharmacist's contribution is the promotion of rational and economical prescribing, as well as dispensing.
- The pharmacist needs evidence-based, unbiased, comprehensive, objective and current information about therapeutics, medicines and other health care products in use, including potential environmental hazard caused by medicines waste disposal.

It is clear from these guidelines that good pharmacy practices requires the existence of good environmental procedures. This is well aligned with the requirements in many regulations, such as the EU directives described in Sect. 38.2 as well as country-specific environmental management acts.

Based on the Environmental Management Act [8] in the Netherlands every citizen should take sufficient care of the

environment and everyone who because of his function or his occupation or trade handles waste has a specific duty to care. This may be interpreted such that the pharmacist has responsibility for all activities in the pharmacy, whether in a community or hospital pharmacy, and hence understand the possible consequences for the environment from the operations. Examples of activities that may impact the environment include, but are not limited to, the storage of hazardous substances and the collection and transport of surplus medicines and medicinal waste. According to the Environmental Management Act community pharmacies in the Netherlands don't need an environmental permit, as would an industrial manufacturer, except when the pharmacy has a laboratory. Usually the environmental permit of the hospital pharmacy falls within the environmental permit of the hospital. If the hospital pharmacy is not part of the hospital (a foundation for example), the hospital pharmacy has to apply for an environmental permit itself.

38.4.2 Preparation from Raw Materials

When medicines are prepared from raw materials, residues will turn up in the cleaning waste. Some guidance about environmental hazards can be found in the safety information forms (The Safety Data Sheets, see also Sect. 26.3.4) of the different substances. The relevant part of the form is called ecologic information.

The EU-GHS system which is mandatory for labelling since 2010 [9] contains H(azard)-statements which relate to aquatic environmental dangers:
H400: Very toxic to in water living organisms
H410: Very toxic to in water living organisms, with long term effects
H411: Toxic to in water living organisms, with long term effects
H412: Harmful to in water living organisms, with long term effects
H413: Can cause long-term harmful effects to in water living organisms
There is also a classification for substances that are dangerous to the ozone layer:
EUH059: Dangerous to the ozone layer.
The EU-GHS uses next to the H-statements, also P(recautionary) statements. For the environment are relevant:
P102: Keep out of reach of children
P273: Prevent from discharging in the environment

The 'old' R(isk)-phrases were legally valid until 2015 [10, 11]:
R 50: Very toxic to living organisms in water
R 51: Toxic to living organisms in water
R 52: Harmful to living organisms in water
R 53: Can cause long-term harmful effects in the aquatic environment
R 54: Toxic to plants
R 55: Toxic to animals
R 56: Toxic to bottom organisms
R 57: Toxic to bees
R 58: Can cause long-term harmful effects to the environment
R 59: Dangerous to the ozone layer
The way the substances are classified and whether H(azard)-statements are being assigned, also for mixtures, is explained in reference [9]. A hazard in combination with an exposure to the substance could generate an environmental risk (risk = hazard × quantity) as discussed in Sect. 38.2.

Starting materials that exceed the expiry date have to be disposed of in a safe manner, because they are a potential burden to the environment. To minimise the risk for materials exceeding expiry date, it is preferable to purchase smaller packages where relevant.

The storage requirements for dangerous substances are discussed in Sects. 26.11 and 36.9. These requirements also aim to protect the environment if a package breaks.

38.4.3 Generation of Waste Such as Overalls and Gloves

When aseptic activities are undertaken as well as the preparation of medicines with highly toxic substances, commonly a lot of waste, such as overalls, gloves, hairnets, masks and mats, will be generated. The waste is usually incinerated because it may be contaminated with toxic substances. Safety is of paramount importance and should never be compromised. It is not, for example, recommended from a health and safety perspective to reuse gloves. It would furthermore create a risk of cross-contamination. Sterile clothes for aseptic work exist in a washable, so reusable, version. Washing these clothes could potentially be less harmful to the environment than incineration of synthetic overalls.

38.4.4 Packaging Material

Pharmaceutical packaging may have an impact on the environment.

Several countries within the EU regard halogenated packaging materials as potentially the most harmful to the environment. Polyvinylchloride (PVC) is commonly used for infusion bags and blister packs. Polyvinylidene chloride (PVdC) is also used for blister packs. During incineration of waste containing PVC, PVdC and other halogenated packaging materials dioxins may be generated. Dioxins are toxic to human health in very low concentrations. Since the start of the twenty-first century, several attempts have been made to replace PVC in infusion bags and blister packs. Potential substitutions are polypropylene and other polyolefins or mixtures of polyamides. There are a few examples of PP (polypropylene) blister packs, but they are limited due to technical challenges during manufacturing and to regulatory reasons. When a manufacturer of medicines wants to change the packaging, the manufacturer needs to submit new shelf life studies and an alteration of the registration is needed. Therefore, innovations in this field of packaging have been restrained.

Aluminium puts a high burden on the environment when it is first manufactured, due to high-energy usage. Recycled aluminium however has a much lower environmental impact. Aluminium is used in the pharmacy in tubes and in blister packs (together with PVC).

Medicines dispensing systems (MDS) cause a relatively large amount of packaging waste, because the medicines are being repacked. Pharmacies that provide the MDS services change from tablets in blister packs to bulk packs.

By choosing the right packaging material, the producer or the pharmacy can enhance the possibilities to recycle the material after the patient has used it. Mono material is easier to recycle than mixtures and laminates. Reusing primary packaging, like blister packs, infusion bags and glass flasks, is not usually recommended because the intensive cleaning process to remove medicine waste before recycling is considered a larger burden to the environment than incineration. Secondary packaging, like carbon boxes, should however be collected separately and recycled.

38.4.5 Laboratory

Many substances used in pharmaceutical analysis and bio-analysis are potentially harmful to the environment. When designing analytical methods it is always recommended to use as environmentally sound substances as possible. Check the part of the safety data form, called ‘ecologic information’ (see Sect. 38.4.2). At the laboratory, the waste can be reduced for example by reusing eluents for chromatographic determinations or by reducing volumes for preparing stock solutions and control solutions.

A laboratory should not dump toxic substances in the sewer. The waste has to be collected, and kept separately where relevant because certain substances must not get into contact with each other. Also, the laboratory has to collect separately certain types of solvents such as halogen-rich ones, since they may be processed separately from halogen-free solvents. The company contracted to process these solvents, will indicate in its acceptance conditions the different categories to be used.

38.4.6 Waste Disposal

Everyone who is responsible for waste has a duty to ensure that the waste is handled, transported and disposed of in a safe way.

Pharmaceutical waste generally can be divided into three types of waste [12]:

- Hazardous waste
- Non-hazardous waste
- Not pharmaceutically active and possessing no hazardous properties

The waste from preparation of, for example, antineoplastics and radiopharmaceuticals is seen as hazardous waste and should be collected, disposed of and processed separately. Solid waste from all other preparations (in hospital pharmacies or local pharmacies) is collected as non-hazardous waste or not pharmaceutically active and possessing no hazardous properties.

Patients who self inject medicines in some countries receive a special container from the pharmacy or the municipality to collect syringes and needles, because of the risk of contamination and accidents. The full containers should be handed in to a pharmacy or a waste management facility (depending on local regulations).

The community pharmacy has to take back from patients medicines that are no longer required, or expired medicines, these are the so-called unused medicines (see Sect. 38.4.2).

Obviously, the pharmacy has to collect chemical waste from its other general functions, e.g. toner cartridges, separately.

The pharmacy will contract to specialised companies to process the waste by means of incineration. These companies have to have a permit and the pharmacy has to ask for confirmation of the permit. The contract with the collector states how the pharmacy has to deliver the waste. In addition, the contract states that the company will destroy all the medicine waste. The forms confirming handing over the waste to the contractor should be kept in the pharmacy for a certain, country-specific, period.

38.4.7 Energy Use

Energy is largely generated in society using fossil fuels. When fossil fuels are combusted, greenhouse gases are emitted which contributes to global warming. Hence,

decreasing energy use in the pharmacy is a good example of caring responsibly for the environment. The temperature in the working areas of the pharmacy probably does not need to be kept at, for example, 20 °C but can more or less follow the seasons. However for storage areas the temperature has to be kept within limits (see Sect. 36.9.4) When electrical devices (for example computers and safety cabinets) are not used, they should be turned off or put in sleep mode/stand-by. In certain situations there can be conflicting interests between environmental burden and both product quality and safety for the pharmacist.

As an example: after working hours a parenteral product has to be prepared, urgently, in the safety cabinet. If the safety cabinet has been switched off at that moment, it takes approximately 30 minutes (depending on which machine and type) before the preparation can be started. If the preparation was to be started too soon, the product quality and the protection of the preparing pharmacist could not be guaranteed.

The pharmacist has to formulate procedures so that the energy consumption is limited to a minimum without putting product quality and health and safety of the preparing pharmacist at risk.

38.5 The Use of Medicines

38.5.1 Patient Excretion

Medicines used by patients turn up, whether metabolised or not, in urine, faeces, vomit and sweat and therefore in waste water. This is true for humans as well as animals (livestock). The quantity of residues from livestock that turns up in water is much higher that the medicine waste from hospitals [13].

The National Institute for Public Health and Environment (RIVM) in the Netherlands carries out periodical analysis to record the distribution of human and veterinary medicines in drinking water. In 2002 and 2003 [14] during measurements, there were remainders of four active substances found in drinking water and drinking water sources. These four medicines were: (acetyl)salicylic acid, carbamazepine, clofibric acid, sulfamethoxazol. In follow-up research in 2005 and 2006 [15, 16] 22 medicines were found and the researchers concluded that this result indicated an increase in quantity. Ethinylestradiol, the active substance of the oral contraceptive, wasn't detected in any of the samples. The concentrations of most medicines are smaller than 50 nanograms/liter and that is by a factor of 200 till 1000 less than the derived toxicological limits for drinking-water. However, there are several reports from around the globe where surface waters have been reported to contain concentrations of medicines in micrograms/liter [17].

The most relevant question is whether the appearance of active substances in drinking water is harmful to humans. The direct risk for humans seems to be negligible at the present time since the concentrations in drinking water are extremely low. However, some concerns have been raised as expressed by Kümmerer and others [18]. Knowledge gaps regard potential effects from constant exposure to very low concentrations in drinking water over long periods of time. Furthermore, little is known about the sensitivity of neonates and of the effect of mixtures of substances. Questions have also been raised whether the release of antibiotics to the environment could contribute to antimicrobial resistance development. The Health Council of the Netherlands has issued a statement on antibiotics in food animal production and resistant bacteria in humans. The statement: "The extensive use of antibiotics in food animal production, the sector that produces food of animal origin, plays an important role in the discussion on resistance development. Since resistant bacteria can be passed on from animals to humans, the use of antibiotics in the treatment of animals contributes to the problem [19].

The risks for any environmental impact from pharmaceutical substances excreted by patients or livestock have been heavily discussed over the recent decade. There are nevertheless still major knowledge gaps about occurrence in the environment and effects from pharmaceutical substances to e.g. water-living organisms.

In order to learn more, and if possibly decrease environmental impacts through adjusted prescription patterns, the Research-based Pharmaceutical Industry in Sweden (LIF [20]) has developed an environmental classification scheme for pharmaceutical substances[21] The model for presenting environmental data was developed in collaboration with Stockholm County Council, the pharmacy chain Apoteket AB, the Swedish Association of Local Authorities and Regions (SKL), and the Swedish Medical Products Agency MPA. The goal was to develop a model, which clearly shows environmental information, both to interested members of the public, to healthcare professionals and pharmacists. The environmental information draws on data from the pharmaceutical companies, often generated in the preparation phase

Table 38.1 Descriptive phrases for environmental risk of substances

Classification phrase	PEC/PNEC value	Examples of active substance
Use of the substance has been considered to result in insignificant environmental risk	Less than 0.1	Omeprazol
Use of the substance has been considered to result in low environmental risk	Between 0.1 and 1	Paracetamol
Use of the substance has been considered to result in moderate environmental risk	Between 1 and 10	Sertralin
Use of the substance has been considered to result in high environmental risk	Higher than 10	Ethinylestradiol

of the environmental risk assessments (see Sect. 38.2.2.2). An independent organisation, the Swedish Environmental Research Institute, IVL, acts as a reviewer of all data and of the assessments and classifications. The environmental information and classifications of different substances can be found on the Swedish prescribing guide called Fass [22].

The relation between the predicted no-effect concentration (PNEC) and the anticipated concentration (PEC, predicted environmental concentration) is described using the phrases within the Swedish classification system, see Table 38.1.

The prescribing guide Fass also provides, in addition to information on environmental risk, information on whether a certain pharmaceutical substance is persistent or biodegradable, and whether it can bioaccumulate in aquatic organisms.

The Swedish classification system uses the following phrases regarding degradability:

- The substance is degraded in the environment
- The substance is slowly degraded in the environment
- The substance is potentially persistent

The Swedish classification system uses the following phrases regarding bioaccumulation:

- No significant bioaccumulation potential
- Potential to bioaccumulate in aquatic organisms

Certain pharmaceuticals are exempted from classification as for various reasons they are considered not to cause any environmental effect. This is in line with the EU's environmental risk assessment guidelines for medicinal products (see Sect. 38.2.2.2).

The exemption covers:

- Vitamins
- Electrolytes
- Amino acids, peptides, proteins
- Carbohydrates
- Lipids
- Vaccines

38.5.2 Unused Medicines

Unused medicines can pose a health and social risk if they come into wrong hands, for example children or addicts; and they can pose an environmental risk if they are not disposed of properly through correct destruction. According to a EU Directive (see Sect. 38.2.2.1) all EU Member States "shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired". Member states that have implemented solid systems for the management of unused medicines have to secure that medicines are transported to approved incineration facilities, and burned under supervision. The gas from incineration is cleaned before release. The ash is placed at approved disposal facilities.

In order to collect unused medicines from the general public it is often recommended to return the unused medicines to a pharmacy. Pharmacists should establish a safe procedure for medicines waste disposal at the hospital or community pharmacy so that patients and the public are encouraged to return their expired and unwanted medicines and medical devices. Alternatively, pharmacists should provide appropriate information to patients on how to safely dispose of expired or unwanted medicines.

The Swedish Medical Products Agency (MPA) have in their report regarding unused medicines from 2013 [23] estimated the quantity of unused medicines, expressed in term of money, as 5 % of the total use of prescribed medicines. In order to secure that unused medicines are brought back to pharmacies and hence correctly managed from a waste management perspective, the Research-based Pharmaceutical Industry in Sweden (LIF) has together with Swedish pharmacies conducted surveys regularly since 2001 to investigate the level of knowledge in the general public on this issue. The campaigns and the surveys from 2001, 2004, and 2007 are described in the reference [24] A general conclusion from these surveys, and confirmed by the MPA report, is that roughly 75–80 % of unused medicines among the general public are brought back to pharmacies for proper waste management. It is also very obvious that information, e.g. campaigns to patients, are important to secure high compliance to the recommendation of bringing unused medicines back to the pharmacy. The pharmacists' role is extremely important for success.

> Some patients want to donate unused medicines to Third World countries. There are even organisations that collect surplus medicines to send. Neither the people, nor the environment of the receiving country wants that. The names and instruction leaflets may

(continued)

cause confusion, the medicines are also taken when the indication isn't conforming the disorder and unused medicines stay in the environment. Therefore, the WHO has formulated guidelines how medicine donations can be useful [25]. In these guidelines there is no place for medicines that have been returned by patients.

38.5.3 Potential Mitigating Measures

Any direct danger for humans from environmental exposure to medical substances is considered negligible at this moment, but the concentrations in the environment may rise over time due to the slow degradation of the substances. It is also important to remember that the knowledge on environmental effects from mixtures of substances is low. Hence protective and mitigating measures could be appropriate. The following measures have been proposed [16, 26]:

- Propagate restrictive prescribing policy
- Give education to patients and health care workers about the effects of medicines on the environment
- Give information about returning and destroying unused medicines
- Production of more easily, biologically, degradable medicines (green pharmacy)
- Extra purification of waste water of health care institutions
- Development of new sanitation systems for drinking water

Physicians and patients can contribute by means of reducing the quantity of unused medicines, and return them to a pharmacy. The Swedish classification scheme has also been used to bring environmental risk and hazard into the decision of the choice of medicine used [27]. For information regarding novel waste water treatment techniques suitable for removal of pharmaceutical substances, e.g. activated carbon, ozonation, and ultraviolet radiation, the reader is referred to the references [28–32].

An approach that tries to solve the problem more at the source is the so-called green pharmacy. In order to stimulate the development of more easily degradable medicines, both for human as well as for veterinary medicines, European guidelines are formulated. At the application stage to get a marketing authorisation the manufacturer has to give information about the effects of the medicine on the environment as well as an evaluation of those effects and measurements which have to be taken to prevent or reduce these effects [33–35]. When veterinary products are concerned, authorities can even deny the registration if the environmental risk is considered too big. Market authorisation can however not be refused for a human medicinal product for too high an environmental risk. The need for mitigating measures, e.g. restricted use or labelling could however be mandated.

38.6 Essentials

The pharmacist can contribute to a better environment during all activities in the pharmacy: during educating patients about returning unused medicines, during raw material management, during drafting preparation methods. However, there is still little scientific research conducted into environmental burden by pharmacies. There are legal guidelines for processing waste from the pharmacy, but on several other environmental topics, there are no concrete rules available which could guide the pharmacist in the daily operations.

The environmental burden caused by medicine use is a subject of increasing research. For now, humans seem to run no direct risk. Nevertheless, humans may run an indirect risk by harming the environment. In the short term, hope is placed upon innovations in the field of waste water treatment, and on the contribution of the patient by returning unused medicines to the pharmacy. The development of 'green medicines', which do not cause harm to the environment, and a responsible use and management of those medicines (green pharmacy) is the ultimate goal.

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Information Sources

39

Doerine Postma and Sin Ying Chuah

Contents

Abstract

Amongst the wealth of information sources, specific ones may be valuable for pharmacists who are concerned with product care, preparation, adapting dosage forms and reconstitution. This chapter presents an authors' and editors' choice of essential references, textbooks, specific references and sources for postgraduate studying. For each source practical information is given.

Keywords

Sources • References • Textbook • Postgraduate education

39.1 Introduction

This chapter gives a selection of sources on product care, and preparation of medicines. The authors and editors consider them valuable and worth to be considered by pharmacists who are involved in product care, preparation and manufacturing, adapting dosage forms and reconstitution.

The focus of this chapter is on those sources that are most useful, apart from Practical Pharmaceutics. Therefore the authors have refrained from mentioning other general textbooks on 'practical pharmaceutics', however valuable they may be.

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3_39,

Input is given by the members of the Editorial Advisory Group, the authors of the other chapters and the editors. The selection of the sources is based on applicability in practice and on experience.

This selection is a suggestion and it is not intended to be complete. There may be more applicable (national) sources that are not listed in this chapter.

The sources in this chapter are subdivided into the themes: essential references, textbooks and specific references. Formularies on pharmacy preparation and quality of preparation are also mentioned in this chapter. Furthermore a few sources for further studying are mentioned.

The sources are described in a similar way: a short explanation on the content and information on the publisher, editor, publication channel, most recent edition, price in 2014 (without VAT), language of the source and ISBN for books or ISSN for journals or series of books.

39.2 Essential References

During daily practice, a pharmacist may advise and instruct patients about handling their medicines. Also a pharmacist may have to manage different aspects of pharmacy preparation and the logistics of medicines. Therefore it is useful to have some reference works at hand:

For the therapeutic relevance of a pharmacy preparation: Martindale and Medline/PubMed.

For information about adapting oral dosage forms: a handbook like Don't Rush to Crush.

For more insight on pharmaceutical excipients: the Handbook on Pharmaceutical Excipients and Fielders Encyclopedia. The Handbook describes the most common excipients in detail. The Encyclopedia describes almost all excipients, but less in detail than the Handbook.

For information on stability of medicines in solution with emphasis on stability and incompatibility of parenteral medicines: Stabilis gives a practical overview of facts based on reliable literature.

39.2.1 Australian Don't Rush to Crush Handbook

This handbook provides Australia-based information for health professionals on how to administer medicines safely to people unable to swallow solid oral medicines.

It contains over 500 monographs on solid oral medicines, which are on the Australian market, listing generic names, brand names, forms and strengths. Separate recommendations for patients with swallowing difficulties and patients with enteral feeding tubes are being given.

Published by:	The Society of Hospital Pharmacists of Australia
Editor:	Burridge N, Deidun D
Publication channel:	ring binder
Most recent edition:	1st, 2011
Price in 2014:	SHPA member: AU$ 110, non-member: AU$ 120
Language:	English
ISBN:	9780987110336
More information:	www.shpa.org.au/Publications

39.2.2 Fiedler Encyclopedia of Excipients

Fiedler Encyclopedia of Excipients describes the properties of more than 17,000 excipients that are used in pharmaceutical and cosmetic industry. The descriptions contain: chemical name, synonyms, structural formula, pharmacopoeial references, CAS Registry number (Chemical Abstract Service), synthesis, properties, use, toxicology, analysis.

Published by:	Editio Cantor Verlag
Editor:	Lang S, Reng A, Schmidt PC
Publication channel:	book
Most recent edition:	6th, 2007
Price in 2014:	€ 385
Language:	English
ISBN:	9783804727977
More information:	http://www.deutscher-apotheker-verlag.de

39.2.3 Handbook of Pharmaceutical Excipients

The Handbook of Pharmaceutical Excipients contains approximately 380 excipient monographs. The data contains information on physical properties, safety and potential toxicity of the excipients.

The monographs include pharmacopoeial information, non-proprietary names and synonyms, chemical name, CAS Registry number, empirical formula, molecular weight, functional category, applications and incompatibilities, material description and typical excipient properties, safety, stability, storage and handling precautions.

Published by:	Pharmaceutical Press
Editor:	Rowe RC, Sheskey PJ, Cook WG, Fenton ME
Publication channel:	book, online
Most recent edition:	7th, 2012
Price in 2014:	book: £ 299; online £ 224 (via MedicinesComplete)
Language:	English
ISBN:	9780857110275
More information:	http://www.pharmpress.com/

39.2.4 Martindale, the Complete Drug Reference

Martindale contains approximately 6,000 monographs on active substances and excipients. It contains information on uses and administration as well adverse effects, treatment of adverse effects, precautions, interactions, pharmacokinetics. For each substance the following characteristics are given: synonyms, pharmacopoeial description and solubility if available, proprietary preparation names.

Published by:	Pharmaceutical Press
Editor:	Sweetman SC
Publication channel:	book, online
Most recent edition:	38th, 2014
Price in 2014:	book: £ 459; online: £ 270 (via MedicinesComplete); book and online: £ 575
Language:	English
ISBN:	9780857111395
More information:	http://www.pharmpress.com

39.2.5 PubMed/MEDLINE

MEDLINE is a bibliographic database of life sciences and biomedical information. It contains references to articles from academic journals covering medicine, nursing, pharmacy, dentistry, veterinary medicine, health care, biology and biochemistry.

PubMed provides free access to MEDLINE. It also includes articles from other sources. Pubmed is helpful for searching additional information on therapeutic relevance of active substances. It contains abstracts and links to full-text articles.

Published by:	National Center for Biotechnology Information (NCBI)
Editor:	not applicable
Publication channel:	online
Most recent edition:	not applicable
Price in 2014:	free
Language:	English
ISBN:	not applicable
More information:	http://www.ncbi.nlm.nih.gov/pubmed/

39.2.6 Stabilis

Stabilis is a database with information about stability and compatibility of parenteral medicines (injectable medicines). For each drug the following information is given: trade names in different countries, stability in solution, stability in admixtures, factors which affect its stability, incompatibilities and routes of administration. Relevant references are also mentioned. The stability information of parenteral medicines can be useful to determine the stability on liquid medicines in general.

Stabilis also gives stability information of some other pharmaceutical preparation, such as eye-drops, ointments, oral solution. Data about stability of the dilutions and the compatibilities are examined by experts, who only include them in Stabilis if the shelf life testing is reliable. Stabilis uses pictograms and the information is translated into 28 languages.

Published by:	Infostab
Editors:	Vigneron J
Publication channel:	online
Most recent edition:	not applicable
Price in 2014:	free
Language:	Arabic, Bulgarian, Chinese, Croatian, Czech, Danish, Dutch, German, English, Estonian, Finnish, French, Greek, Hungarian, Italian, Japanese, Latvian, Lithuanian, Norwegian, Polish, Portuguese, Rumanian, Russian, Slovenian, Slovak, Spanish, Swedish, Turkish.
More information:	http://www.stabilis.org

39.3 Textbooks

For the design of pharmacy preparations it is necessary to understand the scientific principles. These principles are also important for the understanding of the design and production of licensed medicines and to assess the possibilities of adapting these products.

During education Aultons and Martin's are both valuable. Martin's Physical Pharmacy and Pharmaceutical Sciences focuses on the scientific background whereas the focus of Aultons Pharmaceutics may be more on the design of medicines.

Pharmatopia and Rezeptur in Bild can be helpful for learning and improving preparation skills. These sources visualise different preparation methods.

39.3.1 Aultons Pharmaceutics: The Design and Manufacture of Medicines

This textbook is on the design and preparation and discusses the underlying principles. It discusses the design of dosage forms, particle and powder technology, pharmaceutical microbiology and sterilisation, biopharmaceutical principles of pharmaceutical availability and the manufacturing of preparations.

Published by:	Churchill Livingstone
Editor:	Aulton M, Taylor K
Publication channel:	book, e-book
Most recent edition:	4th, 2013
Price in 2014:	book: € 63,99 e-book: € 61,99
Language:	English
ISBN:	book 9780702042904, e-book 9780702053931
More information:	http://www.elsevier.com

39.3.2 Martin's Physical Pharmacy and Pharmaceutical Sciences

Martin's Physical Pharmacy and Pharmaceutical Sciences focuses on the underlying principles of physics, chemistry and biology for the development of dosage forms. The last chapter gives a review of problems, including answers at the end, helping students to understand the content more easily.

Published by:	Lippincott Williams & Wilkins
Editor:	Sinko PJ
Publication channel:	book
Most recent edition:	6th, 2010
Price in 2014:	£ 47
Language:	English
ISBN:	9781609134020
More information:	http://www.lww.co.uk

39.3.3 Pharmatopia

Pharmatopia is an open education site for pharmacists and students. It has a collection of interactive web-based learning modules, containing presentations/lectures, assessments, reference materials, workshops and training etc. The information is subdivided in different subjects: Chemistry/Medicinal Chemistry, Pharmacy practice, Pharmaceutics/Drug Delivery and Pharmacology/ Drug Discovery and Biology. There is also a community for social networking and for exchanging information and knowledge. Universities/pharmacists can share their education resources with each other on this website.

In 2014 the information on preparation is limited but it is expected to expand.

Published by:	Monash University Australia
Editor:	not applicable
Publication channel:	online
Most recent edition:	not applicable
Price in 2014:	The modules are freely accessible to schools and universities, and on a cost recovery basis to industry
Language:	English
ISBN:	not applicable
More information:	http://saber.monash.edu/pharmatopia

39.3.4 Rezeptur im Bild

Six short movies show the method of preparation of the most common dosage forms, emphasising the aspects that have impact on the quality. The subjects are:
Suspension: labelling and dosing a suspension
Solution (oil, alcoholic, water): weighing and packaging of solutions (oil, alcohol, water)
Hydrophilic creams: physical stability of hydrophilic creams
Stock preparation of capsule filling material: documentation
Suppositories: preparation with the squeeze bottle and Occupational Safety and Health issues
Non preserved eye drops: aseptic preparation

Published by:	Govi-Verlag
Editor:	not applicable
Publication channel:	DVD
Most recent edition:	2012
Price in 2014:	Member € 44,90; Non-member € 59,90
Language:	German
ISBN:	9783774112148
More information:	http://www.govi.de

39.4 Specific References

Whereas some references are essential for daily practice, other references can be suitable for background information or contain more in-depth information.

For pharmacy preparation the formularies of other European countries can be an inspiration. This paragraph mentions the formularies that give information on a preparation with sufficient quality. This means that not only the formula and the method of preparation are given but that the formulae are also validated, for instance by stability studies and proficiency studies. The Formulary on Dutch Pharmacists (Formularium der Nederlandse Apothekers) and the German Formulary (Neues Rezeptur-Formularium) are validated and the shelf lives are based on stability studies.

For quality control of the preparation process several references may be relevant. For production quality the EU-GMP is applicable for pharmaceutical industry. For product quality of pharmacy preparations, the monograph "Pharmaceutical Preparations" is applicable. It is a general monograph for the preparation or production of pharmaceutical preparations and it explicitly mentions pharmacy preparation, as preparation of unlicensed medicines.

The Ph. Eur. contains monographs on substances, whereas the British Pharmacopoeia and the United States Pharmacopoeia also contain monographs on pharmaceutical preparations and unlicensed medicines. The Deutscher Arzneimittel-Codex (DAC) contains monographs on active substances and excipients that are not described in the Ph. Eur.

The Kommentar zum Arzneibuch gives more background information on the monographs of the Ph. Eur. and DAC.

For more extensive information on substances several sources can be useful. Profiles of drug substances excipients and related microbiology, Handbook on extemporaneous preparation and Trissel's Stability of compounded formulations are discussed.

The authors of the chapters of Practical Pharmaceutics have recommended specific reference works on the topics: aseptic processing, microbiology, phytotherapy, radiopharmaceuticals and stability studies.

39.4.1 British Pharmacopoeia

The British Phamacopoeia (B.P.) comprises of six volumes. Volume I and II encompass monographs of medicinal and pharmaceutical substances. Volume III contains monographs on formulated preparations. Volume IV is about herbal active substances, herbal preparations and herbal medicinal products, material for use in the manufacture of homeopathic preparations, blood-related products, immunological products, radiopharmaceutical preparations and surgical materials. Volume V contains infrared reference spectra, appendices and supplementary chapters. There is also a single volume of the B.P. (Veterinary) containing monographs on products used in veterinary medicines.

The B.P. contains, besides all monographs of the Ph. Eur. also monographs on other substances and on pharmaceutical preparations and unlicensed medicines.

Published by:	The Stationery Office
Editor:	British Pharmacopoeia Commission Secretariat of the Medicines and Healthcare Products Regulatory Agency
Publication channel:	print, CD-rom and online, online
Most recent edition:	2014
Price in 2014:	print, CD-rom and online: £1.000; online: price on request
Language:	English
ISBN:	9780113229352
More information:	http://www.pharmacopoeia.co.uk

39.4.2 Deutscher Arzneimittel-Codex/Neues Rezeptur-Formularium

Deutscher Arzneimittel-Codex/Neues Rezeptur-Formularium (DAC/NRF) is a German collection of general information about specification and identification of substances, pharmacy preparation and quality control, monographs of substances and formulas including preparation methods.

Subscribers of DAC/NRF also have free access to NRF-Rezepturhinweise; an online collection of 550 documents on not-standardised formula.

Published by:	ABDA – Bundesvereinigung Deutscher Apothekerverbände
Editor:	Kiefer A, Scriba G, Hörnig M, Reimann H
Publication channel:	six loose-leaf bands, six loose-leaf bands and CD
Most recent edition:	two updates per year
Price in 2014:	loose-leaf bands: € 278 loose-leaf bands and CD: € 398
Language:	German
ISBN:	9783774100442
More information:	http://www.govi.de

39.4.3 EU Legislation/GMP

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5. Volume 1 is about EU pharmaceutical legislation for medicinal products for human use and volume 5 for veterinary use.

The basic legislation is compiled in a series of guidelines that are published in Volume 2 till Volume 10. Volume 4 is about guidelines for good manufacturing practices for medicinal products for human and veterinary use, which is also known as European Good Manufacturing Practices (EU GMP).

Since 1991 the EU GMP has been effective. For production quality the EU-GMP is applicable for pharmaceutical industry; but it has no guidelines on the design of medicinal products.

The EU-GMP comprises 3 parts. Part 1 encompasses 9 basic chapters on medicines: Pharmaceutical Quality System, Personnel, Premises and Equipment, Documentation, Production, Quality Control, Outsourced activities, Complaints and Product Recall, Self Inspection. Part 2 is about the production of active substances. Part 3 contains about 20 related documents such as a site master file and several annexes (see also Sect. 35.5.7).

Many European countries refer in their national legislation to the GMP principles.

Published by:	European Commission Enterprise and Industry Directorate-general
Editor:	not applicable
Publication channel:	online
Price in 2014:	free
Language:	English
ISBN:	not applicable
More information:	http://ec.europa.eu/health/documents/eudralex/

39.4.4 European Pharmacopoeia

The European Pharmacopoeia (Ph. Eur.) defines requirements for the qualitative and quantitative composition of medicines, the tests to be carried out on medicines and on substances and materials used in their production.

The eight edition consists of two initial volumes (8.0) and 8 supplements (8.1 to 8.8). Each volume contains a complete table of contents and index. Volume 1 and 2 combined contain 2,224 monographs, 345 general chapters illustrated with diagrams or chromatograms and 2,500 descriptions of reagents. The eight edition of Ph. Eur. contains monographs on active substances, dosage forms and vaccines, biologicals, gasses and radiopharmaceuticals in general.

Since April 1st 2013 the monograph "Pharmaceutical Preparations" is applicable. It is a general monograph for the preparation or production of pharmaceutical preparations and it explicitly mentions pharmacy preparation, as preparation of unlicensed medicines.

In general the Ph. Eur. does not publish monographs on finished products.

Published by:	The Council of Europe, Strasbourg Cedex France
Editor:	Not applicable
Publication channel:	book, USB and online
Most recent edition:	8th 2014
Prices in 2014:	depending on type of package see https://store.edqm.eu
Language:	English and French
ISBN:	English version ISBN/ISSN: 9789287175311
	French version ISBN/ISSN: 9789287175304
More information:	https://store.edqm.eu

39.4.5 Formularium der Nederlandse Apothekers

The Formularium der Nederlandse Apothekers (FNA) is a Dutch formulary that contains about 250 national standardised formulations on pharmacy preparations. Each formulation contains a qualitative and quantitative composition of the preparation, preparation method, the recommended packaging, storage conditions and related shelf life and quality requirements of the preparation.

Each formulation also contains extensive background information to support the design and the correct method of preparation of the product and the therapeutic assessment of each preparation.

Published by:	Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie
Editor:	not applicable
Publication channel:	book, online
Most recent edition:	2013
Price in 2014:	book: € 299 online: € 2,072 (including about 200 procedures on preparation methods, product design, quality control and assay methods of the preparations as well)
Language:	Dutch
ISBN:	9789070605988
More information:	www.knmp.nl

39.4.6 Handbook of Extemporaneous Preparation

This handbook has a part on standards for extemporaneous dispensing and a part containing stability summaries for the 50 most frequent extemporaneously prepared medicines in UK NHS hospitals. It also includes sections relating to clinical risk assessment and advice for procuring unlicensed medicines from manufacturers.

Published by:	Pharmaceutical Press
Editor:	Jackson M, Lowey A
Publication channel:	book, e-book
Most recent edition:	1st, 2010
Price in 2013:	book: € 44,99; e-book: € 29,80
Language:	English
ISBN:	book: 9780853699019 e-book: 9780853699699
More information:	http://www.pharmpress.com

39.4.7 Hugo and Russell's Pharmaceutical Microbiology

Pharmaceutical microbiology discusses all aspects of microbiology in pharmaceutical production from the manufacture and quality control of pharmaceutical products through to an understanding of the mode of action of antibiotics.

This book covers the biology of microorganisms, contamination and infection control, and pharmaceutical production. Also pathogens and host response, and therapeutics are discussed.

Published by:	Wiley-Blackwell
Editor:	Denyer SP, Hodges N, Gorman SP, Gilmore BF
Publication channel:	book, e-book
Most recent edition:	8th, 2011
Price in 2014:	book: £ 53,99/ € 64,80 e-book: £ 42,99/ € 52,99
Language:	English
ISBN:	book: 9781444330632 e-book: 9781118293829
More information:	http://eu.wiley.com/WileyCDA/

39.4.8 Kommentar zum Europäischen Arzneibuch & Kommentar zum Deutschen Arzneibuch

Kommentar zum Europäischen Arzneibuch & Kommentar zum Deutschen Arzneibuch comprises two parts.

Band I is a general volume, with information mainly about formulation, apparatus and reagents. It also gives comment on the analytical methods in the European and German Pharmacopoeia and the background information. Band II contains comments on each monograph of the European and German Pharmacopoeia. Each comment on a specific monograph gives an explanation of all sections of the monograph. It also gives information about the synthesis, the general chemical and physical aspects, the stability, storage conditions and alternative analytical methods. The book has illustrations of IR-spectra, UV-spectra and incidental HPLC-chromatograms.

Published by:	Wissenschaftliche Verlagsgesellschaft Stuttgart
Editor:	Bracher F, Heisig P, Langguth P et al.
Publication channel:	loose-leaf bands
Most recent edition:	47th, 2014
Price in 2014:	€ 980
Language:	German
ISBN:	9783804730533
More information:	http://www.wissenschaftliche-verlagsgesellschaft.de

39.4.9 Principles and Practice of Phytotherapy

Principles and practice of phytotherapy is a reference work with information on western herbal medicine. It provides practical and evidence-based information for the use of herbal treatment in clinical condition and problems. This book includes information on fundamental concepts, traditional use, scientific research, safety, effective dosage and clinical applications of herbal medicines.

Published by:	Churchill Livingstone
Editor:	Bone K, Mills S
Publication channel:	book, e-book
Most recent edition:	2nd, 2013
Price in 2014:	book: € 103; e-book: € 83,33
Language:	English
ISBN:	book: 9780443069925, e-book: 9780702052972
More information:	https://www.elsevier.com

39.4.10 Profiles of Drug Substances, Excipients and Related Methodology

This book series comprises of 38 volumes. It contains information about 533 substances and excipients. The Profiles series include for instance the physical and analytical characterisation of substances and excipients, information of clinical uses, pharmacology, pharmacokinetics, safety or toxicity. The first 29 volumes were published by the name: Analytical Profiles of Drug Substances. Since volume 30 the name was changed into Profiles of Drug Substances, Excipients and Related Methodology. It is recommended for its chemical, physico-chemical and stability information.

Published by:	Academic Press
Editor:	Brittain HG, founding editor Florey K
Publication channel:	book series, e-book, online
Most recent edition:	latest volume (39) 2014
Price in 2014:	book per volume approx. € 180 e-book per volume approx. € 175 per electronic profile of substance: € 31,50
Language:	English
ISSN:	1871–5125
More information:	http://www.elsevier.com/

39.4.11 Quality Assurance of Aseptic Preparation Services

Quality Assurance of Aseptic Preparation Services provides information and up-to-date national guidance on unlicensed

aseptic preparation, from prescription verification to distribution. Appendices give information as to how these standards can be achieved e.g. for validation, microbiological environmental monitoring, capacity planning etcetera.

Published by:	Pharmaceutical Press
Editor:	Beaney AM
Publication channel:	book
Most recent edition:	4th, 2005
Price in 2013:	£ 34,99
Language:	English
ISBN:	9780853696155
More information:	http://www.pharmpress.com

39.4.12 Sampson's Textbook on Radiopharmacy

Sampson's Textbook on Radiopharmacy is a reference work with information on science and practice of radiopharmacy. The book includes information on: physics applied to radiopharmacy; medicinal radio-elements; radiopharmacology and radiopharmacokinetics; radiopharmaceutics: formulation, preparation and quality assurance, radiopharmacy practice and new techniques for design and testing of radiopharmaceuticals.

Published by:	Pharmaceutical Press
Editor:	Theobald T
Publication channel:	book, e-book
Most recent edition:	4th, 2010
Price in 2013:	book: £ 74,99; e-book € 105,28
Language:	English
ISBN:	book: 9780853697893; e-book: 9780857110114
More information:	http://www.pharmpress.com

39.4.13 Stabilitätsprüfung in der Pharmazie: Theorie und Praxis

This book describes extensively the stability testing methods used for synthetic and biotechnical active substances. It portrays the trajectory from development to marketing authorisation in typical cases.

Published by:	Cantor Verlag
Editor:	Grimm WA, Harnischfeger G, Tegtmeier M
Publication channel:	book
Most recent edition:	3rd, 2011
Price in 2014:	€192
Language:	German
ISBN:	9783871934087
More information:	http://www.ecv.de/buecher.php

39.4.14 Trissel's Stability of Compounded Formulations

Trissel's stability of compounded formulations contains monographs on substances and gives an overview of stability information on preparations. Each monograph is organised into three categories: Properties, General Stability Considerations and Stability Reports of Compounded Preparations. Fourth and fifth categories – Compatibility with Other Drug Products and Compatibility with Common Beverages and Foods – are included where information is available.

Published by:	American Pharmacists Association
Editor:	Trissel LA
Publication channel:	book
Most recent edition:	5th, 2012
Price in 2014:	$ 149,95; member APhA: $ 120
Language:	English
ISBN:	9781582121673
More information:	http://ebusiness.pharmacist.com/personifyebusiness/ShopAPhA.aspx

39.4.15 United States Pharmacopeia and The National Formulary

United States Pharmacopeia and The National Formulary (USP-NF) is a combination of two compendia: USP and the NF. USP contains monographs for substances, dosage forms and medicines. Dietary supplements monographs are in a separate section of the USP. NF discusses monographs for excipients.

Each monograph contains the following information: name of the substance or medicinal product, definition, packaging, storage, labeling requirements and specifications (tests, procedures for the tests and acceptance criteria). The USP also contains several general chapters. There are five general chapters about pharmaceutical preparation: sterile preparations, non-sterile preparations, pharmaceutical calculations in extemporaneous preparation, quality assurance, and prescription balances and volumetric apparatus.

USP on Compounding is a guide for pharmacists who are involved with pharmaceutical preparation. It contains preparation-related General Chapters from the USP-NF. It also features supporting General Chapters that are referred to

in the chapters on preparation and in USP-NF General Notices and Requirements.

Published by:	The United States Pharmacopeial Convention
Editor:	Not applicable
Publication channel:	USP-NF: book, online, USB flash drive USP on compounding: 12-month electronic subscription in PDF-format
Most recent edition:	USP 37 – NF 32 2014
Price in 2014:	USP- NF: Book: $ 850, Online (per year): $ 850, USB flash drive: $ 850 USP on Compounding: $100
Language:	USP-NF: English, Spanish, Russian USP on Compounding: English
ISBN: USP-NF:	9781936424221 (01957996 ISSN) USP on Compounding: 9781936424047
More information:	http://www.usp.org/products

39.4.16 World Health Organization Guidelines

The World Health Organization (WHO) has guidelines for good manufacturing practices (GMP), published as Technical Reports. Many countries have formulated their own requirements for GMP based on the WHO GMP or they have harmonized their requirements, for example in the European Union (EU-GMP).

The WHO GMP have no legal value for those countries that have their own GMP. Nevertheless they can be an inspiration. They may also serve as reference for those countries that don't have their own GMP regulations.

The WHO has a Technical Reports on Specifications for pharmaceutical preparations (http://www.who.int/medicines/publications/pharmprep/en/).

For production of medicines, relevant annexes are clustered into good manufacturing practices (main principles and several categories of products e.g. active ingredients, excipients, blood products), risk analysis, technology transfer and training materials.

Published by:	World Health Organization
Editor:	not applicable
Publication channel:	online
Most recent edition:	not applicable
Price in 2014:	free
Language:	English
More information:	http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/

39.5 Further Studying

After graduation pharmacists can refresh their knowledge and keep it up-to-date by attending courses, reading pharmaceutical journals or joining a society. For pharmacy preparation, the following courses and journals are recommended.

Arbeitsgemeinschaft für pharmazeutische Verfahrenstechnik (APV) is an association that organizes congresses and courses and has its own journal. The APV focuses on industrial pharmacists. The International Journal of Pharmaceutics focuses on pharmaceutical scientists and has articles of interest for pharmacists as well.

The European Journal of Hospital Pharmacy has less information on pharmacy preparation, but rather on preparation prior to use or adapting dosage forms.

The Parenteral Drug Association Journal contains peer-reviewed scientific and technical papers in the pharmaceutical and biotechnology industries, but mainly – and extensively – regarding the preparation and manufacturing of parenteral medicines..

International Pharmaceutical Abstracts is a large database containing pharmaceutical science and health related literature, which can be of interest to pharmacists. Since the price is considerably high, it might not be suitable for daily practice in pharmacies.

The International Journal on Pharmaceutical compounding can be of interest to pharmacists who want to know more about pharmacy preparations outside Europe. This journal contains articles about pharmacy preparation in the United States, but only some of the articles are peer-reviewed.

For pharmacists who would like to get into contact with other pharmaceutical and scientific experts and stay up to date with pharmaceutical knowledge, the International Society for Pharmaceutical Engineering (ISPE) can be of interest. The ISPE has its focus on technical subjects but on quality management of manufacturing as well.

39.5.1 Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik: Courses

Arbeitsgemeinschaft für pharmazeutische Verfahrenstechnik (APV) is an International Association for Pharmaceutical Technology. It organises approximately 100 events of various types ranging from expert meetings, seminars and excursions to international scientific congresses and exhibitions. The APV also publishes its own scientific

journal (EJPB – European Journal of Pharmaceutics and Biopharmaceutics).

APV focuses on: Analytics and Quality Assurance, Pharmaceutical Education and Science, Biopharmacy and Pharmacokinetics, Drug Delivery, Drug Regulatory Affairs, Solid Dosage Forms, Liquid and Semi solid Dosage Forms, Information Technology, Pharmaceutical Process Engineering, Pharmaceutical Biotechnology, Process Optimisation and Packaging.

Published by:	International Association for Pharmaceutical Technology
Price in 2014:	for membership € 130, students € 25, retired € 40
Language:	English, German
More information:	http://www.apv-mainz.de

39.5.2 European Journal of Hospital Pharmacy: Science and Practice

The European Journal of Hospital Pharmacy: Science and Practice (EJHP) is the official journal of the European Association of Hospital Pharmacists (EAHP). It is committed to advancing the science, practice and profession of hospital pharmacy. EJHP contains peer reviewed papers, conference reports on all aspects of hospital pharmacy. It also discusses developments in pharmaceutical and biomedical sciences.

Published by:	European Association of Hospital Pharmacy
Editor:	Wiffen P
Publication channel:	journal
Most recent edition:	bimonthly
Price in 2014:	personal print and online access: £ 175 institutional online access: £ 515–700
Language:	English
ISSN: Print:	20479956, Online: 20479964
More information:	http://ejhp.bmj.com

39.5.3 International Journal of Pharmaceutics

The International Journal of Pharmaceutics is the journal for pharmaceutical scientists concerned with the physical, chemical and biological properties of devices and delivery systems for medicines, vaccines and biologicals, including their design, manufacture and evaluation. This includes evaluation of the properties of substances, excipients such as surfactants and polymers and novel materials. The journal has special sections on pharmaceutical nanotechnology and personalised medicines, and publishes research papers, reviews, commentaries and letters to the editor as well as special issues.

Published by:	Elsevier
Editor:	Editor-in-Chief: Florence AT
Publication channel:	journal
Most recent edition:	monthly update
Price in 2014:	E-journal: € 10,078.40 (access for 5 users and to 4 years of archives)
Journal:	€ 10,431 (for one calendar year)
Personal print Journal:	€ 693 (includes Ipad access)
Language:	English
ISSN:	03785173
More information:	http://www.journals.elsevier.com/international-journal-of-pharmaceutics/

39.5.4 International Journal on Pharmaceutical Compounding

The International Journal on Pharmaceutical Compounding is a bi-monthly journal emphasising pharmaceutical preparation. It contains information on formulations and guidelines from the USP. This journal focuses on the American practice (with its guidelines).

Published by:	IJPC print
Editor:	Allen, LV
Publication channel:	journal
Most recent edition:	bimonthly
Price in 2014:	journal: $250; in USA $175; Canada $200 Electronic copies: $175
Language:	English
More information:	https://www.ijpc.com

39.5.5 International Pharmaceutical Abstracts

International Pharmaceutical Abstracts (IPA) indexes articles about the development and use of active substances and professional pharmaceutical practice. IPA covers medicines therapy and pharmaceutical information, and includes articles from more than 800 pharmaceutical, medical and health-related journals. IPA's coverage includes journals published worldwide since 1970.

Published by:	Wolters Kluwer Health/ Thomson Scientific, Inc.
Publication channel:	online

Most recent edition:	monthly update
Price in 2014:	approximately € 6,500 for an account for one user
Language:	English
More information:	http://ovidsp.ovid.com

39.5.6 International Society of Pharmaceutical Engineering

International Society of Pharmaceutical Engineering (ISPE) is a non-profit association for pharmaceutical professionals. ISPE focused on the knowledge of pharmaceutical manufacturing and its quality. It organises discussions, meetings, courses and training on topics on pharmaceutical manufacturing. ISPE also publishes its own journal.

Published by:	International Society for Pharmaceutical Engineering
Price in 2014:	membership €130, students € 25, retired € 40
Language:	English, German
ISSN:	10924221
More information:	http://www.ispe.org

39.5.7 PDA Journal of Pharmaceutical Science and Technology and Technical Reports

Journal articles are categorised into the following areas: editorial, letter to the editor, commentary, review, research, technology/application (or case studies) and conference proceedings.

PDA is also well-known for their Technical Reports. These Reports address a wide area, including use and validation of pharmaceutical filters, sterilisation technologies, non-conformities in glass vials and ampoules, pharmaceutical microbiology, glass defects, process validation and good distribution practices, including cold chain, and quality risk management.

Published by:	Parenteral Drug Association
Editor:	Rao G
Publication channel:	journal
Most recent edition:	bimonthly
Price in 2014:	(one year online access) member: $150, non-member: $399
Language:	English
ISSN:	print 10797440; online 19482124
More information:	http://journal.pda.org

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Y. Bouwman-Boer et al. (eds.), *Practical Pharmaceutics*,
DOI 10.1007/978-3-319-15814-3, © KNMP and Springer International Publishing Switzerland 2015

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