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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. 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.

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-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: the preparation of a homogeneous powder mixture and evenly dividing the powder mixture over the dosage units.

Finally, this chapter discusses recent developments, such as 3D printing of oral solids and the production of orodispersible films. These techniques can be a useful

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addition to the pharmacist's toolbox, as they do not have the disadvantages of traditional compounding methods.

What Is New?

This chapter is based upon the chapter Oral Solids by Minna Helin-Tanninen and João Pinto in the 2015 edition of Practical Pharmaceutics. The text has been updated for clarity and to rectify grammatical errors. Section 12.6.2.3. Solvent Method has been expanded with pros and cons of this particular method. Sections on Orodispersible Films and 3D Printing of Oral Solids have been added to reflect the recent developments in this field. A section on Swallowing Problems is now included, based on the chapter Instructions for use of medicines in the previous edition of Practical Pharmaceutics. The section on Herbal Oral Medicines has been removed, as it did not fit the scope of this chapter.

Learning Objectives

The reader of the chapter

- will be familiar with the most common oral solid dosage forms and their advantages and disadvantages
- will know the excipients commonly used in the preparation of oral solid dosage forms, as well as their function(s)
- will understand the different methods for preparing a homogeneous powder mixture and when each method is applicable
- will be familiar with different kinds of modified-release tablets and their general technical principles
- will be updated on several recent developments regarding oral solid dosage forms, such as orodispersible films and 3D printing

12.1 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].

This chapter first provides the Ph. Eur. definitions for different oral dosage forms and their biopharmaceutical aspects. Next, the general aspects of formulation and preparation of powder mixtures are dealt with. Specific information about the respective dosage forms is 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 is necessary to understand how they are made, should they have to be adapted for the preparation of other oral preparations in pharmacies.

Powders are encapsulated into hard shells (capsules) and are as such 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 these dosage forms, rather than starting 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 when 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.

Hard capsules are normally 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].

Further details on the characteristics and use, advantages and disadvantages of the respective oral dosage forms will be given in the separate Sects. 12.6 (capsules), 12.7 (powders), 12.8 (cachets), 12.9 (tablets), 12.10 (modified-release preparations) and 12.11 (orodispersible films). Section 12.12 briefly discusses the emergence of 3D printing as a method for the production of oral solid dosage forms. Complementary information on packaging, labelling, storage and use is discussed in Sect. 12.13.

12.2 Definitions

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

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, dyes, and flavouring substances. They are generally administered in or with water or another suitable liquid. They are presented as single-dose or multidose preparations" [4].

Similarly, granules are solid, dry agglomerates of powder particles [4]. 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 [4]. 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. According to the Ph. Eur., "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 [4].

Tablets are defined in the Ph. Eur. as "solid preparations each containing a single dose of one or more active substances" [4]. 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 [4]. Modified-release tablets include prolonged-release, delayed-release and pulsatile-release tablets.

Orodispersible films are defined in the Ph. Eur. as "solid oromucosal preparations intended for administration in the mouth, where they disperse rapidly to deliver active substances" [4]. As follows from their definition, orodispersible films are classified in the Ph. Eur. as oromucosal preparations.

12.3 Biopharmaceutics

Active substances are only absorbed from the gastrointestinal tract in the dissolved state (see Chap. 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. 12.1).

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 sulphate 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 [6, 7]. 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 [4]. 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 usually has not been subjected to a compression stage, as is common for most industrially manufactured capsules. Therefore, the content of pharmacy prepared capsules is often 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. Chapter 6 discusses the effects of these factors on the absorption of the active substance.

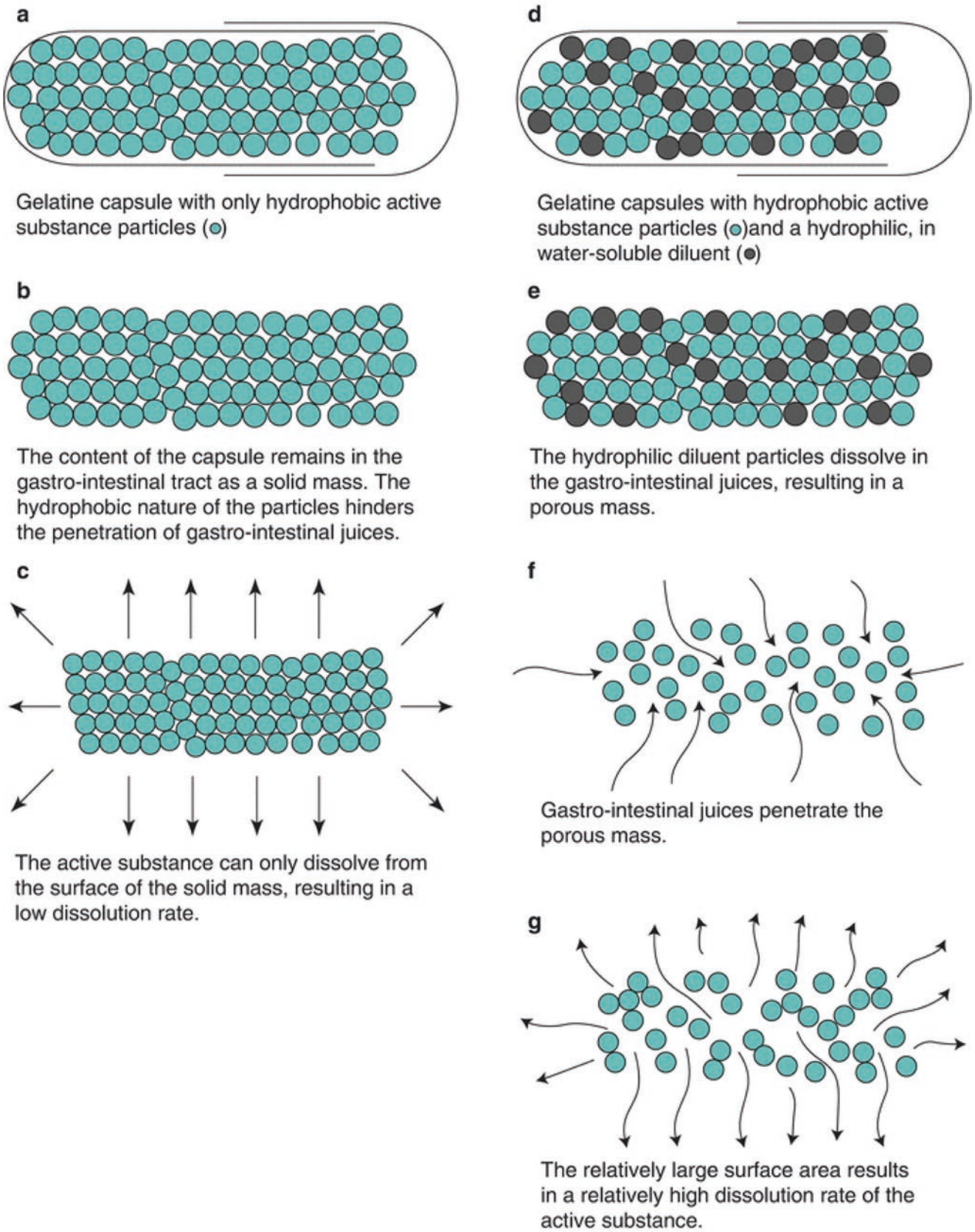

Fig. 12.1 The effect of a hydrophilic diluent on the dissolution rate of a sparingly soluble, hydrophobic active substance in a gelatine capsule. (From McConell and Basit [5], with permission). (**a–c**) Gelatine capsule with only hydrophobic active substance particles. (**d–g**) Gelatine capsules with hydrophobic active substance particles and a hydrophilic, in water-soluble diluent

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 [8]:

- 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 a specific part of the intestine undamaged 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 therapy 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).
- 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 microgranules 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 1500 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) [9].

12.4 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.

12.4.1 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 to handle the powder mixture. Secondly, the active substance may not have good flow properties; and 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 several of these functions, so the number of different excipients can be limited and the potential interactions between materials can be minimised [10]. 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 these 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 [11]. For example, many colouring agents have been associated with hypersensitivity and other adverse reactions.

12.4.2 Active Substance

Solid oral dosage forms are preferably prepared with the original pure active substance. The particle size of active substances in fast-release preparations should, ideally, not be 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 Chap. 29).

When the active substance is not available as raw material, tablets or capsules containing the active substance may be used, provided that both the tablet or capsule and the active substance itself are suitable for processing into a capsule. Sometimes the active substance is extracted by dissolution into a liquid, but these solutions (especially aqueous liquids) unfortunately 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 [12], which do not affect the gelatine.

Any processing of the active substance (e.g. milling, hydration), which may occur during preparation, can modify its physical properties. This probably will not be noticed by the pharmacist, as he will not have methods at his disposal to

confirm changes of the active substances [13]. For this reason, preparation of dosage forms should be preferably carried out starting from 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 risks associated with 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. However, the preparation of an oral solution of the active substance may be a better alternative.

12.4.3 Dilution and Flowability of the Powder Mixture

Solid oral dosage form units are prepared by dividing a mixture of the active substance and excipients evenly over a dosing mould, so that 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 [14]. When the mixture is dusty, sticky, or when segregation of components occurs, other excipients should be used or a glidant must be added. Even if the mixture looks suitable, the powder flow may not be appropriate. Insufficient flow will lead to uneven filling of the separate capsules and tablet molds. This will ultimately result in excessive 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) [15].

Powder flowability is influenced by [16]:

- 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 a 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 a too low moisture content will generate static electricity.
- Electrostatic charge: removing the charge improves the flow properties.

12.4.3.1 Diluents

Addition of excipients such as a diluent with good flow properties may improve the flow properties of a powder. Diluents are also added to powder mixtures 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 [17].

The most often used diluent for capsules and powders is microcrystalline cellulose (Avicel PH 102 or Pharmacel 102, see also Chap. 7). Microcrystalline cellulose has both good flow and disintegrating properties. However, microcrystalline cellulose has some drawbacks. It is insoluble in water, forming a suspension. and certain active substances may adsorb onto cellulose particles. This may reduce both solubility and dissolution rates of sparingly water soluble active substances, and thus the active substance's relative pharmaceutical bioavailability. Microcrystalline cellulose does not cause systemic adverse effects because humans do not absorb it [10, 18].

Lactose (alpha-lactose monohydrate) (see also Chap. 7) 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 whose contents have to be dissolved. Capsules containing lactose disintegrate as a result of the dissolution of lactose (Fig. 12.1). Its use might be limited in patients with lactose intolerance [10].

Dried (corn, rice or potato) starch (see also Chap. 7) 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.

12.4.3.2 Glidants

If insufficient 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. Colloidal anhydrous silica (Aerosil 200 V) at a concentration of 0.5% is the glidant of choice for the preparation of capsules. 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.

Addition of a glidant could be counterproductive because of [19]:

- Segregation: glidants may displace the active substance particles that are bound to a carrier by ordered mixing (see Sect. 12.5.1). 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 can 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.

12.4.3.3 Binding Agents

Binding agents combine the diluent function and thus improve flowability. The binding function is mainly used in the direct compression of tablets. These excipients increase the mass and promote the bonds between particles of other materials in the formulation, so they lead to the 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 grade flows better because half of the particles are granulated.

Granulated grade calcium monohydrogen phosphate dihydrate is used 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 12.1). Despite its hydrophilic nature, calcium monohydrogen phosphate dihydrate has neither disintegrating properties, nor is it water-soluble. Therefore, addition of a disintegrating agent is required. Primojel Capsule diluent FNA is a diluent for capsules that contains, the disintegrating agent sodium starch glycolate A (Primojel®) and the glidant colloidal anhydrous silica, as well as calcium monohydrogen phosphate dihydrate (Table 12.2).

During an investigation to find the optimal formulation of a suitable flowing powder for the preparation of Prednisolone capsules. Microcrystalline cellulose with anhydrous colloidal silica failed to give a mean content meeting the requirements [20]. The electric charge was apparently not neutralised and prednisolone was lost, 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, colloidal silica and the disintegrating agent sodium starch glycolate disintegrated sufficiently to give the desired dissolution rate.

12.4.4 Disintegration

Capsules disintegrate when the capsule shell dissolves and the powder mixture is wetted. Hydrophilic excipients promote the wetting of the powder bed (Fig. 12.1). Due to the

Table 12.1 Prednisolone Capsules 10–40 mg FNA [20]

Prednisolone, micronised	10–40 mg
Primojel capsule diluent FNA (Table 12.2)	>200 mg
Capsules size 2	

Table 12.2 Primojel Capsule Diluent FNA [20]

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®

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. 12.1). Highly compressed powders or granulates in tablets are more difficult to disintegrate. The addition of a disintegrating agent is therefore 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 a 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 [21]. 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. Tablets for immediate release of active substances always contain a disintegrating agent.

12.4.5 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 water-insoluble excipients such as the diluent microcrystalline cellulose. 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 [22].

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 Maillard reaction is slow in absence of water, but may lead to yellow discolouration during storage [23].

The pharmacist must therefore be careful when choosing 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. It is usually safe to dilute a crushed tablet with the excipient used in the tablet formulation, based on the market authorisation holder who has ensured their compatibility.

12.4.6 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 a pharmaceutical preparation's 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 [24].

One cannot simply add a flavour to a dosage form containing an unpleasant tasting active substance and expect it to taste good because the strength of tastes are different or different receptors are sensitised. Flavours are generally complex mixtures that are made from many chemicals. Flavouring agents can be natural (essential oil, derivatives from fruit vegetable juice) or artificial. Natural flavours particularly, 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 clinical trial placebos with an appearance identical to the original tablets. With capsules, it is possible to use coloured capsule shells, or to prepare a coloured powder mixture for use 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. Chapter 7 lists colouring agents for powder mixtures. Tablets can be coloured by using water-soluble (for wet granulation) or water-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 [25].

12.5 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 more complex. Tablets are made with a tableting machine, which imposes extra requirements on the flowability of the powder mixture. To minimise flow and segregation problems, powder mixtures are often granulated before compression.

12.5.1 Homogeneous Powder Mixtures

12.5.1.1 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 should have comparable particle sizes, densities, shapes and equal mixing ratio (see Sect. 12.4.2). 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 poor 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 Chap. 6). 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.

12.5.1.2 Starting from Tablets or Capsules

Real challenges for the preparation of powder mixtures arise when tablets or capsules are used as the active substance. The pharmacist must consider the suitability of the tablets or capsules for grinding or crushing. Then they have to develop a reliable method to produce the required dilution of the ground mass; this dilution sometimes has to be quite considerable, even a 100-fold.

Coated tablets, such as enteric-coated tablets, and modified-release tablets are preferably not split or pulverised, because their specific features may be lost. If it is absolutely necessary to break them, then the pharmacist must understand the implications on the stability of the medicine and on its therapeutic effect (see Sect. 12.9). 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 can readily be processed into a powder mixture.

To obtain the required amount of active substance, the number of whole tablets containing the equivalent amount is 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 use an excess of tablets to pulverise, determine the average tablet weight before pulverisation and then subsequently weigh the required quantity of tablet mass after pulverisation. If an exact number of tablets is used, the resulting mean content of active substance in the final product must be validated.

A strict method of pulverisation 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 or 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 also some loss of active substance 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. 12.2).

Tablets are crushed manually in a non-porous mortar with a pestle, preferably one with a rough surface to aid pulverisation. After careful grinding the resulting powder may be more or less homogeneous (Fig. 12.3).

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 homogeneity. In Sects. 12.9 and

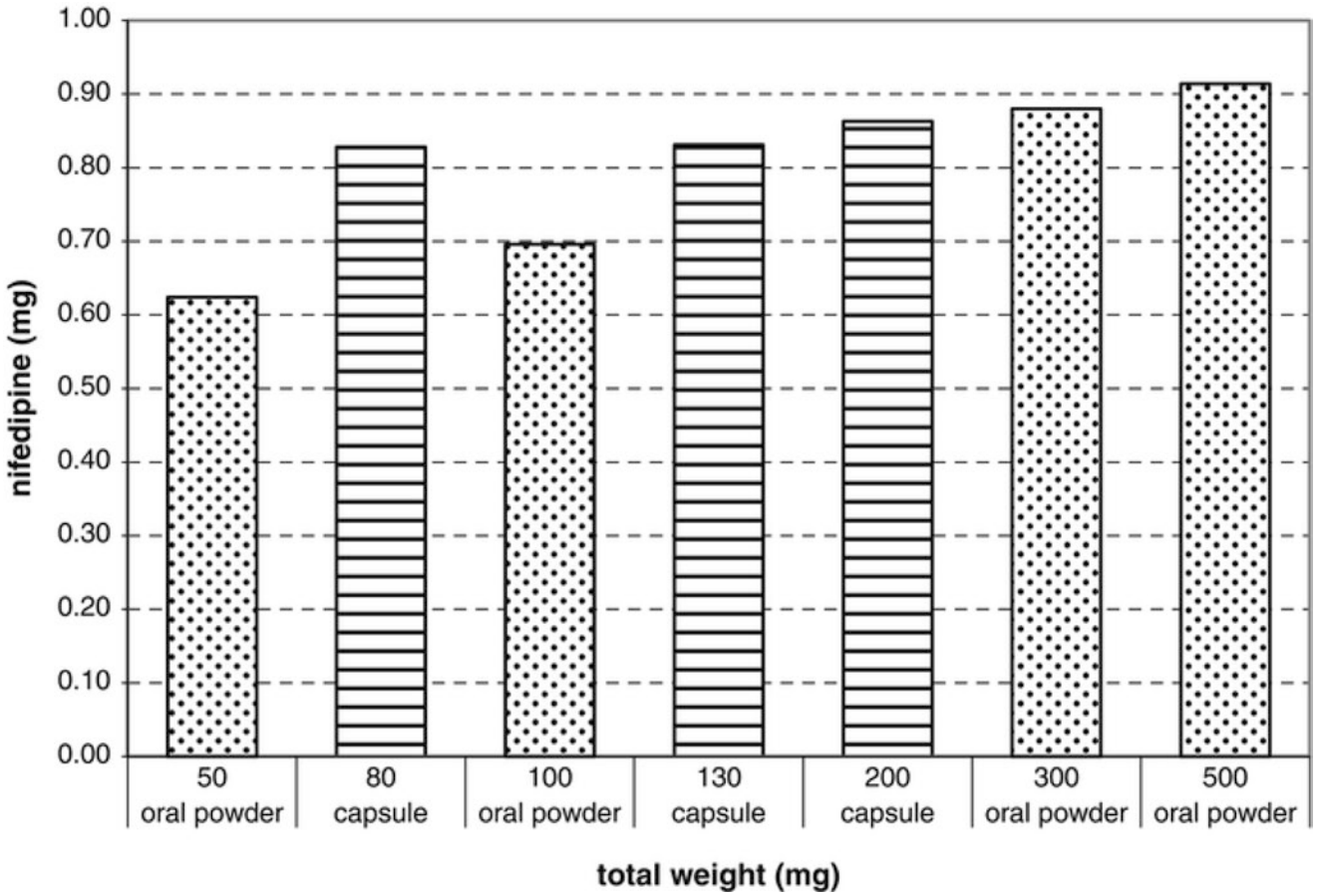

Fig. 12.2 Nifedipine contents in single-dose powders or capsules that were meant to contain nifedipine 1 mg as active substance (from crushed tablets Adalat® 10 mg retard) and microcrystalline cellulose (MCC) as a diluent. The batch size was 50 single-dose powders or capsules and no excess tablets were used. Capsules sizes 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). A 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 [26]

12.10 the formulation of tablets and the possibilities to process coated or modified-release tablets in capsules are discussed.

12.5.1.3 The Mixing Process

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

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. 12.6.2). 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.
2. Suctioning off 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 a minimum, and by avoiding whipping too much air into the mixture. A powder that is too 'fluffy' can be compacted slightly by the addition of a few drops of alco-

Fig. 12.3 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 [27].

hol, water or liquid paraffin to change the surface properties of the powder.

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.

12.5.1.4 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 solvent method can also be used to change the crystalline structure of an active substance to improve its flow properties. An example of this is Phenylbutazone capsules FNA [28].

Phenylbutazone as a raw material is shaped like needles of approximately 80 µm which can hook into one another. This causes poor flowability of the substance, which cannot be improved by the addition of a glidant or an excess of diluent. However, dissolving the phenylbutazone in methylene chloride alters the crystalline structure of the compound, and upon recrystallisation and mixing with microcrystalline cellulose, the flow properties of the resultant mixture have improved. Flowability of the powder mixture is enhanced even further by the addition of heavy magnesium oxide.

The solvent method must be investigated for each new combination of a specific active substance and solvent. Unfortunately, the solvent method often cannot be used, because there is no suitable solvent or because the active substance is not stable in solution. Additionally, a major downside of the solvent method is its reliance on volatile, organic liquids, which can carry environmental and health risks. When using the solvent method, the pharmacist has to ensure that the final preparation contains no remaining traces of the solvent (often by smell) and that any remaining solvent is disposed of properly.

The solvent method basically distributes a small quantity of active substance (generally 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, but not the carrier, has to dissolve well in the solvent.
- 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. 12.6.2.

12.5.2 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 Chap. 7). Water-soluble colouring agents should be dissolved 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, 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.

12.6 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, 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 a few units up to hundreds of thousand units. Further advantages compared 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.

12.6.1 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 to make capsules opaque). Gelatine is often extracted from animals (e.g. pig), which can cause issues for patients with dietary or religious restrictions. As an alternative, vegetarian capsules exist, made of plant-based polymers such as cellulose derivates or pullulan. The pharmacist must consider possible interactions between the active substance or the excipients and the capsule material.

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 [29]. 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 and 2 are used for adults and sizes 3 and 4 are used for children in pharmacy preparations. 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 medicine can be given without the protection of the capsule shell.

12.6.2 Different Methods for Preparing the Powder Mass

In 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 12.3).

The volumes in the table are derived by filling capsules with microcrystalline cellulose and tapping lightly or not tapping at all. However, even under these circumstances the volumes may vary slightly during preparation. Moreover, filling capsules with a different diluent or using a different method may influence the filling volumes.

For small batches of small sized capsules no filling volumes are given, as their preparation cannot be performed reliably. Such batches should not be prepared, because a relatively large loss of powder mass 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, since a small quantity of powder is hard to divide evenly over the capsules.

Table 12.3 Volumes of microcrystalline cellulose needed to fill hard-shell gelatine capsules (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

Another way to determine the volume of capsule shells is by filling them with a liquid of known relative density, such as ethanol 96% V/V. Ethanol of high concentration evaporates quickly, so lower concentrations can also be used. However, if pure water is used, a pharmacist must measure quickly, because the capsule shells will begin to dissolve. From the weight difference between the empty and filled capsules and the density of the liquid used, 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 dripping from a pipette: the volume of liquid dispensed corresponds to the volume of the shell's body.

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.

12.6.2.1 High Dose Method

For capsules with a relatively high dose of active substance (>50 mg per capsule). The active substances and, if necessary, the glidant are mixed following the geometric dilution method (see Sect. 12.5.1.3). Next, the volume of this mixture is determined with a measuring cylinder, and a diluent is added up to the required volume without tapping too firmly, 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 losses are relatively small and a relatively small amount of diluent is needed. The method is based on the bulk density of the powder mixture, i.e. the density of a bulk whose volume has been measured in e.g. a volumetric cylinder.

12.6.2.2 Low Dose Method

The preparation method for capsules with a relatively low dose of active substance (≤50 mg per capsule) has been developed to prevent loss of the active substance. Losses occur mainly 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 or adsorb easily to surfaces. For this method, a layer of diluent is first placed in the mortar. The active substance is then added and covered with 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.

12.6.2.3 Solvent Method

The solvent method is preferably used for mixtures with very unfavourable mixing ratios (<5 mg active substance per capsule). This method (see Sect. 12.5.1.4) needs careful testing and validation. For some active substances, a suitable solvent is known (Table 12.4). If a suitable solvent cannot be found, the powder mixture can only be prepared following the low dose method.

To illustrate the solvent method, the preparation process of Hydrochlorothiazide capsules NRF [32] is quoted:

- Hydrochlorthiazide 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% of acetone has evaporated).

(continued)

Table 12.4 Solvent method developed for some low dose capsules

Active substance and dose:	Solvent and amount:	Deposition and ratio:	Diluent	Reference
Colchicine 0.5 mg	Methylene chloride 2 × 9 mL for 162 mg colchicine	Diluent 100 times the amount of colchicine	Microcrystalline cellulose	[30]
Diazepam	Methylene chloride 2 × 3 mL for 120–300 mg diazepam	Diluent 20 times the amount of diazepam	Microcrystalline cellulose	[31]
Ethinylestradiol	Acetone 2 × 3 mL for 100 mg ethinylestradiol	2 g colloidal anhydrous silica, compressed, for 100 mg ethinylestradiol	Lactose	[31]
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	[32]
Phenylbutazone 100 mg	Methylene chloride 2 x 10 mL for 10 g phenylbutazone	Approx. 8 g diluent	Microcrystalline cellulose with 50 mg heavy magnesium oxide per capsule	[28]

- First portion of diluent is mixed with the hydrochlorthiazide solution, avoiding excess force. The mixture has to be loosened from the side of the mortar and pestle at least twice. The mixture has to be removed from the mortar and kept aside (in process controls: powder mixture should be a fine powder again and not smell 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 pestle at least twice. The mixture has to be removed from the mortar and kept aside (in process controls: powder mixture should be a fine powder again and not smell of acetone).
- Mixing of both powder mixtures, avoiding excess force.
- Et cetera (adding diluent if necessary, mixing, filling capsules).

12.6.2.4 Preparation from Tablets

Tablets may be crushed and the resulting powder used as a source of active ingredient. To prepare the powder mixture, either the high dose or low dose method can be used, depending on the calculated required tablet mass per capsule (see Sects. 12.5.1 and 12.6.1). 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 in a preparation using the pure active substance.

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

12.6.2.5 Preparation from Other Capsules

Capsules available as authorised medicines can be used as the source of the active substance. The capsules have to be opened and emptied to obtain the active substance for further processing 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.

12.6.2.6 Supplementing to Volume

For all methods described above, the final step in preparation of the powder mixture is to add a diluent up to the required volume (see Table 12.3). 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 settling in between larger particles. As a consequence, a relatively large amount of diluent is needed to bring the powder mixture up 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 be emphasised that powder volume measurements in a measuring cylinder should be undertaken with care. Excessive tapping of the cylinder should be avoided, as this will increase the powder bulk density. This may result in a considerable portion of the mixture no longer fitting into the available capsule volume, resulting in a failure of the capsule filling process.

12.6.3 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 is 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. This can be achieved by ensuring good flowability of the powder mixture and a suitable spreading technique. Placing 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 Chap. 28.

12.6.3.1 In Process Controls

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

- Both the weight of the empty measuring cylinder and the weight of the measuring cylinder after adding diluent up to the required filling volume should be noted.
- The absence of lumps or agglomerates in the powder mixture: simple visual control is sufficient to determine whether lumps or agglomerates are present or not.
- A visual test on homogeneity or evenness of the powder mixture: this test is performed after mixing or sieving of powder mixtures.
- The yield (number of capsules).
- When the powder mixture has to be divided over more than one portion, every portion (including the last one) must be weighed separately; each portion should not differ more than 0.5% of the calculated portion weight.

12.6.4 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 [12].

12.6.5 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 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 Chaps. 33 and 38 on the distinction between content variation due to inhomogeneity or to weight variation.

12.6.5.1 Appearance

A simple visual control is sufficient to determine capsule appearance. Filled capsules should be free of dust and closed properly after preparation. Moreover, they should not be dented. A dent may lead to a too low dose delivered to patients.

12.6.5.2 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. 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, usually the ones in the corners 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 capsule weight is calculated from the theoretical quantities of raw materials, except for the diluent, for which the weighed quantity is used. A difference of more than 3% between the theoretical weight and the average weight can imply 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.

12.6.5.3 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 Chap. 33) 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.

The Laboratory of Dutch Pharmacists (LNA) has adapted the Ph. Eur. requirements for the uniformity of mass of capsules to a more practical approach. Ten capsules are weighed and their relative standard deviation is calculated. The batch of capsules can be said to comply with the Ph. Eur. requirements when the following holds true [31]:

- For capsules containing less than 300 mg, the relative standard deviation is below 4%.
- For capsules containing more than 300 mg, the relative standard deviation is below 3%.

12.6.5.4 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. However, 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 Chap. 33.

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 case, it can be concluded that the mixing of the solids was insufficient. Generally, the variation coefficient after mixing should be less than 5% [33].

12.7 Powders

12.7.1 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 the 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 a bitter or salty taste can be presented as effervescent granules [15].

Before ingestion, powders should be dissolved or suspended in a glass of water or milk or mixed with a small amount of suitable soft food 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 most or 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.

12.7.1.1 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 only minor loss of active substance during the process (Fig. 12.2) [26].

The formulation and preparation of the powder mixture for single-dose powders is to a great extent similar to that of powder mixtures as described previously (see Sects. 12.5 and 12.6.2). 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 between the dose units. For single-dose powders this is done by weighing the powders individually on waxed powder papers. Each paper is then 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 the active substance and 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, a soluble sodium salt of the active substance often forms. 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 for single-dose powders are the same as for capsules.

12.7.1.2 Release Control and Quality Requirements

For single-dose powders, the average weight and the uniformity of mass are determined. The specifications for content uniformity and additional Ph. Eur. tests are discussed in Chap. 33.

As with capsules, the Laboratory of Dutch Pharmacists (LNA) has adapted the Ph. Eur. requirements for the uniformity of mass of single-dose powders to a more practical approach. Ten single-dose powders are weighed and their relative standard deviation is calculated. The batch of single-dose powders can be said to comply with the Ph. Eur. requirements when the following holds true [34]:

(continued)

- For single-dose powders containing less than 300 mg, the relative standard deviation is below 4%.
- For single-dose powders containing more than 300 mg, the relative standard deviation is below 3%.

12.7.2 Multidose Powders

Multidose powders for oral use are mainly used when the patient has to take large quantities (grams) of an active substance, 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 with a measuring spoon or cup. Traditionally, spoons and cups are used as cutlery presented standard measures, but nowadays, designers can freely change the sizes, and thus, the volumes. To prevent variations of volume, patients should be given a measuring device with the bulk container. The dose accuracy of multidose powders is nevertheless not as good as single-dose powders, tablets or capsules.

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

Sodium sulphate is an example of multidose powder, which is used as a laxative in cases 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.

12.8 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 many countries they are considered obsolete and not in use anymore due to stability problems and difficulty in industrial manufacturing.

The sizes range from no. 1, the smallest, to no. 6, which is the largest (Table 12.5). In contrast to hard gelatine capsules, they are bigger and flatter in shape (Fig. 12.4). 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 a dry place.

12.8.1 Filling of Cachets

In the pharmacy, cachets are hand-filled with dry powder mixtures. Active substances often require addition of a diluent to achieve the minimum mass of 100–300 mg as in single-dose powders. Lactose is the most common agent used for this purpose. The powder must 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.

12.8.2 Patient Instruction

Despite 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 enables cachets to be administered to children.

Table 12.5 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

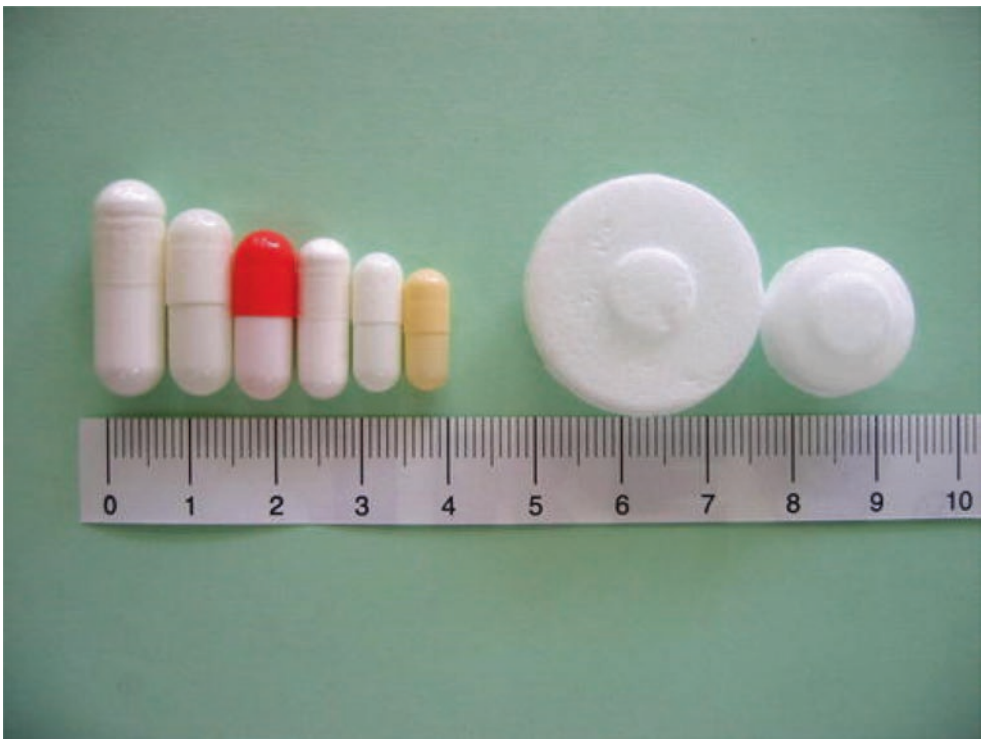

Fig. 12.4 Dimensions of cachets compared to capsule shells, © Department of Pharmaceutical Technology GUMed Gdansk

12.8.3 Stability

Cachets are sensitive to moisture, which causes softening of the shell, improves the potential for chemical degradation and encourages microbial growth. When stability is not confirmed experimentally, the beyond-use date is generally no 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.

12.9 Tablets

12.9.1 Orientation and Definitions

Tablets are the most popular pharmaceutical dosage form and offer 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 usually occurs 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. Most tablets are swallowed whole. Other types of tablets need to be dissolved or disintegrated before ingestion (Table 12.6).

Table 12.6 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 is applied to a tablet (e.g. to protect the tablet 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 has to be dissolved in water prior to administration; may or may not be coated
Dispersible tablet	Tablet has to be dispersed in water prior to administration; may or may not be coated
Orodispersible tablet	Tablet is 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 cavity 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

(continued)

Table 12.6 (continued)

Type of tablet	Characteristics
Chewable tablet	Designed to be chewed
	Is formulated to have a pleasant taste, without leaving an unpleasant aftertaste (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

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 adaptation of these products into other oral dosage forms in pharmacies. The preparation of tablets is complex and specialised, difficult to perform on a small scale and therefore beyond the scope of this book. However, the preparation method is discussed briefly because it determines the possibilities for adaptation.

12.9.2 Formulation

12.9.2.1 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 can be used. Some of these substances are described in the section on capsules. 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 Chap. 7).

Nowadays some tablet excipients present multiple 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 in designing a new formulation.

Diluents with binding properties are used in tablets that are prepared by direct compression. They are designed 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 are used as diluents in tablets. For instance, alpha-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 alpha-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 a 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.

12.9.2.2 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 concentrations 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 used are:

- Sodium starch glycolate (type A) (Primojel®) 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 agents, crospovidone is the better choice.

12.9.2.3 Binders

Binders provide binding in tablets that are prepared by wet granulation. Binders are polymers that transform into a sticky mass in the 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 maximises 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

12.9.2.4 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, but colloidal anhydrous silica (Aerosil® 200 V) can be used if desired. Magnesium stearate also promotes flow, but is mainly used as a lubricant.

12.9.2.5 Lubricants

Lubricants are used to minimise friction between particles and between the particles or the tablet and the mould during tableting. The most 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.

12.9.2.6 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 patients and may be regarded as a defective product by the patient.

12.9.2.7 Disintegration and Dissolution Rate

Most types of tablets should disintegrate in water within a certain time limit (see Chap. 33). Disintegration of tablets is a prerequisite, but not a guarantee for a good bioavailability, for which a good dissolution rate is essential as well.

12.9.3 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 with tablets is that it is hard to produce small batches of good quality tablets. Mixing, granulation (often required) and tableting equipment are suitable for the manufacturing of tablets on a larger scale than required in most pharmacies. 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. Small-scale tableting traditionally has not been common practice in pharmacies, but new equipment allows 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. Usually, direct compressed tablets additionally contain 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 tablet is described in Sect. 12.10.

12.9.3.1 Flow

To evenly fill 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 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 using 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.

12.9.3.2 Mixing

To achieve a good content uniformity, it is essential that a powder does not segregate during mixing or tableting. 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. 12.5.1) 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.12.5.1).

12.9.4 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. Most of these requirements can be found in the Ph. Eur.

12.10 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. Several reasons for the use of modified-release preparations have been presented previously (Sect. 12.9.1).

Modified-release preparations are discussed in this chapter for several reasons. Firstly, 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 aspects 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. [4], but the same care must be taken not to damage the coating when using these in the preparation of other dosage forms.

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

12.10.1 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, 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. by mucoadhesion).

12.10.2 Physicochemical Mechanisms on Active Substance Release

Various physicochemical 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, e.g. through narrow pores or a viscous mass.
- Delayed dissolution by applying a layer that only 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 semipermeable 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 (gastric retention).

12.10.3 Desired Release Rate

The desired release profile can be based on various physicochemical 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 in directing the development of new preparations.

However, the release profile *in vivo* is hard and often even impossible to predict. 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. is generally beneficial. 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 to the influence of pH [4]. The USP also requires testing for the influence of 15% ethanol on the dissolution rate.

12.10.4 Dosage Form

The described physicochemical 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 stomach and intestines, thereby reducing the chance that the dose is (unintentionally) released at once. This could lead to damage of the gastro-intestinal wall. Furthermore, transportation of the particles is independent of the filling of the stomach, provided they are smaller than 2 mm. However, with multi-particulate systems the total surface area is large, resulting in a higher dissolution rate and thus requiring a larger delay. Furthermore, when the particles contain hydrophilic and inert polymers, there is a chance that the system does not disintegrate and thus acts as a monolithic dosage form.

Over the last 30 years many studies have addressed the problem of transit time and active substance absorption site. Factors such as dosage form size, density, shape and the fed versus fast status of the patient have been studied using different techniques (e.g. gamma-scintigraphy). Generally, small-size and low-density dosage forms present a faster transit than large and dense ones [35]. Overall, the time a modified-release dosage form spends 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.

12.10.5 Matrix Systems

In a matrix, the active substance is dispersed in a compressed mixture of excipients (usually polymers) that retains 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 polymers 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

12.10.6 Reservoir Systems

A reservoir system consists of an active substance and a membrane, and 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, 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 with holes of 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®)
- Acid-soluble polymethacrylates and cellulose derivates
- Shellac
- Fats and waxes, such as carnauba wax, glycerol monostearate, hydrogenated ricin oil

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

- Hydrophilic plasticisers: triethyl citrate (TEC), triacetine (GTA), macrogol, propylene glycol, sodium lauryl sulphate, 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, glidants or anti-adhesive agents (titanium oxide, talc, magnesium stearate, etc.) and agents that further influence the release.

12.10.7 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. In Chap. 40 various strategies to modify conventional (fast-release) tablets or capsules are discussed, 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. The pharmacist must answer several questions first: 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 must be administered intact to have its intended effect. Splitting is not an option, unless otherwise specified in the product details by the manufacturer. Sometimes, asking the manufacturer directly may give the desired information, but not all manufacturers are able or willing to help with the specific needs 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 or tablet, or when they require a different dose. To improve this situation, the EMA made the following changes in the guidelines on the content of the Summary of Product Characteristics (SPCs) in 2009 [37]:

- 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 opened, or the content mixed with food or liquid. The manufacturer should also account for patients who receive tube 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 given situation, the pharmacist has to study 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 the section 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 information on the modified-release profile is paramount to making a justified decision.

12.11 Orodispersible Films

In recent years, orodispersible films (ODFs) have emerged as an alternative to the more traditional oral solid dosage forms. ODFs are administered on a patient's tongue, where the film rapidly dissolves upon contact with saliva. The contents of the dissolved film are subsequently swallowed, giving a pharmacokinetic profile similar to that of an oral solution [38].

ODFs offer several advantages over capsules and tablets. As ODFs are thin, flexible sheets, they are less prone to friability issues and therefore easier to store and transport. Additionally, ODFs provide high dosage flexibility, as the sheets can be cut into smaller pieces. Furthermore, as the films completely dissolve before swallowing, ODFs are suitable for patients with swallowing problems or limited fluid intake. However, there are some potential downsides as well. If an API is readily absorbed through the oral mucosa, thereby bypassing the first-pass effect, administration via ODF might lead to higher than expected blood levels. A practical constraint is the limited active substance load per film, which may require multiple ODFs to be administered at once to achieve the required dose [39].

12.11.1 Formulation

12.11.1.1 Polymers

The basic structure of ODFs is provided by a polymer or mixture thereof. The choice of polymer, as well as its concentration, determines both the mechanical properties and the disintegration time of the film. The polymer or polymer mixture should provide elasticity to the film, while also ensuring the film rapidly dissolves after administration. A wide range of both natural and synthetic polymers for the formulation of ODFs have been described in the literature. Natural polymers used include polysaccharides, such as starch, maltodextrin, and alginate, gelatin and collagen. (Semi-)synthetic polymers include cellulose derivatives and vinyl polymers, e.g. polyvinyl alcohol, polyvinyl acetate and polyvidone.

12.11.1.2 Plasticizers

Plasticizers are added to ODFs to improve their mechanical properties, such as tensile strength and flexibility, while at the same time reducing film brittleness. Plasticizers include polyols like sorbitol, mannitol, glycerol and propylene glycol, as well as citric acid esters (e.g. triethyl citrate, tributyl citrate). Additionally, several polyol plasticizers also improve the flavour profile of the ODF.

12.11.1.3 Surfactants

Addition of surfactants, such as sodium lauryl sulphate and polysorbate (Tween®), to ODFs can be required for two reasons. First, surfactants can aid the wetting of the film and therefore its disintegration upon contact with saliva. Second, surfactants lower the surface tension of the ODF mixture. This may be necessary to ensure proper manufacture of the film, especially when using an inkjet-based method. Surfactants usually have an unpleasant taste, which has to be accounted for in the design of an ODF formulation.

12.11.1.4 Expectorants

As the ODF must dissolve in saliva prior to swallowing, the addition of an expectorant to increase saliva production may prove useful. Acidic food additives, such as malic acid, tartaric acid, ascorbic acid and lactic acid can be used as an expectorant.

12.11.1.5 Flavouring Agents

Contrary to other oral solid dosage forms, taste masking may be necessary for ODFs. This is because the API and other excipients will eventually be present in the mouth in a dissolved state and in contact with the palate. Flavoured essences, as well as sweeteners such as sucrose, sorbitol, mannitol and aspartame have been described to flavour ODFs [40]. For more information on flavouring agents, see Chap. 7.

Several medicines have now obtained marketing authorisation as orodispersible films. One example is sildenafil, which has been authorised under the brand names Rabestrom, Silandyl or Xybilun in certain European countries. The film contains maltodextrin as the main polymer. Other excipients include glycerol, polysorbate 20, propylene glycol monocaprylate, polyvinyl acetate, colourants and flavouring agents [41].

12.11.2 Film Production Methods

Different methods have been developed for the production of ODFs. As most of these methods are not easily reproduced at the scale of the individual pharmacy, this paragraph will only provide a basic overview. More details on the different methods can be found in the literature [42, 43].

12.11.2.1 Solvent Casting

In solvent casting, the active pharmaceutical ingredient and all necessary excipients are dissolved or dispersed in a suitable volatile organic solvent. The resulting solution or suspension is then cast in appropriate moulds and dried. The solvent evaporates during the drying process, thus leaving a film, which can be cut into the correct size if necessary. While this method is fairly simple and reproducible, even in a pharmacy, it raises both environmental and health concerns due to its reliance on organic solvents.

12.11.2.2 Hot-Melt Extrusion

In hot-melt extrusion, the active pharmaceutical ingredient and the excipients are first melted. The melted mixture is then extruded to form filaments, which can subsequently be used in other methods, e.g. fused deposition modelling (see Sect. 12.11.2.4). Due to the high processing temperatures, hot-melt extrusion is not suitable for APIs and excipients that are not thermostable.

12.11.2.3 Electrospinning

Electrospinning relies on electric force to create nanofibers from a polymer solution extruded through a metal needle. The active pharmaceutical ingredient can either be incorporated in the polymer solution or applied to the 'blank' nanofibers after spinning. A major advantage of this technique is the high surface area of the resulting nanofibers, which increases the drug dissolution rate. A downside of electrospinning is that it often requires the use of organic solvents to prepare the polymer solution.

12.11.2.4 3D Printing

There are two main methods for the printing of ODFs. The first is inkjet printing, in which an 'ink' containing the active pharmaceutical ingredient is prepared. The solvent depends on the solubility of the API. Additionally, surfactants or viscosity modifying agents may be added to the ink to improve the printing process: the ink should not leak from the printing nozzle, nor should it clog the nozzle. After preparation, the ink is then jetted onto a substrate that is, in effect, an already prepared blank film. The printed films are then dried.

The second printing method is fused deposition modelling (FDM). Polymer filaments containing the API are first prepared, e.g. by hot-melt extrusion. The drug-loaded filaments are then melted and deposited into a film with the required dimensions. Multiple layers can be printed with this method. A disadvantage of FDM is the need for preloaded filaments, which are not readily available. Additionally, like hot-melt extrusion, FDM is unsuitable for film components that are not heat stable.

12.11.3 Release Control and Quality Requirements

The Ph. Eur. classifies orodispersible films as oromucosal preparations; thus, ODFs have to comply with the Ph. Eur. tests on uniformity of dosage units, uniformity of content, uniformity of mass or a combination of these tests. Additionally, the Ph. Eur. requires a dissolution test (see Chap. 33) for ODFs. The Ph. Eur. also states that the films "possess suitable mechanical strength to resist handling without being damaged" [4]. The literature suggests several parameters that can be used to quantify the mechanical strength of ODFs, such as tensile strength, tear resistance, folding endurance, and elongation [40, 44]. Orodispersible films should be packaged in such a way that they are protected from moisture.

12.12 3D Printing of Oral Solids

The emergence of 3D printing as a viable technology for the production of pharmaceutical preparations has opened new avenues for oral solid dosage forms. 3D printing offers a high degree of flexibility in both design and dosage that is generally not found in traditional compounding techniques, especially tableting. Individual dose units, e.g. tablets or films, can be tailored to the specific needs of the individual patient and produced on demand. Moreover, 3D printing requires fewer processing steps than tableting, as milling, granulation and compression are not necessary [45]. Many different 3D printing methods have been developed, which are discussed in more detail in Chap. 28.

3D printing does not rely on moulds or filling apparatus for the production of oral solids and thus it allows for a wide variety in shapes, sizes and structures of the final product. For example, dosage forms can be designed to have a porous structure to enhance disintegration, thus increasing the drug release rate. With 3D printing it is also possible to create oral dosage forms containing multiple active pharmaceutical ingredients in separate layers or segments. These 'polypills' could greatly increase therapy compliance in polypharmacy patients. 3D printing can also be used to produce modified-release tablets: 3D printed controlled release, sustained release and delayed release tablets have all been described in the literature [46].

The composition of 3D printed oral dosage forms is largely dependent on the desired characteristics of the final product and the printing method used. Some traditional excipients in oral solid dosage forms, such as lubricants, are not strictly necessary in 3D printed oral solids, as there are

no moulds or filling apparatus involved in the manufacturing process. In general, a polymer, for example a polyvinyl compound or a cellulose derivative, forms the base of the dosage form. Additional excipients can be added to alter the mechanical properties of the dosage form (e.g. binders and plasticizers), change its release profile or, for orodispersible dosage forms, to improve their flavour [46, 47]. When formulating a 3D printed dosage form, excipients should be selected with care to ensure their compatibility with the chosen printing method.

While 3D printing offers many advantages, there are limitations as well (see also Chap. 28). Heat-based printing methods like fused deposition modelling are not suitable for thermolabile APIs or excipients. Formulations for 3D printing may contain organic solvents or photopolymers, which can carry (unknown) health risks. Several techniques, such as stereolithography, require the use of lasers, and are thus high in energy consumption. Many printing methods generate waste when not all the raw materials are consumed during the printing process. Additionally, depending on the technique used, the printed product may look rough or unfinished, which could negatively affect patient compliance [45].

As the 3D printing of pharmaceutical dosage forms is a relatively new development, there are currently no regulations or guidelines for the design and quality control of 3D printed dosage forms. Different printing methods show a large variation in starting materials, processing of materials and post-processing steps. Furthermore, 3D printing can be used to create a wide array of oral solids, each of which may have distinct quality controls. It is therefore not possible to create one specific set of guidelines that is valid for 3D printing in general [48]. For larger batches of 3D printed oral solid dosage forms, Ph. Eur. tests of comparable dosage forms may be applicable. For small scale preparation of 3D printed oral solids or the production of individual, personalised dose units, non-destructive tests are required, as is the case for other pharmacy preparations [45]. As 3D printing becomes more commonplace in pharmaceutical manufacturing, regulatory bodies will hopefully provide more guidance on 3D printed dosage forms.

In 2015, the FDA approved Spritam® (levetiracetam), the first ever 3D printed pharmaceutical dosage form. Spritam is produced by binder jetting: the powder mixture is deposited in a single layer, after which a binding fluid is applied to create porous tablets that rapidly disintegrate upon ingestion [49].

12.13 Complementary Information

12.13.1 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 cardboard carton, plastic jar or plastic sachet. For packaging of licensed medicines, light-sensitivity of the active substance is taken into account. When such products are repackaged for automated dispensing systems, the function of the original container should be considered and replicated, e.g. 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 must be provided with a label. When the preparation has a primary and a secondary container, both containers must be labelled. The label should meet the requirements described in Chap. 40.

12.13.2 Storage and Stability

The chemical, physical and microbiological stability of solid oral dosage forms is generally good. Chemical reactions, physical degradation processes and microbiological growth hardly occur in the absence of water.

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 absorbing properties (e.g. silicon dioxide) 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.

Capsules should not be stored in a refrigerator, as the humidity inside can vary greatly.

Multidose powders have their containers opened several times during use, 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 should be instructed on the proper use, particularly on having the container 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 smelled in very low quantities. To prevent patients becoming needlessly worried, carbasalate calcium powders should be packaged in lightly ventilating material, such as paper.

12.13.3 Advice 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 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 can it be kept after mixing?

Medicines can interact in many ways with food or liquids (see also Chap. 5). Food or drinks may interfere with the performance of the dosage form, by modifying 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) [50]. Food or drinks or one of their ingredients can influence the stability of the active substance, e.g. calcium ions present in the milk may chelate some active substances [51]. 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, doxycycline) require the label to instruct the patient to take the medicine in an upright position with a full glass of water.

12.13.4 Swallowing Problems

Patients may experience problems with oral solid dosage forms due to swallowing problems. Difficulty in swallowing, also known as dysphagia, is not limited to a specific patient group and may be caused by any number of factors:

- Age: children under 2 years old cannot safely swallow oral solids, while in elderly patients reduced saliva production and weakened muscle function can make swallowing more difficult.
- Morbidity: many diseases and pathologies, such as neurological disorders, a stroke, cancerous growths or oesophageal damage, can cause dysphagia.
- Adverse drug effects: swallowing problems are a side effect observed in a wide variety of medicines, e.g. anticholinergics, antidepressants, muscle relaxants, antibiotics and bisphosphonates.
- Psychological issues, e.g. fear of choking or fear of retching.

Swallowing problems can lead to decreased medication adherence. It is therefore important to accommodate patients when they are experiencing such problems.

Proper instruction on the ingestion of oral solid dosage forms can alleviate swallowing problems. While most patients tend to tilt their head backwards when taking tablets or capsules, this is actually disadvantageous: it makes swallowing harder and increases the risk of choking. Bending the head slightly forwards can ease the swallowing of the medicine. The patient can also try the so-called 'pop-bottle method'. With this method, the patient places the tablet on their tongue and subsequently closes their lips tightly around a plastic bottle filled with water. The patient then takes a sip of water, thus creating a suction effect that helps the tablet go down more easily [52].

The pharmacist can offer alternative dosage forms to bypass the swallowing of a solid object, such as oral liquids, granules, chewable tablets, orodispersible tablets or films. When such alternatives are not available, the pharmacist can prepare capsules. The patient can open these capsules and add their contents to a liquid or a soft food, which they can then ingest. Lactose is the preferred diluent for such capsules, as it readily dissolves in water [31].

When switching to an alternative dosage form or a pharmacy preparation is not an option, licensed products may be adapted to aid their ingestion. This is only possible for immediate-release capsules and tablets, as modified-release preparations will lose their specific pharmacokinetic properties when manipulated (see Sect. 12.10.7). Uncoated capsules can be opened and handled in a similar way to capsules prepared in a pharmacy.

Tablets can be processed in several different ways to make them easier to swallow (see Chap. 40). Tablets with a score line can be broken into separate halves by hand or split using

a mechanical device. Manual breaking requires the patient to have sufficient strength, so splitting may be preferred. If complete disintegration of the tablet is required, it can be ground or crushed using a mortar and pestle, a tablet crusher or a grinder. After use, these devices should be cleaned thoroughly to avoid cross-contamination between medicines. Alternatively, the tablet can be placed in a syringe, which is then filled with lukewarm water and capped. Gently shaking the capped syringe will disintegrate the tablet. This method may be preferable to grinding or crushing, as there is no loss of material and no exposure to the disintegrated tablet. However, this method can be time-consuming, especially with coated tablets [53].

A 2022 study compared the performance of different devices for splitting, crushing or grinding tablets. The study found that tablet splitting is not a reliable and reproducible method, as the resulting tablet fragments show a large variation in size and weight. Screwcap crushers can be difficult to operate due to the manual force required, especially for harder tablets. Manual grinders and electric grinders yield better results, but are generally more expensive. This study shows that the aim of size reduction should be taken into account in choosing the reduction method: while tablet splitting may be fine to ease swallowing, it should not be used for dose adaptation [54].

To aid the swallowing of oral solids, either whole or crushed, a patient can ingest them with readily available (viscous) drinks or soft foods, such as applesauce or yoghourt. However, certain foods can cause interactions with the medication. For example, calcium, found in dairy products, is known to decrease the absorption of certain active substances from the gastrointestinal tract. Alternatively, medication lubricants are available: gels or viscous liquids that are specifically designed to aid the swallowing of tablets and capsules. Different marketed medication lubricants vary greatly in their physicochemical properties, such as viscosity, pH, density and texture. The selection of a suitable medication lubricant therefore depends on the specific needs of the patient, the severity of the dysphagia and any incompatibilities with the dosage form [55]. The pharmacist can advise the patient in choosing the best option.

Questions

1. Which types of excipients can be used in the preparation of powder mixtures for capsules, tablets and cachets, and what is the function of each excipient?
2. Which methods exist for the preparation of homogeneous powder mixtures, and when should each method be used?
3. What are the release control and quality requirements for the different oral solid dosage forms?
4. Which types of modified-release preparations exist, and what are their underlying principles?
5. What solutions can be attempted to accommodate a patient experiencing swallowing problems?

References

1. Pinto JF (2010) Site-specific drug delivery systems within the gastro-intestinal tract: from the mouth to the colon. Int J Pharm 395:44–52
2. Mahato RI, Narang AS (2011) Pharmaceutical dosage forms and drug delivery. CRC Press (ISBN 978-1-4398-7)
3. Sam T, Ernest TB, Walsh J, Williams JL (2012) On behalf of the European paediatric formulation initiative (EuPFI). A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms – an application for paediatric dosage form selection. Int J Pharm 435:115–123
4. Anonymous (2014) European Pharmacopoeia, 10th edn. Council of Europe, Strasbourg
5. McConnell EL, Basit AW (2013) Modified-release oral drug delivery. In: Aulton ME, Taylor KMG (eds) Pharmaceutics. The design and manufacture of medicines, 4th edn. Churchill Livingstone, Edinburgh, pp 550–565
6. Davis A, Begg E, Kennedy M (1993) Application of a simplified method to determine bioavailability of an oral dose of phenytoin. J Pharmacokinet Biopharm 21:195–208
7. Panakanti R, Narang A (2012) Impact of excipient interactions on drug bioavailability from solid dosage forms. Pharm Res 29:2639–2659
8. Porter SC (2013) Coating of tablets and multiparticulates. In: Aulton ME, Taylor KMG (eds) Pharmaceutics. The design and manufacture of medicines, 4th edn. Churchill Livingstone, Edinburgh, pp 566–582
9. Iacucci M, Silva S, Ghosh S (2010) Mesalazine in inflammatory bowel disease: a trendy topic once again? Can J Gastroenterol 24:127–133
10. Rowe R, Sheskey P, Owen S (2006) Handbook of pharmaceutical excipients, 5th edn. Pharmaceutical Press, London
11. STEP Database. European paediatric formulation initiative. http://pharmacyapp-a.ucl.ac.uk:8080/eupfi. Accessed 13 Apr 2015
12. Jones BE (2013) Hard capsules. In: Aulton ME, Taylor KMG (eds) Pharmaceutics. The design and manufacture of medicines. Churchill Livingstone, Edinburgh, pp 583–596
13. Doelker E (2002) Crystalline modifications and polymorphism changes during drug manufacture. Ann Pharm Fr 60:161–176
14. Tan S, Newton J (1990) Powder flowability as an indication of capsule filling performance. Int J Pharm 61:145–155
15. Aulton ME (2013) Powder flow. In: Aulton ME, Taylor KMG (eds) Pharmaceutics. The design and manufacture of medicines, 4th edn. Churchill Livingstone, Edinburgh, pp 187–199
16. Pingali K, Saranteas K, Foroughi R, Muzzio F (2009) Practical methods for improving flow properties. Drug Dev Ind Pharm 35:1460–1469
17. Pawar S, Kumar A (2002) Issues in the formulation of drugs for oral use in children: role of excipients. Pediatr Drugs 4(6):371–379
18. Kotkoskie LA, Butt MT, Selinger E, Freeman C, Weiner ML (1996) Qualitative investigation of uptake of fine particle size microcrystalline cellulose following oral administration in rats. J Anat 189:531–535

19. Twitchell A (2013) Mixing. In: Aulton ME, Taylor KMG (eds) Pharmaceutics. The design and manufacture of medicines, 4th edn. Churchill Livingstone, Edinburgh, pp 170–186
20. Prednisoloncapsules FNA. Formularium der Nederlandse Apothekers. Jaar 2012. Den Haag: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP)
21. Khan K, Rhodes C (1975) Disintegration properties of calcium phosphate dibasic dihydrate tablets. J Pharm Sci 64:166–168
22. Nyqvist H, Lundgren P, Nyström C (1978) Studies on the physical properties of tablets and tablet excipients. I. Adsorption of drugs to cellulose used in tablets. Acta Pharm Suec 15:150–159
23. Eyjolfsson R (1998) Lisinopril-lactose incompatibility. Drug Dev Ind Pharm 24:797–798
24. Cram A, Breitkreutz J, Desset-Brethes S, Nunn T, Tuleu C (2009) On behalf of the European paediatric formulation initiative (EuPFI). Challenges of developing palatable oral paediatric formulations. Int J Pharm 365(1–2):1–3
25. Ten S, New M, Maclaren N (2001) Addison's disease. J Clin Endocrinol Metab 86:2909–2922
26. Helin-Tanninen M, Naaranlahti T, Kontra K, Savolainen K (2007) Nifedipine capsules may provide a viable alternative to oral powders for paediatric patients. J Clin Pharm Ther 32:49–55
27. Helin-Tanninen M, Naaranlahti T, Kontra K, Wallenius K (2001) Enteral suspension of nifedipine for neonates. Part 1. Formulation of nifedipine suspension for hospital use. J Clin Pharm Ther 26:49–57
28. Fenylbutazoncapsules FNA. Formularium der Nederlandse Apothekers. Jaar 2014. Den Haag: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP)
29. Kapselhüllen. DAC K-145. Fassung 2011. In: Deutscher Arzneimittel-Codex/Neues Rezeptur-Formularium (NRF). Govi-Verlag Pharmazeutischer Verlag GmbH Eschborn. Deutscher Apotheker Verlag Stuttgart
30. Colchicinecapsules FNA Formularium der Nederlandse Apothekers. Jaar 2014. Den Haag: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP)
31. LNA Procedure Capsules (2020) Den Haag: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP)
32. Hydrochlorothiazid-Kapseln 0,5 mg/1 mg/2 mg/5 mg NRF 26.3. Fassung 2006. In: Deutscher Arzneimittel-Codex/Neues Rezeptur-Formularium (NRF). Govi-Verlag Pharmazeutischer Verlag GmbH Eschborn. Deutscher Apotheker-Verlag Stuttgart
33. Polderman J, De Blaey CJ (1971) Mengproblemen. Pharm Weekbl 106:773–789
34. LNA Procedure Poeders (2021) Den Haag: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP)
35. Podczeck F, Course N, Newton J, Short M (2007) Gastrointestinal transit of model mini-tablet controlled release oral dosage forms in fasted human volunteers. J Pharm Pharmacol 59:941–945
36. Augsburger L, Hoag S (2008) Pharmaceutical dosage forms: rational design and formulation with excipients. Inform Healthcare, New York
37. EMEA (2009) A guideline on summary of product characteristics. Rev. 2. EMEA/2009. http://ec.europa.eu/health/files/eudralex/vol--2/c/smpc_guideline_rev2_en.pdf. Accessed 13 Apr 2015
38. Krampe R, Visser JC, Frijlink HW, Breitkreutz J, Woerdenbag HJ, Preis M (2016) Oromucosal film preparations: points to consider for patient centricity and manufacturing processes. Expert Opin Drug Deliv 13(4):493–506
39. Visser JC, Woerdenbag HJ, Hanff LM, Frijlink HW (2017) Personalized medicine in Pediatrics: the clinical potential of Orodispersible films. AAPS PharmSciTech 18:267–272
40. Wasilewska K, Winnicka K (2019) How to assess orodispersible film quality? A review of applied methods and their modifications. Acta Pharma 69(2):155–176
41. SmPC Silandyl 25–100, orodispergeerdbare film (2016) 6.1 Lijst van hulpstoffen. Accessed via https://www.geneesmiddeleninformatiebank.nl/
42. Musazzi UM, Khalid GM, Selmin F, Minghetti P, Cilurzo F (2020) Trends in the production methods of orodispersible films. Int J Pharm 576:118963
43. He M, Zhu L, Yang N, Li H, Yang Q (2021) Recent advances of oral film as platform for drug delivery. Int J Pharm 604:120759
44. Khalid GM, Selmin F, Musazzi UM, Gennari CGM, Minghetti P, Cilurzo F (2021) Trends in the characterization methods of Orodispersible films. Curr Drug Deliv 18(7):935–946
45. Okafor-Muo OL, Hassanin H, Kayyali R, ElShaer A (2020) 3D printing of solid Oral dosage forms: numerous challenges with unique opportunities. J Pharm Sci 109(12):3535–3550
46. Karalia D, Siamidi A, Karalis V, Vlachou M (2021) 3D-printed Oral dosage forms: mechanical properties, computational approaches and applications. Pharmaceutics 13(9):1401
47. Konta AA, García-Piña M, Serrano DR (2017) Personalised 3D printed medicines: which techniques and polymers are more successful? Bioengineering 4(4):79
48. Jamróz W, Szafraniec J, Kurek M, Jachowicz R (2018) 3D printing in pharmaceutical and medical applications – recent achievements and challenges. Pharm Res 35(9):176
49. Making Medicine Using 3D Printing. https://spritam.com/making-medicine-using-3d-printing. Accessed 2 July 2022
50. Coupe A, Davis S, Evans D (1991) Correlation of the gastric-emptying of non-disintegrating tablets with gastrointestinal motility. Pharm Res 8:1281–1285
51. D'Arcy P, McElnay J (2011) Drug interactions in the gut involving metal ions. Drug Metabol Drug Interact 5:83–112
52. Schiele JT, Schneider H, Quinzler R, Reich G, Haefeli WE (2014) Two techniques to make swallowing pills easier. Ann Fam Med 12(6):550–552
53. Oralia VTGM (2020). Den Haag: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP)
54. Woerdenbag HJ, Visser JC, Leferink Op Reinink MPAM, van Orsoy RR, Eissens AC, Hagedoorn P, Dijkstra H, Allersma DP, Ng SW, Smeets OSNM, Frijlink HW (2022) Performance of tablet splitters, crushers, and grinders in relation to personalised medication with tablets. Pharmaceutics 14(2):320
55. Malouh MA, Cichero JAY, Manrique YJ, Crino L, Lau ETL, Nissen LM, Steadman KJ (2020) Are medication swallowing lubricants suitable for use in dysphagia? Consistency, viscosity, texture, and application of the International Dysphagia Diet Standardization Initiative (IDDSI) framework. Pharmaceutics 12(10):924