1
Relevance of Solid-state Properties
for Pharmaceutical Products

Rolf Hilfiker, Fritz Blatter, and Markus von Raumer

1.1
Introduction

Many organic and inorganic compounds can exist in different solid forms [1–6]. They can be in the amorphous (Chapter 10), i.e., disordered, or in the crystalline, i.e., ordered, state. According to McCrone’s definition [2], “The polymorphism of any element or compound is its ability to crystallize as more than one distinct crystal species”, we will call different crystal arrangements of the same chemical composition polymorphs. Other authors use the term “polymorph” more broadly, including both the amorphous state and solvates (Chapter 15). Since different inter- and intramolecular interactions such as van der Waals interactions and hydrogen bonds will be present in different crystal structures, different polymorphs will have different free energies and therefore different physical properties such as solubility, chemical stability, melting point, density, etc. (Chapter 2). Also of practical importance are solvates (Chapter 8), sometimes called pseudopolymorphs, where solvent molecules are incorporated in the crystal lattice in a stoichiometric or non-stoichiometric [6, 7] way. Hydrates (Chapter 9), where the solvent is water, are of particular interest. If non-volatile molecules play the same role, the solids are called co-crystals. Solvates and co-crystals can also exist as different polymorphs, of course.

In addition to the crystalline, amorphous and liquid states, condensed matter can exist in various mesophases. These mesophases are characterized by exhibiting partial order between that of a crystalline and an amorphous state [8, 9]. Several drug substances form liquid crystalline phases, which can be either thermotropic, where liquid crystal formation is induced by temperature, or lyotropic, where the transition is solvent induced [10–12].

Polymorphism is very common in connection with drug substances, which are mostly (about 90%) small organic molecules with molecular weights below 600 g mol⁻¹ [13, 14]. Literature values concerning the prevalence of true polymorphs range from 32% [15] to 51% [16, 17] of small organic molecules. According to the same references, 56 and 87%, respectively, have more than one
solid form if solvates are included. When a compound is acidic or basic, it is often possible to create a salt (Chapter 12) with a suitable base or acid, and such a salt can in turn often be crystallized. Such crystalline salts may also exist as various polymorphs or solvates. Obviously, solvates, co-crystals and salts will have different properties from the polymorphs of the active molecule. Since salts generally have higher water solubility and bioavailability than the corresponding uncharged molecule, they are popular choices for drug substances. About half of all active molecules are marketed as salts [14, 18]. Polymorphs, solvates, salts, and co-crystals are schematically depicted in Fig. 1.1. We will use the term “drug substance” for the therapeutic moiety, which may be a solvate, salt or a co-crystal, while the single, uncharged molecule will be called the “active molecule”.

Most drug products (formulated drug substances) are administered as oral dosage forms, and by far the most popular oral dosage forms are tablets and other solid forms such as capsules. Drugs for parenteral application are also often stored as solids (mainly as lyophilized products) and dissolved just prior to use since in general the chemical stability of a molecule in the solid form is much higher than in solution. Drugs administered by inhalation have become increasingly popular, and dry powder inhalers are now commonly in use. Evidently, therefore, both the solid form of the drug substance and the selected excipients have a strong impact on the properties of the formulated drug. Even if the envisaged market form of the drug is a solution, information about the solid-state properties of the drug substance may still be necessary [19]. If different forms have significantly different solubilities, it may be possible to unintentionally create a supersaturated solution with respect to the least soluble form by creating a concentrated solution of a metastable form. Also, the drug substance will in most cases be handled as a solid in some stages of the manufacturing process, and its handling and stability properties may depend critically on the solid form.

Fig. 1.1 Schematic depiction of various types of solid forms.
In fact, the whole existence of a drug is affected by the properties of the solid form, and the final goal of solid form development is to find and select the solid with the optimal characteristics for the intended use.

Initially, when the drug substance is first produced, one has to be certain that the desired solid form is obtained in a consistent, pure and reproducible manner. Subsequently, when it is formulated to obtain the drug product, one has to make sure that no undesired transitions occur (Chapter 13). For this phase, a profound knowledge of potential solvate formation is especially useful. It is highly advisable to avoid using solvents that can form solvates with the drug substance in the formulation process. Otherwise, such solvates might be generated during formulation and subsequently desolvated in a final drying step. In such a situation the final polymorph would probably differ from the initial one—an undesirable effect in most cases. Similarly, the energy-temperature diagram (Chapter 2) of the polymorphs and the kinetics of the change from one polymorph into another should be known so that one can be sure that temperature variations during the formulation process will not lead to an unacceptable degree of change in the solid form.

In the next step, when the drug substance or drug product is stored during its shelf-life, it is imperative that the solid form does not transform over time. Otherwise, important properties of the drug might change drastically. Stability properties have to be evaluated with respect to ambient conditions, storage, and packaging. Thermodynamic stability depends on the environment. A solvate, for example, represents a metastable form under ambient conditions but is likely to be the most stable form in its solvent. Thermodynamically, any metastable form will eventually transform into a more stable form. The kinetics under which this transformation occurs, however, are polymorph specific. Therefore, the existence of a more stable polymorph does not necessarily imply that a metastable polymorph cannot be developed.

In the final step, when the patient takes the drug, the solubility and dissolution rate of the drug substance will be influenced by its solid form. This will affect the bioavailability if solubility is a rate-limiting step, i.e., if the drug belongs to class 2 or 4 of the biopharmaceutics classification system (BCS) [20]. Because a change of solid form may render a drug ineffective or toxic, regulatory authorities demand elucidation and control of solid-state behavior (Chapter 15).

Finally, thorough, experimentally obtained knowledge of the solid-state behavior also has the advantages that a good patent situation for a drug substance can be obtained and that valuable intellectual property can be generated (Chapter 14). Although in hindsight everything may appear to be easy and straightforward, crystalline molecular solid-state forms are non-obvious, novel and require inventiveness. For instance, typically, many attempts to crystallize an amorphous drug substance fail until, suddenly, a stable crystalline form is obtained. Once seed crystals are available, the crystallization becomes the simple last step of a production process.
1.2 Drug Discovery and Development

Typically, it takes eight to twelve years, or sometimes even longer, for a molecule with biological activity to progress from its first synthesis to market introduction as an efficacious, formulated drug [21]. This process is normally divided into two main phases: (a) research or discovery and (b) development [22]. In the research phase, the appropriate target for a particular disease model is identified and validated, and candidate molecules are synthesized or chosen from libraries. They are primarily tested with respect to binding affinity to the target or, if possible, directly for their potential to alter a target's activity. Sometimes other parameters, such as selectivity, are also considered. Promising candidates are usually termed “hits”. As a rule at this stage, limited attention is paid to the possibility to formulate a drug for a certain administration route. Often, from a drug delivery aspect, simple vehicles like DMSO solutions are used. As a result, the activity of especially poorly water-soluble drugs may not be identified at all because they precipitate under the used in vitro conditions [23]. In a medicinal chemistry program the “hits” are then modified to improve physicochemical parameters such as solubility and partition coefficient. This is the first time that solid-state properties come into play. When solubility is evaluated, it is critical to know whether the solubility of an amorphous or crystalline substance was measured. Permeation measurements are performed using, e.g., Caco-2 [24], PAMPA [25] or MDCK [26] assays, and dose–response studies are conducted in in vitro models. Selectivity is assessed in counter screens. At the same time, preliminary safety studies are carried out, and IP opportunities are assessed. Structure–activity relationship (SAR) considerations play a large role at this stage.

Molecules that show promise in all important aspects are called “leads”. Often several series of leads are identified and are then further optimized and scrutinized in more sophisticated models, including early metabolic and in vivo studies. Both pharmacokinetics (PK, the quantitative relationship between the administered dose and the observed concentration of the drug and its metabolites in the body, i.e., plasma and/or tissue) and pharmacodynamics (PD, the quantitative relationship between the drug concentration in plasma and/or tissue and the magnitude of the observed pharmacological effect) are studied in animal models to predict bioavailability and dose in humans. Simultaneously with characterization of the drug substance, a proper dosage form needs to be designed, enabling the drug substance to exert its maximum effect. For freely water-soluble drugs this is less critical than for poorly water-soluble drugs, which without the aid of an adequate dosage form cannot be properly investigated in the research stage. In the discovery phase, high-throughput methods play an increasingly important role in many aspects, such as target identification, synthesis of potential candidate molecules, and screening of candidate molecules. Considering that only about 1 out of 10 000 synthesized molecules will reach the market [21], high-throughput approaches are a necessity. The optimal molecule arising from these assessments is then promoted to the next stage, i.e., development.
The development process of a pharmaceutical product is depicted in Fig. 1.2. It consists of a non-clinical and a clinical phase. While drug companies' approaches to the non-clinical phase can differ somewhat, the clinical phase is treated very similarly due to regulatory requirements. In the non-clinical phase enough data is gathered to compile an Investigational New Drug Application (IND) in the US or a Clinical Trial Application (CTA) in the European Union, which is the prerequisite for the first use of the substance in humans. For obvious reasons, particular emphasis is placed on toxicology studies during this phase, including assessment of toxicity by single-dose and repeated-dose administration and evaluation of carcinogenicity, mutagenicity and reproductive toxicity. An absolute necessity at this stage is that the drug is maximally bioavailable, resulting in sufficient exposure of the animals to the drug to obtain an adequate assessment of its toxicity profile. Whenever possible, the need for animal studies is reduced by using, e.g., human cell in vitro tests. The non-clinical development phase lasts between one and two years, and the attrition rate is ca. 50% (Fig. 1.2). At the end of the non-clinical phase, the decision has to be made whether the neutral molecule, a salt, or a co-crystal will be developed. If a salt form or co-crystal is chosen, it has to be clear which salt (Section 1.4.1) or co-crystal is optimal. In the clinical phases the product is first tested on healthy volunteers and then on small and large patient populations. For certain disease indications, like oncology, Phase I studies are performed directly on patients. Approximate population sizes are given in Fig. 1.2. One has to bear in mind, however, that these numbers depend significantly on the indication the drug is intended to treat. Attrition rates during the clinical phases are between 80 and 90%. During the clinical phases, analytical, process and dosage-form development continues in parallel with long-term toxicology studies. Of course, solid-state properties continue to play a crucial role dur-
ing both chemical development of the drug substance and pharmaceutical development of the dosage form.

1.3 Bioavailability of Solids

An issue that has to be addressed for every drug product, and which is closely related to its solid-state properties, is whether its solubility and dissolution rate are sufficiently high. This leads to the question of what the minimal acceptable solubility and dissolution rates are.

Bioavailability essentially depends on three factors: solubility, permeability and dose [27], and the question of minimal acceptable solubility can only be answered if the other two factors are known. According to the BCS a drug substance is considered highly soluble when the highest strength dosage is soluble in 250 mL of aqueous media over the pH range 1.0–7.5 [28].

A valuable concept for estimating what the minimum solubility of a drug substance for development purposes should be uses the maximum absorbable dose (MAD) [29, 30]. MAD corresponds to the maximum dose that could be absorbed if there were a saturated solution of the drug in the small intestine during the small intestinal transit time (SITT $\approx$ 270 min). The bioavailable dose is smaller than MAD due to metabolism of components in the portal blood in the liver (first pass effect) and in the intestinal mucosal tissue [20]. MAD can be calculated from the solubility, $S$, at pH 6.5 (corresponding to typical conditions in the small intestine), the transintestinal absorption rate ($K_a$), the small intestinal water volume (SIWV $\approx$ 250 mL) and the SITT.

\[
\text{MAD (mg)} = \frac{S \text{ (mg mL}^{-1}) \times K_a \text{ (min}^{-1}) \times \text{SIWV (mL)} \times \text{SITT (min)}}{100}
\]  

(1)

Human $K_a$ can be estimated from measured rat intestinal perfusion experiments [30, 31]. It is related to the permeability ($P$) through SIWV and the effective surface of absorption ($S_{abs}$) [20].

\[
K_a \text{ (min}^{-1}) = \frac{P \text{ (cm min}^{-1}) \times S_{abs} \text{ (cm}^2\text{)} / \text{SIWV (mL)}}{100}
\]  

(2)

In the absence of active diffusion, permeability is related to the diffusion coefficient ($D$), the partition coefficient $K$ ($= c_{in \text{ membrane}} / c_{in \text{ solution}}$) and the membrane thickness ($\delta$).

\[
P \text{ (cm min}^{-1}) = \frac{D \text{ (cm}^2\text{ min}^{-1}) \times K / \delta \text{ (cm)}}{100}
\]  

(3)

In reality, proportionality between the partition coefficient and the permeability is only found for a rather small range of partition coefficients [24, 32]. This is because the model of a single homogeneous membrane is an oversimplification. The intestinal wall is better represented by a bilayer membrane consisting of an
aqueous and an adjoining lipid region. Therefore, for highly lipophilic substances, the water layer becomes the limiting factor and leads to a decrease in permeability as $K$ is increased [33].

Implicit in Eq. (1) is that the solution stays saturated during the SITT and therefore that there is a large excess of solid drug in the small intestine. In deriving this equation as a limiting case, the authors [29] took into account the dissolution kinetics of a polydisperse powder and showed how the percentage of the dose that is absorbed is influenced by solubility, particle size and permeability. They showed that for highly soluble drugs, as defined above, the percentage of dose absorbed is only limited by permeability. For smaller solubilities, the dissolution rate and hence the particle size become important factors as well. The influence of particle size is greatest for low-solubility and low-dose drugs.

MAD readily translates into minimal acceptable solubility [30].

$$\text{Minimal acceptable solubility} = \frac{S \times \text{target dose (mg)}}{\text{MAD}} = \frac{\text{target dose}}{\left(\frac{K_a \times \text{SIWV} \times \text{SITT}}{C_{180}}\right)} \quad (4)$$

Realistic values for $K_a$ lie between 0.001 and 0.05 min$^{-1}$ and vary over a much narrower range than typical solubilities ($0.1 \mu g \text{ mL}^{-1}$ to 100 mg mL$^{-1}$) [30]. Considering these facts and assuming a typical dose of 70 mg, i.e., 1 mg kg$^{-1}$, minimal acceptable solubilities between 20 $\mu g \text{ mL}^{-1}$ and 1 mg mL$^{-1}$ are obtained. When making these estimates, one has to keep in mind that the assumptions of the model break down if there is possible absorption in other parts of the gastrointestinal tract or if the diffusivity of the drug is changed due to the meal effect, etc. [34]. Furthermore, it is important to realize that $S$ represents a “kinetic” solubility. A weakly basic drug might be freely soluble in the stomach while its equilibrium solubility in the small intestine might be very low. Nevertheless, it may remain in the supersaturated state in the small intestine, in which case that “kinetic” solubility would be the relevant one for calculating the MAD.

1.4 Phases of Development and Solid-state Research

Normally, solid-state research and development involves the following stages, which may also overlap:

- deciding whether the uncharged molecule or a salt should be developed;
- identifying the optimal salt;
- identifying and characterizing all relevant solid forms of the chosen drug substance;
- patenting new forms;
- choosing a form for chemical and pharmaceutical development;
- developing a scalable crystallization process to obtain the desired form of the drug substance;
• developing a method to determine the polymorphic purity of the drug substance;
• formulating the drug substance to obtain the drug product;
• developing a method to determine the polymorphic purity of the drug substance in the drug product.

Not all of these stages may be necessary for every drug substance, and the order of the stages may be varied according to the specific properties and behavior of the drug. Particularly for drugs that are poorly water soluble, polymorphism in formulations can play a crucial role since it could significantly influence the dissolution rate and degree of dissolution required to achieve adequate bioavailability.

1.4.1 Salt Selection

Clearly, the first decision is whether it is more desirable to develop the uncharged molecule or, if possible, a salt thereof (Chapter 12). In general, salt formation will be possible if the molecule contains acidic or basic groups, which is the case for most active molecules. Since making a salt will normally involve an additional step in the synthesis and since the molecular weight of a salt will always be higher than that of the neutral molecule, salts will only be chosen if they promise to have clear advantages compared with the free acid/base. As a rule, a salt is chosen if the free acid/base has at least one of the following undesirable properties:

• very low solubility in water;
• apparently not crystallizable;
• low melting point (typical cutoff 80°C [35]);
• high hygroscopicity;
• low chemical stability, etc.;
• IP issues.

Low water solubility is relative and always has to be assessed in the context of dose and permeability (Section 1.3). A very low water solubility may mean a high lipophilicity, enabling efficient passage through membranes, or a very large binding constant with the receptor, allowing a low dose. Also, the amorphous state of a neutral molecule may be the best option to get high oral bioavailability, provided the amorphous form can be kinetically stabilized over a reasonable time scale. Therefore, the decision to develop a salt should be based on a head-to-head broad comparison, taking into consideration both in vivo performance and physicochemical properties. If the decision has been made to develop a salt, it is obviously important to carry out a broad salt screening and salt selection process to identify the optimal salt. Potential counterions are chosen based on pKₐ differences, counterion toxicity (preferably GRAS status [18, 36]), etc. (Chapter 12). Desirable properties of the salts include crystallinity, high water solubility, low hygroscopicity, good chemical stability, and high melting
1.4 Phases of Development and Solid-state Research

<table>
<thead>
<tr>
<th>non-clinical</th>
<th>clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Develop-ment</td>
<td>Phase 0</td>
</tr>
<tr>
<td>salt selection</td>
<td>crystallization development</td>
</tr>
<tr>
<td>polymorphism screening: form for development</td>
<td>extended polymorphism screening</td>
</tr>
<tr>
<td>early formulation</td>
<td>final formulation</td>
</tr>
<tr>
<td>method development: polymorph purity</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1.3 Rough guideline of when the various issues related to solid-state properties generally should be taken care of in the development process. Depending on company policies, obtained results and other circumstances, large shifts are possible. In particular, certain steps may have to be repeated due to unanticipated experimental results.

...point. The relative importance of these properties may vary from project to project. At this stage it also has to be decided whether co-crystals are to be considered. Co-crystals can offer valuable alternatives, especially for very weak bases or acids. Very often, salt screening and salt selection are performed in stages: first a large number of salts is produced on a microscopic scale and characterized with a limited number of methods (e.g., birefringence, Raman, XRD) to identify a few promising candidates, which are then produced on a scale of a few 100 mg and characterized in more detail.

Different companies perform salt screening in different phases of development. Some even move the salt selection process to the research phase [35], but clearly the decision on the salt form should ideally be made no later than the beginning of the long-term toxicology studies, i.e., at the start of Phase I (Fig. 1.3).

1.4.2 Polymorph Screening

The objective of the next important step with respect to solid-state development is identifying all relevant polymorphs and solvates (Chapter 11), characterizing them (Chapters 3 to 7), and choosing the optimal form for further chemical and pharmaceutical development. In the absence of solvents and humidity, the thermodynamically stable polymorph is the only one that is guaranteed not to convert into another polymorphic form. This is why this form is most often chosen for the drug product [31]. The disadvantage of the thermodynamically stable form is, of course, that it is always the least soluble polymorph (Chapter 2) and therefore has the lowest bioavailability. But in most cases this is a small price to pay for the very large advantage of absolute kinetic stability. Differences in the solubility of various polymorphs are typically lower than a factor of 2 (see Ref. [37] for a re-
view of literature data), but sometimes as much as a five-fold difference can be observed [38]. In cases where several enantiotropically related forms exist and where the transition temperature is around room temperature, the choice may be difficult, but it is based on the same criteria as for all solid forms. The kinetics of interconversion from one form into the other and the reproducibility of producing consistently the same ratio of polymorphs are important.

Apart from the thermodynamically stable polymorph of a drug substance, hydrates are also very popular components of the final dosage form. Owing to the ubiquity of water vapor, hydrates are often the thermodynamically stable form at ambient conditions. If a certain hydrate is stable within a rather large range of humidities, it may therefore be much easier to formulate the hydrate in a controlled way and to subsequently store and package it.

In a few cases, a metastable form might be preferable [31], normally for one of the following reasons:

1. too low a solubility (and bioavailability) of the stable form;
2. high dissolution rate needed for quick-relief formulations;
3. manufacturing difficulties;
4. IP issues;
5. chemical instability of the thermodynamically stable form due to topocchemical factors.

(1) If the solubility of the stable polymorph is critically low (Section 1.3) and no salt is feasible, several options exist [39]. Liquid-like formulations (emulsions, microemulsions, liposomal formulations) or soft gelatin capsules filled with solutions of the drug in a non-aqueous solvent may be used. Alternatively, a metastable solid form, a solvate or a co-crystal might be selected for development. If a solid form with a higher solubility than the thermodynamically stable form is desired, it is often better to use the amorphous form rather than a metastable polymorph, provided that the glass transition temperature (T_g) of the amorphous form is sufficiently high (Chapter 10) [40]. Firstly, the amorphous form often has a ten-fold or higher increased solubility relative to the stable form [41], while metastable polymorphs typically have a less than a two-fold higher solubility, as mentioned above. Secondly, it is normally impossible to stabilize a metastable form reliably by excipients, since they can only interact with the surface of the crystals of the metastable drug substance. This will change the surface free energy, but for crystal sizes larger than some tens of nanometers, the contribution of the surface free energy to the total free energy is negligible. The best way to stabilize a metastable form kinetically is to ensure the absence of any seeds of the stable form because such seeds have a very large effect on the kinetics of transformation [42]. The amorphous form, however, can be stabilized, for example, by creating a solid dispersion with a polymer [43, 44]. Such a dispersion will be highly kinetically stable if two conditions are fulfilled: if it remains in the glassy state under the storage conditions, thus blocking all translational diffusion, and if the
drug substance molecules are molecularly dispersed within the matrix. In any case, irrespective of whether a crystalline or disordered metastable form is to be developed, very careful kinetic stability studies will be necessary. For amorphous solids, particular attention has to be paid to the lowering of the glass transition temperature due to humidity.

(2) In some instances, quick onset of action of a drug is of particular importance. In such cases, metastable forms with a higher dissolution rate may accelerate the uptake of the drug and may therefore act faster.

(3) Different polymorphs will also have different mechanical properties, such as hardness, powder flow properties, compressibility and bonding strength. A well-known example is acetaminophen (also known as paracetamol), where the thermodynamically stable form (monoclinic form I) cannot be compressed into stable tablets while the metastable form II (orthorhombic) can as it shows more favorable properties with respect to plastic deformation [45]. In very rare cases, this might lead to a decision to develop a metastable form.

(4) If the thermodynamically stable polymorph is protected by patents, while other forms are free, the respective drug substance can be marketed as a metastable form without obtaining a license from the patent owner (Chapter 14) [5].

(5) Generally, the thermodynamically most stable polymorph is also the most stable chemically (Chapter 2) [31]. This has been attributed to the fact that its density is typically higher, but it could also be explained by its lower free energy. Only in extremely rare cases, where the arrangement of atoms in the stable polymorph favors an intermolecular chemical reaction, could its chemical stability be lower. In such cases, development of a metastable form might be advisable.

A very important question is, of course, when a polymorphism screening should be carried out and when the choice of form to develop should be made. Since different solid forms have different properties and may have different bioavailabilities, it is definitely advisable to select the final form together with the accompanying formulation before carrying out pivotal clinical studies [19, 46]. It is, therefore, critical to have at least identified the thermodynamically stable form along with important hydrates by the end of Phase I at the latest (Fig. 1.3). Accordingly, by that time a polymorphism screening that is primarily designed to identify these forms with a large probability should have been completed. Owing to economic reasons and the expected attrition rate of up to 90% of potential drug candidates after this stage, a full polymorphic screening, which identifies all relevant metastable forms as well, may need to be deferred. However, this should only be the exception because knowledge of metastable phases, thermodynamic stability as a function of temperature and conditions for solvate formation is crucial for the design of crystallization and formulation processes.
While the kinetic stability of dry metastable forms is not much influenced by additives, as mentioned above, additives and impurities can influence their kinetic stability in solutions and suspensions [47] by affecting both nucleation and growth rates. Therefore, a polymorphism screening that is performed with an early batch of drug substance still containing many impurities may provide different results from a screening performed with a later, purer batch. In particularly unfortunate cases, important forms may not be discovered in the initial screening. Therefore, it is highly advisable to repeat at least a limited polymorphism screening with a batch of drug substance produced with the final GMP procedure, which has the impurity profile of the product to be marketed.

Clearly, the unexpected appearance of a new form at a late stage can be disastrous. A very well publicized example is that of ritonavir (Norvir) [38, 48]. When it was launched on the market, only form I was known. One marketed formulation consisted of soft gelatin capsules filled with a nearly saturated solution of form I. About two years after market introduction, some capsules failed the dissolution test due to precipitation of a new, thermodynamically more stable form of ritonavir (form II). The solubility difference between forms I and II is about a factor of 5 [38], which is unusually high. In the end, the original formulation had to be taken off the market, and a new formulation had to be developed with considerable effort and expense [38]. While this is certainly an extreme case, there are many instances of new polymorphs appearing in Phase II and Phase III studies, leading to considerable difficulties [49].

1.4.3 Crystallization Process Development

After selecting the appropriate solid form for the drug substance, a reliable large-scale process to produce that form has to be developed. Parameters such as yield, chemical purity, polymorphic purity, solvent class (preferably Class 3 solvents according to ICH Q3C [50]), residual solvent content and cost need to be optimized. As a rule, it is also necessary to obtain solids with a consistent particle size and morphology (external shape, habit). The crystal habit can have a profound impact on important processing parameters such as filterability, flowability [46] and bulk density. It can sometimes be controlled by choosing the appropriate solvent and method for crystallization [51].

Crystallization, even of a drug substance precursor, is generally by far the most efficient and economic way of obtaining chemically pure compounds. Solvates can also be useful for obtaining crystalline material with increased purity if a drug substance is difficult to crystallize in a solvent-free form. The formation of a solvate with subsequent drying to produce the desired form by desolvation might be feasible as an intended process. However, this usually corresponds to a rearrangement of the lattice, which is generally susceptible to loss of crystallinity.

Precise knowledge of the thermodynamic stability relationships among the various forms as a function of temperature (ET diagrams, Chapter 2) is a prerequisite for designing reliable crystallization processes [52, 53], where parameters
such as solvent composition, concentration, cooling rate, etc. are optimized [54]. In addition, the metastable zone width of all relevant forms has to be known [55–58]. Often a seeding process provides the only reliable way to obtain the desired form [1, 59]. Even if a drug substance does not show polymorphism, seeding is often applied to control the crystallization process. Seeding can also be very useful for controlling the crystal size. Other ways to control crystal size include the use of ultrasound [60] in the crystallization process and, of course, milling as a processing step. In milling processes, care must be taken that no phase changes are induced due to increases in pressure or temperature although an exact understanding of phase changes induced by milling is still incomplete [61]. A common phenomenon is amorphization upon micronization. Samples with several percent of amorphous content are frequently produced. Depending on the intended use, e.g., for inhalation purposes, such amorphous parts have to be quantified, as requested by regulatory authorities. Particular attention also has to be paid to drying processes. It must be assured that, at the drying temperature used, no conversion into an undesired form takes place. Regulatory authorities like to know the rationale for the choice of a particular condition [19]. Again, ET diagrams are very helpful for establishing such criteria.

Crystallization development normally is carried out as a part of synthesis process development (see Figs. 1.2 and 1.3) [62, 63].

1.4.4 Formulation

Different formulations are used at the various stages of drug development. The first formulations of the drug substance are made for pharmacokinetics (PK) and toxicology studies. At this stage, it is important that the formulation is quick and easy to produce, and other aspects such as shelf-life or ease of application play a minor role. Often, a tiered approach is used to test the drugs orally. Drug suspensions are the first choice [35], followed by pH-adjusted aqueous solutions, solutions in non-aqueous solvents and self-emulsifying lipid-based systems [41]. When using suspensions, it is very important to control particle size as this might have an effect on bioavailability. In many cases, parenteral administration of test compounds is a better method because the resulting absolute bioavailability information allows a better assessment of the efficacy of the lead compounds. The oral route may be hampered by first-pass effects and/or low oral absorption. Evidently, therefore, during the early research phase, the drug can be properly profiled only by using adequate formulations with both the oral and the parenteral route. In general, the preclinical screening of poorly water-soluble compounds is more challenging than for freely water-soluble compounds. The formulation that is used for these preclinical studies has implications for the possible final formulations [41]. For Phase II or, at the very latest, for Phase III, the final formulation must be developed. Final oral formulation types include tablets as the most popular form, capsules, syrups and solutions.
Other possible formulations include solids for inhalation, creams, gels, patches, nasal sprays, suppositories, solids for reconstitution prior to injection, etc. [64]. Choosing the final formulation can be difficult, and the solid-state properties of both excipients and the drug substance again play a key role. As mentioned in the Introduction, phase changes in the formulation process induced by solvate/hydrate formation or temperature must be avoided. This can be particularly difficult if wet granulation is used with a substance that can form hydrates [65]. In such a case, one may have to assure by post-process controls that the desired form is present in the formulation. Solvation/desolvation processes during formulation may also change particle size [65, 66]. The influence of the process parameters temperature and pressure on solid-state properties has to be monitored carefully. Of particular concern is unintended formation of amorphous parts due to their generally much lower chemical stability and higher solubility [19]. Of course, chemical compatibility between excipients and the drug substances must be checked as well. Particularly challenging are formulations intended for inhalation [60]. There, particle size is important not only for dissolution kinetics but also for absorption. Only particles within a narrow size range of about 1 to 5 μm can be deposited in the lungs.

1.4.5
Method Development

In cases where differences in polymorphic form affect drug performance, bioavailability or stability, the appropriate solid state form must be specified (Chapter 15, ICH Q6A) [67]. It may even be necessary to specify acceptable levels of undesired forms mixed with the desired form. In such cases the crucial question is what the acceptable level is. It depends both on solubility differences and chemical stability differences between the possible forms. From the production process it is generally known which forms can be present as “phase impurities” in the selected form. Other forms can often be regarded as uncritical or very unlikely to be formed by the chosen crystallization process, and method development can be focused on critical forms. For instance, the amorphous form is normally the solid form that shows the most pronounced differences to the most stable crystalline form. Therefore, requests to assess the content of amorphous form have often been made by regulatory authorities.

Suitable methods to determine solid-state compositions include differential scanning calorimetry, microcalorimetry, solution calorimetry, thermogravimetry, moisture sorption, IR, Raman, powder X-ray diffraction, solid-state NMR, solubility and dissolution rate measurements, and light and electron microscopy (Chapters 3 to 7) [42, 68]. Which method is optimal depends on both the drug substance and the excipients. If the polymorph composition is used as a release parameter, the appropriate method has to be validated [42] with respect to linearity, accuracy, precision, intermediate precision, limit of quantitation and limit of detection (ICH Q2A, Q2B) [69, 70].
1.5 Solid-state and Life Cycle Management

Exploiting superior properties of new solid forms of a certain active molecule may also be used for life cycle management. An example is the sodium salt of diclofenac. It was marketed as Voltaren® by Ciba-Geigy. Before the patent expired, other salts with properties enabling substantially better penetration of the skin were discovered and patented [71]. These salts, in appropriate formulations, are particularly suitable for topical applications. So discovering and patenting new salts and formulations enabled retention of an exclusive position in this market segment.

1.6 Conclusions

The solid-state form can drastically alter the properties of a pharmaceutical product. It may change its effectiveness, stability and suitability for a particular formulation. Therefore, developing the “right” solid form is critical for the success of a product. Finding this form and assuring that it is successfully delivered is part of an integrated approach to solid-state issues, all the way from salt screening to quality control. The ultimate goal of solid form screening (free molecule, salt or co-crystal) is to identify and to select the optimal solids for the intended use. This is independent of whether amorphous or crystalline solids are to be used. Necessary controls for different solid forms need to be established on a case-by-case basis.

The solid-state behavior of a drug plays an important role during the whole life span of a drug, from discovery through to the life cycle management stage. While understanding the solid-state behavior is particularly an issue in development, there are increasing efforts to carry out preliminary solid-state investigations already in the research phase [35]. Timing, available amount of substance and attrition rate suggest that the effort of solid-state development should be staged. It makes sense to adapt the solid-state development effort to the preclinical and clinical development phases.

Furthermore, once the product is on the market, concerns about solid-state issues do not end. Discovering new forms, possibly in combination with new formulations, may provide opportunities for the life cycle management of the product. Also, if changes in the manufacturing process are made, consistent quality in terms of solid-state properties and adequate quality control method development must be ensured [19].
**Acknowledgments**

We acknowledge the valuable comments and suggestions of Peter van Hooge-vest.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS</td>
<td>Biopharmaceutics classification system</td>
</tr>
<tr>
<td>c</td>
<td>Concentration</td>
</tr>
<tr>
<td>Caco-2</td>
<td>Human colon adenocarcinoma cell line</td>
</tr>
<tr>
<td>CTA</td>
<td>Clinical trial application</td>
</tr>
<tr>
<td>δ</td>
<td>Membrane thickness</td>
</tr>
<tr>
<td>D</td>
<td>Diffusion coefficient</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>ET diagram</td>
<td>Energy–temperature diagram</td>
</tr>
<tr>
<td>GMP</td>
<td>Good manufacturing practice</td>
</tr>
<tr>
<td>GRAS</td>
<td>Generally regarded as safe</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational new drug application</td>
</tr>
<tr>
<td>IP</td>
<td>Intellectual property</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>K</td>
<td>Partition coefficient</td>
</tr>
<tr>
<td>K_a</td>
<td>Transintestinal absorption rate</td>
</tr>
<tr>
<td>MAD</td>
<td>Maximum absorbable dose</td>
</tr>
<tr>
<td>MDCK</td>
<td>Madin Darby Canine Kidney</td>
</tr>
<tr>
<td>NDA</td>
<td>New drug application</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>P</td>
<td>Permeability</td>
</tr>
<tr>
<td>PAMPA</td>
<td>Parallel artificial membrane permeability assay</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>S</td>
<td>Solubility</td>
</tr>
<tr>
<td>S_{abs}</td>
<td>Effective surface of absorption</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure–activity relationship</td>
</tr>
<tr>
<td>SITT</td>
<td>Small intestinal transit time</td>
</tr>
<tr>
<td>SIWV</td>
<td>Small intestinal water volume</td>
</tr>
<tr>
<td>XRD</td>
<td>X-ray diffraction</td>
</tr>
</tbody>
</table>
References


References

