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

Polymorphism: in the Pharmaceutical Industry. Edited by Rolf Hilfiker

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.

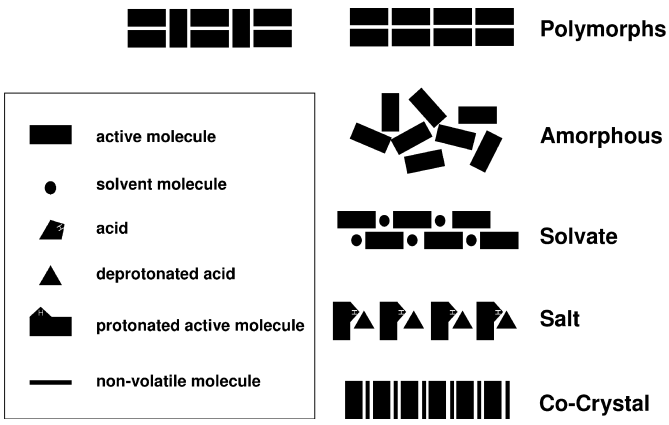

Fig. 1.1 Schematic depiction of various types of solid forms.

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.

	non-clinical		clinical			
		IND				NDA Approval
	Early Development	Phase 0	Phase I	Phase II	Phase III	Submission and Approval
description	pre-formulation	short term toxicology	first in humans, safety, PK long term toxicology	efficacy, dose finding synthesis redesign, process development	efficacy and safety comparison against standard, data for registration	-
# patients	-	-	10-100 healthy volunteers	100-500 patients	300-3000+ patients	-
duration	0.5 to 1 year	0.5 to 1 year	1 to 2 years	1 to 2 years	2 to 4 years	1 year
# compounds at beginning of phase (per approved compound)	9 to 20	7 to 15	5 to 12	3 to 7	1.5 to 3	1.1

Fig. 1.2 Drug development process with a description of respective phases, approximate number of test persons, timelines and attrition rates. These numbers are a rough guideline only and can differ significantly according to the specific indication, the characteristics of the drug substance, etc.

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-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.