Polymorphism

in the Pharmaceutical Industry

Edited by
Rolf Hilfiker

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Rolf Hilfiker

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Editor

Dr. Rolf Hilfiker
Solvias AG
Klybeckstrasse 191
4002 Basel
Switzerland

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Contents

Preface

Polymorphism, a term derived from the Greek words for "much/many" (poly, πολύ) and "form" (morphē, μορφή), is used in disciplines as diverse as linguistics, computer science, biology, genetics, and crystallography. In the life sciences industry, two completely different types of polymorphism play a major role: polymorphisms in DNA sequence and polymorphs of crystalline substances. In the former, great strides are being made using polymorphisms in their DNA sequence to predict an individual's susceptibility to disease and response to drugs, making it possible to design and select appropriate drugs. In the latter, the polymorphic form of a drug substance or excipient can have a profound impact on a spectrum of aspects, such as biological action, production, formulation and intellectual property protection. This book deals exclusively with the polymorphs of solids, covering not only polymorphs in the narrow sense, i.e., different crystalline forms of the same molecular entity, but also other solid-state forms relevant to industry, such as solvates, salts, and the amorphous form.

Interest in the solid-state properties of drugs has grown tremendously in recent decades as can be seen, for example, by the numerous conferences and workshops organized by various scientific and commercial institutions. This interest is well deserved. Anyone who has worked in the field for some time can point to examples where insufficient understanding of solid-state properties has led to serious setbacks. Problems encountered range from the sudden unexpected inability to produce reliably a form that has been used for pivotal clinical studies and is the basis for registration documents to variations in the drug product properties due to seemingly random changes of the solid form during processing or storage. Conversely, a thorough understanding of solid-state properties can create opportunities, which are increasingly being exploited for the benefit of both the company and the patient. Not only can patent protection be broadened or prolonged, and production made more efficient and cheaper, but the properties of the drug can also be improved to the advantage of the patient.

Increasing recognition of the importance of polymorphism to the life sciences industry has generated a great deal of interest and the field has been evolving rapidly. Given the pace of recent developments, an update is both useful and timely. This book discusses the whole breadth of the subject, covering all relevant aspects of solid-state issues for the pharmaceutical industry. It should act as a manual and a guideline for scientists dealing with solid-state issues, and

serve both as an introduction to people new to the field and as a source for experts to round off their knowledge. It also provides valuable information for scientists working in other areas where solid-state issues are important, such as animal health, agrochemical, and specialty chemical industries.

Chapters are organized according to the following aspects of polymorphism: relevance, tools, properties, practical approaches, and legal issues. Chapter 1 discusses the relevance of solid-state forms in the pharmaceutical industry and makes recommendations on how best to approach solid-state issues. Chapter 2, on the thermodynamics of polymorphs, provides the theoretical tools needed to understand solid-state behavior. Chapters 3 to 7 give detailed descriptions, instructions, and hints on how to characterize solids, since solid-state behavior can only be understood after thorough characterization. Such an understanding is crucial to making the right decisions at key stages of drug development and production. Chapters 8 to 10 highlight the properties and importance of solid-state forms that are not included in the narrow definition of polymorphism, namely, solvates, hydrates and the amorphous form. Essential practical aspects for development scientists are described in Chapters 11 to 13, which deal with identifying relevant polymorphs, finding optimal salts and controlling solid-state behavior during processing. The last two chapters discuss legislative aspects of solid-state properties. Often, solid-state forms can be protected by patents, which may create significant financial benefits. Chapter 14 outlines the principles of intellectual property protection and provides relevant examples. Finally, since the solid form can have an impact on the safety and efficacy of drugs, Chapter 15 explains regulatory issues in connection with solid-state behavior. Rules, based on scientific considerations, are elucidated.

The broad range of topics discussed in this text, from thermodynamics to legal issues, emphasizes the complexity of the subject. It also demonstrates that the challenges and opportunities connected with solid-state properties can only be addressed successfully through an integral approach that considers all these aspects.

The strength of this volume lies in the quality of its contributions. My sincere thanks go to every author for the excellent standard of their submissions and their engaged cooperation. The balance of contributions from industry, academia and government highlights the far-reaching importance of the subject. From a personal perspective, I very much appreciated the fact that after developing the concept for this book and inviting authors to submit chapters on specific themes, colleagues willingly agreed to do so despite their very busy schedules. Finally, I thank Wiley-VCH for recognizing the timeliness of such a volume and Dr. Elke Maase and Dr. Bettina Bems for an enjoyable collaboration in the preparation of this book.

Basel, January 2006 *Rolf Hilfiker*

List of Contributors

Joel Bernstein
Department of Chemistry
Ben-Gurion University of the Negev
Beer Sheva 84105
Israel

Fritz Blatter
Solvias AG
Klybeckstrasse 191
4002 Basel
Switzerland

John M. Chalmers
VS Consulting
14 Croft Hills
Tame Bridge, Stokesley TS9 5NW
United Kingdom

Gérard Coquerel
Sciences et Méthodes Séparatives,
EA 3233
Université de Rouen
IRCOF, Rue Tesnière
76821 Mont Saint Aignan Cedex
France

Duncan Q. M. Craig
School of Chemical Sciences and
Pharmacy
University of East Anglia
Norwich, Norfolk NR4 7TJ
United Kingdom

Susan M. De Paul
Solvias AG
Klybeckstrasse 191
4002 Basel
Switzerland

Geoffrey Dent
GD Analytical Consulting
53 Nudger Green
Dobcross, Oldham OL3 5AW
United Kingdom

Ramprakash Govindarajan
Department of Pharmaceutics
University of Minnesota
308 Harvard Street SE
Minneapolis, MN 55455
USA

David J. W. Grant
Department of Pharmaceutics
College of Pharmacy
University of Minnesota
308 Harvard Street SE
Minneapolis, MN 55455
USA

Ulrich J. Griesser
Institute of Pharmacy
University of Innsbruck
Innrain 52
6020 Innsbruck
Austria

Rolf Hilfiker
Solvias AG
Klybeckstrasse 191
4002 Basel
Switzerland

Sachin Lohani
Department of Pharmaceutics
College of Pharmacy
University of Minnesota
308 Harvard Street SE
Minneapolis, MN 55455-0343
USA

Joseph W. Lubach
Department of Pharmaceutical Chemistry
University of Kansas
2095 Constant Ave.
Lawrence, KS 66047
USA

Stephen P. F. Miller
Office of New Drug Quality Assessment
Food and Drug Administration – Center for Drug Evaluation and Research
Bld. 22, Mail Stop 2411
10903 New Hampshire Ave.
Silver Spring, MD 20993
USA

Eric J. Munson
Department of Pharmaceutical Chemistry
University of Kansas
2095 Constant Ave.
Lawrence, KS 66047
USA

Ann W. Newman
SSCI, Inc.
3065 Kent Avenue
West Lafayette, IN 47906
USA

Gary Nichols
Pharmaceutical Sciences
Pfizer Global R&D
Ramsgate Road
Sandwich, Kent CT1 3NN
United Kingdom

Philippe Ochsenbein
Sanofi-Aventis
371, rue du Professeur J. Blayac
34184 Montpellier Cedex 04
France

Samuel Petit
Sciences et Méthodes Séparatives, EA 3233
Université de Rouen
IRCOF, Rue Tesnière
76821 Mont Saint Aignan Cedex
France

Markus von Raumer
Solvias AG
Klybeckstrasse 191
4002 Basel
Switzerland

Andre S. Raw
Office of Generics Drugs
Food and Drug Administration – Center for Drug Evaluation and Research
Metro Park North II, Room E204
7500 Standish Place
Rockville, MD 20855
USA

Susan M. Reutzel-Edens
Eli Lilly & Company
Pharmaceutical Research & Development
Lilly Corporate Center
Indianapolis, IN 46285
USA

Kurt J. Schenk
École Polytechnique Fédérale
de Lausanne
LCr1–IPMC–FSB
BSP-521 Dorigny
1015 Lausanne
Switzerland

Peter Heinrich Stahl
Private Consultant
Lerchenstrasse 28
79104 Freiburg
Germany
Former business address:
CIBA-GEIGY/Novartis Pharma
Basel, Switzerland

Raj Suryanarayanan
Department of Pharmaceutics
University of Minnesota
308 Harvard Street SE
Minneapolis, MN 55455
USA

Bertrand Sutter
Novartis Pharma AG
PHAD Analytical R&D
WSJ-360.508
Lichtstrasse 35
4056 Basel
Switzerland

Martin Szelagiewicz
Solvias AG
Klybeckstrasse 191
4002 Basel
Switzerland

Lawrence X. Yu
Office of Generics Drugs
Food and Drug Administration –
Center for Drug Evaluation
and Research
Metro Park North II, Room 285
7500 Standish Place
Rockville, MD 20855
USA

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.

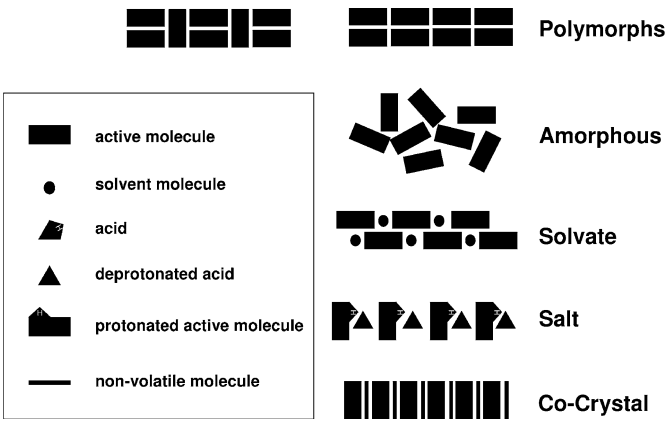

Fig. 1.1 Schematic depiction of various types of solid forms.

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.

	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-

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 (Ka), the small intestinal water volume (SIWV $\approx$ 250 mL) and the SITT.

$$\text{MAD (mg)} = S\ (\text{mg mL}^{-1}) \times K\text{a}\ (\text{min}^{-1}) \times \text{SIWV (mL)} \times \text{SITT (min)} \tag{1}$$

Human Ka 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].

$$K\text{a}\ (\text{min}^{-1}) = P\ (\text{cm min}^{-1}) \times S_{\text{abs}}\ (\text{cm}^2)/\text{SIWV (mL)} \tag{2}$$

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

$$P\ (\text{cm min}^{-1}) = D\ (\text{cm}^2\ \text{min}^{-1}) \times K/\delta\ (\text{cm}) \tag{3}$$

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].

$$\begin{aligned}\text{Minimal acceptable solubility} &= S \times \{\text{target dose (mg)}/\text{MAD}\} \\ &= \text{target dose}/\{Ka \times \text{SIWV} \times \text{SITT}\}\end{aligned} \tag{4}$$

Realistic values for Ka lie between 0.001 and 0.05 min^{-1} and vary over a much narrower range than typical solubilities (0.1 μg 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 μg 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 pK_a 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