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Solid State and Polymorphism of the Drug Substance in the Context of Quality by Design and ICH Guidelines Q8–Q12

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1.1 Introduction

The way in which the pharmaceutical industry is approaching technical development has evolved very much in the recent years. Fresh concepts coming from other industries have been introduced with the desire to push for a more science and risk-based development approach throughout the product life cycle. Quality by design (QbD) in the pharmaceutical industry is an outcome of the efforts to harmonize development quality concepts and understandings by regulatory agencies and resulted in the International Conference of Harmonization (ICH) guidelines Q8 [1], Q9 [2], Q10 [3], Q11 [4], and Q12 [5]. Although first devised for pharmaceutical development (Q8), the QbD concepts and related tools were rapidly recognized as being very helpful for chemical development. A result of this process was the Q11 guideline that provides guidance for drug substance as defined in the scope of the ICH guideline Q6A [6] (this guideline contains the well-known decision trees for polymorphism).

The scope of this chapter is to give a short introduction to the solid-state development process in the pharmaceutical industry and to QbD. Questions on how QbD principles can be applied to solid-state development will be discussed, highlighting how the solid state is an important parameter to be considered in the pharmaceutical development process. For that purpose, some general insights into the relevance of the drug substance (DS) solid state throughout various fields of pharmaceutical development will be given.

1.2 A Short Introduction to Polymorphism and Solid-State Development

Only a brief overview of solid-state development and polymorphism shall be given here. Subsequent chapters in this book will discuss the various aspects in more detail.

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Many organic and inorganic compounds can exist in different solid forms [7–12]. They can be in the amorphous (Chapter 7), i.e. disordered [13], or in the crystalline, i.e. ordered, state. In accordance with McCrone's definition [8], "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 (Figure 1.1). Especially in the pharmaceutical context, the term "polymorph or polymorphism" is used more broadly by many authors and regulatory agencies. The amorphous state, as well as hydrates or solvates (both of which do not have the same chemical composition), are tacitly included by the term. Because 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 4). Hence, the crystal form of a solid material in development is often considered a critical quality attribute (CQA, see next section). Of practical importance are also solvates [14], sometimes called pseudopolymorphs, where solvent molecules are incorporated in the crystal lattice in a stoichiometric or nonstoichiometric [12, 15] way. Hydrates (Chapter 6), where the solvent is water, are of particular interest because of the omnipresence of water. In addition to the crystalline,

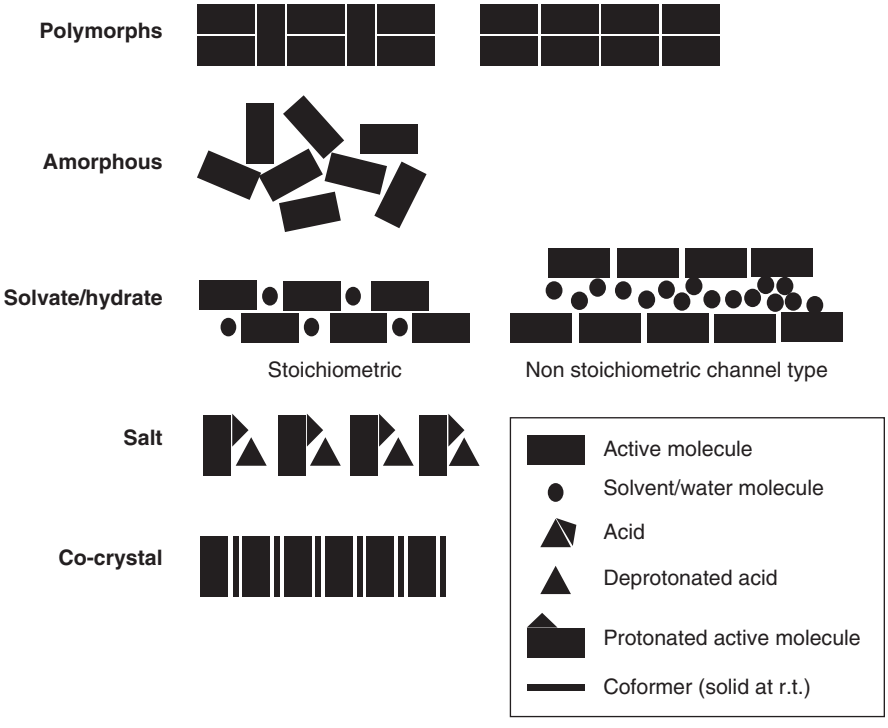

Figure 1.1 Schematic depiction of various types of solid forms.

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 [16, 17]. Several drug substances are known to form liquid crystalline phases, which can be either thermotropic, where the liquid crystal formation is induced by temperature, or lyotropic, where the transition is solvent induced [18–20].

Polymorphism is a very common phenomenon [11, 21–25] in connection with small-molecule drug substances. The literature values concerning the prevalence of true polymorphs range from 32% [26] to 51% [27–29] of small organic molecules (molecular weight $<600\,g\,mol^{-1}$). According to the same references, 56% and 87%, respectively, have more than one solid form if solvates are included in the count.

In the context of pharmaceutical solid-state development, polymorph considerations are made subsequent to general considerations like salt [30] (Chapter 2) or co-crystal [31] (Chapter 3) formation. When a compound is acidic or basic, it is often possible to create a salt with a suitable base or acid, and such a salt can, in turn, often be crystallized. Crystalline salts may then again be able to exist as various polymorphs or solvates. From the scientific perspective, solvates can be considered as co-crystals of the active molecule and solvent. In the pharmaceutical industry, the term co-crystal is used in a slightly different way, however. A pharmaceutical co-crystal is a solid, where the constituting molecules are in the solid phase as single components at room temperature. Obviously, solvates, co-crystals and salts will have different properties than the polymorphs of the active molecule. About half of all active molecules are marketed as salts [25, 30, 32]. Recently, also the first co-crystal composed of two active molecules reached the market (Entresto from Novartis [33]). Polymorphs, solvates, salts, and co-crystals are schematically depicted in Figure 1.1. We will use the term "drug substance" for the therapeutic moiety, which may be a solvate, salt, or a co-crystal, whereas the single, uncharged molecule will be called the "active molecule."

1.3 A Short Introduction to Quality by Design (QbD)

Only a brief overview of QbD shall be given here. Pharmaceutical applications thereof were described in a far more detailed and applied way elsewhere [34, 35].

QbD is not a new concept. Indeed, it was introduced in the manufacturing industry in the 1950s. The automobile and electronic industries were early users of QbD as shown in a comprehensive textbook on the subject by Juran [36]. This industry rapidly realized that the process of QbD provides a systematic and structured framework for documenting and presenting a development rationale while acquiring knowledge about the product and the process. As a result, it could be ensured that products were manufactured, which consistently fit the desired quality (and safety, and efficacy, if applied to pharma). In addition to being

safe and cost effective, any process must be robust in order to be successfully implemented and transferred. In contrast to the traditional approach for process development, QbD leads to robust processes. Because of its business benefits, many pharmaceutical companies have already implemented or are now implementing QbD methodologies. QbD has recently evolved from a purely regulatory initiative to an industry initiative with strong encouragement from the regulatory agencies who are concerned about product quality issues and possible drug shortages [37].

QbD introduces a formalism for development based on first understanding the product, then understanding the processes leading to the product, and finally of controlling the process over the product life cycle. It starts with defining the development goal in a quality target product profile (QTPP). As in any other discipline, knowing what is to be developed makes the development easier or possible at all. This means that, for instance, for the development of a drug product (DP), the route of application (oral), the dosage form (tablet, immediate release), and the strength (efficacy and safety) should be defined and justified at the beginning of the process. Although definition is somehow easy, justification is more complicated as it requires quite a lot of prior knowledge. Here, knowledge management and the transfer of knowledge throughout the pharmaceutical development help to justify decisions that are taken. For example, preclinical pharmacokinetic results, possibly coupled with *in silico* considerations, can help to make informed decisions on the DS. A rationale for the solid form and, for example, target particle size can be gained here. Refined with the human PK data of clinical phases I and II, a rationale for phase III and market product can be developed. A QTPP can contain input from all stakeholders, i.e. the patient, the physician, and the pharmacist. Next comes the CQA, which should encompass various aspects related to quality, efficacy, and safety. Any physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (or efficacy, or safety) is a CQA. As an example, the assay of a DP should be, for example, between 90% and 110% as a target. Assay variability would potentially affect safety and efficacy, and this quality attribute is hence set as critical. Process variables may affect the assay of the DP; hence, assay is to be evaluated throughout formulation development. Other CQAs can be the polymorphic form and the particle size distribution of the DS to name only few of them. Indeed, all DS attributes are candidates of being defined as CQA in a first round of contemplation. Generally, every DP CQA, except maybe appearance, is affected by DS attributes. Also the purity, the solid-state form, the morphology, and the particle size distribution impact more than one DP CQA. In a next step, a risk assessment for critical material attributes (CMA) and critical process parameters (CPP) is conducted. Risk assessment and criticality are words that encompass quite some room for interpretation and they deserve some short discussion. A material attribute or a process parameter is deemed critical if its variability has an impact on a CQA and therefore has to be controlled within narrow specifications to ensure that the DS, or DP, will meet specifications. Risk assessment is done regularly in other industries and various tools and ways exist in doing so. One of the possibilities is a split in risk identification, risk analysis,

and risk evaluation. Risk identification consists of identifying potential factors causing an overall effect. A popular way of doing so is a cause-and-effect analysis that can be graphically represented by an Ishikawa, or fishbone, diagram. The causes are traditionally grouped in six major categories, which are related to men (people), methods, machines, materials, measurements, and milieu (environment). For example, for a crystallization process and final particle size distribution as effect, the reactor with its baffles, stirrer, heat transfer characteristics, etc., would fall under the machine category and the crystallization process itself (concentration profiles, temperature, stoichiometry, addition rate, etc.) would fall in the method category. Risk analysis then picks up all process parameters and material attributes and links them to CQAs in a matrix-type table (see Table 1.1 as an example). High risks are then further evaluated. Various tools and approaches exist for risk evaluation. One often cited in pharmaceutical QbD is the failure mode effect analysis (FMEA). The goal of this exercise is a ranking and priority ranking of risks. This is done by attribution of a risk priority number based on probability, severity, and detectability of the failure. For example, having a wrong polymorph would be severe, highly probable (obviously dependent on the compound and the underlying crystallization process, let us take this as an example), but also easily detectable. This would lead to a high risk priority number and consequently to a high priority on the "to do list" of items to be analyzed in more depth, e.g. by development of a robust crystallization process, which again would require good knowledge of the polymorph landscape and associated properties of the polymorphs. The unit operation of granulation in a high shear granulator can serve as another example. A critical process parameter could be the rate of the impeller; the respective failure mode would be a too high rate and a too long mixing time. As a consequence, larger granules could be obtained that, in turn, could lead to an undesired dissolution profile for the final tablet, which was defined earlier in the QTPP, and that was identified as a CQA (as an example). Again a high risk priority number would call for a deeper investigation of this issue.

Table 1.1 Risk analysis as a part of risk assessment.

	DS material attribute							
DP CQA	**Salt co-crystal**	**Poly-morph**	**Crystal-linity**	**Morph-ology**	**Purity**	**Solvent content**	**Particle size**	**Hygros-copicity**
Appearance	Low	Low	Low	Low	Low	Low	Low	Low
Identity	High	Low	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	High	Low	Low	High
Impurity	Low	High	High	Low	High	High	Low	Low
Content uniformity	Low	Low	Low	High	Low	Low	High	High
Dissolution	High	High	High	High	Low	Low	High	Low

Material attributes and their possible impact on quality attributes of the drug product are exemplified (case-by-case matrix).

As many of the CMAs and critical process parameters are influenced by multiple variables, a meaningful and common way of investigation of the identified high risk priority numbers consists of using statistical experimentation and analysis of results. Design of experiments (DoE) is a very useful tool for that. Use of screening designs helps to identify the statistically significant contributors to a process. This is, in general, followed by an optimization DoE (response surface designs) to obtain good mathematical models of the investigated experimental space. The art in all this exercise consists of finding and describing the right parameters and attributes that are to be studied. For instance, in the development of a scale-up crystallization process, it is not the stirring rate that is to be varied but rather a characteristic and relevant mixing time [38]. Results of such studies generally lead to understanding of the process and help to identify how close to a possible edge of failure a "standard parameter" process is and to define a design space, i.e. an ensemble of parameters which, if varied within a certain range, still lead to the desired process outcome as defined by its specifications. The whole process can then be continued by introducing control. Use of process analytical technologies (PAT) and the introduction of a control space within the design space coupled to a control strategy will help to keep processes within the desired boundaries. QbD also leaves some room for continuous improvement. As with any process that is repeated many times, experience will lead to identification of small improvements, which might lead to increased efficiency without impact on any CQA. The possibility to introduce continuous improvement to pharmaceutical processes without a huge regulatory burden is currently in preparation by the ICH.

The beauty of QbD is that the concept can be applied at various levels: from a top line holistic view level down to very specific single activities. The philosophy and its associated tools allow, for example, the development of an analytical method under such principles [39, 40].

As mentioned earlier, QbD is a systematic procedure that leads to understanding of the product, understanding of the process leading to that product, and finally providing the knowledge to control that process. Many things that are described above are logical and common sense from a scientific point of view. Because the justifications needed for the QTPP, for the CQA, and the risk assessment are based on a scientific rationale, a deep understanding of the matter is needed. And the matter that is discussed in this book in depth is molecular crystals and their bulk appearance in powders. Calling for a deep understanding, in turn, opens the door to science, and this encompasses any aspect related to this topic, from thermodynamic questions to kinetic considerations, from analytical questions to crystallization process scale-up problems, and from surface and mechanical properties to intellectual property-related questions (to name only a few aspects).

From the perspective of the pharmaceutical solid-state development, this means that answers and rationales for many questions and decisions need to be elaborated. This always with the goal in mind to understand, possibly predict, and quantify the outcome of any subprocess to ultimately ensure safety, efficacy, and quality of the medicine brought to patients.

1.4 The Solid State in the Context of Pharmaceutical Development

1.4.1 Typical Drug Discovery and Development

Typically, it takes 8–12 years [41, 42], or sometimes even longer, for a molecule with biological activity to progress from its first synthesis to market introduction as an efficacious, formulated drug. This process is normally divided into two main phases: (i) research or discovery and (ii) development. 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 considered at this stage as well. 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 [43]. 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 [44], PAMPA [45], or MDCK [46] 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, 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, quantitative relationship between the drug concentration in plasma and/or tissue and the magnitude of the observed pharmacological effect) are studied in animal models in order to predict bioavailability and dose in humans. Simultaneously with the characterization of the DS, a proper dosage form needs to be designed, enabling the DS to exert its maximum effect. For freely water-soluble drugs, this is less critical than for poorly water-soluble drugs, which cannot be properly investigated in the research stage without the aid of an adequate dosage form. 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, high-throughput approaches are definitely a necessity. The molecule that is found to be optimal after these assessments is then promoted to the next stage, i.e. development.

The development process of a pharmaceutical product is schematically depicted in Figure 1.2. It consists of a preclinical and a clinical phase. Although drug companies' approaches to the preclinical phase can differ somewhat, the clinical phase is treated very similarly everywhere because of regulatory requirements.

In the preclinical phase, enough data is gathered to compile an Investigational New Drug Application (IND) in the United States 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. An absolute necessity at this stage is that the drug is bioavailable, resulting in sufficient exposure of the animals to the drug to obtain an adequate assessment of its toxicity profile. The duration of the preclinical development phase is between one and two years [47], and the attrition rate is approximately 30% [41]. In the clinical phases, the product is first tested on healthy volunteers and then on small and large patient populations. For certain disease indications, such as oncology, clinical phase I studies are performed directly on patients. Approximate population sizes are given in Figure 1.2. One has to bear in mind, however, that these numbers depend significantly on the indication the drug is intended to treat. Overall attrition rates during the clinical phases and submission to launch are between 80% and 90% [41, 48].

In order to perform clinical development, obviously some clinical trial material (CTM) needs to be available in the required amount at the required quality and appropriate time. As a consequence, chemistry, manufacturing, and controls (CMC) activities are to be conducted at risk, much ahead of any clinical results.

Considering the high investment costs it takes to develop new innovative medicines [49], it is of major interest to manage the pharmaceutical development risks. To lower the risk that an active molecule falls into the attrition funnel, developability criteria are to be considered upon selection. For that purpose, a close interaction of discovery and development teams helps to create mutual understandings. Developability assessment should comprise the identification and selection of the optimal DS (including the optimal solid form for the intended application route and use) and should consider the feasibility of required formulation principles that allow delivering the required dose. Potential hurdles should be identified early on [50–52]. A good understanding of the dose-dependent PK profile and related parameters such as solubility, stability, permeability, first-pass effect, clearance, etc., will help to evaluate risks for DP development as a function of extrapolated needed doses (based on potency, receptor occupancy, exposure profile, etc.). Luckily, modern software tools are used more and more to provide development guidance and to support decision making. *In silico* modeling and simulation help to visualize and understand the interplay of a multitude of parameters and variables of underlying principles. Such tools include physiologically based PK modeling and also population balance-based equation solving for generation of absorption profiles throughout the gastrointestinal tract of different solid forms or formulation principles.

As a consequence of introducing rational developability criteria for selection (which is very much in the spirit of QbD), the classical flow of development

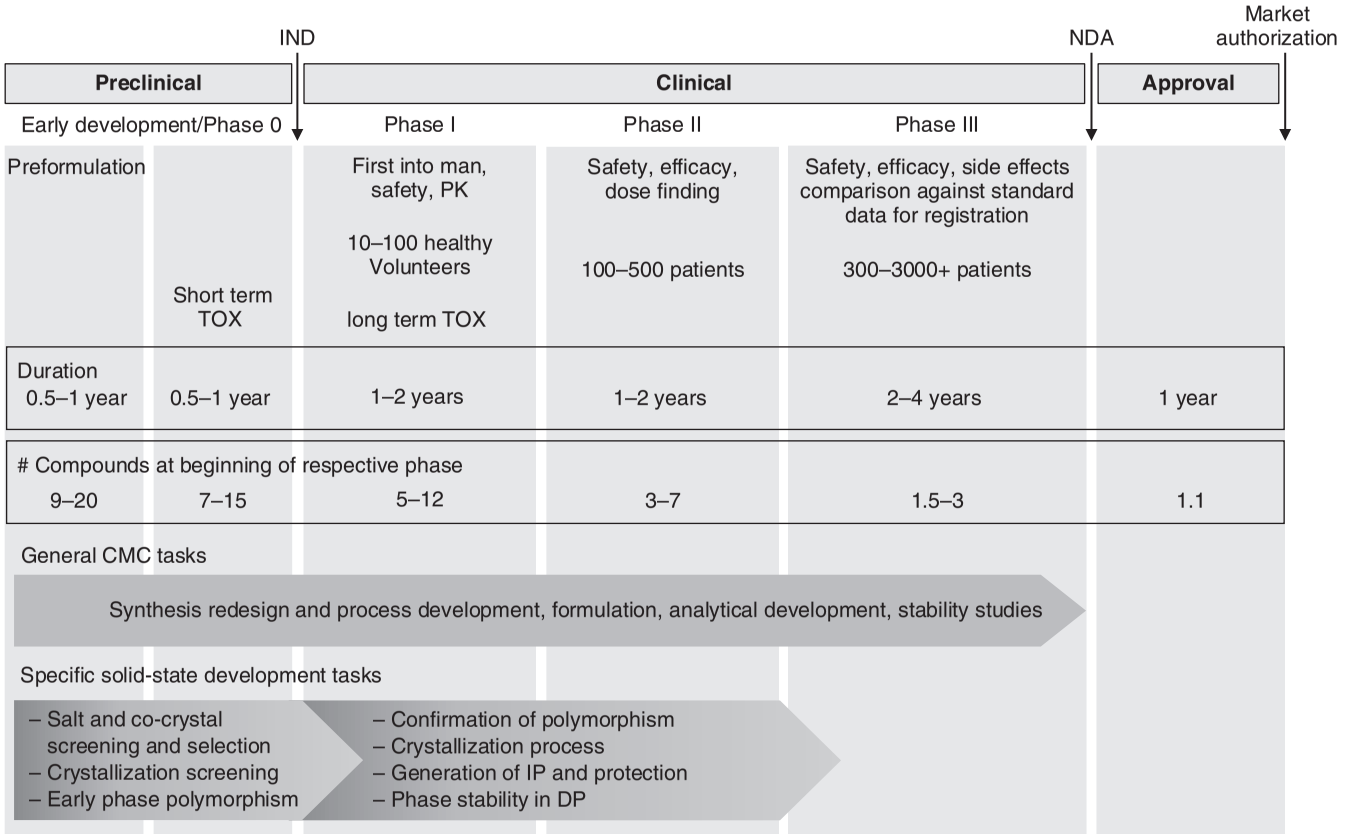

Figure 1.2 Typical development process of a pharmaceutical product and related solid state.

sequences might need to be rearranged. Frontloading of certain key CMC activities will allow getting a better overall understanding of limitations and help avoiding long-term manufacturing issues.

1.4.2 The Solid State at the Interface of Drug Substance and Drug Product

The majority of DPs (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 before 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 more and more popular, and dry powder inhalers are now commonly in use. It is, therefore, evident that the solid form of the DS 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 DS is still necessary [53]. If different forms have a significantly different solubility, 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.

When discussing solid-state development and polymorphism in the context of pharmaceutical development, it has to be pointed out that solid form selection and polymorphism should not be a tick box exercise performed in an isolated way. Although the active molecule is the primary focus and interest of chemists, it is the solid material obtained that will define many of the parameters influencing the absorption of the active molecule from a DP. Careful examination of available options will possibly allow tuning solid-state properties by, e.g. salt [30] or co-crystal [31] formation. At the end of the development chain is the marketed medicine. Because a solid oral dosage form is desired in most cases, the DS physicochemical properties will influence many of the subsequent manufacturing processes. The M3 mnemonic (Molecules–Materials–Medicines) [54] nicely brings it straight to the point; pharmaceutical development needs a holistic approach: chemical development – solid-state development – DP development. These three disciplines are tightly interconnected and have the same goal of making products of the highest standard with respect to quality, safety, and efficacy.

For a defined active molecule, the F3 mnemonic (Form–Formation–Formulation) also nicely describes the interconnectivity of development disciplines (Figure 1.3). The molecular arrangement in a crystal lattice, governed by thermodynamics, will define the polymorphic form (i.e. the Form), that will exhibit a natural habit. The formation of the material, which is governed by kinetics (i.e. the processes of crystallization, isolation, and drying), will define the habit and size of singular particles. Singular particles will express surfaces, and these surfaces, which are the boundary of the molecules to a different environment, will define many of the physicochemical properties and behaviors [55–57]. Many particles together will yield a powder, and properties of powders can be invariant or variant. Properties that are invariant are thermodynamic values such as melting point or solubility. These are defined by the polymorph.

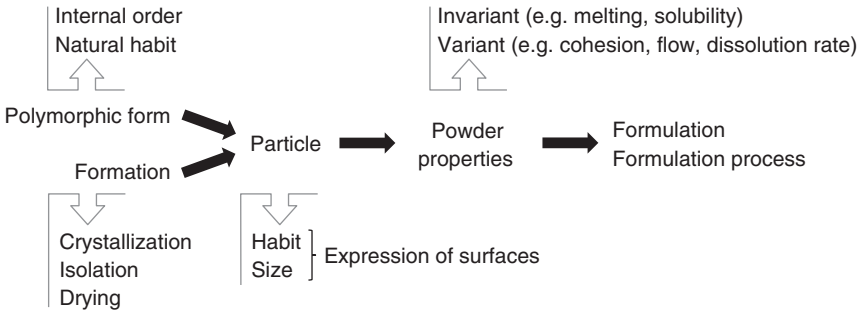

Figure 1.3 The interplay of form and formation resulting in powders that are further processed to the DP.

Variant properties of a powder are, e.g. particle size distribution, flow properties, cohesion, and dissolution rate [58, 59]. It is a DS powder that will be finally used for making a DP. Pharmaceutical unit operations such as powder blending, dry or wet granulation, and ultimately tableting will, therefore, depend on the properties of the powder [57, 60, 61]. Properties such as melting point and mechanical properties such as brittleness or ductility, particle size, surface energy, etc., will influence the tabletability, compactability, and compressibility of the powders. It is clear that the appropriate selection of excipients as a function of dose/drug load will help to mitigate the influences of the DS powder properties. The selection of appropriate formulation processes as a function of DS powder properties was recently described in the "manufacturing classification system" (MCS) [62]. The MCS is intended as a tool for pharmaceutical scientists to rank the feasibility of different processing routes for the manufacturer of oral solid dosage forms, based on the selected properties of the drug substance and the needs of the formulation.

1.4.3 Biopharmaceutics and Bioavailability of Solids

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

An absorption profile of a drug from the gastrointestinal tract essentially depends on three factors: solubility, permeability, and dose [63], and the question of minimal acceptable solubility can only be answered if the other two factors, i.e. permeability and dose, are known. These three factors, via the absorption number A_n (product of the mean residence time in the small intestine and the effective absorption rate constant), dose number D_o (ratio of the dose divided by the liquid volume and the solubility), and dissolution number D_n (ratio of the mean residence time in the small intestine and the time required for a particle to dissolve), are the pillars of the Biopharmaceutical Classification System (BCS) as proposed by Amidon [64, 65]. In his article, the in vitro DP dissolution in vivo bioavailability correlation (IVIVC) was discussed and BCS classes as a function of solubility and permeability of the drug substance

were described. Yu [66] looked at the causes of poor oral drug absorption and categorized into dissolution-limited, permeability-limited, and solubility-limited absorption and proposed some boundary values for classification. This concept was later picked up and modified by Butler and Dressman [50] to result in the developability classification system (DCS). Application of biopharmaceutics concepts resulted in a rationale-based guidance to formulators for classification in dissolution rate-limited or solubility-limited absorption. Intestinal solubility (using fasted state-simulated intestinal fluid), the compensatory nature of solubility and permeability in the small intestine, and an estimate of the particle size needed to overcome dissolution rate-limited absorption were considered. Furthermore, the term "solubility-limited absorbable dose" (SLAD) was proposed that considers the solubility in the small intestine, the fluid volume, and a permeability-dependent multiplier.

According to the BCS, a DS is considered highly soluble if the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range from 1.0 to 7.5 [65]. Solubility in the BCS is defined as the minimum solubility of drug across that pH range. This is a conservative approach that has a big impact for ionizable drugs. Indeed, the BCS and DCS are nice tools for nonionizable or weakly acidic molecules. As soon as ionizable molecules and especially weak bases are contemplated, an additional layer of complexity is added. Dissolution of low soluble bases will be favored by the gastric acidic environment. Transfer to the small intestine will result in a gradual pH shift to neutral conditions. Based on the ionization constants, the solubility of the nonionized species and the propensity of a molecule to supersaturate or to precipitate (be it via amorphous phase separation or via a nucleation and growth mechanism), quite different scenarios can be developed. To account for the distinct behavior of ionizable molecules, subclasses to the BCS were proposed by Tsume in 2014 [67]. With the aim of IVIVC and in vivo predictive dissolution in mind, subclasses for acids, bases, and neutrals were created. Furthermore, the type of required dissolution experiment for being predictive for *in vivo* was listed for every BCS class and subclass. Indeed, dissolution methodologies have much evolved from the simple USP II-type dissolution vessels to take into account various compartments such as gastric and intestinal compartments, as well as an absorption compartment. Transfer-type setups of various kinds [68], sometimes referred to as artificial stomach duodenum system [69, 70], and biphasic dissolution methods [71] have become increasingly popular to cope with the challenges of IVIVC. Very much linked to this, the BioRAM concept (biopharmaceutics risk assessment road map) [51] has as target to optimize DP development and performance by using therapy-driven target drug delivery profiles as a framework to achieve the desired therapeutic outcome.

Independent of a formulator's need of guidance for DP development, physiology-based pharmacokinetic (PBPK) modeling became more and more popular. It was rapidly recognized that the absorption part of the model would deserve some special attention. Sugano makes use of four processes that are the key to drug absorption and that are used for mechanistic considerations, i.e. dissolution, permeation, nucleation, and gastrointestinal transit. All four processes were reduced to molecular-level mechanisms described by mathematical equations that have physical meanings. The whole network of theoretical

equations of drug absorption was called the gastrointestinal unified theoretical (GUT) framework in his biopharmaceutical modeling and simulation book [72].

The wish to use the biopharmaceutic concepts for more predictability and less trial and error in technical pharmaceutical development is also reflected by the ORBITO (Oral Bioavailability Tools) initiative (http://www.orbitoproject.eu/) [73–75]. A large European consortium of private and public stakeholders started this five-year project in 2012 with the vision to "Transform our ability to predict the *in vivo* performance of oral drug products across all stages of drug development" and further "The ORBITO project aims to enhance our understanding of how orally administered drugs are taken up from the gastrointestinal tract into the body, and apply this knowledge to create new laboratory tests and computer models that will better predict the performance of these drugs in patients."

From the pharmaceutical solid-state perspective, the better understanding of human absorption from orally taken drugs is an important aspect, as it provides rationales for selection of a specific species (salt/co-crystal vs neutral), which is, from a QbD side, a desirable state.

However, let us come back to our initial question of what is the minimal or the adequate solubility for a certain dose of an orally taken DP. The short excursion above illustrates that there is no easy answer and that this is a case-to-case consideration. Nevertheless, some very simple assumptions can be made. A valuable concept for estimating what the minimum solubility of a DS for development purposes should be uses the maximum absorbable dose (MAD) [76, 77]. MAD corresponds to the maximum dose that could be absorbed if there was a saturated solution of the drug in the small intestine during the small intestinal transit time (SITT ≈ 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 [64]. 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 ≈ 250 mL), and the SITT.

$$\mathrm{MAD(mg)} = S(\mathrm{mg\,mL^{-1}}) \times K_a(\mathrm{min^{-1}}) \times \mathrm{SIWV(mL)} \times \mathrm{SITT(min)} \quad (1.1)$$

Human K_a can be estimated from measured rat intestinal perfusion experiments [77, 78]. It is related to the permeability (P) through SIWV and the effective surface of absorption (S_{abs}) [64].

$$K_a(\mathrm{min^{-1}}) = P(\mathrm{cm\,min^{-1}}) \times S_{abs}(\mathrm{cm^2})/\mathrm{SIWV(mL)} \quad (1.2)$$

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).

$$P(\mathrm{cm\,min^{-1}}) = D(\mathrm{cm^2\,min^{-1}}) \times K/\delta(\mathrm{cm}) \quad (1.3)$$

In reality, the proportionality between partition coefficient and permeability is only found for a rather small range of partition coefficients [44, 79]. This can be explained by the fact that 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 [80].

Implicit in Eq. (1.1) 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 [76] took into account the dissolution kinetics of a polydisperse powder and showed how the percentage of the dose that is adsorbed 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 [77].

$$\begin{aligned}\text{Minimal acceptable solubility} &= S^{*}(\text{target dose(mg)}/\text{MAD}) \\ &= \text{target dose}/(K_{\text{a}} \times \text{SIWV} \times \text{SITT}) \end{aligned} \quad (1.4)$$

Realistic values for K_{a} lie between 0.001 and 0.05 min^{-1} and vary over a much narrower range than typical solubility (0.1 $\mu\text{g mL}^{-1}$ 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 solubility between 20 $\mu\text{g mL}^{-1}$ 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 because of the meal effect, etc. [81]. Furthermore, it is important to realize that S represents a "kinetic" solubility. As mentioned above, 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.

Big efforts are currently being made in the fields of *in vivo* predictive dissolution [82] that includes better understanding and assessing supersaturation and precipitation behavior of drugs [83–85]. Enabling formulation technologies such as amorphous solid dispersions or lipid-based systems, the use of co-crystals as well as salts, and the solubilization of basic molecules in acidic environment, will possibly lead to supersaturation in the gastrointestinal tract. The possible advantage of such principles stands and falls with the degree and the time that supersaturation can be maintained; this is sometimes referred to as "spring and parachute" effect [83]. Induction times, nucleation, and growth rates of solids in physiological media and conditions are difficult to assess and various approaches are followed in this particular domain of research [68, 86–88].

1.4.4 Pharmaceutical Quality Assessment

With the wish to strengthen pharmaceutical quality on a global scale, the FDA's Center for Drug Evaluation and Research (CDER) created a new Office for Pharmaceutical Quality (OPQ) [37]. The FDA's analysis revealed among other unacceptably high occurrence of problems attributed to inherent defects in

product and process design. Furthermore, the data indicated failures in the implementation of manufacturing process scale-up as well as routine production. The OPQ, seen as a super-office, will ensure a holistic and advanced team-based integrated quality assessment, including among other things, drug substance, DP, and biopharmaceutics. This clearly demonstrates that coordinated, cross-functional, rational development without perceived "classical" boundaries of standalone drug substance or DP development is an absolute necessity. Some examples of science and research activities in OPQ were recently described [89].

1.5 Solid-State Development at Various Stages of the Pharmaceutical Development Process

Although it may be possible to design a theoretical best process of how things should be done, reality often imposes deviations on the best theoretical way. Nevertheless, keeping in mind the "at risk" development described earlier and the high associated investments [49], a certain rigor is needed in order not to miss the essentials.

Based on the time lines imposed by the overall development as shown in Figure 1.2, typical timing for solid-state activities can be deduced. The type of activities and the focus are different at the various development stages, and assuring a good knowledge collection and transfer over the various stages to the various involved parties will help to maintain a consistent understanding. Why some things are done as they are done in specific processes should be transparent to all parties. Indeed, knowledge management is one important aspect of the QbD guidelines and the immediate utility is easily understandable. Solid-state activities, as any other development activity, have to serve the overall development interest, which is providing consistent quality for making safe and efficacious drugs. As discussed in the QbD section, risk assessment helps to prioritize activities.

In general and independent of the overall development, solid-state development encompasses the following activities:

- Identifying and deciding whether the uncharged molecule or a salt or a co-crystal should be developed (based on the rationales as developed in the previous sections).
- Identifying and characterizing all relevant polymorphs, hydrates, and solvates of the chosen drug substance.
- Selecting the crystalline form for chemical and pharmaceutical development according to its intended use.
- Patenting new forms of interest (Chapter 16).
- Developing a scalable manufacturing process to obtain the desired form of the drug substance and fulfilling all specifications. This includes the crystallization process, the filtration and drying steps, and potential operations such as micronization and conditioning.
- Developing a method to determine physical purity of the drug substance. This includes polymorphs, amorphous fraction, salt disproportionation, etc.

- Formulating the drug substance to obtain the DP and investigation of potential processing-induced phase transformations (Chapter 12).
- Developing a method to determine the physical purity of the drug substance in the DP.

Not all of these points may be necessary for every drug substance, and the order and depth of investigations may be varied according to the specific properties and behavior of the drug as identified by a QbD-type risk assessment. It also makes sense that along the overall development phases, a staged approach is chosen for the depth of investigations. Revisiting of some aspects is needed if new findings or new goals contribute to a different risk assessment result.

1.5.1 The Solid State in the Discovery Phase

Even before preclinical development, medicinal chemists should be sensitized to the solid state. Although the first few milligrams of new molecules are often amorphous, the latest when the active molecule shows some potential, a batch tracking by X-ray powder diffraction or similar to identify and track if the DS is amorphous or crystalline, or if different polymorphs exist, makes sense. Questions on what the various material formation processes looked like or what they should look like help to identify early on some possible issues, e.g. solubility wise, like for amorphous and crystalline batches. The more and the more often material is made; consistent properties are required. Hence, batch characterization is often expanded to include, e.g. thermal, spectroscopic, and microscopic methods. Special emphasis can also be put into the interaction with moisture as hydrate formation or strong moisture sorption due to residual salts might impact the assay of the material. Obviously, the more the project is advancing, the more specific such tests have to be, ultimately leading to specification setting according to the criticality of quality attributes.

1.5.2 Salt and Co-crystal Screening and Selection

Clearly, the first decision that has to be made is whether it is more desirable to develop the molecule as a free form or, if possible, as a salt (Chapter 2) or a co-crystal (Chapter 3) thereof. As making a salt or a co-crystal will normally involve an additional step in the synthesis and since the molecular weight of a salt or a co-crystal will always be higher than that of the neutral molecule, salts or co-crystals will only be chosen if they promise to have clear advantages compared to the free acid/base. As a guidance, a salt or a co-crystal is chosen if the free acid/base has at least one of the following undesirable properties:

- BCS/DCS/BioRAM flags, e.g. unfavorable solubility profile
- Apparently not crystallizable
- Low melting point (typical cutoff 80 °C [90])
- High hygroscopicity or unmanageable hydration states
- Poor chemical stability,
- IP issues

An unfavorable solubility profile is relative and always has to be assessed in the context of dose and permeability (Section 1.4.3). In addition, the amorphous state of a neutral molecule may be the best option to get high solubility, provided the amorphous form can be kinetically stabilized over a reasonable time scale. Therefore, the decision to develop a salt or co-crystal should be based on a head-to-head broad comparison taking into consideration both *in vivo* performance (modeled or experimental) and physicochemical properties. If the decision has been made to develop a salt or a co-crystal, it is obviously important to carry out a broad salt and co-crystal screening and selection process in order to identify the optimal salt or co-crystal. Different companies perform salt and co-crystal screening in different phases of development. Some move the salt and co-crystal selection process to the research phase [90], but clearly, the decision on the solid form should ideally be made no later than the beginning of the long-term toxicology studies (Figure 1.2).

1.5.3 Polymorph Screening, Polymorph Landscape, and Polymorph Transformations

The objective of the next important step with respect to solid-state development is to choose the optimal form for further chemical and pharmaceutical development. For that purpose, first all relevant polymorphs, hydrates, and solvates are to be identified in a polymorphism screening (Chapter 8). Characterization of polymorphs and related solid forms will allow understanding the polymorph landscape and possible transformations between polymorphs (and hydrates and solvates). In the absence of solvents and humidity, the thermodynamically stable polymorph at room temperature is the only one that is guaranteed not to convert into another polymorphic form. This is the reason why this form is most often chosen for the DP [78]. The disadvantage of the thermodynamically stable form is, of course, that it is always the least soluble polymorph and therefore has the potentially lowest bioavailability. However, 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 [91] for a review of literature data), but sometimes as much as a fivefold difference can be observed [92]. 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 to the other and the reproducibility of producing consistently the same ratio of polymorphs are important.

Development of new algorithms coupled to increased computing power made the use of *in silico* tools more and more reliable, and polymorph *in silico* prediction has reached a remarkable level (Chapter 5). These tools can help to fully understand polymorph systems (Chapter 15).

Apart from the thermodynamically stable polymorph of a drug substance, hydrates are very popular components of the final dosage form as well. Because of 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 humidity, 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 [77], normally for one of the following reasons:

1. Too low 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 because of topochemical factors

1. If the solubility of the stable polymorph is critically low and no salt or co-crystal is feasible, several options to solve the problem exist [93]. Liquid-like formulations (emulsions, microemulsions, and liposomal formulations) or soft gelatin capsules filled with solutions of the drug in a nonaqueous solvent may be used (e.g. lipid-based formulations). 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 [94]. Firstly, the solubility advantage of an amorphous form is often x-fold relative to the crystalline stable form [95–97], whereas the metastable polymorphs typically have less than a twofold higher solubility as mentioned above. The solubility advantage of an amorphous form as compared to a crystalline form can be estimated by a simple calculation based on melting point and melting enthalpy [96]. Secondly, it is normally impossible to stabilize a metastable form reliably by excipients, as 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. This was recently confirmed for acetaminophen [98]. 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 very large effect on the kinetics of transformation [99]. The amorphous form, on the other hand, can be stabilized, e.g. by creating a solid dispersion with a polymer [100–102]. Such an amorphous solid dispersion will be highly kinetically stable if two conditions are fulfilled: if it remains in the glassy state under 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. Big advances have been made in recent years in the development and understanding of amorphous solids.
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 (Chapter 13). A famous example is acetaminophen, where the thermodynamically stable form (monoclinic form I) cannot be compressed into stable tablets, whereas the metastable form II (orthorhombic) can, as it shows more favorable properties with respect to plastic deformation [103]. 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 [11].
5. Generally, the thermodynamically most stable polymorph is also the most stable chemically [77]. This has been attributed to the fact that its density is typically higher, but it could also be explained by the fact that its free energy is lower. 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 done and when the choice of which form to develop should be made. As different solid forms have different properties and therefore may lead to a different absorption profile, it is definitely advisable to select the final form together with the accompanying formulation before carrying out pivotal clinical studies [53, 104]. 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. Accordingly, by that time, a polymorphism screening that is primarily designed to identify these forms with a large probability should have been completed. Because of 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 to a later date. 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.

Although 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 [105] 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 the one of ritonavir (Norvir) [92, 106]. 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 because of the 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, 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. Although this is certainly an extreme case, there are many instances of new polymorphs appearing in phases II and III studies and leading to considerable difficulties [107] (Chapter 15).

1.5.4 Crystallization and Downstream Processes

Rapid availability of material of sufficient purity by a fit-for-purpose chemical process is perceived as being a key for preclinical development and entry into human clinical studies. Time constrains often impose an incomplete knowledge and hence a certain risk. Close collaboration of material scientists with process and pilot plant chemists will help to mitigate the risk and will allow reacting rapidly to unexpected findings.

For later clinical phases, a reliable large-scale crystallization process has to be developed (Chapter 11) [108–111]. Parameters such as yield, chemical purity, polymorphic purity, solvent class (preferably class III solvents according to ICH Q3C [112]), 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 [104], and bulk density. It can sometimes be controlled by choosing the appropriate solvent and method for crystallization [113].

Crystallization, even of a drug substance precursor, is generally by far the most efficient and economical way for 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 then be feasible as an intended process. However, this corresponds to a rearrangement of the lattice, which is generally susceptible to loss of crystallinity.

A precise knowledge of the thermodynamic stability relationships among the various forms as a function of temperature (energy–temperature diagrams) is a prerequisite for designing reliable crystallization processes [114, 115], where parameters such as solvent composition, concentration, cooling rate, etc., are optimized [116]. In addition, the metastable zone width of all relevant forms might need to be known [108, 110, 117–119]. Often a seeding process provides the only reliable way to obtain the desired form. 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 [120] in the crystallization process.

Similar to biopharmaceutics or polymorphism, big progress has been made in the modeling of crystallization processes. Crystallization processes, consisting

of nucleation (Chapter 9) and growth, can be described by population balance equations (Chapter 10). Precise measurements of certain parameters allow feeding mathematical models that lead to an impressive predictability of crystallization trajectories. Experience shows that a not well-understood crystallization process is notoriously difficult to upscale and to transfer. The key to understanding upscale factors is the application of engineering calculations and fluid dynamics. Reactor design and operation will have a direct impact on energy input and characteristic mixing times [38]. First, it has to be found out which fluid dynamics parameter will influence a crystallization outcome. This can be studied at smaller scale, while paying attention to choose scales where similar turbulent regimes can be reached as encountered at larger scale. Help of modern online analytical tools such as focused beam reflectance measurements (FBRM) will provide information on when and how particles are generated and will contribute to the understanding of the process under investigation.

Although crystallization development is often carried out as a part of synthesis process development [121, 122], it is advisable to study the crystallization in a more dedicated way, in close collaboration with plant engineers, process chemists, material scientists, and analysts. This certainly applies if the crystallization process should deliver a very specific particle size distribution.

Crystallization is only the first part of the story; once the material is made, it needs to be isolated. Harvesting the material consists of several operations such as filtration, drying, and packaging. Potentially, the material is even further processed, e.g. the material is micronized or needs a conditioning step. All these downstream operations can potentially lead to a processing-induced phase transformation [123] and have, therefore, to be considered with the same rigor as the crystallization itself. Temperature, humidity, and mechanical energy input are different for different types of equipment. Again, a close collaboration and information exchange between all involved parties (plant engineer, process chemist, material scientist, analyst, and formulation expert) will allow identifying the criticality of operations for specific drug substances. As an example, particular attention has to be paid to the drying processes. It must be assured that at the drying temperature used, no conversion to an undesired form takes place. Again, phase diagrams are very helpful for establishing such criteria. As another example, the process parameters for jet micronization should not only be optimized for particle size distribution but also incorporate the quantification of amorphization [124]. Samples with several percent of amorphous content are frequently produced, if the process parameters are not set adequately. Even low levels of amorphous content can lead to particle growth and caking [125] upon long-term storage or can directly impact pharmaceutical manufacturing operations (Chapters 12 and 13).

1.5.5 Formulation

Consideration of the solid state of the drug substance in the context of formulation has to be adapted to the stage of development as well as to the application route and dosage form. In discovery and during preclinical studies, compounds are often administered as suspensions or solutions given either

orally or parenterally. From the solid-state perspective, particle size and solid form identity are then in focus. Other aspects such as shelf life or crystallization route are only of secondary interest. The focus of interest changes with the continuing development of the active molecule. Final oral formulation types include tablets as the most popular form, as well as capsules, syrups, and solutions. Other possible formulations include solids for inhalation, creams, gels, patches, nasal sprays, suppositories, solids for reconstitution before injection, etc. [126]. Different application routes and different dosage forms pose different questions with respect to the solid state. Different types of formulations require different sequences to manufacture them. Within such a sequence, any of the processing operations can potentially induce a phase transformation (Chapter 12). Risk assessment tools coupled with strong material science knowhow, as elaborated during the respective polymorphism investigation, will help to identify criticality of material attributes or process parameters. A compilation of unit operations and break down to individual steps was recently published by Yu et al. [35].

1.5.6 Analytical Methods for Characterization and Physical Purity Determination

Many physicochemical methods are used to characterize solid materials as powders [127]. Some of the most important analytical methods are further described in Chapter 14. Different methods help to understand different properties, e.g. gravimetric moisture sorption for the understanding of interaction with moisture or inverse gas chromatography for surface energy aspects. Other methods can be used as fingerprint methods to provide identification of a solid form or to be used as a quantification tool for solid form mixtures. Suitable methods to determine solid-state compositions include differential scanning calorimetry, microcalorimetry, solution calorimetry, moisture sorption, IR and Raman spectroscopy, powder X-ray diffraction, and solid-state NMR.

In cases where differences in polymorphic form affect drug performance or stability, the appropriate solid state must be specified (ICH Q6A [6]). 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. It is generally known from the production process 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, including chemical stability.

Which analytical method is optimal for quantification of polymorphic purity depends on the drug substance. A variety of analytical techniques are generally screened to identify sensitivity, robustness, and suitability. This is important if the polymorph composition is used as a release parameter, as the appropriate method has to be validated [99] with respect to linearity, accuracy, precision, intermediate precision, limit of quantitation, and limit of detection (ICH Q2R1 [128]).

The same kind of thoughts has to be applied to the identification of a polymorph in a DP. As the drug load within a DP can be very low, it can be very difficult or impossible to identify the solid form within a DP. Obviously, this becomes even more complex if polymorph mixtures would have to be identified and quantified. The use of surrogate testing is strongly suggested in such cases. This can, for example, consist of dissolution testing.

1.6 Conclusions

The pharmaceutical solid state and polymorphism has to be seen and understood in a wider context of general solid form selection. The solid-state form can drastically alter the utility and 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 are part of an integrated approach to solid-state issues all the way from the very first synthesis to quality control. The ultimate goal of solid-form screening and selection is to identify and to select the optimal solids for the intended use, which is guided by biopharmaceutical and physicochemical considerations.

In the context of ICH guidelines Q8–Q12, pharmaceutical QbD is defined as being "a systematic approach to the development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."

A good understanding of polymorphism of a drug substance is the key for many QbD-based risk assessments referring to the production of the solid (crystallization process development, filtration, and drying), storing the solid (packaging and conditions), and processing the solid (micronization and pharmaceutical manufacturing processes) that ultimately will lead to high quality, safe, and efficacious medications.

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