1

Solid-State Properties and Pharmaceutical Development

1.1   Introduction

Solid-state chemistry and the solid-state properties of pharmaceutical materials play an ever-increasing and important role in pharmaceutical development. There is much more emphasis on physical characterization since the ICH Q6A guidance on specifications was released. This guidance directs the scientist to determine what solid form is present in the drug substance (API) and drug product. It directs the manufacturer to "know what they have." Additionally, the ICH Q8 guidance on development and the ICH Q9 guidance on risk require a firm understanding of how the medicine was developed and any risks involved.

There are many more poorly soluble drugs under development. In many cases, the solid form of the API and the solid form and formulation in the drug product determine apparent solubility, which in turn determines blood levels. That is, the formulation determines bioavailability and therapeutic response. In these cases, it is even more important to physically characterize the API form and the formulations. Furthermore, most medicines (drug products) are solids, and those drug products that are not solids often start with solid APIs. In addition to solubility and bioavailability, the solid form may affect stability, flow, compression, hygroscopicity, and several other properties.

This book focuses on solid-state properties of pharmaceutical materials and methods of determining these properties. The authors have made every effort to include examples and case studies to illustrate the importance of knowing what you have. This book will focus on solid-state properties and general strategies for physical characterization. Case studies and practical examples will be emphasized. This book will illustrate that a medicine is more than a molecule in many aspects. Additional goals include providing a full physical/analytical/operational definition of the different solid forms, as well as other terms frequently used in pharmaceutical materials science, including polymorph, solvate, amorphous form, habit, nucleation, transformation, dissolution, solubility, and stability.

1.2   Solid-state Forms

Pharmaceutical materials can exist in a crystalline or amorphous state. Figure 1.1 illustrates the crystalline state as a perfectly ordered solid with molecules (circles) packed in an orderly array. Figure 1.1 also illustrates an amorphous material as a disordered material with only short-range order. Crystalline materials give an X-ray diffraction pattern because Bragg planes exist in the material (see Figure 1.2). Amorphous materials do not give a diffraction pattern (see Figure 1.2). Of course, there are many interesting cases where a pharmaceutical material shows an intermediate degree of order falling somewhere between the highly ordered crystalline state and the completely disordered amorphous state. From a thermodynamic point of view, crystalline materials are more stable, but the rate of transformation of amorphous materials to crystalline materials can be highly variable [1].

Crystals of a pharmaceutical material from different sources can vary greatly in their size and shape. Typical particles in different samples may resemble, for example, needles, rods, plates, prisms. Such differences in shape are collectively referred to as differences in morphology. This term merely acknowledges the fact of different shapes. It does not distinguish among the many possible reasons for the different shapes. Naturally, when different compounds are involved, different crystal shapes would be expected as a matter of course. However, when batches of the same substance display crystals with different morphology, further work is needed to determine whether the different shapes are indicative of polymorphs,
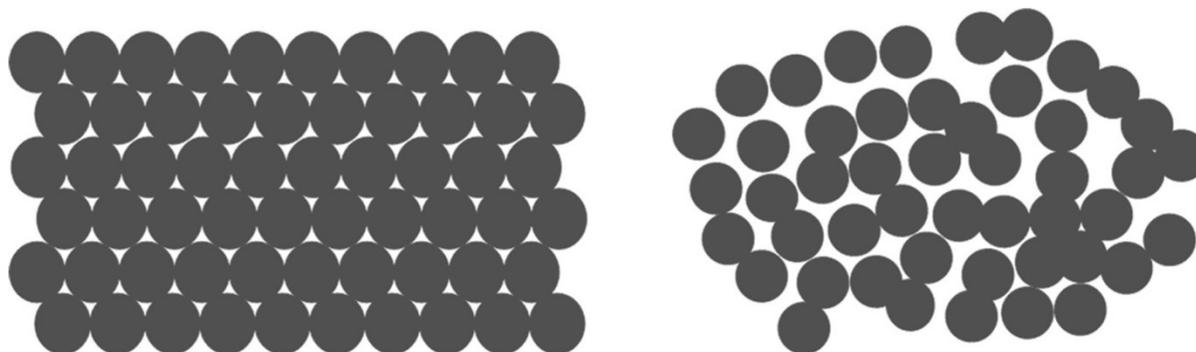
Figure 1.1 Idealized view of crystalline (left panel) and amorphous (right panel) material. In this two-dimensional figure, the molecules are viewed as circles.
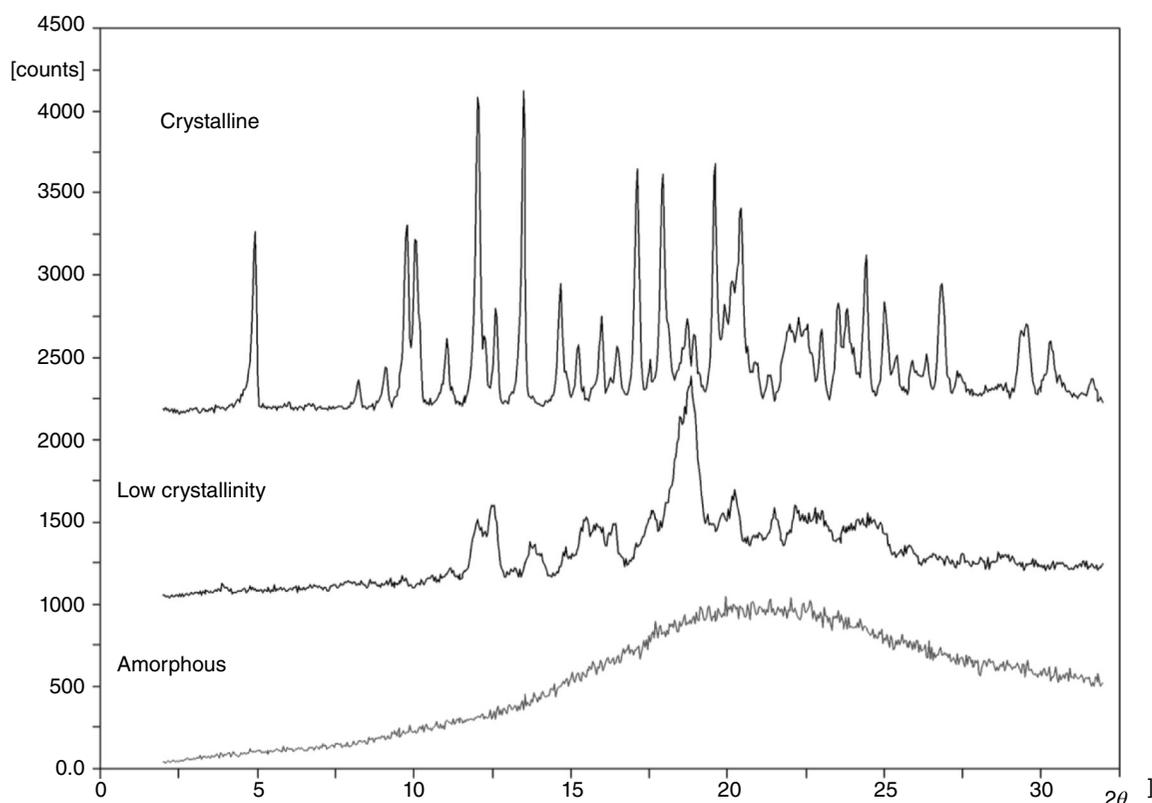

Figure 1.2 X-ray diffraction pattern of three samples: crystalline, low crystallinity, and amorphous.

solvates, or just habits. Because these distinctions can have a profound impact on drug performance, their careful definition is very important to our discourse. At this time, only brief definitions are presented:

- Polymorphs – When two crystals have the *same chemical composition* but *different internal structure* (molecular packing), they are polymorphic modifications or polymorphs (think of the three forms of carbon: diamond, graphite, and fullerenes). Polymorphs can result from different molecular packing, different molecular conformation, tautomeric structure, or combinations of these.
- Solvates – In addition to containing molecules of the same given substance, these crystal forms contain *molecules of solvent* regularly incorporated into a unique structure (think of wet, setting plaster: $CaSO_4 + 2H_2O \rightarrow CaSO_4 \cdot 2H_2O$).
- Habits – Crystals are said to have different habits when samples have the *same* chemical composition and the *same* crystal structure (i.e. the same polymorph and unit cell) but display different shapes (think of snowflakes).
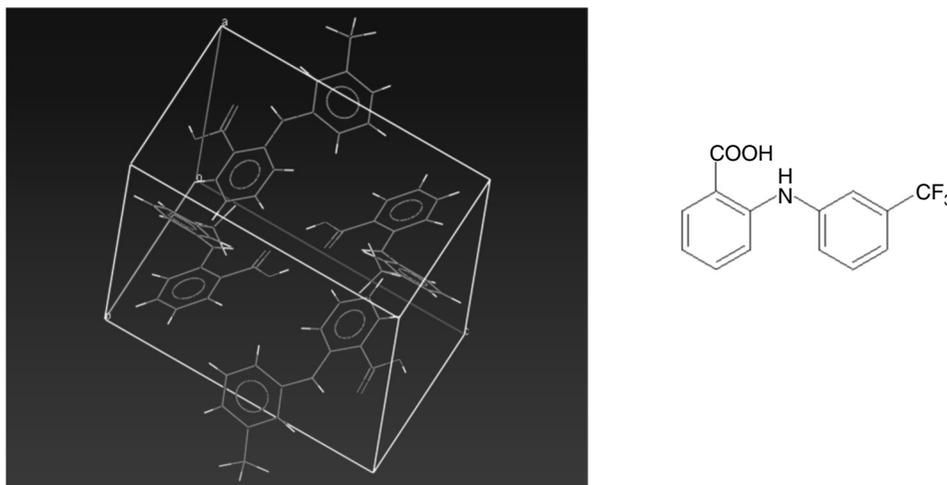
Figure 1.3   Single crystal structure of the Form I polymorph of flufenamic acid (structure shown on right panel).

Together, these solid-state physical modifications of a compound are referred to as crystalline forms. When differences between early batches of a substance are found by microscopic examination, for example, a reference to "form" is particularly useful in the absence of information that allows the more accurate description of a given variant batch (i.e. polymorph, solvate, habit, or amorphous material). The term "pseudopolymorphism" is applied frequently to designate solvates. These solid-state modifications have different physical properties.

To put these important definitions into a practical context, we consider two cases (aspirin and flufenamic acid) in which a drug was crystallized from several different solvents, and different-shaped crystals resulted in each experiment. Although dramatically different shapes were sometimes obtained on changing solvents for the various crystallizations, the final interpretations in the two cases are different. For aspirin, X-ray powder diffraction showed that all crystals regardless of shape had the same diffraction pattern. Thus, the different-shaped crystals are termed crystal habits. For flufenamic acid, the different-shaped crystals had different X-ray powder diffraction patterns. Subsequent analysis showed that the crystals did not contain solvent. Thus, these different crystals are polymorphs.

Further analysis of the crystals from this case provides the single crystal structure. The single crystal structure gives the locations of the atoms relative to a hypothetical unit cell. The unit cell is the smallest building block of a crystal. Figure 1.3 shows the unit cell of Form I of flufenamic acid. This unit cell contains four flufenamic acid molecules. Figure 1.4 shows a space-filling model of the contents of the flufenamic acid Form I unit cell. This figure illustrates Kitaigorodski's close packing theory, which requires that the molecules pack to minimize free volume [2].

Amorphous materials will be discussed in Chapter 6. In this introductory chapter, as previously mentioned briefly, amorphous materials have no long-range order and are thermodynamically metastable. An amorphous solid is characterized by a unique glass transition temperature T_g, the temperature at which it changes from a glass to a super-cooled liquid or rubbery state. When T rises above T_g, the rigid solid can flow, and the corresponding increase in molecular mobility can result in crystallization or increased chemical reactivity of the solid. Several historic papers describe some additional details of amorphous materials. Pikal and coworkers [3] at Eli Lilly showed that amorphous materials can have lower chemical stability, and Fukoka et al. [4] showed that amorphous materials had a tendency to crystallize. Nevertheless, in some cases, amorphous forms have been historically used as products. An excellent example is novobiocin [5], which exists in a crystalline and an amorphous form. The crystalline form, when administered orally, is poorly absorbed and does not provide therapeutic blood levels; in contrast, the amorphous form is readily absorbed and is therapeutically active. Further studies show that the solubility rate of the amorphous form is 70 times greater than the crystalline form in 0.1 N HCl at 25°C when particles <10 microns are used.

Making a "top 10" list of the differences between crystalline and amorphous materials is possible. Crystalline materials have the following characteristics:

1. higher purity,
2. more physically and chemically stable, *crystalline hydrate > anhydrous crystal > amorphous*,
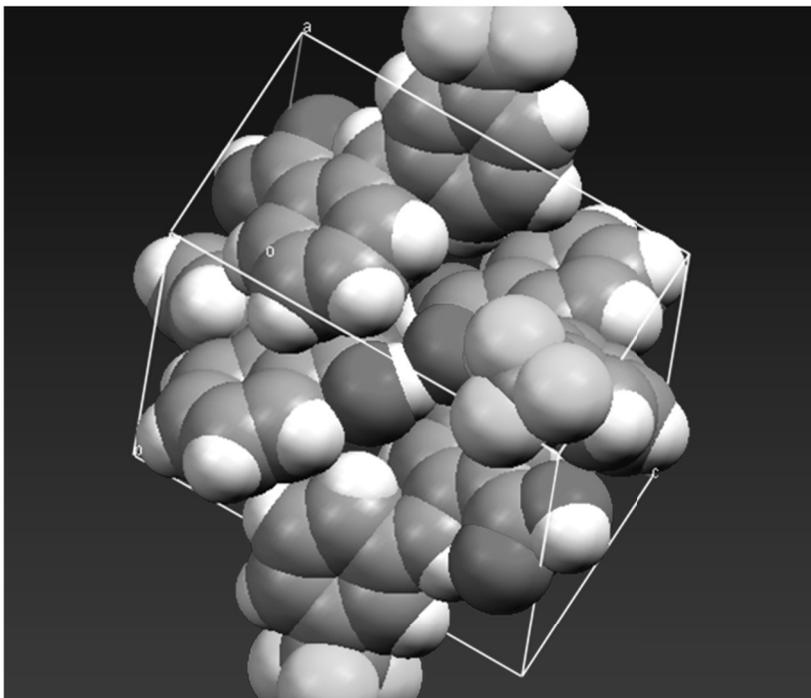3. lower solubility,

Figure 1.4 Space-filling drawing of the unit cell of flufenamic acid form I.
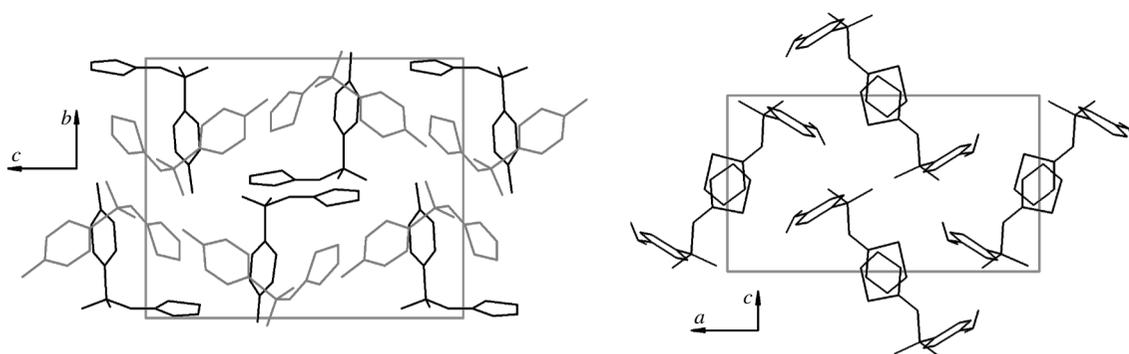

Figure 1.5 Crystal packing and unit cells (gray) of Forms I (left panel) and II (right panel) of sulfathiazole. The grey and black molecules in Form I indicate two unrelated molecules in the asymmetric unit. *Source*: Kruger and Gafner [7, 8]. Redrawn from data published.

4. narrow and (usually) higher melting point range,
5. harder,
6. brittle – slip and cleavage,
7. directionally dependent properties – anisotropy,
8. less compressible,
9. better flow and handling characteristics, and
10. less hygroscopic.

From this list, crystalline materials are generally more desirable unless they are so insoluble that they cannot be used as medicines.

Not only do polymorphs show different X-ray powder diffraction patterns, but they also have different unit cells and different properties, including thermal properties [6]. Figure 1.5 shows the different crystal packing of the Forms I and II of sulfathiazole [7, 8].

Additionally, polymorphs are characterized as monotropic or enantiotropic depending on their thermal properties [9, 10].

- Monotropic polymorphs exist if the transition temperature between forms occurs after the melt. In monotropic polymorphs, one form is most stable throughout the temperature range.
- Enantiotropic polymorphs exist if the transition temperature between forms occurs before melting. In this case, one form is more stable at one temperature. At a different temperature, the other form is most stable. For flufenamic acid, Form I is most stable above the transition temperature of 42 °C, and Form III is most stable below the transition temperature. Practically, this means that slurrying at room temperature will convert Form I to Form III.

Crystalline solvates contain solvents regularly incorporated into the crystal lattice. When the solvent is water, the solid form is called a hydrate. Solvates and hydrates do not have the same composition as unsolvated materials. Solvates and hydrates are sometimes referred to as pseudopolymorphs or solvatomorphs. Interestingly, solvates and hydrates can be polymorphic. In such a case, polymorphic solvates exist. Kuhnert Brandstatter in her 1971 book showed photomicrographs of 16 solvates of estradiol [11]. Figure 1.6 shows the crystal structure of caffeine monohydrate. The crystal of caffeine is built up by stacking the layers shown in Figure 1.6 on top of each other. Thus, the hydrate molecules are in tunnels in this solid form.

It is important to note that the Food and Drug Administration (FDA) has defined polymorphs as "different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Per the current regulatory scheme, different polymorphic forms are considered the same active ingredients." Thus, for purposes of registration, scientists are directed to define polymorphs more broadly to include amorphous forms, solvates, and hydrates.

Cocrystals, that is, two-component crystals, are another solid material of interest. Like solvates, the new crystalline structure imparts different properties to the material, including solubility, stability, and mechanical properties. Of special interest are cocrystals with altered solubility or stability. Figure 1.7 shows the crystal structure of a cocrystal of 2-methoxy-4-nitrophenol–4-(dimethylamino)pyridine and phenol (2:1) [12]. The FDA has recently released a guidance defining cocrystals as "solids that are crystalline materials composed of two or more molecules in the same crystal lattice."

Pharmaceutical salts are substances formed by the reaction of an acid and a base. The FDA has suggested the following definition of salts: "Any of numerous compounds that result from replacement of part or all of the acid hydrogens of an acid by a metal or a radical acting like a metal: an ionic or electrovalent crystalline compound. Per the current regulatory scheme, different salt forms of the same active moiety are considered different active ingredients." When a carboxylic acid reacts with an amine, a salt is typically formed (Scheme 1.1). However, the degree of proton transfer can vary depending on the acidity and basicity of the reacting groups. The FDA definition seems to encompass all these materials.
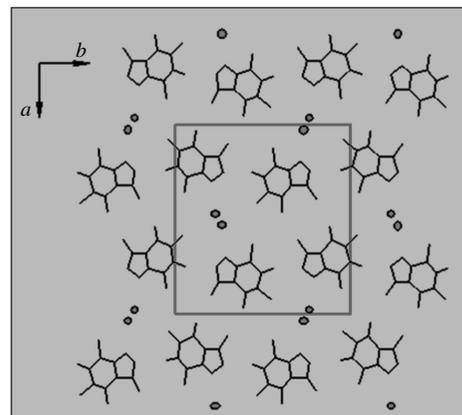
Figure 1.6 Projection of the crystal structure of caffeine hydrate on the *ab* plane. *Source*: Burger and Ramberger [9, 10]. Reproduced with the permission of Springer.

Figure 1.7 Crystal structure of a cocrystal (2-methoxy-4-nitrophenol–4-(dimethylamino) pyridine and phenol (2 : 1)). The unit cell parameters are $a = 6.880$, $b = 38.40$, $c = 8.454$, and the space group is Pna2$_1$. *Source*: Reproduced from [12]/with permission of Royal Society of Chemistry/CC BY 3.0.

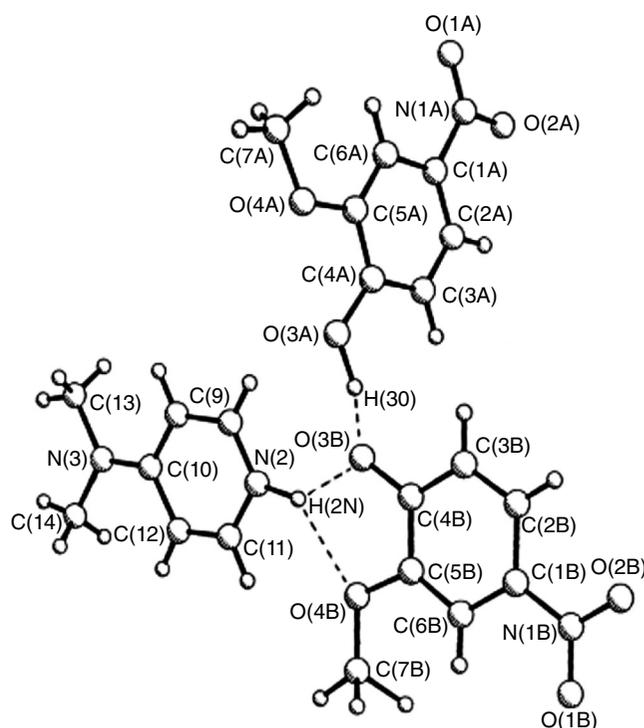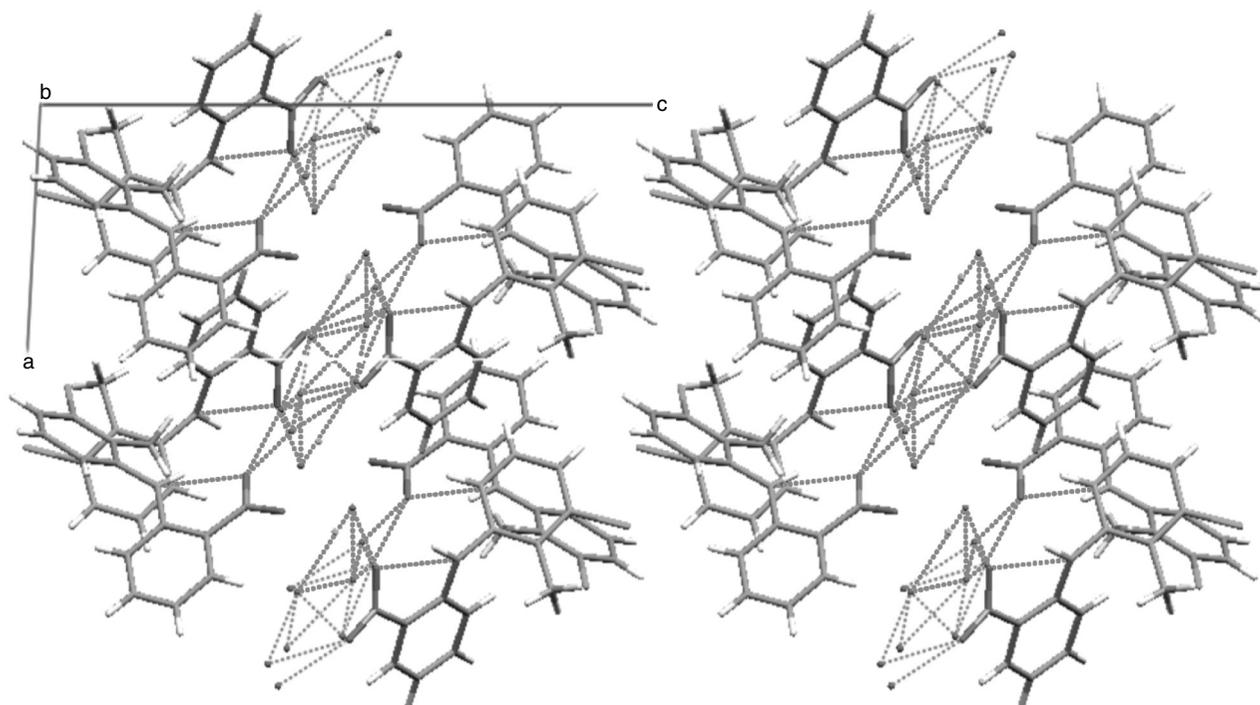**Figure 1.8** Crystal packing of calcium tolfenamate trihydrate showing hydrogen bonding network. The directions of the unit cell axis are (a) vertical, (c) across, and (b) out of the plane of the paper. *Source*: Adapted from [13].

Scheme 1.1

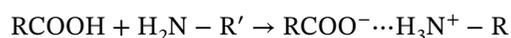$$RCOOH + H_2N - R' \rightarrow RCOO^- \cdots H_3N^+ - R$$

Figure 1.8 shows the crystal structure of calcium tolfenamate trihydrate [13]. The unit cell is composed of regions containing mostly hydrocarbon functional groups and regions containing polar functionalities. This type of crystal packing is typical for salts.

1.3 Bulk and Surface Properties of Solids

As we can anticipate from this previous discussion of solid forms, molecules in the solid state, whether in a crystalline or amorphous state, will pack together in various geometric arrangements with different interaction energies, which ultimately determine their various physical and chemical properties. Such arrangements and interactions will primarily depend on the chemical structure, molecular size and shape, and modes of bringing about solidification, that is, modes of crystallization or vitrification. Most importantly, such structural features will determine physical and chemical properties, described in this book, such as rates of crystallization, polymorphic transformations, chemical instability, solubility and dissolution, mechanical responses to various stresses, liquid crystal formation, protein denaturation, and modes of hygroscopicity. It is also important to recognize that such properties will be quite different for molecules in the bulk and surface phases. In the bulk phase, a molecule is generally locally surrounded in all dimensions by other molecules, as schematically illustrated in Figure 1.1, and forces on any molecule will be evenly balanced. On the other hand, interactions across an immiscible phase boundary will generally be unbalanced and greater in the direction of the bulk phase, giving rise to lower densities and greater molecular mobility at the surface. This gives rise to the surface tension not only observed with liquids but also demonstrated in solids [14]. Usually, the mass of molecules in the bulk phase is much greater than that at

the surface; that is, there is a very small surface-to-volume ratio, and surface properties will not necessarily be important in determining overall thermodynamic and dynamic properties. However, for extremely small particles with very high surface-to-volume ratios, such as nanocrystals, porous solids, or crystal nuclei, surface properties can be the determining factor in influencing both surface and bulk physical and chemical properties. Such surface properties include vapor adsorption by solids, the rate of crystal nucleation, and the ability of liquids to spontaneously spread over solid surfaces or penetrate highly porous structures, that is, wetting [15, 16]. Throughout this book various properties of solids will be discussed in the context of structural arrangements and intermolecular interactions in the bulk phase, with additional surface effects under certain conditions.

1.4   ICH Q6A Decision Trees

In 1995, Byrn, Pfeiffer, Ganey, Poochikian, and Hoiberg from Purdue University and the FDA published a paper using decision trees to describe a strategy to identify the best solid form early in development. In this way, it is possible to ensure uniformity of a solid form in clinical trials and resolve solid-state issues before critical stages of development. The decision trees also suggested appropriate analytical methods for control. Four decision trees were presented: polymorphs, hydrates/ solvates, desolvated solvates, and amorphous forms [17].

In the late 1990s, the International Committee on Harmonization (ICH) used a similar decision tree approach to describe how specifications for the solid form in drug substances (API) and drug products should be determined. The ICH Q6A document presented several decision trees, including decision trees on particle size and polymorphs [18]. The ICH utilized the broadened definition of polymorphs that includes hydrates, solvates, and amorphous forms. The ICH decision trees are divided into three questions, as shown in Figures 1.9–1.11.

These three decision trees outline a strategy widely used during drug development. Most firms conduct an early polymorph screen to address question number 1. Once new forms have been identified, they are physically characterized (solubility, stability, melting point), and an effort is made to understand whether these differences in properties will affect drug product safety, performance, or efficacy. If the different solid forms can affect safety, efficacy, or performance, then question 3 is addressed by determining whether drug product testing can detect changes in ratios of these forms. Additionally, the ratios of forms are monitored during stability studies to make sure changes that affect performance, safety, or efficacy do not occur. Using this strategy, it is possible to find the best solid form for rapid development.
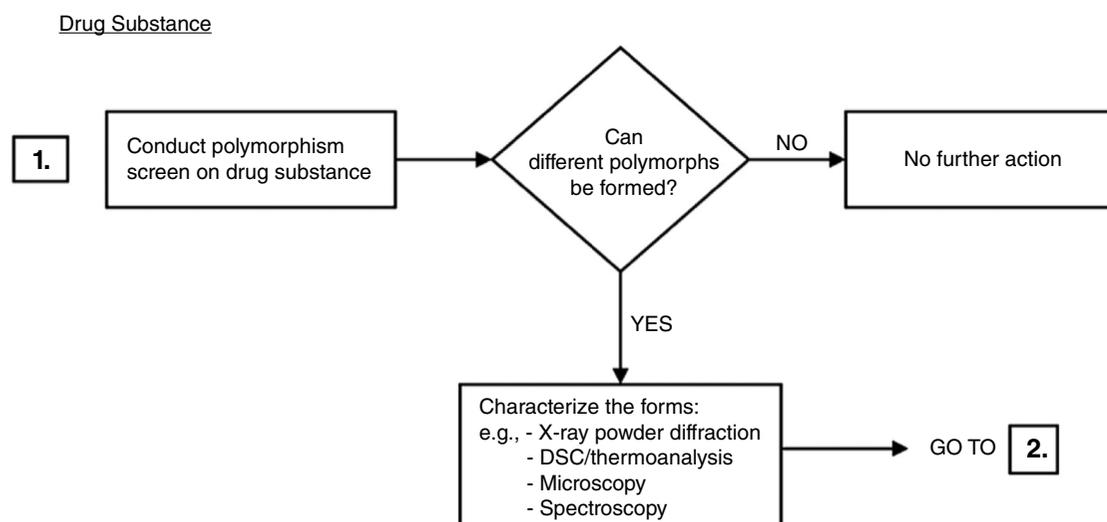

Figure 1.9   ICH Q6A question 1 on polymorphs: Can different polymorphs be formed? *Source*: ICH Harmonized Tripartite Guideline [18]. Reproduced with the permission of ICH.
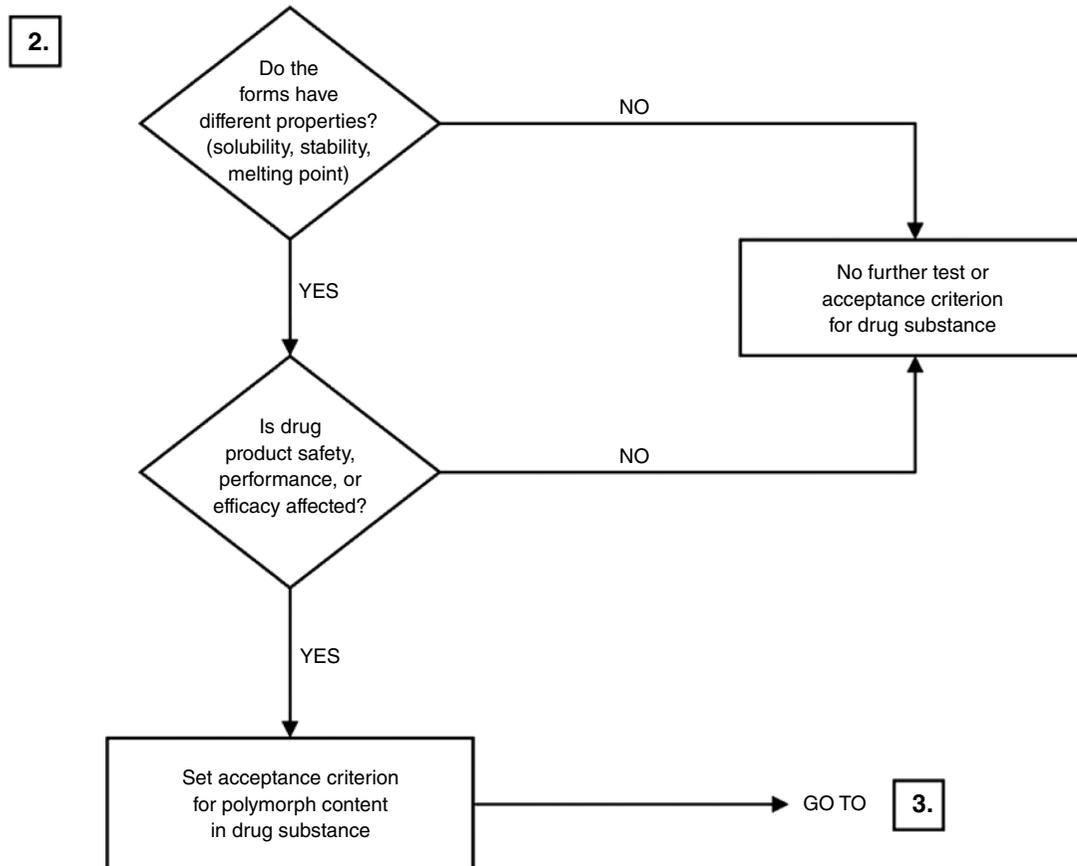
Figure 1.10 ICH Q6A question 2 on polymorphs: Do the forms have different properties (solubility, stability, and melting point)? *Source*: ICH Harmonized Tripartite Guideline [18]. Reproduced with permission of ICH.

1.5 "Big Questions" for Drug Development

In addition to selecting the solid form, Table 1.1 lists other critical issues/measurements required for drug development.

Another way to think about drug development is to think of this process in terms of answering a series of questions we call the "Big Questions." These must be answered to be able to develop a drug for clinical trials and beyond. These questions are:

- What is the structure of the compound?
- What is the likely dose?
- What is the route of administration and desired dosage form?
- What is the indication?
- How difficult is it to synthesize?
- How soluble is the compound/formulation?
- How well is the compound absorbed? What is its Biopharmaceutical Classification System (BCS) class?
- What is the toxicology of the compound? What is its no-observed-adverse-effect-level? What is its maximum tolerated dose (MTD)?
- What biomarkers are available to monitor clinical trials?
- What doses should be used for the Phase 2 clinical trial?
- What are its solid-state properties and physical characterization?
- How chemically stable is the compound?
- How physically stable is the compound?
- How well will the powder flow?
- Is moisture an issue?
- What is the design, composition, and manufacturing procedure of the formulation/product?

3.
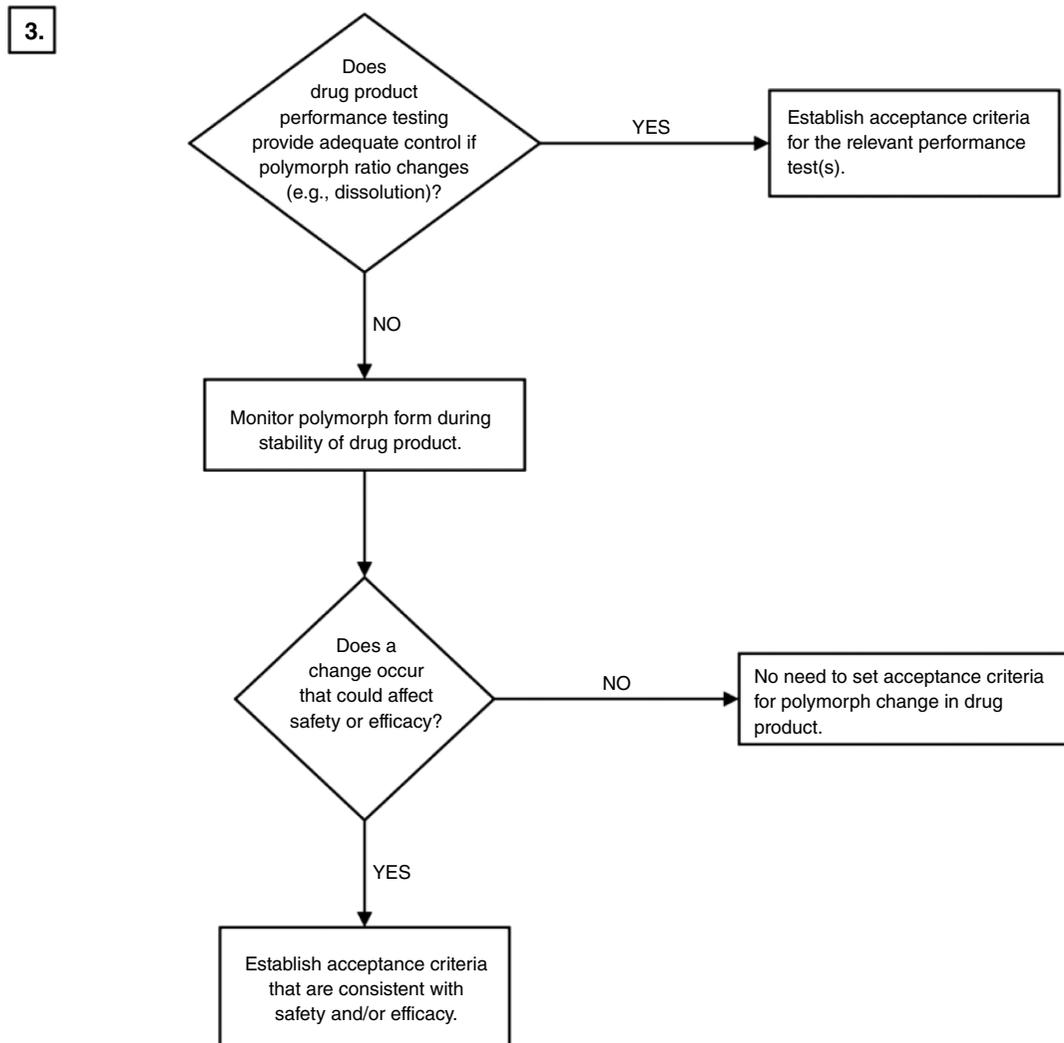
Figure 1.11 ICH Q6A question 3 on polymorphs: Does product performance testing provide adequate control in polymorph ratio changes (e.g. dissolution)? *Source*: ICH Harmonized Tripartite Guideline (1999) [18]. Reproduced with permission of ICH.

Table 1.1 Critical issues for accelerated drug development.

Polymorph selection

Chemical synthesis

Salt selection (optional)

Assay/impurities

Particle size

Physical characterization and properties

Dissolution/solubility

Consistency

Stability

Validated methods/processes

Regulatory issues

Intellectual property

Table 1.2   Biopharmaceutical classification system (BCS).

BCS classification	Solubility	Permeability
BCS class I	High	High
BCS class II	Low	High
BCS class III	High	Low
BCS class IV	Low	Low

As has already been discussed, the solubility of the compound is a critical quality attribute important for specifications and development. The solubility of a solid substance is the concentration at which the solution phase is in equilibrium with a given solid phase at a stated temperature and pressure. Under these conditions, the solid neither dissolves nor continues to crystallize. Note that the definition implies the presence of a specific solid phase. Once determined under the stated conditions, however, we can talk about the "solubility" of a given phase (e.g. a specific polymorph or pseudopolymorph) as a quantity, even in the absence of that solid phase. The use of the term "equilibrium" in connection with crystallizing systems requires clarification. When a substance exists in more than one crystal form, that is, when other polymorphs are possible, only the least soluble of these at a given temperature is considered the most physically stable form at that temperature; all others are metastable forms. In given cases, a solution of a substance may be in apparent equilibrium with one of these metastable phases for a long time, in which case, the system is in metastable equilibrium and is expressing the thermodynamic solubility of that solid form.

It is important to stress the difference between polymorphs and solvates (pseudopolymorphs) at this point. If a solvate/pseudopolymorph exists, it is always (with few exceptions) the most stable form in the solvent that produces the pseudopolymorph.

Undersaturation pertains to solutions at a lower concentration than the saturation value (i.e. diluted solutions). Crystals will dissolve in undersaturated solutions. Saturation is the state of a system where the solid is in equilibrium with the solution, or, in other words, the solution will neither dissolve crystals nor let them grow (i.e. the concentration of the solution represents the solubility value for that crystalline phase). Supersaturation pertains to solutions that, for one reason or another (e.g. rapid cooling of a saturated solution without forming crystals), are at a higher concentration than the saturation value. Supersaturation is required for crystals to grow.

The solubility and permeability are combined to determine the BCS class (Table 1.2). BCS class I drugs dissolve easily and are easily transported into the bloodstream because they are highly permeable with respect to the membranes in the gastrointestinal (GI) tract. BCS class III and IV drugs have poor permeability and are generally difficult to develop. BCS class II drugs are of the greatest interest to pharmaceutical scientists because the structure of the solid, the formulation, its physical character, and many other factors are likely to have a significant effect on bioavailability and ultimately safety, performance, and efficacy. Several important drugs that are widely prescribed are BCS class II, including atorvastatin calcium, celecoxib, efavirenz, irbesartan, lopinavir, medroxyprogesterone acetate, raloxifene hydrochloride, simvastatin, and warfarin sodium. Of the marketed drugs nearly 70% are in BCS class I or II with 31% being in BCS class II. It has been estimated that as high as 80% of the drugs under development are BCS class II.

1.6 Accelerating Drug Development

Accelerating drug development has been a goal of pharmaceutical scientists for many years. One of the earliest discussions of accelerated development can be traced back to 1958 when the National Cancer Chemotherapy Program reported that the pharmaceutical industry was launching major anticancer drug development efforts to accelerate the search for effective agents [19]. This early program was, of course, responsible for the major advances in the treatment and eradication of cancer. In 1995, Colin Gardner of Merck introduced a flow chart showing the synthesis of the API and the development of clinical supplies for first-in-human trials in 1 year. In this early flow chart, drug substance synthesis and process development were carried out in parallel with preformulation/formulation design/development and safety studies. Despite the early introduction of the concept that an investigational new drug (IND) can be submitted in 1 year, it has been difficult to achieve this goal except in very favorable cases. One of the difficulties is the availability of the API, and another one of the difficulties is accelerating toxicology studies. In 1997, Pisano wrote a book for Harvard University Press entitled *The Development Factory* that addressed rapid drug development. Many of his examples came from Bristol Myers Squibb

(BMS) [20]. He described drug development as a learning process and concluded that learning before doing was the most reliable approach to rapid drug development.

In 2007, Aptuit/Solid State Chemical Information (SSCI) introduced their IND-I-GO (INDIGO) program, offering fast development in a Contract Research Organization (CRO) environment. INDIGO was tailored to work with BCS class II compounds and poorly soluble compounds. This INDIGO offering was supported by an example case study on the poorly soluble drug itraconazole and was summarized in a recent publication [21]. Additionally, Byrn et al. and Byrn and Henck outlined strategies based on solid-state chemistry for reducing development time [22, 23]. These publications contained much more detail on how to carry out screens and are discussed in more detail in the following text. In this same time-frame, Chorus, a Lilly-based firm, focused on fast development, introducing their strategy for accelerated development to Phase II [24]. In this early publication, they suggested that it was possible to develop a compound to Phase II in 30 months for $3 million in contrast to the industry average of 42 months and $30 million. The Chorus approach involves a virtual company that heavily uses preferred CROs. Chorus has been quite successful, and Lilly has now established Chorus as an independent entity. In 2015 the success of Chorus over the past 10 years was summarized [25]. Chorus has developed 41 molecules over the years and maintains a portfolio of 15–17 active projects at any one time.

In this same timeframe, PricewaterhouseCoopers introduced a concept of limited launch with what they have termed a "live license" that permits a company to market a drug under very restricted conditions. In one manifestation of this concept, they suggested the launch of a drug after 1.5 years. The details of this strategy are not clear, but it appears that the proposal involves introducing the drug for a limited population and then expanding use as clinical data allows. This, of course, would require the FDA to license drugs differently. The main point of this strategy for our context is that the introduction of a medicine after 1.5 years would require very rapid development and very rapid FDA review. Regardless of the details, the solid form, the formulation, the synthesis of the drug, and all of the other critical steps outlined in Table 1.1 would have to be accomplished quite rapidly.

Recently, the National Institute for Pharmaceutical Technology & Education held a conference aimed at addressing the question: What does Industry Need to Accelerate Drug Product and Process Development? [26] The workshop identified five fundamental barriers to overcome: (1) an intermediate designation by the FDA for accelerated development (This designation would not be an emergency use authorization but also not be a standard NDA. It would be something in between); (2) a mechanism to allow faster stability testing based on artificial intelligence (AI) and structural analysis of the drug; (3) flexible development and manufacturing including continuous and semi-continuous manufacturing; (4) advanced enabling technologies including process analytical technology (PAT) and on-line methods; and (5) integrated product and process development similar to the INDIGO methods outlined earlier and including formulation by design. They also suggested the possible use of AI methods and other technologies to advance animal testing.

Regardless of the model, it is clear that the development process must be accelerated in the future. Accelerated development is especially dependent on the first year of activities. During the first year, three critical steps must be accomplished. The drug must be synthesized. The toxicology must be determined to figure out the initial dose for first-in-human trials, and the solid form and formulation must be developed so that a medicine is available for first-in-human trials. This requires three groups to work together: API synthesis, toxicology, and pharmaceutical sciences. Figure 1.12 shows a detailed 52-week strategy.

The top three bars show the synthesis of the API. Depending on the dose, several kilograms of API will be required for toxicology studies, which are shown in the fourth bar. A key aspect of the toxicology study is the determination of the toxicology formulation. As pointed out by the Merck group, the toxicology formulation can be critical for poorly soluble drugs. If not enough of the drug can be dissolved, then it is impossible to advance that lead [27]. The four bars on the bottom outline the formulation and manufacture of clinical supplies and the regulatory activities needed to file an IND. Engers, Byrn, Newman, and coworkers were able to meet the timelines in Figure 1.12 and develop a mock IND for itraconazole [21].

Even more acceleration of the development timeframe can be achieved if, during the first year, adaptive clinical trials are designed, biomarkers for the clinical trial endpoints are defined, and assays for these biomarkers are developed. Adaptive clinical trials allow merging of phase I and phase II studies and can sometimes accelerate proof-of-concept studies [28]. Adaptive clinical trials are often considered in two phases, exploratory and confirmatory, and use biomarkers. Biomarkers are quantifiable substances that can be correlated to a clinical response, for example, glucose levels for diabetes. Biomarkers can include genes, gene products, enzymes, cytokines, or even cells. Finding a biomarker can greatly advance early decision making and accelerate clinical trials.

One of the goals of accelerated development is to eliminate compounds that are clinically unacceptable or cannot be developed early, so that more resources are available to focus on compounds that are truly acceptable. For example, if a material is so insoluble that its maximum absorbable dose (MAD) or MTD cannot be determined in animal studies, then this must be determined as early as possible. Likewise, if a compound has unacceptable neurotoxicity, this needs to be determined as early as possible. Thus, a strategy that focuses on the most soluble formulation early in the process will provide important
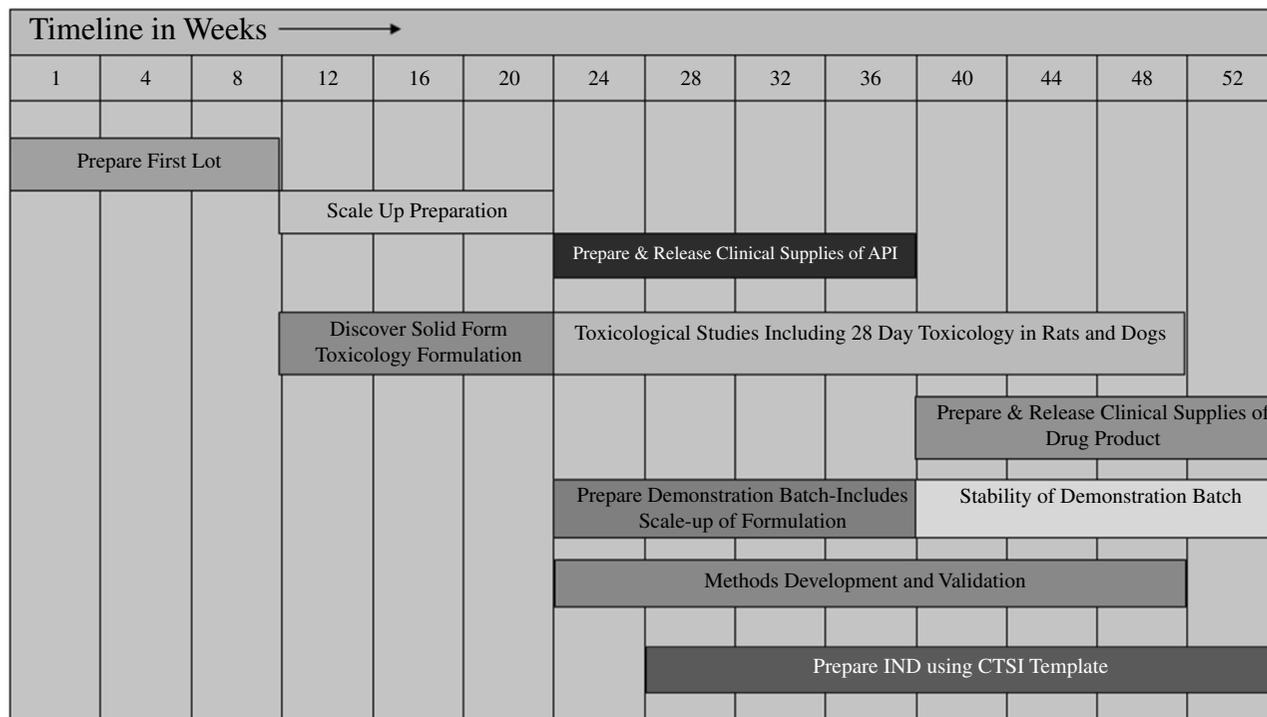
Timeline in Weeks ⟶													
1	4	8	12	16	20	24	28	32	36	40	44	48	52

Figure content (Gantt chart):
- Prepare First Lot (weeks ~1–10)
- Scale Up Preparation (weeks ~10–24)
- Prepare & Release Clinical Supplies of API (weeks ~24–38)
- Discover Solid Form Toxicology Formulation (weeks ~10–24)
- Toxicological Studies Including 28 Day Toxicology in Rats and Dogs (weeks ~24–40)
- Prepare & Release Clinical Supplies of Drug Product (weeks ~40–52)
- Prepare Demonstration Batch-Includes Scale-up of Formulation (weeks ~24–40)
- Stability of Demonstration Batch (weeks ~40–52)
- Methods Development and Validation (weeks ~24–48)
- Prepare IND using CTSI Template (weeks ~28–52)

Figure 1.12 Detailed 52-week strategy for accelerated drug development.

Figure content (diagram):
Solid-State Technology (central), with spokes to: Dosage Choice, Manufacturing, Purification and Process Development, Formulation & Drug Delivery, Marketing & Further Product Improvements, Patents, Regulatory, Stability, Quality Control, Research, Toxicology.
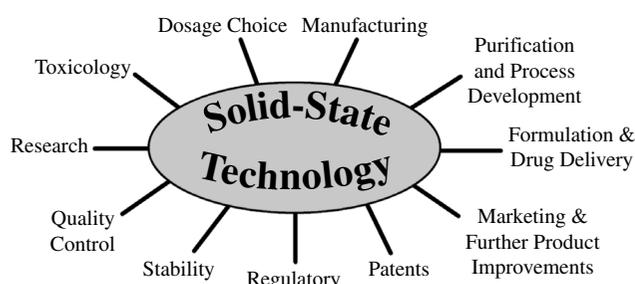
Figure 1.13 Role of solid-state technology in the pharmaceutical industry.

information in both cases. For this reason, some experts suggest that initial formulations should use amorphous forms to identify poorly soluble and highly toxic materials.

1.7 Solid-state Chemistry in Preformulation and Formulation

Figure 1.13 illustrates the important role that solid-state technology plays in the entire development process, including research. In fact, a group from Merck (see above) in a *Journal of Medicinal Chemistry* review has advocated moving solid-state chemistry earlier in drug discovery to ensure that a developable solid form is discovered [27]. As mentioned earlier, the solid form is important in toxicology since an insoluble solid-state form will appear to be nontoxic, perhaps falsely. The solid form is important in dosage choice, manufacturing, purification, development, and formulation. In some cases, product improvements and marketing can be facilitated by finding the best solid form. For example, the Kaletra product (containing lopinavir and ritonavir) is now marketed in an amorphous form that is stable and does not require refrigeration, as did the previous soft gel capsule. Solid forms are quite important for patents and regulatory filings, as discussed earlier. Finally, the stability of the product can be critically related to the solid form.

Particle size, like polymorphism, is one of the most critical aspects of solid-state chemistry. The incorrect particle size can cause a change in the rate of dissolution and affect safety, efficacy, and performance. Figure 1.14 shows a classic study of the effect of particle size of a suspension on blood levels of phenobarbital [29]. This data, as well as the ICH Q6A document on specifications, make it clear that the particle size of APIs (drug substances) must be controlled, especially if they are poorly soluble.

Figure 1.12 illustrates one possibility for when solid-state chemistry is done during preformulation and formulation design. It is important to find a form with acceptable aqueous solubility during this study. In many cases, a form with fast kinetic solubility must be found. If possible, the high solubility should be maintained until the drug is absorbed
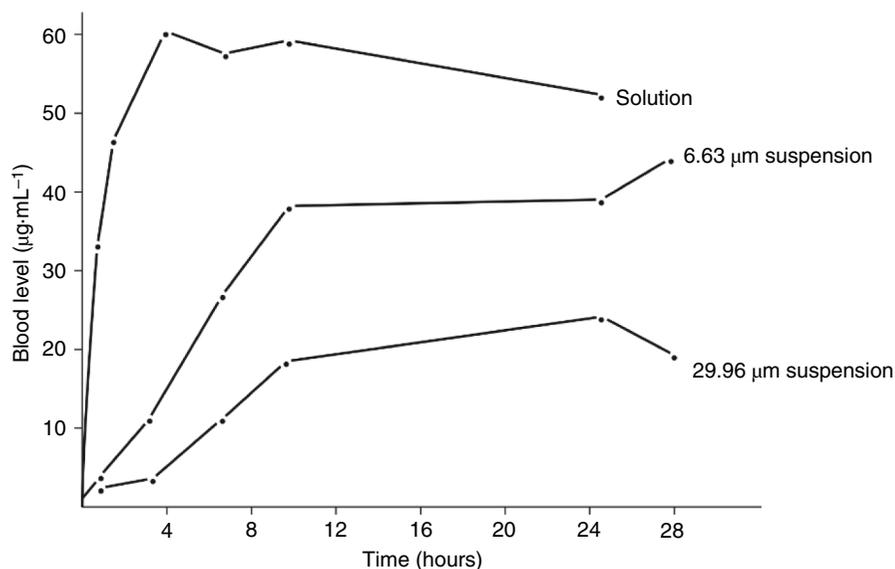
Figure 1.14 Effect of particle size on blood levels. *Source*: Adapted from [29].

from the GI tract. It may be necessary to use crystallization inhibitors to prevent premature precipitation of the solid form. Additionally, the solid form must be chemically stable enough not to decompose during an IND trial. An important goal is to find the form before the final step of the API synthesis. In this way the final form can be prepared in the last step. Additionally, if this can be achieved, the same form can be used for both toxicology and first-in-human studies.

After the first year, additional solid-state and particle size studies will be needed. First, it will be important to confirm the results of the early solid-state studies. It is especially important to do some additional screening to confirm that the best solid form has been selected. There is time for additional salt screening studies and perhaps even cocrystal or nanocrystal screening studies. Furthermore, more complex formulations can be developed. For example, if possible, a simple granulation process should be developed. Alternatively, a roller compaction procedure can be investigated.

In many cases, when the dose of the drug is dissolved, it will be in a supersaturated solution with respect to the most stable crystal form. Thermodynamically, there will be a tendency for this most stable form to crystallize. This system has been termed a supersaturating drug delivery system [30].

Screening is the approach to use to find the best solid form, a manufacturing process, and a crystallization inhibitor, if needed. Polymorph screening was suggested in the mid-1990s for regulatory purposes and to find the form that resulted in the most desirable bioavailability. During the intervening years it has become clear that screening is critical. In the early studies, during the first year, abbreviated screens should be used.

A typical abbreviated screen was described in the early review by Byrn et al. [17]. Solvents should include those used in the final crystallization steps and those used during formulation and processing, such as water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane, and mixtures if appropriate. New crystal forms can often be obtained by cooling hot, saturated solutions or partly evaporating clear, saturated solutions. The solids produced are analyzed using X-ray diffraction and at least one of the other methods. In these analyses, care must be taken to show that the method of sample preparation (i.e. drying, grinding) has not affected the solid form.

Later, more complete screening studies are recommended. If a supersaturated solution is created it is important to screen for a crystallization inhibitor [30]. As indicated, screening is typically done for polymorphs, including amorphous forms, salts, cocrystals, and nanoparticulate formulations.

In addition to screening and selection of the best solid form and optimization/control of particle size, preformulation experiments are carried out. These experiments include the determination of the partition coefficient (log *P*). This reflects the hydrophobicity of the drug and can be useful in determining the BCS class. The solubility of all available forms and the degree of precipitation of any solid forms are determined. Since solubility can depend on solid form, the solubility is typically determined in aqueous buffers, organic solvents, surfactant solutions, and perhaps cyclodextrins and lipids. Solubility can be difficult to determine and should be determined under equilibrium conditions. The solution and solid-state stability
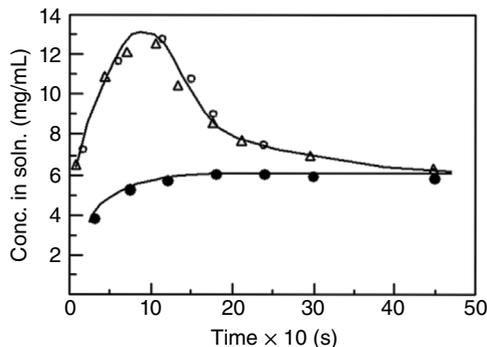
Figure 1.15 Dissolution study of two different forms of theophylline. *Source*: Shefter and Higuchi [31]. Reproduced with the permission of Elsevier.
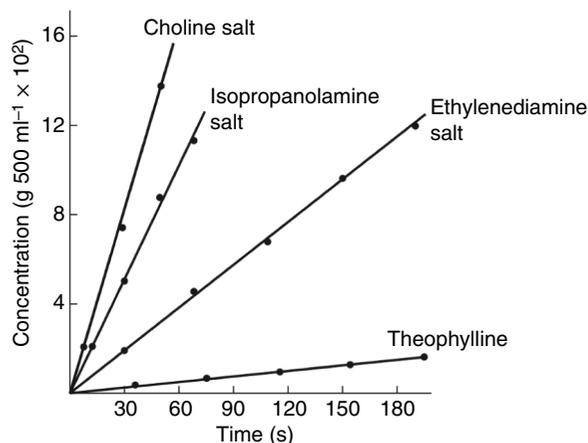

Figure 1.16 Enhancement of solubility and dissolution rate by salt formation. *Source*: Nelson [32]. Reproduced with the permission of Elsevier.
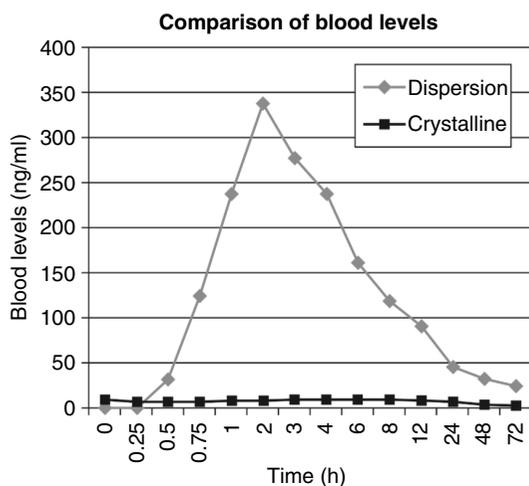

Figure 1.17 Comparison of the bioavailability of a 2:1 HPMC-P:itraconazole dispersion in dogs. *Source*: Adapted from [21]. Redrawn from data published.

of the API is determined under stress conditions, including extreme pH, temperature, light, and humidity. This provides information on the system's intrinsic chemical stability; this knowledge is critical in formulation development. The pK_a is also determined or calculated. This provides important information on the acidity or basicity of the material.

Once the initial solid form has been selected based on the previous screening experiments, the stability of that form is determined under stress and accelerated conditions. This provides important information on how to handle that particular form. The dissolution properties of this form are also monitored. This provides important information on what might happen in the GI tract.

Figure 1.15 illustrates the importance of studying the dissolution rate of different forms [31]. In this study, the hydrate showed normal dissolution behavior, reaching a solubility of about 6 mg/mL. In contrast, the anhydrate showed rapid kinetic dissolution to form a supersaturated solution. This solution then crystallized after about 100 seconds into the hydrate. At the end of the experiment (500 seconds), equilibrium had been reached, and the solubilities of both forms were the same and equal to the hydrate form, which was the solid form present.

Figure 1.16 shows a similar experiment by Nelson on salts of theophylline [32]. This experiment's timeframe was short enough that theophylline hydrate did not crystallize. This figure shows the rapid dissolution rate achieved by some salts. In fact, for some pharmaceutical salts, such as sodium phenytoin, a solubility enhancement of about 1 000 000 is achieved. This clearly shows the desirability of finding salt forms and explains why many drugs are developed as salts. Of course, salt forms are also known to increase the bioavailability of solid forms greatly.

A viable alternative to salt formation, especially in cases where a salt cannot be formed, is to develop an amorphous form/formulation. There are several products containing amorphous forms on the market, including Kaletra and Sporanox. A review reports that amorphous formulations can result in as much as an 82× increase in bioavailability [33]. Law and coworkers reported greatly enhanced plasma concentrations of amorphous ritonavir over crystalline material. Ritonavir is one of the components in Kaletra [34]. Figure 1.17 shows the results of studies of a 2:1 hydroxypropyl methylcellulose (HPMC)-P:itraconazole dispersion in dogs. Clearly, the dispersion results in a large increase in bioavailability.

An alternative to salt formation is cocrystal formation. Figure 1.18 shows that a cocrystal enhanced the bioavailability of an amide-containing API by about 4× [35].

In another interesting study of cocrystals, Childs and coworkers at SSCI showed that cocrystals of fluoxetine hydrochloride could be formed that had faster and slower dissolution rates than the parent [36]. This remains one of the only examples where cocrystals resulted in both enhanced and reduced dissolution rates.

As discussed earlier, amorphous and cocrystalline formulations are classified as supersaturated drug delivery systems. Crystallization inhibitors are sometimes used to prevent premature crystallization for these formulations.
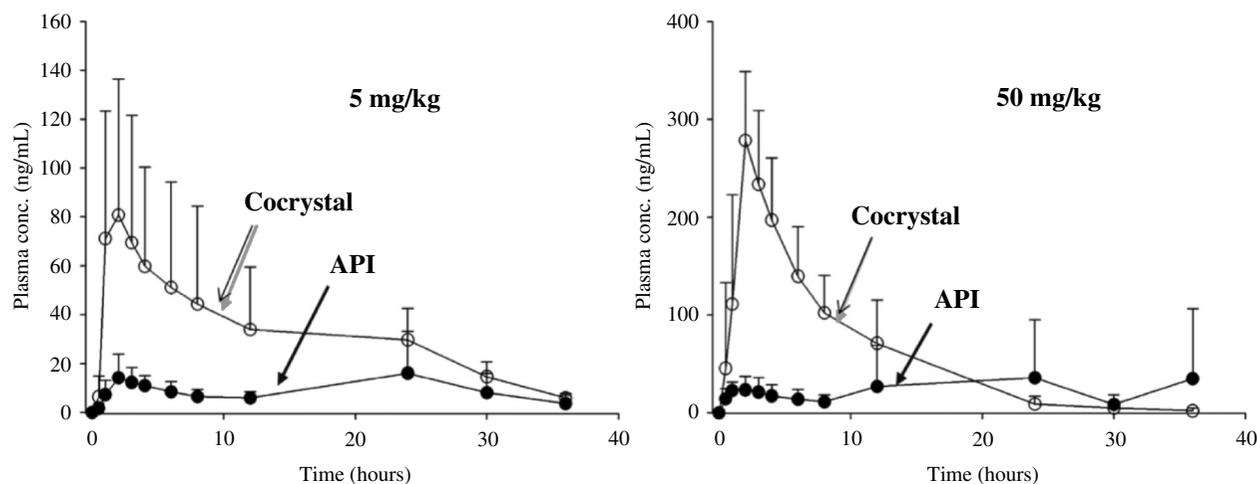
Figure 1.18 Enhanced bioavailability of a cocrystal over the parent drug. *Source*: McNamara et al. [35]. Reproduced with the permission of Springer.

In addition to increasing solubility/dissolution rate, the solid form can influence several other properties important for formulation, including milling, blending, tableting, dry filling, suspension formulation, and lyophilization. Transformations to other forms can also occur during these processes.

1.8 Solid–Lipid Nanoparticles

Solid–lipid nanoparticles (SLNs) provide another strategy for the formulation of drugs and nucleic acids. As the name implies, SLNs are lipidic compositions that are in a solid form. The COVID vaccines, SpikeVax and Comirnaty, contain SLN composed of the cationic lipid, distearoylphosphatidylcholine (DSPC), cholesterol, and polyethylene glycol (PEG) lipid. PEG lipid is a class of polyethylene glycol derivatives attached to a lipid moiety. C&E News stated that, without these lipid shells, there would have been no COVID vaccine. These vaccines have been administered to millions of people with minimal side effects. Cationic lipid-based SLN have been introduced into clinical medicine because of the rapid development of SARS-CoV-2 vaccines. These vaccines utilize second-generation cationic lipids that are easily metabolized and do not exhibit many of the side effects of earlier cationic lipids [37]. The cationic lipids in the SARS-CoV-2 vaccines encapsulate the anionic mRNA by forming a hydrophobic ion pair between the lipid's amine group and the phosphate groups on the nucleic acid backbone [38].

There has been a significant interest in SLN materials for many years before the COVID pandemic. Mehnert and Mader provided an excellent review of the development of SLN up to 2012 [39]. In this review they mention many SLN incorporating drugs, but, curiously, they do not describe the incorporation of nucleic acid and RNA in SLN. A more recent review by Duan and coworkers describes the use of SLN as a dominant formulation strategy with the advantages of liposomes and polymeric nanoparticles, partly because they are non-biotoxic and stable [40]. Montoto describes the current state of this field as the "Golden Age of Pharmaceutical Nanocarriers" [41]. He also points out that SLNs are easy to produce and non-toxic and describes a wide range of diseases that SLNs can treat, including infectious diseases, CNS diseases, and a variety of site-specific treatments. Additionally, nucleic acid SLNs can be used to develop gene therapies, cancer vaccines, malaria vaccines, and a wide range of other therapies.

SLNs have a range of advantages in their use, including improved active agent stability, the potential for controlled release, the potential to increase the solubility of poorly soluble drugs, reduced drug leakage, and more specific drug targeting. SLNs can also often be easily manufactured, for example, freeze-dried and, in favorable cases, reconstituted for injection or utilized directly. For example, celecoxib SLN were freeze-dried with cryoprotectants to yield an acceptable non-collapsed, freeze-dried cake with good redispersal properties, minimal changes in particle size, and long-term stability at refrigerator temperatures [42]. Santonocito and coworkers also reported successful freeze drying of SLN [43]. Freeze drying has also been used to prepare dry powder SLN containing siRNA for inhalation to treat pulmonary disorders. One study successfully used thin film freeze drying to produce SLNs with good inhalation properties [44]. Spray drying is another well-known method for preparing dry powder SLN. In one study lactose and sodium dodecyl sulphate (SDS)
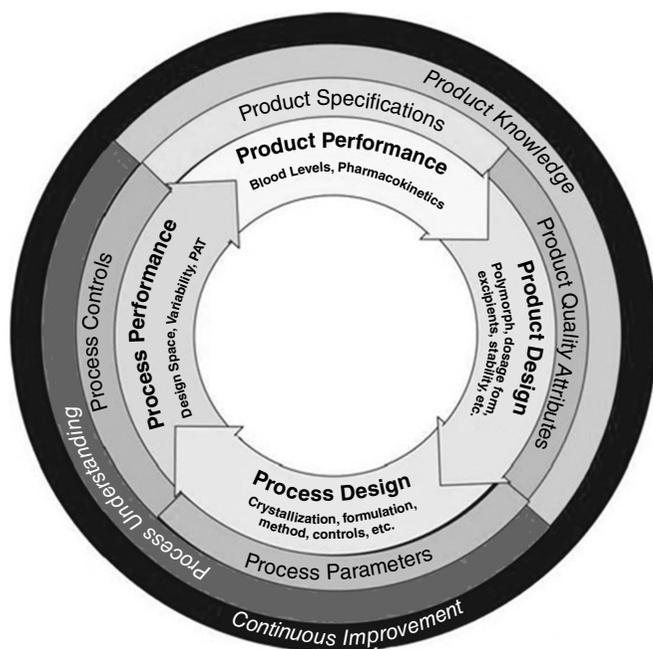
Figure 1.19 Quality-by-design strategies. *Source*: Byrn and Henck [23]. Reproduced with the permission of Elsevier.

were used as a matrix material in the spray drying of tristearin containing fenofibrate [45]. The spray-dried product had good re-dispersibility and produced particle sizes less than 300 nm. Spray drying has also been used to prepare siRNA SLN for pulmonary use. The nanoparticles contained an ionizable cationic lipid, which is a sulfur-containing analog of DLin-MC3-DMA, a helper lipid, cholesterol, and PEG-DMG encapsulating siRNA [46].

1.9 Learning Before Doing and Quality by Design

It is possible to achieve accelerated development using quality by design. Details are presented in Chapter 26. Figure 1.19 shows the quality-by-design wheel used by both the FDA and Pfizer. This wheel illustrates the importance of product design and process design. In effect, we have been discussing product design in this chapter. Using the optimum solid form, it is possible to design a product with the desired solubility. Once this has been achieved, the goal is to develop a formulation that optimizes other properties (e.g. flow) to make a viable product available. Additionally, a process that can reproducibly make the formulation must be achieved. As outlined earlier, often, with proper attention to the solid form, a quality product can be rapidly designed. Thus, in many respects, quality by design is based on preformulation studies.

A simple crystallization/amorphization process followed by filling a solid form in a capsule is often sufficient for early studies. This type of product can be manufactured from solid produced in a variety of ways including spray drying or crystallization followed by capsule filling using one of the commercially available automated capsule-filling machines.

First, good analytical methods for the physical characterization of the designed product must be developed. Then, critical sources of variability in the designed product need to be addressed: Is the solid form stable during its shelf life? What about extremes in temperature or humidity? What factors affect stability?

Stability issues, both chemical and physical, are a major impediment to quality by design. Often it is possible to identify stability problems during preformulation. Exposing the solid form to stress conditions and accelerated stability conditions can provide invaluable information on stability. Armed with this information, adjustments in the designed product can be made.

As development progresses beyond the initial product design and process design stage, multivariate experiments using sensors are typically used to develop a robust process for producing the medicine. If possible, PAT methods are used. A control strategy based on risk is developed to reduce the probability of catastrophic failures. Specifications based on desired product performance are established.

All this information is filed according to the ICH Common Technical Document (CTD). Table 1.3 shows where important quality-by-design data are submitted in an IND. Material submitted in the summary section for drug substance (S.2.x) and drug product (P.2.x) includes a description of critical quality attributes like dissolution rate, process description, process controls, and development history.

Table 1.3 shows the location of quality-by-design elements in the quality overall summary of the CTD, a prescribed format for submissions developed by the ICH.

Figure 1.20 shows the areas of study (learning) and then the formulation, product, and process design in a quality-by-design regime. The formulation is designed by utilizing information about the solid-state chemistry (polymorph), biopharmaceutics, stability, and mechanical properties. This is the product design. Then, a process is designed to make the dosage form.

Table 1.3 QbD elements in the quality overall summary, Section 2.

Question	Drug substance (DS)	Drug product (DP)	Comment
How do the manufacturing processes and controls ensure consistent production of the drug substance/product?	2.3.S.2	2.3.P.3	
How were potential impurities identified and characterized?	2.3.S.3		Impurity analysis is not always included in the drug product
What is the drug substance/product specification?	2.3.S.4	2.3.P.5	Includes explanation of how specifications ensure quality
What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?	2.3.S.7	2.3.P.8	
Pharmaceutical development		2.3.P.2	Includes discussion of polymorphic form and particle size
What attributes should the drug product possess? How was the product designed to have these attributes? Were alternative formulations or mechanisms investigated?		2.3.P.2.2	Includes quality-by-design elements. Includes contour plots for QbD
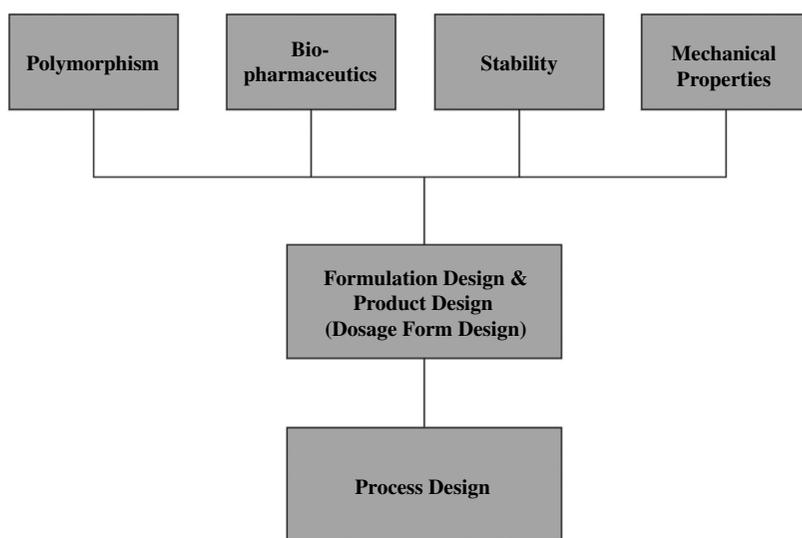
Figure 1.20 Strategy for product and process design.

As outlined in Figure 1.20, the product is designed to meet the target profile based on the system's biopharmaceutics, stability, and mechanical properties. Typically, the target profile is defined by blood levels or biomarkers. The biopharmaceutics includes the BCS class, the solubility, and the permeability. The stability target is a product that is stable throughout clinical trials. Ultimately, a product with 2-year stability is most desirable. The mechanical properties of the system must be addressed. A formulation that does not flow or cannot be compressed will be rejected and must be redesigned to meet the target mechanical profile. In many cases, the initial product design is a powder in a capsule or a powder in a bottle. Typically, modern capsule-filling equipment can fill more than 90% of the available powders into capsules.

For these initial studies the maxim "simple is best" applies. It is important to examine the mechanical properties of the drug substance and/or simple formulation. If the drug substance cannot be filled into capsules, then it is necessary

to prepare trial formulations. In this case excipient compatibility must be determined. Also, the formulation should be designed with the manufacturing method in mind. In some cases, a wet or dry granulation will be needed. Alternatively, soft gels containing dissolved API are a viable alternative to improve solubility and bioavailability.

For the initial studies other factors also influence development considerations. In all cases the polymorph in the formulation must be known and controlled. In many instances, it should be possible to prepare a drug product on a small scale and assess its stability and dissolution rate in laboratory equipment. Dissolution studies on formulations filled in capsules can be facilitated very early in development. In some cases, it is helpful to determine the pharmaco-kinetics of the early formulation in animals. Also, preliminary stability studies are always helpful in understanding the drug substance and drug product. All the initial studies must be done with an eye to the final manufacturing process.

Other challenges faced during initial development are also apparent. Of paramount importance is the short time-line. Another potential problem is that a broad dose range is required. This is because the MTD and MAD are not known. These dose levels will be determined in animal studies and in the first-in-human clinical trials. Until that time, solid-state chemistry and polymorphism studies, as well as formulation design, must be able to accommodate a broad dose range. Additionally, usually minimal amounts of API are available, and sometimes APIs with different attributes are obtained. The early formulation design and solid-state chemistry work must be able to accommodate these variations.

Once the dosage form and formulation have been identified, a process is designed. The process is designed to prepare a drug product that consistently meets the critical quality attributes (design space). Early on, the goal is to have a process that works with the currently available lots of API. As development progresses, the impact of starting materials on the process is understood, and the critical sources of process variability are identified and controlled. The mechanical properties of the formulation must also be understood at this stage. Flow is particularly important as the formulation must flow well to be handled in modern high-speed tablet presses or capsule-filling equipment. Appropriate control strategies are applied to make sure the process is reproducible. Additionally, methods for assessing process performance and product performance are developed, validated, and applied.

As the medicine nears launch and commercial sale, continuous learning occurs. In this process all the elements of Figure 1.20 are reinvestigated in a feed-forward feed-backward process. This allows the development of the final design space. Data are developed to support the design space and control strategy, and all this information is documented.

For polymorphism, the solid-state chemistry of the drug substance (API) and drug product is thoroughly identified. With respect to screening, as discussed earlier, first an accelerated screen is done to develop a dosage form for IND first-in-human trials. Later an intermediate screen should be carried out to make sure the phase II supplies are well con-trolled. Finally, a comprehensive screen that includes all crystallization solvents and other conditions should be done to try to ensure that all the important solid forms are known. This comprehensive screen is also important for intellectual property purposes.

All the work outlined in Figure 1.20 must be carried out from a risk management perspective. The largest risk is that a successful formulation cannot be reproduced. Thus, no matter how short the timeline the formulation developed must be reproducible. Other risks include unstable formulations with unacceptable purity levels. In addition, it is important to carry out a formal risk assessment at each stage of development (Phase I/IND), Phase II, and Phase III. This risk assessment should be documented and communicated to all affected parties.

One strategy that can be quite helpful during the development process outlined in Figure 1.20 is to utilize a sameness/equivalence protocol. A sameness/equivalence protocol is useful in comparing APIs and formulations made during the development process. A sameness/equivalence protocol includes the parameters outlined in Figure 1.20. If an API or a formulation can be shown to be the same according to measurements of polymorphism, biopharmaceutics, stability, and mechanical properties, then switching between these materials is clearly supported.

In conclusion, it is important to realize that the work outlined in Figure 1.20 is a learning process. Scientists are learning about the compound and its properties. Like any learning process, understanding occurs in stages. During early development, the level of understanding is just enough to answer early questions of clinical efficacy and toxicity. Later learning must also be able to address manufacturability, stability, and polymorphism. In all stages, it is important to maximize learning before doing. Learning before doing emphasizes learning on a laboratory scale and using com-puter models, if possible. Learning before doing enhances performance and can greatly accelerate drug development programs.

1.10 Performance and Stability in Pharmaceutical Development

Physical characterization is a critical aspect of evaluating the performance and stability of materials under development. The performance of a pharmaceutical material is intimately related to its dissolution in a GI tract full of variability (e.g. variable pH). For this reason, it is important to determine solubility and whether a supersaturated solution is formed. If a supersaturated solution is formed, then it is important to determine if precipitation occurs. Other studies important to evaluating performance include dissolution tests and tests in animals.

As outlined in Figure 1.15, theophylline hydrate dissolves to reach a constant concentration of about 6 mg/mL. In contrast, theophylline anhydrate dissolves to give a significantly higher concentration, but then the theophylline hydrate precipitates. The theophylline anhydrate solution ultimately reaches a final concentration equivalent to that of the hydrate. This physical transformation and precipitation is a slurry conversion of one physical form to another. If such a precipitation occurs in the body, it could affect blood levels. Clearly, an understanding of slurry conversions and precipitation in the GI tract is important.

As with the precipitation (solution-mediated transformation) discussed earlier, solid forms can interconvert in the solid state on storage, in dosage forms, and during processing. Thus, it is important to understand physical stability and these physical interconversions. Of particular interest is conversion from a less stable form to a more stable form, which would have lower solubility and perhaps lower bioavailability. Of particular interest are crystallization of amorphous forms, Oswald ripening of nanocrystalline products, and conversion of polymorphs to more stable forms or hydrates.

In addition to physical stability, solids can transform chemically. Although the historic rule of thumb is that solid-state reactions are 10–100 times slower than solution reactions, solid-state reactions can occur at a rate that can affect the stability of the compound. Overall, solid-state reactions can be broadly classified into three groups:

- Thermal reactions and degradations
- Photochemical reactions
- Oxidation

Each of these reactions can be important for a given compound. Solid-state chemical reactions can be characterized using X-ray diffraction since the solid structure changes, solid-state NMR since the chemical connectivity changes, and by dissolution of the solid and HPLC analysis. A key question with respect to solid-state chemical reactions and solid-state stability is, "Does your product have an acceptable shelf life?"

A detailed examination of physical transformations shows that the system will always tend to produce only the less soluble of the two forms. To be sure, the time it takes to express this tendency depends on kinetic factors and may be quite variable, but, in any event, a less soluble form never converts to the more soluble form under rigorously defined conditions.

A few illustrations of the dissolution behavior of some polymorphic drugs may help to review these relationships as they apply to solutions at constant temperature. When temperature is introduced as a variable, however, further distinctions concerning the relative stability of alternative forms need to be made. The thermodynamic activity (usually observed as solubility) of each form may change quite differently as a function of temperature. Monotropic systems are defined as systems where a single form is always more stable regardless of the temperature. Enantiotropic systems are defined as systems where the relative stability of the two forms inverts at some transition temperature.

In actual practice, it is customary to plot log solubility versus $1/T$ for each solid phase (i.e. as a so-called van't Hoff plot). These plots give, in most cases, the data in a linear form that lends itself to extrapolation, so that transition points can be determined even when complete data for a given solid phase are unreliable or unavailable. Figure 1.21 shows a van't Hoff plot of solubility versus $1/T$ [47]. In this case, there is a transition point where the lines cross and the relative stabilities of the two forms are the same ($\Delta G = 0$). Extrapolation of data 10 K beyond the experimental range is prone to producing large errors and is not reliable.
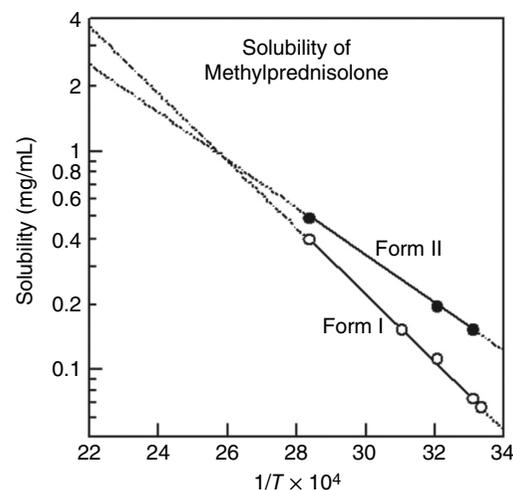

Figure 1.21 A van't Hoff plot of the water solubility of two methylprednisolone crystal forms (log of the solubility as an inverse function of temperature). *Source*: Higuchi et al. [47]. Reproduced with the permission of Elsevier.

Transitions from one solid phase to another can occur in the absence of solvent. The mechanisms and kinetics of such solid-state transitions can be very complex. For example, Kitaigorodskii et al. showed that a pin-prick can initiate the solid-state transformation of *a-p*-dichlorobenzene to *b-p*-dichlorobenzene within a single crystal [48]. The transformation of *a*- to *b-p*-dichlorobenzene is delineated by the spread of the reaction front from the nucleation site through the crystal. A related process is the thermally induced rearrangement of the *a*- to *b*-form of *p*-nitrophenol [49]. In this reaction, needle-shaped single crystals rearrange with the phase boundary moving approximately perpendicular to the needle axis. Grinding or other input of mechanical energy induces the polymorphic transformation of chlorpropamide [50], fostedil [51], chloramphenicol palmitate [52], and several other drugs [53].

1.11 Moisture Uptake

Some crystalline solids take up water from the atmosphere and are termed hygroscopic solids in the literature. Chapter 15 provides a detailed discussion of these materials. Here, the topic is briefly introduced.

Unfortunately, there can be no clear definition of hygroscopic solids because hygroscopicity is a relative term. Hygroscopicity is determined by both a kinetic and a thermodynamic term and is a function of the atmospheric relative humidity. At high relative humidities, many solids are hygroscopic. In atmospheres of low humidity, only a few solids will be hygroscopic. Another factor influencing hygroscopicity is surface area and porosity. The larger the surface area of the solid, the more rapid the uptake of moisture. This is because solids with larger surface areas have more sites for the sorption of water molecules.

When solids that are not solvates contain large amounts of water, it has been hypothesized that water must be taken up into the solid by disordered or high-energy regions, such as defects and amorphous sites. Such effects might be exaggerated by manufacturing processes that reduce particle size, such as micronization, milling, or related processes known to increase the number of high-energy sites. Of course, some solids can take up so much water during these processes that they become damp or even liquefy at RH_0 [54]. This tendency is usually easily detected by microscopic observation.

The formation of crystal hydrates, of course, is another way for water to be incorporated into a solid. In these cases, the water molecules generally occupy a specific crystallographic site in the solid. This site can be determined by X-ray crystallography, which thus unequivocally proves the existence and composition of the hydrate. However, many hydrates exist in which the water is in tunnels within the crystal. The water can be located accurately only by the determination of the crystal structure at low temperatures (if even then). In these cases, the water content may change rather easily with changes in relative humidity.

Plots of vapor pressure versus relative humidity are an excellent way to determine the nature of a solid with respect to water sorption. The different kinds of behavior that these plots may be expected to show include the following:

1. virtually no water uptake,
2. gradual water uptake, characteristic of an amorphous material or a nonstoichiometric hydrate (a hydrate without a simple ratio of water to host molecule), and
3. "stair-step" water uptake, characteristic of a stoichiometric hydrate.

Figure 1.22 shows the behavior of two stoichiometric hydrates (a monohydrate and a sesquihydrate) as well as a nonstoichiometric hydrate of sodium cefazolin [55]. In addition, amorphous sodium cefazolin exists and takes up and gradually loses water as described in the following text.
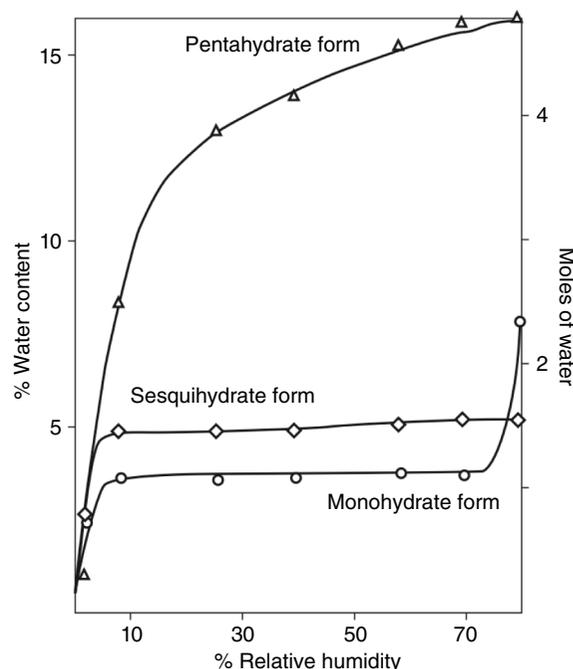

Figure 1.22 Vapor pressure versus relative humidity diagrams for three hydrates of sodium cefazolin. The sesquihydrate and monohydrate behave normally, and the "pentahydrate" is actually a nonstoichiometric hydrate. *Source*: Adapted from [55].

Sorption of water into amorphous solids or regions of a solid involves dispersion or dissolution of the water molecules within a solid. The more polar a solid is, the greater the amount of water it takes up. Obviously, in such systems, the water content depends on relative humidity.

In summary, Zografi et al. made the following recommendations with regard to water specifications [54]:

1. A complete profile of relative humidity versus water content (weight) should be reported for all reference standards.
2. For amorphous solids, both T_g and W_g should be reported.
3. For deliquescent solids, the RH_0 and an appropriate warning on the label should be provided.
4. For stoichiometric hydrates, the water specifications should reflect the stoichiometry.
5. Attention should be paid to materials that do not form well-defined hydrates and can take up or lose water as the humidity is varied. Any structural changes that accompany changes in water content should be noted. (Some hydrates can lose water without changing their crystal structure. This is due to the formation of an extremely stable crystal packing network by the host molecule.)

1.12   Solid-state Reactions

The scientific discipline of solid-state chemistry of drugs emphasizes the studies of the chemical and physical properties of the various solid forms just discussed. These studies include solid-state phase transformations (polymorphic transformations), reactions in which solvent of crystallization is lost or gained, and a broad range of solid-state chemical reactions.

It is necessary to establish criteria for solid-state reactions to focus on true solid-state reactions. This will avoid a liquid-state reaction being identified as a solid-state reaction. Morawetz suggested four criteria for determining whether a reaction is a true solid-state reaction [56] and a fifth very important criterion can be added from Paul and Curtin [57]:

1. A reaction occurs in the solid when the liquid reaction does not occur or is much slower.
2. A reaction occurs in the solid when pronounced differences are found in the reactivity of closely related compounds.
3. A reaction occurs in the solid when different reaction products are formed in the liquid state.
4. A reaction occurs in the solid if the same reagent in different crystalline modifications has different reactivity or leads to different reaction products.
5. A reaction occurs in the solid phase if it occurs at a temperature below the eutectic point of a mixture of the starting material and products.

Once it has been established that the reaction is occurring in the solid state, the reaction can be understood in terms of a four-step process [57]:

1. Loosening of the molecules at the reaction site
2. Molecular change
3. Solid solution formation
4. Separation of the product phase

It is important to realize that many solid-state reactions of drugs involve drug degradations that have been studied mostly on the macroscopic level. In fact, few studies aimed at determining the molecular aspects of the solid-state chemistry of drugs have been published. These reactions are of interest because of a desire to prevent such degradation. Even for such common drugs as vitamin D_2 and vitamin A, the structures of only a few of the solid-state degradation products have been published. Therefore, in many respects, the solid-state chemistry of drugs is synonymous with drug degradation.

1.13   Noninteracting Formulations – Physical Characterizations

Noninteracting formulations are those in which the components do not interact or alter in any meaningful way the particles of the API. Thus, the term "noninteracting formulations" applies to solid dosage forms. Physical characterization of noninteracting formulations is important, in part, because it shows there is indeed no meaningful interaction between the API and the formulation components.

Hypothetically, it would be impossible to have no interaction between the formulation components. Figure 1.23 shows the functional groups on the surface of R,S-alanine [58]. It is clear that the 001 plane has carboxyl groups exposed, whereas
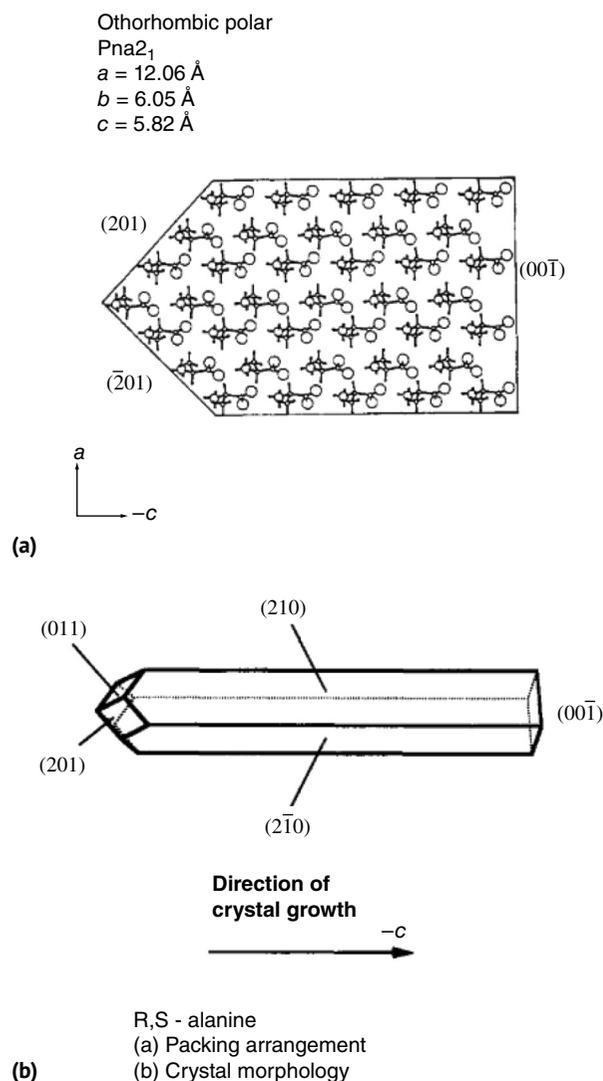
Othorhombic polar
Pna2$_1$
a = 12.06 Å
b = 6.05 Å
c = 5.82 Å

(201)

(00$\bar{1}$)

($\bar{2}$01)

a

$-c$

(a)

(210)

(011)

(00$\bar{1}$)

(201)

($2\bar{1}$0)

**Direction of
crystal growth**

$-c$

R,S - alanine
(a) Packing arrangement
(b) (b) Crystal morphology

Figure 1.23 Functional groups on the surface of crystals of R,S-alanine. *Source*: Weissbuch et al. [58]. Reproduced with the permission of the American Chemical Society.

Figure 1.24 A Raman map of cyclobenzaprine showing an oblong particle of API in the center of the figure near the surface of the tablet. *Source*: Adapted from SSCI, West Lafayette.

the 201 plane has amino groups exposed. Curtin and coworkers confirmed that carboxyl groups were on the 001 plane by reacting these crystals with ammonia gas. In such reactions the ammonia reacted preferentially with the 001 face [59].

Consider the situation where R,S-alanine is formulated with a cellulose derivative. Cellulose has many hydroxyl groups. It is reasonable to hypothesize that the OH groups on the cellulose will hydrogen bond to the C=O group of the alanine carboxylic acid (which, in fact, is likely to be ionized due to the zwitterionic nature of the crystals). Likewise, the NH$_3^+$ group is also likely to hydrogen bond to the OH group of a cellulose molecule. This suggests that there might be surface interactions between solid particles in a formulation. Liversidge and coworkers took advantage of this type of interaction to stabilize nanocrystals using surface modifiers [60].

Raman mapping is a good method for analyzing noninteracting formulation or any formulations for that matter. Figure 1.24 shows a Raman map of cyclobenzaprine drug product. In this map, an oblong drug particle of about 20 microns by 5 microns is visible. This figure clearly shows an intact particle. This figure suggests that Raman mapping can be used to estimate particle size.

Solid-state NMR (SSNMR) is another good method. As shown in the solid-state NMR chapter, different solid forms can be distinguished relatively easily using SSNMR. X-ray diffraction is another powerful method for analyzing formulations. Both SSNMR and X-ray diffraction lack the spatial information available from Raman mapping.

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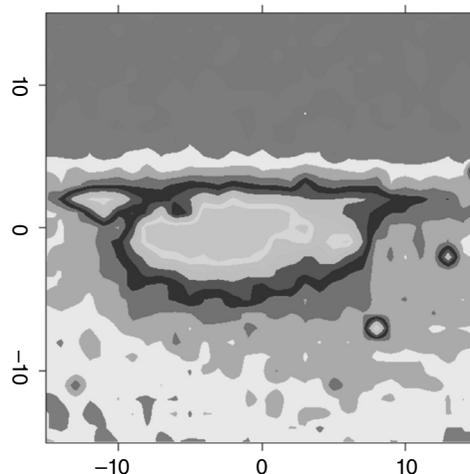2 Kitaigorodskii AI. *Organic Chemical Crystallography*. New York: Consultants Bureau; 1961.

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