Crystal Polymorphism in Chemical Process Development

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Abstract

Polymorphism in molecular crystals is a prevalent phenomenon and is of great interest to the pharmaceutical community. The solid-state form is a key quality attribute of a crystalline product. Inconsistencies in the solid phase produced during the manufacturing and storage of drug substances and drug products may have severe consequences. It is essential to understand the solid-state behavior of the drug and to judiciously select the optimal solid form for development. This review highlights the pervasiveness and relevance of polymorphism and describes solid form screening and selection processes. Moreover, case studies on controlling polymorphs from a chemical development perspective are provided.

INTRODUCTION

API: active pharmaceutical ingredient

Most pharmaceutical products are formulated with excipients and drug substances [or active pharmaceutical ingredients (APIs)] as solids in the crystalline state. Developing molecular crystals in various dosage forms is preferred for stability and manufacturability reasons. Generally, drug molecules are more chemically stable in the solid state compared with solution, where degradation occurs more easily and readily. This, however, does not suggest that pharmaceutical solids do not present their own challenges. In the solid state, molecules can adopt more than one packing arrangement and/or conformation in the crystal lattice, which gives rise to the phenomenon of polymorphism (1). The first observation dates back to the end of the eighteenth century when Klaproth (2) was working with the aragonite and calcite solid phases of calcium carbonate, but recognition of this fascinating and mystifying subject is often ascribed to Mitscherlich's (3) work on isomorphous metallic sulfates. Besides the pharmaceutical realm, this phenomenon has also directly impacted the agrochemical, electronic, explosive, fine chemical, food, pigment, and polymer industries, among others. Because the solid material's properties are closely linked to its three-dimensional crystal structure, variations in the lattice arrangement may result in different chemical and physical properties, which ultimately may affect the application of the material. Generally, when the drug product does not perform as expected (e.g., slower dissolution rate), when manufacturing takes longer than normal (e.g., increased cycle time), or when the drug substance exhibits inconsistent physical and chemical characteristics, the culprit may be the appearance of another solid phase (crystalline or amorphous). At times, this can be a nuisance for chemical engineers, formulators, medicinal and process chemists, and materials scientists alike. Successful development of a drug product requires a comprehensive understanding of the solid-state behavior of all the materials involved, including the API and excipients.

Polymorphism in molecular crystals can be divided into two categories: conformational and packing polymorphism. In the former, conformationally flexible molecules adopt more than one conformation in the solid state (4). Two well-documented examples of drugs that exhibit conformational polymorphism are the antidepressant venlafaxine hydrochloride (Effexor) (5) and the antipsychotic olanzapine (Zyprexa) (6). Packing polymorphism arises from different possible packing arrangements of conformationally rigid molecules. Cases in which the solid state is composed of molecules with different configurations such as geometric isomers and tautomers are known as configurational polymorphism. Strictly speaking, because the isomeric molecules are essentially different, the term polymorphism should not be applied. However, given the molecular sameness, the crystals are typically classified as polymorphs (7). Desmotropy is a term that is frequently encountered with tautomeric (8) or tautomerizational (9) polymorphism; it refers to crystallization of molecules in two different tautomers (10). A well-known example of a desmotropic system is the tetrazole-containing antihypertensive drug irbesartan (Avapro) (11); its two phases are stable in the crystalline state, but the tautomers are in equilibrium in solution.

Crystalline solids that involve the inclusion or incorporation of solvent molecules in the crystal lattice are known as solvates (7), pseudopolymorphs (12), or solvatomorphs (13), although the latter two terms are by no means widely accepted (14–17). Solvates in which the solvent molecule is water are known as hydrates. Given the ubiquitous nature of water in the environment as well as the inclusion of water in solvent mixtures during crystallization, the formation of hydrated crystal structures is common. Moreover, water's small size and ability to serve as both a hydrogen bond donor and acceptor make it likely to be incorporated in many locations within the lattice either as a space filler or as a stabilizing force whose departure would eventually lead to the collapse of the crystal structure (18). A survey of the 1999 European Pharmacopeia, which contained 808 organic compounds, revealed that approximately a third of the molecules listed can form hydrates (19).

Several well-known pharmaceutical products in which the drug substance is a hydrated phase are alendronate sodium trihydrate (Fosamax), amoxicillin trihydrate (Amoxil), atorvastatin calcium trihydrate (Lipitor), and pantoprazole sodium sesquihydrate (Protonix). Conversely, there are cases in which a hydrate exists but the anhydrate has been chosen because of improved physical properties, processability, and/or stability. Examples of anhydrate commercial drug products include mometasone furoate (Elocon), pazopanib hydrochloride (Votrient), and seratraline hydrochloride (Zoloft).

Solvates can contain either a stoichiometric or a nonstoichiometric amount of solvent in the crystal lattice. Generally, desolvation of a stoichiometric solvate results in either a disordered noncrystalline state or a different crystalline form (19). Nonstoichiometric solvates involve solvent molecules that are accommodated in the structure to fill intermolecular voids. Variations in pressure, temperature, and/or humidity may result in solvent exchange, loss, or uptake. Solvates other than hydrates are not normally selected for development owing to risk of desolvation, toxicity concerns with organic solvents that are not Class III and not regarded as safe, and International Conference on Harmonisation (ICH) guidelines for limits on residual solvents. Sometimes, however, the only crystalline phase of a drug molecule is a solvate, and as such, it is necessary to understand the desolvation behavior from both a kinetics and a thermodynamics standpoint before developing a solvated form is considered because processing, handling, and storage may be impacted. Considering that amorphicity may occur upon desolvation, chemical stability may also be a concern owing to the enhanced reactivity of amorphous solids relative to their crystalline counterparts. For instance, angiotensin-converting enzyme (ACE) inhibitors including moexipril, quinapril hydrochloride, and spirapril hydrochloride are more susceptible to chemical degradation in the disordered state than in the crystalline phase (20). Nonetheless, there are marketed drug products that contain solvates such as darunavir ethanolate (Prezista), indinavir sulfate ethanolate (Crixivan), and warfarin sodium isopropanol solvate (Coumadin). Solvates can also be polymorphic, as exemplified by olanzapine (6) and nitrofurantoin (21), which have three dihydrate and two monohydrate forms, respectively. In other cases, solvates can have different stoichiometries in their crystal lattices, which may result in varying packing arrangements. Channel hydrates are one such example, as water molecules interact with one another in the cavities. Depending on the relative humidity, loosely bound water can roam in (hydration) or out (dehydration) of the channels, which may lead to expansion or contraction of the crystal lattice, respectively. In contrast, there are also channel (or variable) hydrates, such as the antitumor drug topotecan hydrochloride (Hycamtin), that can accommodate additional guest water molecules with a minimal effect on the cell dimensions of the crystal lattice (22).

The formation of solvates occurs frequently during drug synthesis and manufacturing, and it is common to isolate intermediates as solvates because these solid phases may purge impurities more effectively than anhydrates as well as provide particles with improved filterability (23). Selection of which intermediate solid phase to isolate is driven more by chemical purity (or quality) and processability. The fate of impurities can be controlled through manipulation of the crystal form, as demonstrated by a piperidene-based intermediate for which crystallization of the hydrate selectively discriminated against an undesired impurity whereas the anhydrous form was less successful in purging the impurity (24). Close examination of the crystal chemistry of these two phases revealed that in the hydrate crystal lattice the impurity was unable to participate in hydrogen bonding with piperidene molecules while the structure of the anhydrous form contained more void volume than the hydrate, which allowed for impurity occlusion. Similarly, manipulation of the polymorphic forms of dirithromycin (25), a macrolide antibiotic, and (*R,R*)-formoterol tartrate (26), a long-acting β2-agonist, through crystallization of the acetone solvate and a hydrated intermediate phase, respectively, enabled the development of an effective purification process.

Analogous to polymorphs, solvates may also impart different chemical and physical properties. Consequently, it is essential to identify and understand the conditions necessary to form a solvate as well as the transformation pathways to other solid phases including amorphous, anhydrates, and other solvates.

Over the past two decades, discussion of the subject of polymorphism has grown immensely in the chemical and pharmaceutical literature, as evident from the increasing number of journal articles on polymorphic compounds, the four monographs (1, 7, 9, 27), and the countless book chapters, commentaries, perspectives, and review articles devoted to this important and continually expanding field. Polymorphism is of great interest to the pharmaceutical community, and since 2004, an annual review has been published that summarizes polymorphism- and solvatomorphism-related papers and patents that were cited in the previous year (13, 28–31). Moreover, special journal issues have been dedicated to this topic including those of *Advanced Drug Delivery Reviews* (32, 33), *Crystal Growth & Design* (34–36), *New Journal of Chemistry* (37), and *Organic Process Research & Development* (38–41). This contribution highlights the prevalence and importance of crystal polymorphism in drug development, briefly describes the solid form selection process, and provides case studies on controlling polymorphs from a chemical process development perspective.

PERVASIVENESS AND SIGNIFICANCE OF POLYMORPHISM IN DRUG DEVELOPMENT

The strong interest in crystal polymorphism within the pharmaceutical landscape can be attributed to its frequent occurrence and the fact that significant differences in chemical and physical characteristics may arise with changes in the solid-state form, thus affecting the manufacturability, performance, and/or quality of the drug product. Some have suggested that virtually all chemical compounds have more than one crystalline form. The prevalence of polymorphism is often linked with McCrone's (12) statement "that every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound." Others have made similar suggestions, including Buerger & Bloom (42), who commented in 1937 that "polymorphism is an inherent property of the solid-state and it fails to appear only under special conditions," and Kuhnert-Brandstatter (43), who more recently noted in 1975 that "probably every substance is potentially polymorphous. The only question is, whether it is possible to adjust the external conditions in such a way that polymorphism can be realized or not." These comments likely are a bit exaggerated, as isolation of new polymorphs is most often a result of chance or serendipity. Moreover, for some small molecules such as naphthalene, only one crystalline form exists even though the molecule has been crystallized many times, and for others such as dibenzylidene sorbitol, a nucleating agent or clarifier used in polymer manufacturing, a crystalline phase is unattainable.

Examination of the polymorphs and solvates of the top ten best-selling small-molecule drugs in 2009 (**Table 1**) and common over-the-counter (OTC) drugs (**Table 2**) would suggest that most drug molecules exist in multiple polymorphic and/or pseudopolymorphic forms. This is consistent with an earlier review on polymorph screening by Stahly (44) in which he noted that out of 245 small-molecule organic compounds screened for polymorphs, approximately 90% of these showed evidence of multiple crystalline and noncrystalline forms, with approximately half of these exhibiting polymorphism. An earlier survey of 62 drug compounds at Bayer AG revealed a higher frequency of polymorphism, as four out of five molecules were polymorphic (45). Regardless of the statistical percentages, polymorphism is a widespread phenomenon and may strike all types of compounds including salts, cocrystals, and those that are chiral and racemic.

Table 1 The top ten best-selling small-molecule drugs in 2009[a]

Rank	Brand name	Companies	Active pharmaceutical ingredient(s)	Indication	Sales ($ in billions)	Minimum number of solid phases[b]	Reference
1	Lipitor	Pfizer, Astellas	Atorvastatin calcium	High LDL cholesterol	12.5	41	108
2	Plavix	Bristol-Myers Squibb (BMS), Sanofi Aventis	Clopidogrel bisulfate	Atherosclerosis	9.3	6	109, 110
3	Advair	GlaxoSmithKline	Fluticasone propionate Salmeterol xinafoate	Asthma	7.8	2[c] 2[d]	111, 112
4	Diovan	Novartis	Valsartan	Hypertension	6.0	10	113
5	Abilify	Otsuka, BMS	Aripiprazole	Schizophrenia	5.6	9	114
6	Nexium	Astra Zeneca	Esomeprazole magnesium	Ulcer	5.0	4	115
7	Zyprexa	Lilly	Olanzapine	Schizophrenia	4.9	25	6
8	Seroquel	Astra Zeneca, Astellas	Quetiapine fumarate	Schizophrenia	4.9	2	116
9	Crestor	Astra Zeneca, Shionoggi	Rosuvastatin calcium	High LDL cholesterol	4.7	3	117
10	Singulair	Merck	Montelukast sodium	Asthma	4.7	4	118

[a]Sales data according to Reference 119.
[b]Includes both anhydrates and solvates.
[c]Minimum number of fluticasone propionate solid phases.
[d]Minimum number of salmeterol xinafoate solid phases.

Table 2 Solid-state forms of common over-the-counter (OTC) drugs

Brand name	Active pharmaceutical ingredient	Indication	Polymorphs/solvates/hydrates	Reference
Tylenol	Acetaminophen (paracetamol)	Pain	Forms I, II, and III; monohydrate; trihydrate; dioxane hemisolvate; methanolate	120, 121
Bayer	Aspirin	Pain, arthritis	Forms I and II	122
Tagamet	Cimetidine	Ulcer	Forms A, B, C, and D; hydrated Forms M1, M2, and M3	123
Pepcid	Famotidine	Ulcer	Forms A and B	124
Advil, Motrin	Ibuprofen	Pain	Forms I and II	125, 126
Imodium	Loperamide hydrochloride	Diarrhea	Forms I, II, and III; tetrahydrate	127, 128
Claritin	Loratadine	Allergy	Forms I and II	129
Aleve	Naproxen sodium	Pain	Form 1; monohydrate; dihydrate Forms I and II; tetrahydrate; methanolate; ethanolate; 1-propanolate; 2-propanolate; 1-butanolate; isobutanolate	130, 131
Zantac	Ranitidine hydrochloride	Ulcer	Forms 1 and 2	132

CSD: Cambridge Structural Database

Similarly, formation of solvates is frequently encountered with organic molecules. Given the ubiquity of water, hydrates are the most common solvates found. A survey of the Cambridge Structural Database (CSD) Version 5.26 by Motherwell and coworkers (46) showed that approximately 6.5% (6,558) of the crystal structures of organic compounds in the database (101,244) are in the hydrated form. Interestingly, pharmaceutical salts, in particular hydrochloride and sodium salts, formed hydrates more frequently than non-salts (47). This can be attributed to the propensity of water to bind to ionic sites. In contrast, non-salts are more prone to form solvates and polymorphs (19).

There are many types of organic solvate-forming solvents including alcohols, aromatics, esters, ethers, and ketones. Nangia & Desiraju (48) searched the CSD and elegantly showed that after applying a usage correction, the organic solvents most likely to form solvates are *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and 1,4-dioxane. This is probably because all three solvents may participate in hydrogen bonding with the solute molecules. It is quite common to encounter cases in which a particular molecule is prone to form multiple solvates. One classic example of a promiscuous solvate former is sulfathiazole, a potent antibacterial sulfonamide compound, which has been described in more than 100 solvated forms (49). In some instances, the solvent molecules simply fill the channels (or cavities) and are innocuous bystanders, thereby forming isostructural solvates; in other cases the solvent molecules play an integral role in stabilizing the crystal lattice.

Variations in the solid form will most likely lead to alterations in the material's chemical and physical properties. **Figure 1** summarizes properties that may be affected in crystal polymorphs. One of the most apparent differences in physical properties is polychromism (i.e., different colors). The synthetic intermediate to olanzapine, 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, also known as ROY, is a classic example of polychromism (50). ROY refers to the red, orange, and yellow crystals that can be crystallized. The difference in colors is a result of the conformational differences among the polymorphs (51).

Key drug properties vital to the development of a quality drug product are the bioavailability and solid-state stability. Solubility and dissolution rate are physical characteristics that are directly related to the bioavailability. It has been reported that the solubility ratio between polymorphic

Chemical	Kinetic	Mechanical
• Chemical reactivity/stability • Photochemical reactivity	• Rate of dissolution • Solid-state reaction kinetics • Stability • Rate of crystal growth	• Compactability • Hardness • Powder flow • Tableting • Tensile strength
Packing/physical	**Surface**	**Thermodynamic**
• Conductivity • Density (or molar volume) • Hygroscopicity • Refractive index • Color • Particle morphology	• Interfacial tensions • Surface area • Surface free energy	• Chemical potential, free energy, and solubility • Enthalpy and entropy • Heat capacity • Melting and sublimation temperature • Vapor pressure

Figure 1

Properties that may vary with different solid forms and solvates of the same material.

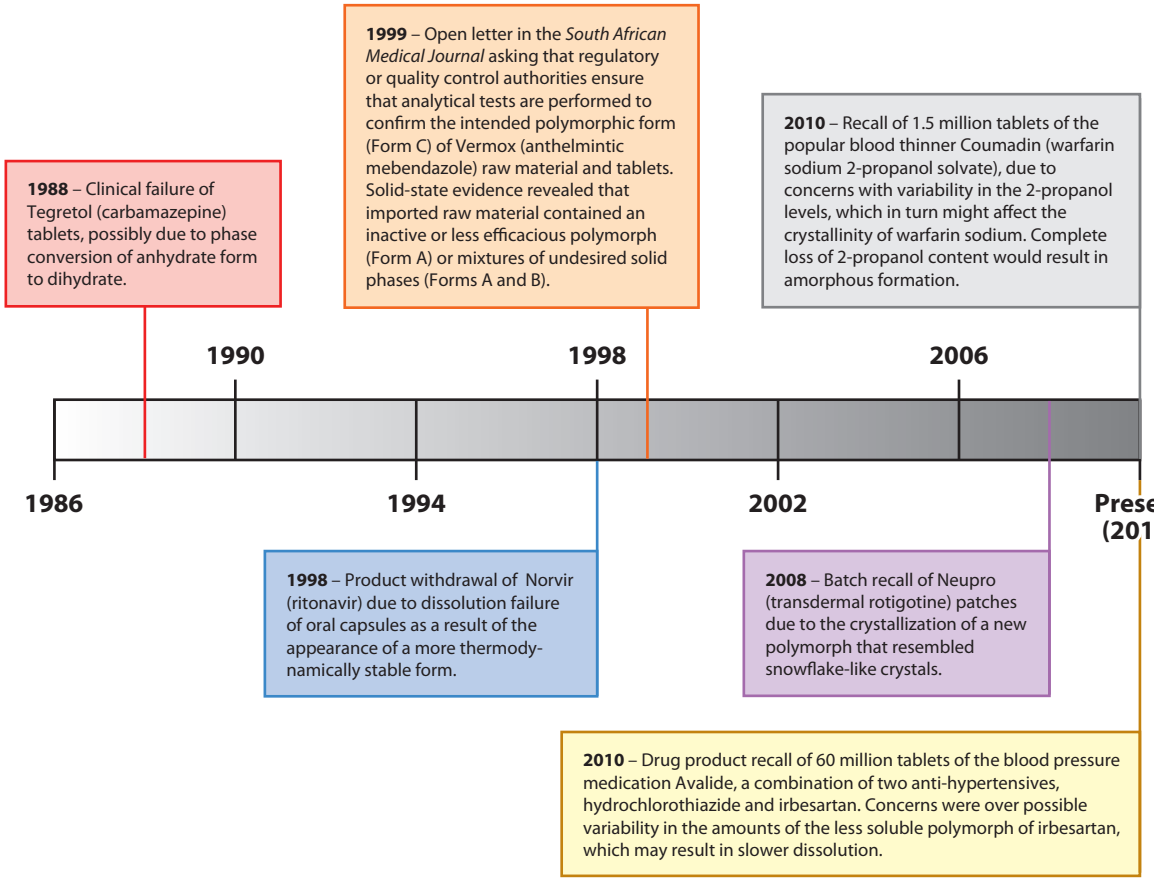

Figure 2

A timeline of events concerning solid-state issues with polymorphism of pharmaceutical drugs over the past 25 years.

pairs is generally less than two, although in certain cases, higher ratios were observed (52). In the simplest form, differences in solubility are a reflection of the free energy differences between polymorphs. The most famous example of polymorphs influencing the solubility and dissolution profile of a pharmaceutical is the antiretroviral drug ritonavir (Norvir) (53). In 1998, a more stable, less soluble crystalline phase appeared in the formulation vehicle that resulted in dissolution failures of the soft gelatin capsules. Ultimately, the pharmaceutical product was withdrawn from the market because the manufacturing process was no longer able to reliably produce the desired polymorph. Eventually the product was reformulated with the most stable polymorph and relaunched.

A timeline of events involving solid-state polymorphism over the past 25 years is shown in **Figure 2**. In most of the cases, the products were recalled owing to ambiguous product performance and quality as a result of a phase conversion. There are probably many more events, most of which have not been reported in the public domain, in which crystal polymorphism has occurred and led to manufacturing troubleshooting, batch rework, and delays in project or clinical timelines.

The packing arrangement may also influence the chemical reactivity of molecular crystals. Generally, metastable solid forms are less chemically stable than thermodynamically stable

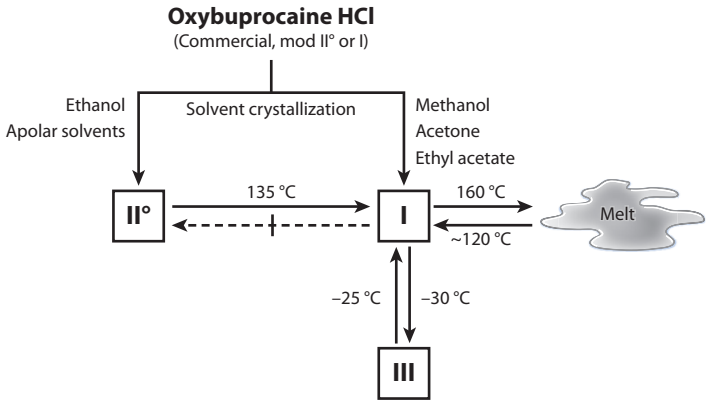

Figure 3

Crystallization and transformation pathways of oxybuprocaine hydrochloride polymorphs. Caption and figure reprinted with permission from Reference 55. Copyright © 2008 by the American Chemical Society.

polymorphs. This can be partially explained by the fact that stable polymorphs are more densely-packed and have higher crystal packing density. For instance, the photolytic degradation of the widely used diuretic furosemide (Lasix) to 4-chloro-5-sulfamoylanthranilic acid occurs more rapidly for the metastable phase, as the thermodynamically favored polymorph has slower photodegradation kinetics (54). Given the loss of the drug substance and the potential appearance of toxic degradants, chemical stability is an essential element of quality requirements. It can also be a deciding factor within the solid form selection process.

Another aspect of solid-state stability is the physical stability of the solids, which is often related to the physical transformation of the solid to a new phase. The most common physical changes are amorphization, dehydration-hydration interconversion, desolvation, and polymorph transformation. These changes may occur during handling, manufacturing, processing, and/or storage of the solid material and are a response to variations in humidity, pressure, and temperature. The local anesthetic drug oxybuprocaine hydrochloride (55) is an example of a pharmaceutical compound whose physical stability can vary with different conditions (**Figure 3**). The commercial form, mod II°, is the thermodynamically favored polymorph at room temperature and may convert to mod I near 135°C. Mod I is kinetically stable and reverts back to mod II° in solvent-mediated processes in which the temperature is below 90°C. At low temperature (<−30°C), mod I can reversibly convert to a third polymorph, mod III. The three polymorphs exhibit significant conformational differences and are an example of conformational polymorphism. Evaluation of the physical stability is a critical activity and is necessary to ensure that the efficacy, performance, and safety of the formulated product are not compromised. To minimize the risk of any physical instability, selection of the most thermodynamically stable, lowest-energy polymorph for development is generally preferred.

Mechanical properties including compressibility, elasticity, hardness, and yield pressure may also differ with modifications in the crystal structure. Information on the three-dimensional solid-state structures may be valuable and provide helpful clues for assessing the mechanical strength as well as the compaction and tableting behavior of molecular crystals. For instance, the monohydrate form of theophylline is less brittle than the anhydrous phase owing to the greater number of intermolecular hydrogen bonds in its crystal lattice (56). More recently, it has been demonstrated that polymorphs of the calorie-free sweetener acesulfame exhibit unique mechanical properties. In particular, the needle-like polymorph bends upon mechanical stress, whereas the other

polymorph, which is a prismatic crystal, is brittle and breaks under the same applied mechanical stress (57). In contrast to bioavailability and solid-state stability, the mechanical properties of solid forms are secondary factors in deciding with which polymorph to move forward, as in most cases the poor mechanical properties of polymorphs may be overcome through careful selection of excipients and choice of formulation processes.

FDA: Food and Drug Administration

DPI: dry powder inhaler

Owing to the importance of how variations in the polymorphic forms of the drug substance may impact the bioavailability, manufacturability, and stability of the pharmaceutical product, the Food and Drug Administration (FDA) and other regulatory agencies require close attention to be paid to crystal polymorphism (58) and mandate that drug substance manufacturers have robust drug substance and drug product manufacturing processes to reliably and consistently produce the intended product. Moreover, identification and characterization of all possible polymorphs are expected, and relevant information on the polymorph landscape, drug stability, and solid-state properties of the drug substance must be included with the appropriate analytical methodology as part of the regulatory submission process.

The relevance of crystal polymorphism also extends to the intellectual property domain, as different crystal forms are considered patentable inventions. Generally, brand-name pharmaceutical manufacturers (or innovators) will patent every viable polymorph of a drug molecule in addition to filing patents related to methods of use and process of manufacture to ensure that the innovators have exclusive rights to the invention. Consequently, solid form screening has been regarded as an essential activity in the drug development process. Nonetheless, in hope of gaining early access to the marketplace, generic pharmaceutical manufacturers continually search for novel polymorphic forms of a drug and increasingly challenge the originator's patents in order to circumvent the drug's intellectual property protection. A recent example highlighting the patent battle over polymorphs between brand-name and generic manufacturers is the antibiotic cefdinir (59). Brand-name pharmaceutical companies have used composition of matter patents to extend the life of a drug and impede competition from generic manufacturers. SmithKline Beecham Corporation (now known as GlaxoSmithKline PLC) took such actions in the case of the antidepressant drug paroxetine hydrochloride (or Paxil) where the company filed and was granted a patent protection on the hemihydrate form that expired much later than the original patent on the anhydrous form. Thus, when a generic firm, Apotex Corporation, filed an abbreviated new drug application for a generic anhydrate Paxil, litigation followed, with SmithKline demonstrating that the Apotex product contained the hemihydrate form and therefore infringed on SmithKline's patent. Eventually SmithKline lost market exclusivity owing to separate and unrelated technicalities.

Polymorphism is not limited to drug substances; it also can strike antioxidants (or polymer additives) used in polymer-based medical devices as well as excipients, thereby having profound implications for the drug products. In the former case, antioxidants are a source of extractable and leachable compounds for medical devices, and the solid-state properties of the stabilizer may impact the diffusion coefficient, dissolution rate, solubility, and transport properties of the additive in the polymer (60). Saunier and coworkers (61) recently reported that commercial polyurethane catheters containing the antioxidant Irganox 1076 may bloom on the surface of the device. It was observed that the nucleated form was different from the commercially available polymorph. Moreover, the study highlighted the importance of understanding polymorphic behavior in connection with investigating leachable compounds.

Excipients are also prone to have multiple crystal forms, which may have implications for the processability or manufacturability of a formulated product. For instance, the most widely used lubricant in capsule and tablet formulation, magnesium stearate, has several hydrated forms, and it has been reported that magnesium stearate with high moisture content has the best lubricity (62). In the case of the excipient carrier lactose, which is often used for dry powder inhalers (DPIs),

the solid form of the carrier particles can be critical to performance of the formulated product. Traini and coworkers (63) recently reported that the excipient's functionality varies with which crystalline phase is used. With salbutamol sulfate-lactose capsule blends, α-lactose monohydrate showed the best aerosolization performance of the drug followed by the anhydrous form of β-lactose and then the anhydrous form of α-lactose. The variation in the aerosolization efficiency was attributed to differences in the physical properties of different lactose crystal phases, in particular the surface energy, that ultimately affected the drug-carrier particle adhesion. At times, the choice of excipients in pharmaceutical formulations is exploited to overcome challenges of the drug substance (e.g., poor powder flow, salt disproportionation, poor compactability, high level of static charge). However, inappropriate excipient selections can negatively impact both the manufacturability and the performance of the pharmaceutical formulation. Consequently, knowledge of the solid-state properties of the excipient is essential and must be taken into consideration in the selection process.

SOLID FORM SCREENING AND SELECTION

Screening and Generation of Multiple Solid Phases

Given the significance of polymorphism, solid form screening of drug substances is an essential activity and is initially carried out at the drug discovery-development interface (64). The intent of the screen is to uncover all possible crystalline phases and to identify an optimal solid form suitable for development. However, due to the high attrition rates of drug candidates in early development and in the interest of conserving resources (i.e., material, personnel, and time), there is little incentive to conduct an exhaustive polymorph screen. Nonetheless, the early screen should be comprehensive enough to understand the solid-state behavior of the drug substance and to determine which solid form is the most developable and has the most favorable properties. Failure to conduct an early screen increases the potential for modifications during chemical and formulation development, which in turn increases the resources needed to troubleshoot issues related to the solid-state properties. A solid form screen does not guarantee that all polymorphs of a drug substance have been unearthed, but it does provide assurance that an optimal form has been selected and minimizes the risk of late-appearing, unwanted polymorphs.

As a general rule, chemically pure material (>99% purity) should be used in a solid form screen because the presence of impurities can influence the solid-state outcome and/or inhibit phase transformation. There are countless examples including ritonavir in which impurities can inhibit or trigger the nucleation and crystal growth of a specific polymorph over another crystalline phase (65). As a consequence, the use of impure starting material may yield misleading results, as new solid phases may be missed. The unexpected appearance of a low-energy solid form and disappearance of a high-energy, metastable polymorph are often associated with the absence or removal of key impurities that might have stabilized the transient solid phase. It is not unexpected that a new, more stable solid form could appear owing to an improved impurity profile as a result of development of a new synthetic route, improvements to the synthetic process, scale-up, or use of a new chemical intermediate supplier (66–68).

Generally polymorph screening involves a diverse range of approaches including recrystallizing the drug substance from solution via antisolvent addition, cooling, and evaporation; crystallization from the melt or amorphous phase; slurrying (and slurry bridging); grinding (neat and liquid assisted); spray drying; sublimation; vapor diffusion; thermal desolvation of solvates; and subjecting the drug to various process-induced stresses (heat, pressure, and shear). **Figure 4** illustrates the classical methods; slow crystallization processes favor thermodynamically stable phases, and kinetic

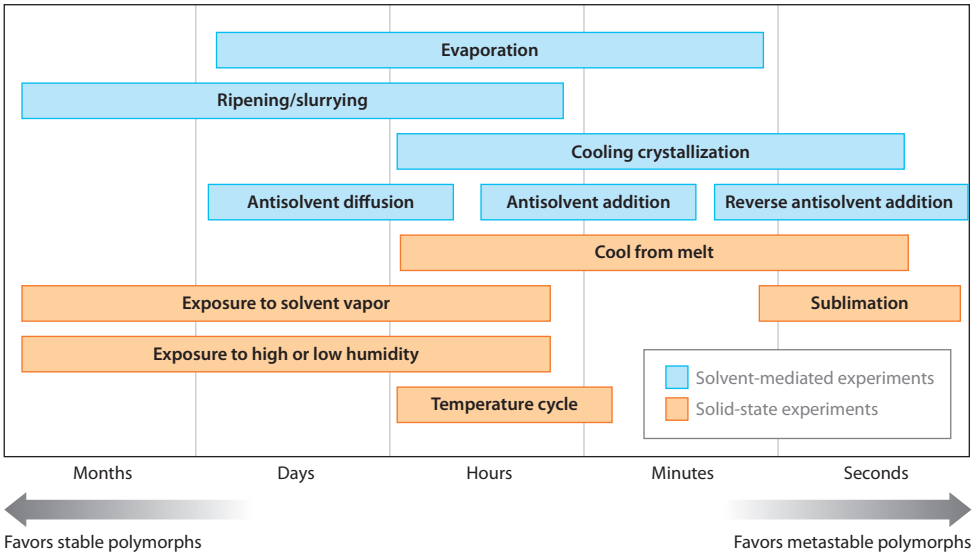

Figure 4

Timescales of different crystallization methods used to screen solid phases. Figure reprinted with permission from Reference 69. Copyright © 2004 by Russell Publishing Ltd.

forms are more likely to nucleate in processes in which crystallization occurs immediately (69). Most of the traditional methods are amenable to automated high-throughput technology. As a result, large sets of crystallization experiments can be performed using small amounts of APIs in a short period of time using robotic platforms for sample generation and analysis (70). The different methods to derive multiple solid forms have been extensively reviewed (44, 71–74). It is necessary to exploit different approaches, as one method may produce a specific polymorph exclusively.

Solvent-based approaches, in particular solution crystallization methods and slurry experiments, should incorporate a diverse set of solvents and solvent mixtures covering a wide range of properties (e.g., hydrogen bond acceptors/donors, polarity, dipole moment, dielectric constant, viscosity). Similar to impurities, solvent can promote or inhibit the hydrogen bonding networks found in molecular crystals, thereby directing the nucleation and growth of a specific solid form via molecular recognition. In slurry ripening studies, the choice of solvents is crucial, as inadequate solubility in a solvent system may hinder the solvent-mediated phase transformation of a metastable polymorph to a stable solid form. It has been suggested that a solubility of at least 8 mM is needed for conversion to a stable polymorph in a reasonable timeframe (75). The slurry technique is quite effective for identifying low-energy polymorphs and improving the drug substance's crystallinity, as amorphous solids or metastable polymorphs cascade to the next-lowest-energy solid phase according to Ostwald's rule of stages. Moreover, it has been demonstrated that for water-soluble compounds, neat aqueous slurries are effective in finding hydrated forms, whereas for poorly water-soluble drugs, slurries in mixed solvent systems containing water are more successful in generating hydrates (76) because the drug is often more soluble in the solvent mixture than in water, thus allowing equilibrium to be reached earlier. Solvents commonly used for the development of a crystallization process or in processing should be included as part of the screen.

The nature of the solid-state phase is also dependent on the driving force for crystallization, supersaturation. The level of supersaturation influences both the crystal nucleation and growth rate. Generally, stable polymorphs are the slowest to nucleate and tend to precipitate at low

supersaturations, whereas kinetic polymorphs favor a high degree of supersaturation. In a single-solvent polymorph screen of the anticonvulsant drug carbamazepine Lodaya and coworkers (77) manipulated the solid-state outcome via variations in the nucleation temperature and the degree of supersaturation at which nucleation occurred. In a few instances, several polymorphic pairs concomitantly nucleated.

For compounds with multiple solid forms, the relative stability of the polymorphs should be identified. The most common method to evaluate physical stability is slurry bridging (or competitive slurry). The approach involves slurrying at least two different solid forms in various solvents or solvent mixtures that are saturated with the drug. According to Ostwald's rule of stages, the high-energy polymorph will dissolve and convert eventually to the lowest-energy (or lowest-solubility) solid form. Use of multiple solvents is recommended to minimize any potential solvent effects, as the polymorph stability order is independent of the solvent system. Slurry bridging can be conducted over a wide temperature range, and in the case of enantiotropically related polymorphs, competitive slurry can be carried out to bracket the transition temperature. Generally, additional techniques (e.g., solubility, eutectic melting point depression, intrinsic dissolution rate, melting data, solution calorimetry) should be used to confirm the thermodynamic stability relationships of polymorphs (78). Slurry bridging can also be extended to anhydrates/solvates to identify the critical solvent activity for solvate formation. This technique is frequently applied to hydrates to determine the phase boundary, understand the solid-state stability, and identify appropriate storage conditions because the water activity is directly related to the relative humidity (79).

When the drug compound progresses further along the development timeline and reaches key milestones, it may be prudent to revisit and conduct a more wide-ranging, exhaustive polymorph screen to ensure that the polymorph landscape is thoroughly covered from both a process robustness and an intellectual property perspective. Nonclassical approaches, which include crystallization under high pressure, supercritical fluid crystallization, additive-induced heteronucleation, crystallization in confined volumes, template-directed nucleation, microfluidic crystallization, potentiometric cycling, and crystallization under an external effect, may also be valuable in searching for new polymorphs and should be considered as part of the comprehensive polymorph screen. Several of these methods should also be considered in cases in which a particular drug molecule is difficult to crystallize, as these approaches can reduce the activation barrier for nucleation and thus accelerate the crystallization process. Llinas & Goodman (80) provide an excellent summary of controlling polymorphs with these different methods.

Polymorph Selection—Deciding Which Solid Form to Develop

Form selection is generally a collaborative process involving various key personnel including formulators, materials scientists, and process chemists and engineers. Physiochemical properties of each solid phase are evaluated and compared to decide which one should be selected. Key physical properties that are carefully scrutinized are the chemical and physical stability, dissolution rate, bioavailability, solubility, and hygroscopicity. In addition, the manufacturability and processability are considered. Information on the sensitivity of the drug substance to heat, pressure, and shear is vital, as each of these aspects may have implications for chemical and formulation processing. For instance, shear-sensitive materials may undergo a loss in crystallinity or a phase conversion upon milling; hence, particle size control will rely solely on the crystallization process. Most of the time, the decisive factors in the selection process are stability and solubility. The thermodynamically stable polymorph is generally preferred and developed, as it has the lowest risk for a phase conversion during manufacturing, packaging, and storage. In some instances, for efficacy reasons it may not be viable to develop the lowest-energy solid form, whereupon it may be more desirable

to develop a metastable polymorph or a stabilized amorphous phase (i.e., solid dispersion) (81). The susceptibility of the high-energy polymorph to undergo an unwanted phase transition can outweigh any benefits it might offer. However, this does not imply that the development of a metastable form will not be viable. The metastable polymorph is indeed developable but will require a detailed understanding of the impact of numerous factors including storage temperature, process-induced stresses, humidity, and processing variables on the phase transition, and this form is often considered more challenging compared with the most stable polymorph (82).

The selection process between an anhydrate and a hydrated phase is more complex, as various factors are considered including the solubility, dissolution profile, processability, dehydration-hydration behavior, and solid-state stability. Information on the phase boundaries and the stability conditions, namely the humidity and temperature conditions in which the phases are stable and exist, is also necessary. Owing to the slower kinetics of solid-solid phase transition, slurry bridging in aqueous-organic solvent mixtures with varying water activities can provide prompt and useful information for identifying the critical relative humidity (or water activity) and understanding the thermodynamics of the anhydrate-hydrate relationship.

Generally, hydrates are less soluble and have slower dissolution profiles in water than anhydrous forms. Moreover, channel hydrates can present challenges, as inconsistencies in the moisture content as a result of absorption or desorption of water vapor may lead to issues in content uniformity in the drug product and also result in materials with dissimilar powder properties (e.g., powder flowability). If possible, structural determination of the hydrate crystal lattice can provide valuable insight on the role of water in the crystal structure. Thermal analysis and humidity desorption of the hydrate can shed information on the strength of the hydrate, that is, how loosely or tightly water is bound in the crystal structure. To highlight the potential risks with each solid phase, a thorough understanding of the solid-state properties is required.

Solvates are also potentially viable solid phases, but similar to hydrates, factors including hygroscopicity, desolvation behavior, solid-state stability, manufacturability, and dissolution behavior must be evaluated. Solvates chosen for development are restricted to certain solvents that are regarded as safe. Generally Class III solvents are ideal relative to the other two solvent classes owing to lower toxicity concerns. Commonly accepted solvates include ethanolate, 2-propanol, and acetone solvates. Although solvates outside of hydrates tend to offer enhanced apparent solubility in water over nonsolvated solid phases, the main hurdles are the risk of desolvation and the ICH guidelines for limits on residual solvents, which are related to the desired dose of the formulation.

CONTROLLING POLYMORPHISM DURING DRUG SUBSTANCE MANUFACTURING

In API manufacturing, the finishing steps (or technologies) typically include crystallization, isolation, and drying. Each unit operation may impact the quality, powder properties, and final crystal form of the drug substance. Crystallization from solution is the primary separation and purification method, and it defines the crystal size, particle habit, and solid form of the crystalline product. The outcome and information derived from the solid form screen are critical in designing a robust crystallization process to produce the selected solid phase, which usually is the most thermodynamically stable phase, consistently. For compounds with multiple solid phases, the polymorph relationship (monotropy or enantiotropy), relative thermodynamic stability, and/or phase transition kinetics should be established along with the phase diagram/behavior/map, which includes vital information on the thermodynamic stability regions.

In the case of monotropically related polymorphs, the most stable solid form can be crystallized exclusively through monitoring and control of the supersaturation profile by ensuring that the

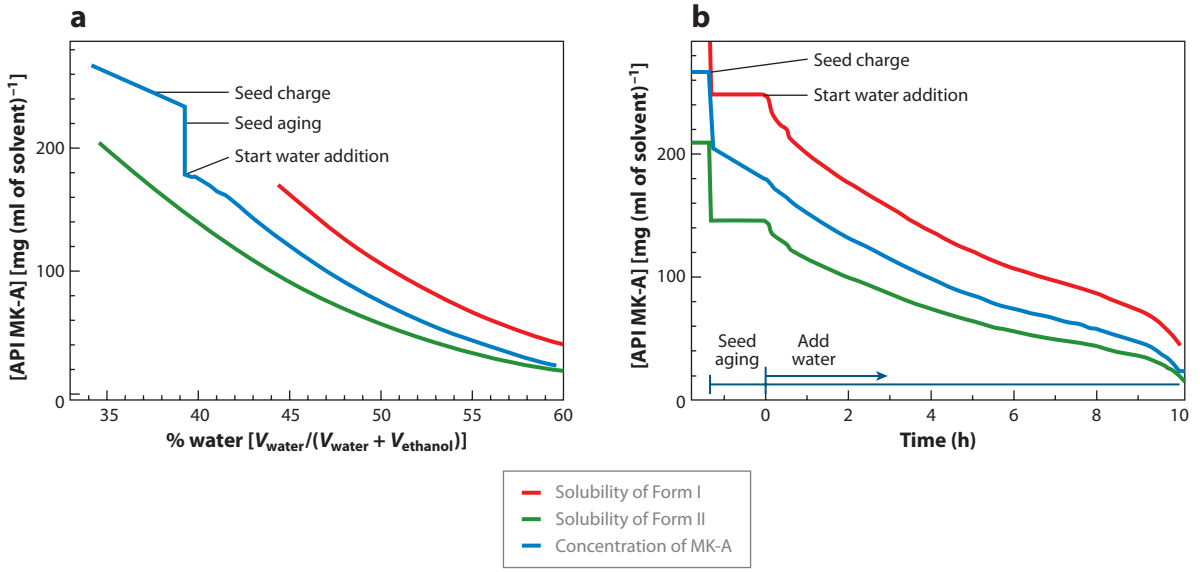

Figure 5

Solubility curves and crystallization profiles at 65°C for an active pharmaceutical ingredient feedback-controlled addition applied to maintain 33% supersaturation: (*a*) versus % water and (*b*) versus time. Figure and caption reprinted with permission from Reference 83. Copyright © 2009 by the American Chemical Society. MK-A is a generic descriptor of a Merck compound.

solution concentration does not exceed the solubility of the less stable (or more soluble) polymorph while the homogeneous solution is supersaturated with respect to the stable solid phase. Cote and coworkers (83) elegantly demonstrated this approach in a feedback-controlled manner in an antisolvent crystallization process for an API. Combined with the use of milled seeds and operation of the process at a high temperature to enhance the growth rate, the most stable form was selectively crystallized with satisfactory cycle times. **Figure 5** shows the crystallization profiles of the API; a constant supersaturation is maintained within the solubility window where only the stable phase can crystallize, as the metastable form cannot nucleate as a result of undersaturation. The approach can also extend to enantiotropic systems; however, knowledge of the transition temperature is required, as crystallization should occur in the temperature range in which the desired solid form is thermodynamically favored.

The most effective and straightforward technique to control polymorphism in molecular crystals is to seed a supersaturated solution with the desired polymorph. Information such as the solid-liquid equilibria and the supersaturation limits (or metastable zone width) would be needed to develop a seeded crystallization process (84, 85). Otherwise, if the solution is undersaturated the seeds will dissolve or in the event where spontaneous nucleation occurs, a mixture of solid forms may be obtained, as the initial nucleation may result in the appearance of a kinetic phase according to Ostwald's rule of stages.

Seeding enables nucleation to be bypassed, and the polymorphic form and particle size and habit can be controlled by the seed loading, conditioning, and type as well as by the conditions at which the seeds are introduced (86). Seeds should be chemically pure as well as polymorphically pure; otherwise, a mixture of polymorphs may be obtained (87). In the case of abecarnil, small amounts of the stable polymorph, Form C, in seeds of the metastable phase, Form A, resulted in the isolated material containing a mixture of both Form A and Form C solids, whereas pure Form

A seeds were able to suppress the formation of Form C crystals and to produce the desired Form A solids exclusively (88). For an enantiotropic polymorphic compound, Müller and coworkers (89) highlighted the importance of identifying the transition temperature and devised a seeding strategy that involved seeding at low supersaturations below the transition temperature to manufacture the desired stable solid form consistently. However, at times seeding may not succeed in crystallizing the target polymorph. For example, Yu and coworkers (90, 91) demonstrated that cross-nucleation occurred between D-sorbitol, D-mannitol, and ROY polymorphs in seeded melt crystallization of each system. Seeds of one polymorph were able to nucleate a different crystal form regardless of the thermodynamic stability. As a consequence, seeding is futile in controlling the polymorphic outcome when cross-nucleation strikes.

Inclusion of a diverse set of solvents in a solid form screen is enormously valuable in identifying solvated phases, and the outcome of the screen is potentially helpful in guiding the selection of appropriate crystallization and washing solvents. For instance, solvents that favor unwanted solvates can be ruled out as prospective solvent systems. However, there may be times when, despite the existence of a solvate, the solvent is required in the crystallization process to remove impurities. At this point, a phase diagram or map is tremendously important in pinpointing stability regions where other solid phases might lie. Recently, Black and coworkers (92) reported a crystallization design space that enabled the isolation of an anhydrate and the avoidance of a hydrated form in an aqueous process. Water could not have been excluded as it served a dual purpose: purging inorganic impurities and achieving adequate solubility. Thermodynamic equilibrium of the anhydrate and hydrate in aqueous mixtures was determined through a series of slurry experiments, and a ternary phase diagram was constructed to identify the design space in which the anhydrate was the most stable. Knowledge of the stability region allowed the process to operate in a zone where the anhydrate was thermodynamically favored and could be produced robustly and consistently.

Solution-mediated phase transformation is a common and effective strategy to transform high-energy forms to least-soluble polymorphs, particularly in cases in which concomitant polymorphism (93) occurs as the less-soluble phase grows at the expense of the more soluble form. The phase transition process involves three main steps: dissolution of the metastable phase, nucleation of the stable form, and crystal growth of the stable phase (94). The driving force of the conversion is the difference in the free energy between the metastable and stable solid phases, which is generally reflected as the solubility difference between phases. The greater the solubility difference, the more rapidly the transition proceeds. The choice of a solvent system is important, as adequate solubility is needed for the kinetic phase to cascade to the low-energy solid form (75).

Various factors including solvent, impurities (or additives), temperature, agitation rate, seed type, and particle size can accelerate or slow the phase conversion rate. Temperature is an important parameter, as solubility of a drug in a particular solvent is dependent on temperature. Hence, temperatures at which the solubility is low may delay the phase transition. Moreover, in enantiotropic systems the process temperature is more significant because temperatures approaching the transition temperature will yield slow transformation kinetics as the solubility difference between the two phases approaches zero. At the transition temperature, both solid phases persist in solution. Conversely, decreasing or increasing the temperature away from the transition temperature will lead to faster phase conversion kinetics as the magnitude of the solubility difference increases.

Particle size can also influence the transformation rate between solid phases. As particle size decreases, there is an increase in the ratio of surface area to volume, whereby the dissolution rate of the solids is enhanced as a result of an increase in their mass transfer rates. Furthermore, according to the Ostwald-Freundlich equation, the saturation solubility increases with decreasing particle size. This is particularly relevant for metastable polymorphs in which dissolution and solubility

of the less stable phase can be enhanced, which in turn accelerates the transformation process. Bristol-Myers Squibb scientists (95) employed this strategy in the crystallization of an API where a high-shear mixing force from a homogenizer was applied to a slurry consisting of a less stable solid phase. The more soluble solid phase was reported to transform quickly to the stable polymorph in the high-shear environment.

PPAR: peroxisome proliferator-activated receptor

Impurities or additives can selectively inhibit the phase transition process by hindering the nucleation and growth of the stable phase and thereby stabilizing the metastable form. In the case of L-glutamic acid, Davey and coworkers (96) rationally designed additives that mimic the conformation of molecules in the thermodynamically stable polymorph in order to stabilize the kinetic α-form. Later, it was observed that in the absence of additives the phase transformation of L-glutamic acid from the metastable α-form to the stable β-phase involves secondary nucleation of the stable form on the surface of the kinetic form and eventually results in the encapsulation (or inclusion) of the β-phase within the α-form (97). Additives can also alter the solubility of polymorphs. In the case of L-phenylalanine, additives that decreased the solubility of the anhydrous form or inhibited the mass transfer of solute molecules to the growing monohydrate surface in solution were effective in reducing the rate of transformation of the anhydrate to the monohydrate phase (98). Similarly, solvents can retard the phase transformation process by interfering with the crystal nucleation and growth of the least soluble phase. Careful choice of solvent may be a useful approach to isolate less stable polymorphs. Kline and coworkers (99) employed a high-throughput automated solvent screen to identify solvent systems that are effective in stabilizing the metastable form of a PPAR (peroxisome proliferator-activated receptor) inhibitor. With this screening approach, a suitable solvent was found, and a controlled seeded cooling crystallization process was developed that enabled the exclusive manufacture of the least stable polymorph. Important aspects of solution-mediated phase transformation process have been summarized elsewhere (100, 101).

Phase transition in solution is an efficient method for converting solvated phases to anhydrous forms. One tactic is to reduce the solvent activity below the critical activity at which the solvate is no longer thermodynamically preferred. This can be achieved by introducing a second solvent to the slurry or by reslurrying the solvate in a different solvent system (102). An alternative approach relies on the fact that the critical solvent activity of the solvate is a function of temperature. With increasing temperature, the critical solvent activity is expected to increase, and the anhydrous phase is preferred. In contrast, temperature reduction favors the solvate, as the critical solvent activity diminishes (103). Generally, a solvate-anhydrate pair can be considered enantiotropically related if a transition temperature exists above which the anhydrate is thermodynamically favored and below which the solvate is the preferred solid phase. Recently, the two approaches were applied to axitinib, a promiscuous solvate former, as desolvation pathways to crystallize the stable anhydrous form (102, 103).

Phase transitions that have direct implications for both processing and storage of the drug substance can also occur in the solid state. Numerous factors can affect the kinetics of the phase transition including temperature, pressure, humidity, particle size, impurities, and crystalline defects. In API manufacturing, a solid-solid phase transition can occur during drying and/or milling. There are many types of phase transitions including transformation between crystalline and amorphous phases; transformation between polymorphs; and transformations between solvates and neat anhydrates, solvates with different stoichiometry, or solvates composed of different solvent molecules.

During drying, residual solvents are removed with heat; for solvated phases, thermally induced desolvation is a concern. Efforts should be made to ensure that the solvate is maintained. This can be realized by avoiding overdrying via determination of drying end points; identifying an appropriate drying scheme, for instance, humidified drying for hydrated forms; and understanding

the interaction of process parameters (e.g., temperature, pressure) with the residual solvent content and physical properties (104). Desolvation processes generally occur via one of two mechanisms. In the first, subtle changes in the crystal lattice occur with the loss of the solvent molecules. This leads to the appearance of solvent-free isomorphic desolvates or desolvated solvates (105). The second mechanism revolves around a destructive and potentially reconstructive mechanism in which the original crystal structure collapses to a glassy or intermediate state in which all information on the crystal lattice is lost. The metastable state may then potentially reorganize, nucleate, and grow into a new crystalline phase. Given that thermal stress may induce physical transformations of organic solids, thermal analysis is an essential aspect of the screening process for generating new crystalline forms and understanding the solid-state behavior.

In some cases the pathway to a particular phase can be achieved only through a solid-solid phase transition. For instance, the hydrate form of the inhaled drug TRK-720 was obtained from a solvent exchange process with a methanolate phase whereby the solvate goes through a desolvation-hydration step in which water substitutes for methanol molecules in the crystal lattice (106). The water molecules penetrated into the crystal and filled the empty space available as a result of the methanol departure. Solid form screening results revealed that nine solvates of TRK-720 can exist; however, owing to concerns with the residual solvent limit, the solvates were not considered viable candidates. Attempts to desolvate the solid via drying were unsuccessful in producing anhydrates; amorphous solids were generated instead. The desolvation-hydration process was successfully scaled up and was able to manufacture the hydrate phase reproducibly.

Milling is a common top-down approach to reduce the particle sizes of drug substances. Milling involves cutting/shearing, compression, and attrition of particles. High energy is generally required to break crystals to micrometer- and submicrometer-sized particles. The process is quite effective in diminishing the size of the particle; however, it sometimes results in a polymorphic change or a decrease in the crystallinity of the pharmaceutical solids. Mechanical stresses are applied to crystals that can result in crystal defects, lattice disorder, or reorganization within the lattice arrangement. The occurrence of solid-solid phase transitions during mechanical processing is not uncommon, and general aspects of mechanical stress on phase behavior have been reviewed (107).

SUMMARY POINTS

1. The existence of multiple solid phases is inevitable for most small-molecule drugs. Knowledge of the solid-state properties of all solid phases is necessary to judiciously select the optimal phase.
2. Solid form screening is a critical activity initially carried out at the drug discovery-development interface. It enables the discovery of all potential crystalline phases and includes the evaluation of the solid-state properties of these phases. The phase selection process involves a cross-functional team from various scientific disciplines, as the selection of a developable phase depends on the solid-state stability, solubility, dissolution, hygroscopicity, processability, and manufacturability of the drug substance.
3. Polymorphic control in a crystallization process requires understanding the kinetics and thermodynamics of the polymorphic system. Establishing phase diagrams or maps is beneficial in identifying thermodynamic stability regions to selectively crystallize the most stable phase.

4. Phase transitions not only are solution mediated but may also occur in the solid state as a response to variations in humidity, pressure, and temperature. The solid-state behavior of the drug substance must be thoroughly investigated to understand the risks associated with process-induced stresses (e.g., heat, pressure, and shear).

DISCLOSURE STATEMENT

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