

# From Form to Function: Crystallization of Active Pharmaceutical Ingredients

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## Introduction

Since the introduction of aspirin in 1899, and more particularly since the advent of antibiotic “wonder drugs” in the 1940s, society has come to rely on the widespread availability of therapeutic drugs at reasonable prices. It was a tremendous challenge to bring penicillin to market and could not have been done without the simultaneous development of both product and process under the inspired leadership of Howard Florey over a 10 year period starting in the early 1930s, as revealed in the riveting story told by Eric Lax.<sup>1</sup> In the interim, much has changed in drug development, but the timelines remain long, and the obstacles to success remain high.

For drugs delivered to patients in crystalline form, the physical properties of the active pharmaceutical ingredient (API) including crystal form, size and shape have the potential to impact bioperformance, particularly for low-solubility compounds, where the rate-limiting-step in drug uptake may be the dissolution of the API in the gut. These physical properties of the API are often controlled in the final API crystallization step. Because most small molecule drugs (>90%) are delivered in crystalline form, and currently about 90% of new API's being pursued are classified as having low solubility in water, a well-controlled crystallization of the API is often a vitally important operation in pharmaceutical manufacturing. Moreover, it is a difficult operation because of uncertainty in the crystal forms that will appear, and because of the many challenges associated with scaling-up crystallizations from laboratory to manufacturing scale.

Although great emphasis is placed on the therapeutic and chemical discovery aspects of new APIs, it must be emphasized that the successful entities will eventually need to be

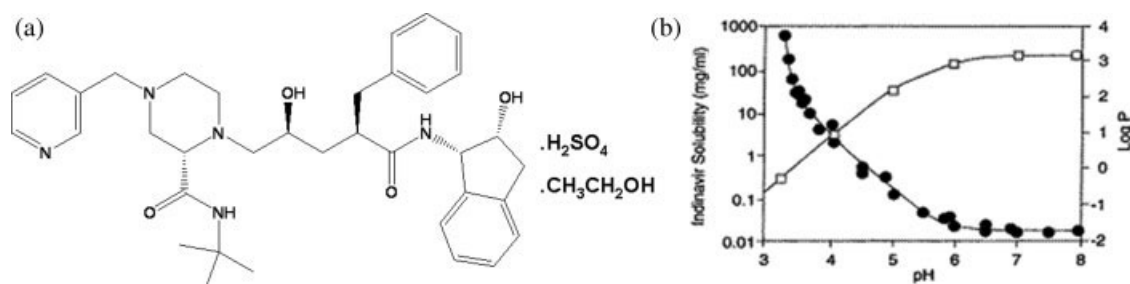
manufactured. Pisano<sup>2</sup> has made a detailed study of the strategic value of process development and concludes that the benefits of a superior manufacturing process can include early product launch and consistent, higher product quality. Most companies seek to minimize manufacturing costs and maximize process portability by applying the simplest manufacturing process capable of producing their drug product with desired attributes. Because only 10% of the compounds in development survive the efficacy and safety hurdles in the clinic and become marketed drugs, there is also great value in minimizing R&D costs (including clinical trials), which are estimated to be about \$1 billion per launch, with a remaining life protected on-patent of typically only 6–10 years.

In this perspective, we describe the state-of-the-art in API crystal product and process design, highlight barriers that currently prevent the production of better, cheaper crystalline products, and give our best estimate of where the field is going and should go during the next decade.

## Crystal Form

The ultimate efficacy of a drug molecule depends on its interactions with the appropriate target in the human body at the molecular level. However, the delivery of the drug in a safe and economical way partly depends on the properties of its solid-state, at least in those cases involving a solid dosage form. Small molecular drug entities (which typically have molecular mass in the range 200–600) are normally isolated as crystalline or, in some cases, as amorphous solids for delivery, although the ultimate formulation may be a solution or suspension. Crystallinity confers various advantages during isolation, processing and storage of the drug, such as better impurity rejection, improved handling characteristics, such as sticking and flow and, in the majority of cases, better physical and chemical stability. These factors are particularly important in defining a robust processing platform and storage conditions so that a stable product can be delivered to patients. Solid

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**Figure 1.** (a) Structure of indinavir sulfate ethanolate. (●) pH-solubility and (□) pH-logP profile for indinavir, where P is the octanol-water partition coefficient for indinavir.<sup>11</sup>

dose API's can be prepared as native free base (or free acid) moieties or as salts; they can be anhydrous, hydrates, or solvates; they may be crystalline or amorphous; they may even be prepared as a single component or as a cocrystal. Each has its advantages and disadvantages.

Most critical to the performance of a drug in humans is its plasma concentration profile, frequently referred to as bioavailability. It is the fraction of administered dose of drug that reaches systemic circulation and is an important pharmacokinetic property of the solid-state of the drug. Hence, the formulation needs to be optimized to ensure that sufficient drug will be available to engage the target in humans and, hence, be efficacious. Since the crystalline state is thermodynamically more stable than the amorphous state, its solubility and dissolution rate can be expected to be lower than that of the amorphous phase.<sup>3</sup> In addition, the solubility and dissolution rate of a more stable polymorph (most crystalline solids are capable of existing in several molecular packing configurations called polymorphs, e.g., carbon has two-diamond and graphite) will be lower than that of a less stable form. While this could potentially have a negative impact on bioavailability (in cases where bioavailability is limited by the solubility and/or dissolution rate), it is still preferable to develop the polymorph with lowest free energy into a drug product due to physical stability considerations.

An effective way to anticipate the existence of multiple forms, including solvates and hydrates, is to preinvest in experimental crystal form screening, which may also include salt screening in cases where the drug molecule is a free acid or free base. Almost every pharmaceutical company has some form of high-throughput approach to perform these screens. There have also been some efforts at so-called "polymorph predictions",<sup>4-7</sup> but this is a very nascent field in terms of being practically relevant to current drug development. The only example the authors found of a stable crystalline form that was predicted *in silico*, and subsequently produced experimentally in the laboratory is the case of racemic progesterone.<sup>8</sup> A similar case for a marketed drug has not been found. This is a reflection of the immense complexity of anticipating packing arrangements of organic molecules in crystal lattices, our inadequate understanding of subtle yet important non-bonded molecular interactions (e.g., van der Waals interactions, hydrogen bonds, zwitterionic interactions, etc.) that can influence such packings and inadequacies in accurate energy calculations of molecular crystals. For example, the energy difference between polymorphs could be smaller than the accuracy level of parametric force-fields.<sup>9,10</sup> *Ab initio* methods

are not yet capable of accurately computing energetics of even rigid molecules. This fascinating theoretical problem is sure to engage the imagination of academics for the foreseeable future and, should a successful method be developed, could change the way polymorph screening is conducted in the pharmaceutical industry. However, a pessimistic view of the whole process involves asking the question — Even if free energies could be adequately calculated for crystals as a function of temperature, will this lead to a successful prediction? For practical purposes, one would want to predict the experimentally observed structure, which need not exactly coincide with the thermodynamically most stable structure.<sup>10</sup>

Another important factor to consider when selecting the API phase is that the pH-solubility profile of a drug with a pKa in a pH range that is physiologically relevant can play a major role in determining pharmacokinetics. For example, the HIV protease inhibitor, indinavir (Figure 1), has a solubility of 0.02 mg/mL at pH 7.4, which increases to 60 mg/mL at pH 3.5 due to protonation of the pyridinyl nitrogen, i.e., an acidic environment increases the probability of absorption of indinavir.<sup>11</sup> However, HIV-infected patients frequently suffer from low-levels of HCl in the stomach. Hence, it is critical to develop an acidic salt of indinavir, such as the sulfate, which is the commercially marketed solid form, to ensure optimal serum concentrations for anti-HIV activity.

Crystallization often represents a convenient and scalable method to purify a drug substance, and the extent of impurity rejection could depend significantly on the particular crystal form that is isolated. The purifications of dirithromycin,<sup>12</sup> and (R, R)-formoterol tartrate,<sup>13</sup> represent two examples, where it was possible to vastly improve impurity rejection by selective crystallization of an acetone solvate in the penultimate step in the first case, and a high-temperature hydrated crystalline form in the second. In both cases the subsequent processing step involved the isolation of an anhydrous polymorph of the API through a solvent-mediated crystal form conversion in which the less stable form dissolves, and the more stable form simultaneously crystallizes, as explained in the context of other systems by Cardew and Davey,<sup>14</sup> and by Veessler et al.<sup>15</sup>

The intriguing case of ritonavir (an important ingredient in the AIDS medication cocktail) is presented as a case study to justify preinvestment in crystal form screening, in order to improve the probability of discovering the most stable polymorph early in the drug development cycle.<sup>16</sup> In this instance, the formulated product, Norvir<sup>TM</sup>, a semisolid capsule, failed dissolution tests after being launched in the market due to the



**Figure 2. Solution mediated conversion of orthorhombic paracetamol to monoclinic paracetamol in benzyl alcohol.**  
The scale bar represents 250  $\mu\text{m}$ .<sup>21</sup>

appearance of a new, more stable crystalline polymorph of ritonavir, Form II, which possessed a lower thermodynamic solubility than the marketed Form I. Abbott was forced to reintroduce the product formulated with Form II, but encountered serious challenges in maintaining the drug supply of this life saving treatment for AIDS. The new form was believed to have been templated by the production of a degradate of ritonavir base, the cyclic carbamate, with an analogous structure.<sup>17</sup> This case highlights the difficulty faced by the industry in forecasting with any scientific certainty whether the crystal form in development is the most stable form, hence, resistant to form changes as drug development goes through clinical trials followed by large-scale manufacture of the product during the marketed lifetime. It also exemplifies the highly stochastic nature of nucleation, which may lead to the undesirable scenario in which an undiscovered form appears during late-stage development or manufacturing.

Another aspect of crystal forms in an emerging area that has recently received a great deal of attention is that of cocrystals. These represent crystals containing two or more distinct components that are held together by either hydrogen-bonding or strong dispersive interactions. Solvates and hydrates are typically excluded from this list. Such crystal forms could offer advantages in terms of bioavailability,<sup>18,19</sup> stability, and the ability to extend the product portfolio if sufficient advantages can be demonstrated by developing the cocrystal compared to the neutral form.

## Crystal Shape and Size

Certain crystal habits are notoriously difficult to handle in both the laboratory and in manufacturing — needles and flakes being the worst. While it is normal to have a suspension

density of 15 wt % solids for equant-shaped crystals, it is difficult to reach even 5 wt % for needle-shaped crystals. Moreover, needles and flakes are difficult to filter, dry, handle in powder form, and formulate.

It is well-known that crystals grow in a variety of shapes in response to both internal (crystal structure) and external factors. Some of these factors can be manipulated (e.g., solvent type, impurity or additive concentrations, solution temperature and supersaturation, etc.) by crystal engineers to steer crystals toward a target shape or away from undesired shapes. The importance of crystal shape to processing and product quality/functionality has been discussed in the context of ibuprofen by Gordon and Amin.<sup>20</sup> The primary interest in this system is the existence of high-aspect ratio rods when grown from nonpolar hydrocarbon solvents, such as hexane or heptane. Equant, low-aspect ratio crystals are formed when grown from polar solvents, such as methanol or ethanol. The resulting crystals have better dissolution behavior and improved processing properties relative to the rods grown from nonpolar solvents. This was discovered by researchers at the Upjohn Company, who patented the change in solvent as a process and product improvement.<sup>20</sup>

It is well-known that different polymorphs may exhibit substantially different crystal morphologies. For example, Figure 2 presents an instant in time during the solvent-mediated conversion of orthorhombic paracetamol (needles) to the monoclinic form, which exists as prisms and plates in benzyl alcohol.

Dramatic changes of crystal shape can also be induced by changes in solvent or solvent mixture (see Winn and Doherty<sup>22</sup> for a review of solvent effects) and by the presence of quite small amounts of surface active impurities in solution that act as growth inhibitors for certain crystal planes. Growth inhibitors may be added deliberately to modify the crystal

shape, or may be present as a result of the manufacturing conditions (e.g., due to reaction chemistry). A classic example of this is the case of paracetamol (also called acetaminophen) crystallization, whereby small amounts of reaction byproducts, such as metacetamol, change the paracetamol crystal shape from equant to needle-like.<sup>23</sup> Changes in supersaturation may also induce changes in shape, but this is typically not as dramatic (e.g., again the case of paracetamol).<sup>24</sup> Consequently, the potential for engineering changes in crystal shape is enormous, although this is an area that has not been as extensively cultivated by drug companies as one might expect. In fact, the authors are not aware of any marketed drugs for which the API shape has been intentionally altered by the addition of a growth inhibitor to the final API crystallization. More commonly, the growth inhibitors that are at play in API crystallizations are naturally occurring byproducts of upstream chemical steps, and there is generally limited capacity to predict the extent to which low-levels of these impurities may alter crystal habit.

Particle-size distribution (PSD) may determine the rate of plasma uptake of an API when the process is dissolution rate limited. The PSD may also affect API processing parameters, such as filtration and drying rates and product formulation parameters, such as flow, compactability, sticking, and segregation, which ultimately affect key product/process attributes, such as content uniformity, tablet strength, and productivity. From the bioavailability perspective, small particles are preferred as they provide faster dissolution, but small particles can be challenging to handle. From a manufacturing perspective, larger particles are preferred, but not so large as to cause content uniformity issues in the formulated product, which can be a particular concern for low-dose drugs. As a general rule, broad or bimodal particle-size distributions are to be avoided as they have a higher tendency to yield slow filtration rates and often have poor flow properties. In most cases, narrow distributions about an optimal mean size are desired.

Typically, for both seeded and unseeded crystallizations, the particle-size distribution is set by the balance between crystal growth and nucleation, which is ultimately controlled by the level of supersaturation prevailing during the course of the crystallization. This is true whether the supersaturation is created by cooling, antisolvent addition, evaporation, or chemical reaction. Ward et al.<sup>25</sup> present an example of a seeded batch crystallization operated in cooling mode, for which a significant degree of control over the PSD could be obtained by selecting an appropriate cooling policy. The cooling profile determines whether nucleation or growth processes dominate at each instant of time during the crystallization. If the system nucleates early, those crystals have a chance to grow, and relatively large particles are produced. If the system nucleates late, they do not, so one is likely to generate a PSD rich in fines.

Current practices of API particle-size control often involve some type of size reduction subsequent to crystallization in order to achieve some or all of the following objectives: break up needles or elongated rods into smaller aspect ratio particles, reduce the mean particle size significantly from that achieved during crystallization, reduce batch-to-batch variations, or create a more monodisperse distribution of sizes. One emerging technology in the “wet-milling” arena is sonication, generally applying ultrasound frequencies in the 20–50 kHz range in order to break particles and reduce crystal aspect ratio. Several cases of this application are reported in the litera-

ture, including an article by researchers at Bristol-Myers Squibb Company<sup>26</sup> who report that such an approach has been used to reduce the size of API particles from an initial size of 100–200 microns to particles smaller than 20 microns.

## Process Development

The development of a process to crystallize the bulk API is generally driven by the desire to achieve the following: (1) sufficient product purity to meet established quality standards, (2) isolation of the chosen crystal form, which is typically (with very few exceptions) the most thermodynamically stable form, (3) a specific target PSD and crystal shape, as these may affect both bioavailability and processability, (4) a high-yield, (5) good volume productivity with final slurry concentrations typically targeted for  $10 \pm 5$  wt %, and (6) reasonable cycle time (generally < 24 h) for the crystallization, as well as for the associated filtration and drying processes. Typically these factors would be prioritized as listed earlier, with (1) being absolutely critical to ensure patient safety, while (2) and (3) are frequently required, depending on their impact on chemical stability and bioavailability. While factors (4)–(6) are not expected to have direct impact on the patient, the pressures of operating in an increasingly cost-conscious world provide significant incentive to seek operational efficiency, bringing goals (4)–(6) to the forefront of consideration, particularly for high-volume drugs.

Unfortunately, these factors are not independent, and achieving one may render it impossible to achieve the others. As unsatisfying as it may be, there are some cases where process development simply becomes a matter of making rationally chosen compromises.

The other critical factor that plays heavily on this effort is the need to develop processes very quickly, often with very small quantities of material in order to facilitate early formulation development activities geared toward establishing a preliminary market formulation. With a premium placed on getting to market as rapidly as possible, the goal is to keep the process development activities off the critical path. Additionally, because the vast majority of the processes being developed are for compounds that will never become marketed drugs, there exists a strong driver to applying a resource-sparing approach to this process development. From this perspective, there is certainly great value in “doing it right the first time”, recognizing that the “right” solution represents a global optimum where two of the critical parameters being optimized are time and resources.

In addition to speed, a premium is also placed on acquiring a high-degree of scientific understanding of the process during development, as this knowledge can be leveraged into increased regulatory flexibility under the new Quality-by-Design (QbD) paradigm. While at first glance these two seem like conflicting objectives, our ability to realize both of these may be facilitated by the thoughtful application of scientific and engineering fundamentals, new enabling technologies, such as process analytical technology (PAT), process modeling tools including population balance and computational fluid dynamics (CFD) models,<sup>27,28</sup> and innovative solutions in the area of continuous processing. The last of these concepts deserves a brief discussion as continuous processing has found

limited application in the pharmaceutical industry relative to the rest of the chemical industry, and there are many who feel that this has been a missed opportunity.<sup>29</sup> While there are certainly interesting examples of continuous API processes (such as the impinging jet crystallization work of Midler et al.<sup>30</sup>), API processes have historically defaulted to batch or semi-batch mode as the industry standard. Because continuous processes have the potential to offer economic and/or safety advantages, or to even achieve results not accessible via batch processes, interest in this topic has increased significantly over the last few years. The most publicly visible example of this interest is the recently established Novartis-MIT Center for Continuous Manufacturing, supported by a \$65 million 10-year grant from Novartis.

One highly touted enabling technology is the microreactor, noted for its potential to offer significant advantages in the control of many chemical reactions, while offering unique simplicity in “scale-up”.<sup>31,32</sup> However, the application of this technology to crystallization has, thus far, been rather limited, with the vast majority of the publications in the area focused on generating nanoparticles of inorganic molecules. The small channel sizes (which give microreactors their unique capabilities) are highly prone to plugging, and create practical limitations on the size of the particles that can be produced.

## Scale-Up

The goal of any process development effort should be a robust, reproducible, scalable process. For crystallization processes, it is the last of these criteria that is often most difficult to achieve or to predict. Traditionally, the vast majority of final API crystallizations have been conducted in simple stirred-tanks via processes involving a complex combination of growth, secondary nucleation, agglomeration, and particle breakage. With the exception of growth, the rates of these processes are all highly dependent on the system’s agitation, as poor micromixing leads to high local supersaturation, which can drive nucleation and agglomeration, while overly intense agitation can lead to particle breakage/secondary nucleation. Complicating the situation considerably is the fact that agitation is notoriously challenging to scale-up, because as one moves across scales, geometric similarity between vessels is difficult to achieve, and one can not match both tip speed (which affects peak shear, and, therefore, particle breakage) and power per unit volume (which affects blending time, particle suspension, and frequency of exposure to the high-shear zones) simultaneously. As a result, scale-up of these processes from laboratory to factory often results in significant changes in both PSD and crystal morphology. While, in principle, CFD modeling could eliminate some of this uncertainty by mapping out the shear fields and providing insights into the mixing times, the state-of-the-art lacks comprehensive crystallization models that can predict process performance across scales.

In response to this lack of control, the vast majority of processes have relied on terminal milling to adjust the particle size and shape, thus, providing the batch-to-batch consistency needed to ensure target performance in patients. However, dry milling (pin or jet milling) has a number of liabilities, including: (1) the operations present serious industrial hygiene con-

cerns due to dust generation, (2) crystal form/crystallinity may be impossible to preserve across the milling step, (3) the product from dry milling is often rich in fines and/or highly electrostatic, making downstream processing difficult, and perhaps most importantly, (4) dry milling is a very expensive operation. These drivers are leading the industry to adopt strategies that incorporate particle size and shape control into the final crystallization directly so that terminal dry milling can be eliminated from factory processes.

One such approach is to develop growth-dominated processes in which nucleation, agglomeration, and particle breakage are minimized. Two elements are critical to minimizing nucleation: (1) providing ample seed surface area, and (2) providing rapid micromixing in order to avoid locally high-supersaturation at the feed point, where antisolvent or reagent is being introduced. The first point can be accomplished by providing a large amount of seed in what is often referred to as a “heel” process in which a portion (generally ~10%–30%) of the final crystallized slurry from batch “*n*” is left in the crystallizer to serve as seed for batch “*n*+1”. Alternatively, more moderate amounts (0.1–10%) of high-surface area seed (> 2 m<sup>2</sup>/g) can be used. In either case, by providing sufficient supersaturation control to ensure a growth process, one can “dial in” final API particle size by changing the seed loading. Critical to the success of this approach is a seed conditioning step that ensures consistent seed from batch to batch. The second point is accomplished by charging reagents to the system via a recycle loop set up to circulate locally around the crystallizer. By incorporating mixing tees, static mixers, or other such devices, one can achieve very rapid micromixing in the loop, thus, removing this burden from the vessel agitator, which can instead be designed and operated to provide low-shear blending and solids suspension. In some cases, particularly when high surface area seed is applied and the growth kinetics are very rapid, particle agglomeration can be an issue; and since agglomeration reduces seed surface area and shifts the PSD unpredictably, it is an issue that must be addressed. Agglomeration can generally be mitigated through proper energy input to the system via a rotor/stator wet-mill, sonicator, or other device incorporated into the recycle loop. In the case of shear-sensitive compounds, the recycle loop should be set up with a low-shear alternative to the centrifugal or diaphragm pumps commonly used for such operations.

At Merck, this general approach to API crystallization<sup>33</sup> has become the “standard”, and line-of-sight from research laboratory all the way to commercial scale has been achieved via the design of standardized equipment trains and careful process control enabled by PAT tools, such as the closed loop feedback control module described previously.<sup>34</sup> Not only does this strategy allow a consistent PSD to be established during the crystallization, but the utilization of crystallization best practices reduces the risk of nucleating unwanted crystal forms or occluding impurities that could compromise product quality.

## The Future

*For also knowledge itself is power.* Thus, wrote Francis Bacon.<sup>35</sup> In the field of pharmaceutical crystallizations, this statement has never before rung truer than it does today. The fact that regulatory agencies are providing a strong incentive

for companies to know their processes, and the ultimate impact of those processes on the patients under the new Quality-by-Design paradigm places a premium on knowledge. A comprehensive understanding of the crystal form landscape and crystallization processes of drug molecules will greatly enable several pieces of the drug development puzzle to fall into place—optimizing pharmacokinetics through salt formation, improving impurity rejection in synthesis schemes, providing opportunities for delivering a drug product with impeccable physicochemical stability and adequate shelf-life, and the potential to diversify a product portfolio. Layered on top of this is the need to develop drugs more rapidly and more efficiently than ever before in an environment that has become increasingly competitive. So, the challenge that drug companies face is the need to minimize process development and manufacturing costs and to reach markets quickly, while simultaneously mitigating risk. Accomplishing these goals is of great value to both the patients and the pharmaceutical industry—the ultimate manifestation of success being high-quality, low-cost drugs getting onto the market and to the patients who need them faster than previously believed possible.

The goal of this article was to highlight the complexity of the problem, while providing the authors' perspective regarding the challenges, gaps in knowledge or capabilities, and opportunities for improvement in the development of pharmaceutical crystallization processes. While many of the tools that may ultimately reshape the landscape in this field are in the early stages of their development, most are far from ready to handle the complexity of drug molecules being crystallized from real process streams in large-scale equipment. Specific technologies or methodologies that have the potential to revolutionize API product and process design include: (1) tools to select the most bioavailable salt form or cocrystal particularly with an understanding of the solubility and possible form conversion in biorelevant dissolution media, such as simulated gastric fluid and simulated intestinal fluids, (2) *ab initio* prediction of all the polymorphs of an API in their correct relative order of stability, (3) scientific understanding of the basis of impurity rejection by solvates and hydrates compared to the anhydrous free base or acid, (4) tools to manipulate crystal size or shape in a predictable manner, (5) process modeling methodologies to facilitate reliable scale-up, and (6) better understanding and tests for detecting and predicting late-stage appearing polymorphs, especially those appearing in liquid formulated capsules or solid dispersions. Some of these tools may be generated within the pharmaceutical industry, but most are likely to be the fruit of productive, focused collaborations between academia and industry.

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