

## REVIEWS

# Engineering of Pharmaceutical Materials: An Industrial Perspective

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**ABSTRACT:** Crystal engineering provides a rational approach to solving formulation, processing and product performance problems. This review discusses how the concept of crystal engineering can be judiciously utilized to manipulate the solid-state properties of drugs and excipients for successful pharmaceutical formulation and process development. Existing and emerging manufacturing as well as co-processing technologies being applied in the pharmaceutical industry are also presented together with selected examples of crystal form design, crystal form selection and crystal modifications for illustration purposes. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 97:2855–2877, 2008

**Keywords:** crystal engineering; crystallization; polymorphism; selection of salt forms; particle size; preformulation; pharmaceutical manufacturing; formulation

## INTRODUCTION

Crystal engineering addresses crystal structural design and its fabrication to the end product. It was pioneered by Schmidt in photochemistry where photodimers, dislocations, crystal modification as well as packaging were discussed.<sup>1,2</sup> Desiraju defined crystal engineering as the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with the desired physical and chemical properties.<sup>3</sup> It is a highly interdisciplinary field that involves various and often uncorrelated areas.<sup>4</sup>

Many recent publications on crystal engineering are based on supramolecular chemistry that entails the study of noncovalent intermolecular interactions, for example, pharmaceutical cocrystal research. In addition, a number of topics such as crystal packing, molecular interactions, crystal structure and shape prediction, crystallinity, polymorphism, crystal nucleation and growth, synthetic process, and crystallization modeling have also been included in crystal engineering research.<sup>3,5–10</sup>

From an industrial perspective, crystal engineering encompasses broadly the application of basic principles of crystal chemistry and materials science to the production of tailor-made pharmaceutical materials. It constitutes an important component of a drug development program where the drug crystal (or solid) structure is defined and optimized, followed by formulation development

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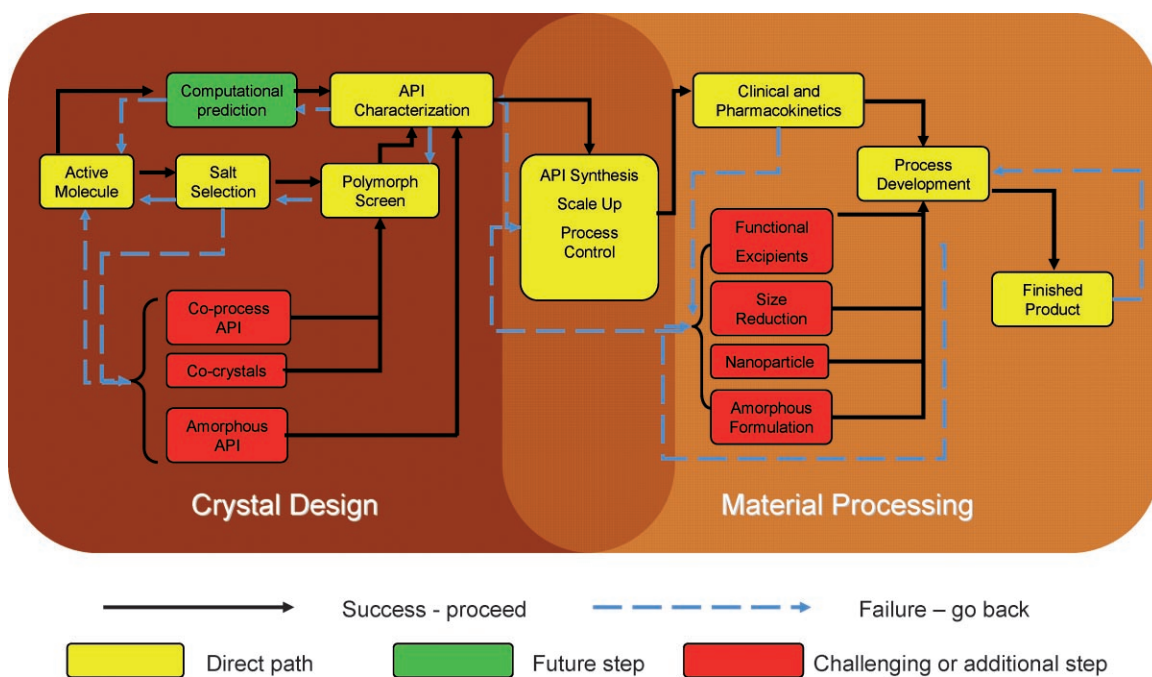
and process design (Fig. 1). Solid-state knowledge covering important material properties such as polymorphism,<sup>11–16</sup> size and morphology,<sup>17–19</sup> amorphous structure,<sup>20–23</sup> solvates and cocrystals,<sup>12,13,24,25</sup> salt/polymorph selection<sup>26,27</sup> can be applied, and appropriate crystallization/manufacturing processes can then be engaged to design and produce a pharmaceutical product.

At present, a ‘Throw Off The Wall’ approach is generally practiced where a molecule in development is passed through discovery, preformulation, formulation development and chemical development (development stages) when it meets a limited set of criteria with little contribution from other functional areas and knowledge of developability. Drug candidates are often advanced to human testing with insufficient information on potential crystal forms, salts, physical properties, and manufacturing capabilities. Traditionally, almost all formulation and processing problems are empirically handled by increasing the excipient to drug ratios; applying granulation techniques; or using complex processing technologies and delivery systems. The present review is intended to provide an overview of selected material design and fabrication technologies based on the concept of crystal engineering that are currently applied in the pharmaceutical industry. Our main objectives are to highlight the applications and merits of these proven or

emerging technologies and to illustrate how crystal engineering can be applied in the pharmaceutical industry to help improve the design and development of solid materials for processing, manufacturing and drug delivery.

## DESIGN OF CRYSTAL STRUCTURE

The packing of drug molecules (not only the chemical structure) is known to affect profoundly the stability, ease of manufacture and biopharmaceutical performance. Typical drug molecules have complex chemical structures with multifunctional groups and conformations. They are prone to form different packings with small local free energy minima differences<sup>28</sup> either by themselves (polymorphs), or with other molecular components (cocrystals or solvates) or counter ions (salts), producing materials with different physical, chemical, mechanical and biopharmaceutical properties. Development of an undesirable crystal form (e.g., in the case of metastable ritonavir) may result in production failures and product performance problems<sup>29</sup> Suitable utilization of crystal forms, however, may be advantageous in terms of improving product quality, generating intellectual properties and avoiding occasionally catastrophic failures in development or manufacturing.



**Figure 1.** Relationship between crystal and process design in new drug development.

Crystal habit (and size) are often not considered when the crystal structure of a (lead) drug candidate is finalized for further development. Particle shape may cause problems in (1) mixing and de-mixing,<sup>30</sup> flow,<sup>31</sup> and milling;<sup>32</sup> (2) tablet lamination or capping as a result of particle slippage,<sup>33,34</sup> particle bonding,<sup>35,36</sup> preferred orientations<sup>37,38</sup> and pressure transmission;<sup>39</sup> (3) dissolution;<sup>40,41</sup> and (4) aerodynamic properties of respiratory particles.<sup>18</sup> Analysis of anisotropic structural strain or polymorphic transitions during compression of organic crystals such as paracetamol by X-ray diffraction or spectroscopic means have been reported.<sup>42</sup> Further studies on the influence of crystal shape and molecular interactions on compaction may provide better prediction of the mechanical properties and stability of tablets.

Crystal habit is a direct manifestation of its point group symmetries and crystallization conditions. The Law of Rational Indices states that crystal faces of low energy are stable, more commonly observed in nature (i.e., slower rate of crystallization), characterized by high densities of atoms, and perpendicular to a large interplanar spacing (related to the crystal structure), which corresponds to small Miller Indices.<sup>43</sup> The shape of a crystal is also determined by the relative growth rate of the crystal faces, which can be influenced by mass and heat transfer, the API manufacturing process (e.g., fluid shear and milling) involved and interaction with the crystallization solvents.<sup>17,44</sup> Inclusion of crystal habit in the design and modeling of crystal structure and crystallization process paves the path to successful development of a functional drug substance.

### Prediction of Crystal Structure and Habit

Different packings and habits of pharmaceutical crystals alone or with other components were mostly discovered by empirical approaches or by serendipity. Computational crystal structure prediction may remove some of the uncertainties in formulation development. It has the potential of not only supporting candidate screening and lead optimization but also providing valuable information on the chemical stability, mechanical properties, thermodynamic stability (between polymorphs) and synthesis (growth and nucleation) of crystals. Due to a lack of understanding of molecular interactions and conformations, as well as crystallization kinetics that are required for

obtaining confirmatory polymorphs, predicting polymorphs from molecular structures is a long-term goal.<sup>45–48</sup> Most methods of crystal structure prediction rely on the search for local minima for identifying energetically feasible polymorphs (2 kcal/mol between observable polymorphs). The outcome of the prediction depends on the molecular, force, and search modeling.<sup>45</sup> Computational prediction of crystal structures and polymorphs for rigid molecules was reported to be reasonably reliable<sup>46</sup> and the associated software is commercially available (Accekryst<sup>®</sup>). Prediction of equilibrium morphology and mechanical properties based on crystal structure is becoming a reality.<sup>17,49–51</sup> It may also be possible to include specific interactions of solvents or impurities for morphology predictions.<sup>17,51</sup> Hence the crystal habits of APIs (active pharmaceutical ingredients) may be engineered by a suitable choice of crystallization solvents. The concept of Bravais–Friedel Donnay–Harker and attachment energy models for predicting equilibrium crystal shape and how solvents may modify crystal habits has been reviewed by Winn and Doherty.<sup>17</sup> With the availability of crystal structure and habit information, prediction of processing capability, for example, compaction<sup>37</sup> and milling (Accelrys<sup>®</sup> technical document), has also been reported.

### Salt Selection and Polymorphic Screening for Lead Optimization

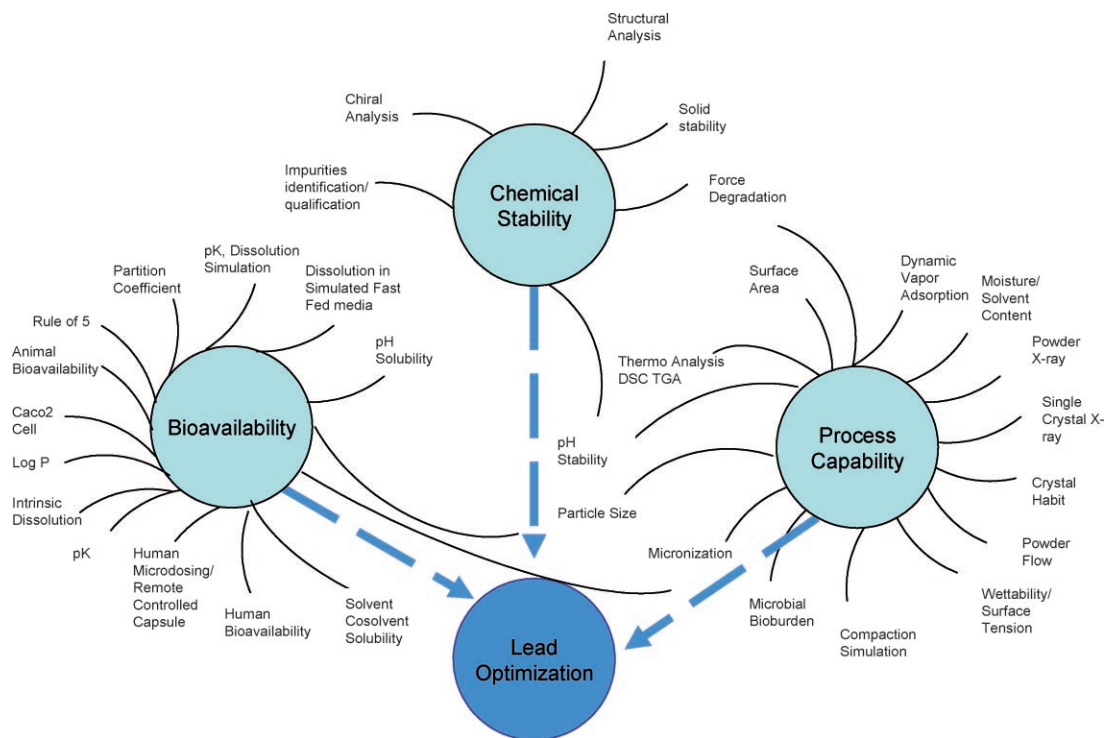
Judicious design of packing structure in the salt selection and polymorph screening program is often under appreciated in the industry. A hastily chosen material may jeopardize the development program if it fails to meet the formulation, processing, synthesis or bioavailability requirement. At present, a semi-empirical approach is being employed for most salt selections/designs<sup>52</sup> with the common objective to increase drug's solubility and dissolution rate using counter ions such as chloride, bromide, and nitrate. On the other hand, sparingly soluble salts, such as pamoate, resinate, and xinafoate, are used to slow absorption so as to avoid acute toxicity. Such salts have also been selected to reduce hygroscopicity, improve taste, reduce corrosiveness to manufacturing equipment, improve compaction, increase melting points, and enhance stability.<sup>26,27</sup>

Based on our experience, the impact of pharmaceutical forms might be underreported, although there have been quite a few documented

cases with blockbuster drugs such as atorvastatin, indinavir, ritonavir, and paroxetine.<sup>53</sup> A paradigm shift of form selection and lead optimization strategies appears to be emerging in the industry. Hybrid programs (Transform, Symyx, Avantium, Solvias, and SSCI) that combine high-throughput technologies, statistical design of experiment and crystal growth knowledge have recently been exploited commercially.<sup>53–55</sup> These programs provide more crystal form screening and material characterization than conventional studies. Because of the limited drug substance available and a potentially large number of permutations of solvents and crystallization conditions, expertise in crystallization, statistics, and software/hardware design is often utilized to limit the number of trial runs required. X-ray diffraction and Raman spectroscopy are commonly used to define the hits.

A key objective of the crystal structure design program is to confirm the developability of the crystal form by conducting downstream experiments (Fig. 2) that are valuable to the clinical performance, formulation and manufacturing efficiency.<sup>56,57</sup> Pharmaceutical manufacturing is currently viewed as being inefficient and costly, and improvements are expected to bring an

annual saving of US\$90 billion.<sup>58</sup> Part of the saving could be realized by selecting better drug forms. Existing (staged) approaches for assessing developability using structural/stability characterization, bioavailability and thermodynamics data have been reviewed.<sup>26,56</sup> These approaches prioritize the developability testing based on defined selection criteria and drug substance availability for early screening to initial clinical program. Using miniaturized analytical technologies and setting testing criteria, Balbach reported that quality data can be generated with as little as 100 mg per active for candidate selections.<sup>57</sup> Despite these advances, our experience suggests that there is a general dearth (with some exceptions) of pre-formulation data in the industry to predict the developability for clinical and commercial formulations. It is advantageous to introduce formulation relevant tests such as miniature equipment processing or compaction simulation as soon as possible. Computational prediction<sup>34,37</sup> and computer simulation of compression process (both of which require good understanding of molecular interactions) based on crystallographic data may also be useful. Partnership between chemical and pharmaceutical



**Figure 2.** Developability assessment for pharmaceutical formulation development. The scope of the studies will depend on the nature of the drug candidate and its therapeutic indication.

development teams often brings overall success to the program.

Polymorph selection strategies premised on the knowledge of chemical structure, kinetics, thermodynamic and molecular packing have been discussed by Blagden and Davey<sup>16</sup> as a crystal engineering exercise. To assess thermodynamic stability, a number of techniques such as quantitative thermal analysis using differential scanning calorimetry (DSC)<sup>59,60</sup> and application of the Burger's Rule (with few exceptions); solubility determination of the crystal forms and the use of van-Hoff plot to determine the transition temperature;<sup>61</sup> as well as solvent and temperature cycling have been used in the industry.<sup>56</sup> Polymorph prediction software (Molecular Simulations, Inc., San Diego, CA) was reported to be reliable for small molecules with molecular weight <500.<sup>26</sup> Solubility data may give good estimate of the thermodynamic stability between different morphic forms but thermal analysis can be readily performed with less drug substance. Although a more stable polymorph is usually preferred, it is not often the rule until bioavailability, processing capability and stability results are evaluated (Fig. 2). For polymorph-sensitive products, formulation composition, primary packaging and secondary process need to be designed in accordance with regulatory requirements<sup>62-64</sup> to prevent unwanted polymorphic transitions during manufacturing<sup>65</sup> or storage.

At present, lead optimization programs for pharmaceutical forms are experimentally based. In each program, lead molecular form(s) are evaluated using a limited number of tests selected from an overwhelming list of experiments after preliminary screening (Fig. 2). The list of experiments can be viewed as a series of probes for defining the properties expressed by the chemical and solid-state structures. The scope of tests to be conducted may be defined by material science knowledge. For example, more solubility work will likely be performed on high molecular weight compounds<sup>66</sup> and crystal structure data may help define the need for early compaction evaluation for tablets.<sup>67</sup> However certain physical properties, such as particle size distribution and bulk density, are difficult to predict from the solid-state structure alone. An extensive testing program may still be required to assess the developability of a compound with confidence. It may be somewhat idealistic at this stage to expect pharmaceutical scientists to engineer the desired materials with fewer tests, less time and reduced

cost although this is probably the eventual goal of crystal engineering.

### Multicomponent Systems: Cocrystals, Solvates, and Co-Processed Materials

The design of crystal structure may also involve the development of cocrystals, solvates or coprocessed materials to achieve the development goal. Cocrystals containing two stoichiometric components (each component is a solid at room temperature before preparation) are reported to exhibit more or less desirable stability,<sup>68</sup> *in vitro* dissolution profile<sup>69</sup> and *in vivo* performance<sup>70-72</sup> than the acid, base or salt of a drug substance. They may have less tendency to form polymorphs or to recrystallize, unlike metastable polymorphs or amorphous systems.<sup>55</sup> Engineering of cocrystals could entail crystal design, pharmaceutical properties testing and manufacturing process development.

Understanding the formation of cocrystals may help support their crystal design, define pharmaceutical applications and develop manufacturing processes. Kitaigorodsky suggested that molecular-compound crystals (e.g., cocrystals) normally occur in molar ratio of 1:1 or 2:1. Their free energy is lower than the average energy of the components because of hydrogen bonding and crystal packing.<sup>73</sup> Cocrystals contain self-assembly units and may be designed using hydrogen bond based supramolecular synthons that could involve high-throughput screening.<sup>53-55,74</sup> A number of synthons based on carboxylic acids, amine HCl, carbonyl and hydroxyl groups, and saccharin have been employed to produce pharmaceutical cocrystals.<sup>75,76</sup> Cambridge Structural Database showed a respectable number of cocrystals of therapeutically active substances<sup>77</sup> and other compounds.<sup>25</sup> Synthons are identified by commonly found motifs in crystal structures and H-bond based synthon is believed to produce large enthalpy of interaction on crystallization. Crystallization is a spontaneous process where the free energy is reduced because the reduction of entropy (e.g., affected by crystal packing) is outweighed by the much larger decrease of enthalpy (e.g., affected by bonding, notably H-bond). Cocrystal formation in favor of the pure components is often the result of cooperative effect of strong (e.g., H-bond) and weak molecular interactions.<sup>78</sup> Use of both molecular modeling and H-bond synthons

may enhance the chance of success of developing commercializable cocrystals.

The fate of cocrystals both *in vitro* and *in vivo* may be difficult to predict because of the differences in thermodynamic activity coefficient of their binary components in solutions. For example, a glutaric acid cocrystal was demonstrated to improve the oral bioavailability of a low solubility API in animals. The dissolution rate was increased by 18-fold despite the occurrence of some solid–solid transformation in the dissolution media.<sup>72</sup> Childs et al. also reported that the increase and decrease of melting points and dissolution rates of fluoxetine HCl cocrystals depended on the properties of the guest molecules. Recrystallization of fluoxetine HCl:succinic acid<sup>76</sup> and conversion of celecoxib:nicotinamide<sup>69</sup> cocrystals during dissolution were also reported.

Cocrystal formation may be best effected by allowing component assembly in a thermodynamically favorable environment. Solvent evaporation, milling and melt processing (unconventional API manufacturing processes) have been proposed<sup>15,79</sup> although a solvent crystallization method has been reported.<sup>80</sup>

Solvates (including hydrates) are similar to cocrystals except one component is a liquid at room temperature.<sup>25</sup> Their crystal structures may be classified into isolated site, channel, or ion-associated type.<sup>3,81</sup> Spontaneous crystallization of solvates produces crystals of lower free energies than their corresponding nonsolvates. Therefore solvates have lower solubilities in their solvents of crystallization.<sup>61,82</sup> Solvates may display different physicochemical properties, manufacturability and bioavailability compared with their nonsolvated counterparts. Their characteristic crystal properties may exert positive or negative impacts on pharmaceutical formulation and processing. For instance, beclomethasone dipropionate solvates are useful for micronization, and for formulation as nasal spray suspensions and aerosol inhalers.<sup>82–85</sup> In contrast, magnesium stearate hydrates<sup>86</sup> may cause batch-to-batch variations. Solvation or desolvation, for example, conversion of anhydrous lactose to monohydrate, is a common manufacturing problem for solvates. The physical stability of a solvate may be related to the solid-state solvent mobility and the molecular interactions (e.g., specific interactions), both of which can be studied by single crystal X-ray diffraction<sup>87</sup> and solid-state NMR spectroscopy.<sup>88</sup>

Co-processing of excipients and drugs is a practical way of producing desirable input materials

for pharmaceutical manufacturing. A list of common co-processed actives and excipients is presented in Table 1. These common excipients have demonstrated significant benefits in improving mixing, flow, compression, and formulation drug loading.<sup>89</sup> Co-processing of APIs is employed for direct compression (e.g., common generic drugs such as ibuprofen and acetaminophen) and to improve chemical stability (e.g., co-processed with antioxidants).<sup>90</sup> The properties of co-processed materials are often different from the physical mixtures of individual components, and the crystallization or manufacturing of these co-processed materials is not well studied or reported.

## AMORPHOUS ACTIVES, EXCIPIENTS, AND FORMULATIONS

In some pharmaceutical applications, advantages can be taken of packing disorders for dissolution-controlled bioavailability improvement by designing less crystalline or even amorphous materials. In 2001, up to 35 amorphous active ingredients, excipients or dosage forms (e.g., Accupril<sup>®</sup>, Accolate<sup>®</sup>, Ceftin<sup>®</sup>, and Solu Medrol<sup>®</sup>) are listed in the European Pharmacopoeia, United States Pharmacopoeia and Physicians' Desk Ref.<sup>91</sup> Bioavailability enhanced solid dispersions such as griseofulvin (Gris-PEG<sup>®</sup>), nabilone (Cesamet<sup>®</sup>), itraconazole (Sporanox<sup>®</sup>), tacrolimus (Prograf<sup>®</sup>) and troglitazone (Rezulin<sup>®</sup>, Romozin<sup>®</sup>, and Noscal<sup>®</sup>) were introduced. More than 30 fast dissolving products were developed by freeze drying, molding and compression for improving patient compliance.<sup>92</sup> Many drug molecules, being large (with multifunctional groups) and conformationally flexible, are difficult to crystallize.<sup>20,28</sup> Therefore, amorphous drugs are also used in clinical formulations when crystalline forms are not available (e.g., amorphous atorvastatin) or to enhance drug release. Because of thermodynamic instability, developing amorphous or partially crystalline products is inherently risky. However, the benefits of using amorphous or partially crystalline (metastable) components may outweigh the risks. A number of good reviews on the properties of pharmaceutical amorphous solids have been published.<sup>20,21,23</sup> The following provides a brief overview of recent research and development strategies for amorphous products. Knowledge of crystallization and molecular interaction of drug

**Table 1.** Typical Engineered Excipients and Drug Substances

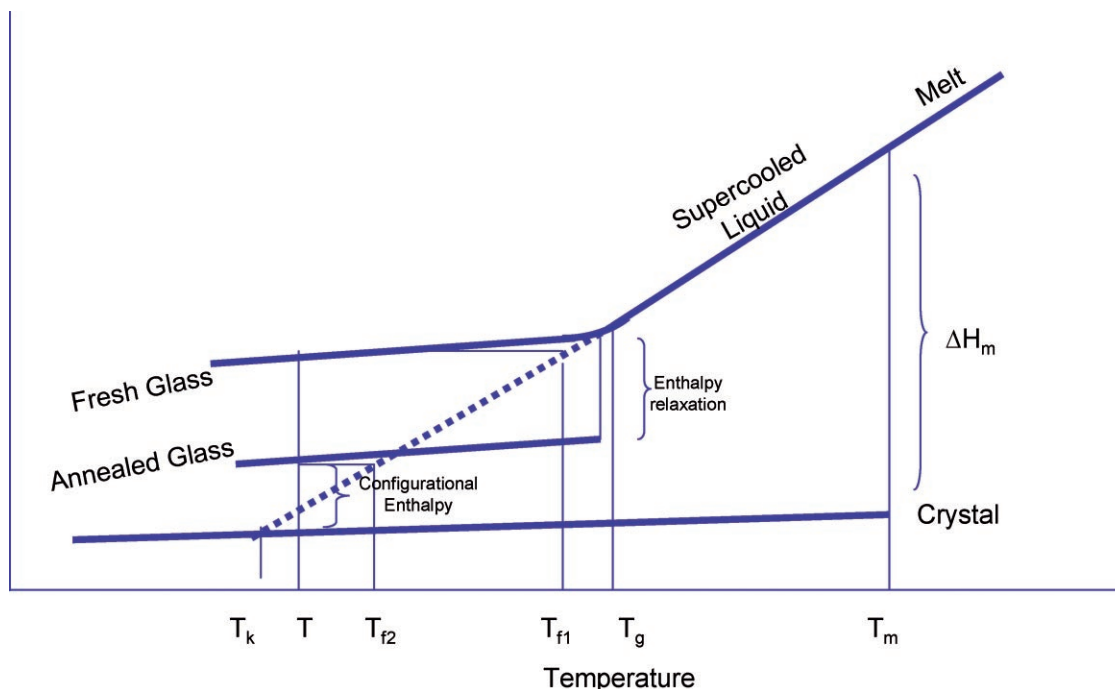
Excipient/Drug Substance	Crystal Engineering Approach(es)	Benefit(s)	Source/Supplier
Microcrystalline cellulose	Crystallinity, size	Improve compression behavior and flow property	FMC BioPolymer
Silicified microcrystalline cellulose	Co-processing of colloidal silicon dioxide and microcrystalline cellulose	Improve compactibility, flow, lubrication efficiency, blending properties	JRS Pharma
Cellactose	Spray drying of microcrystalline cellulose and lactose	Improve compression and flow	Meggle
Lactose monohydrate, spray dried	Spray drying mixture of crystalline and amorphous lactose	Improve compression and flow	Foremost, DMV
Granulated lactose	Fluid bed granulation	Improve compression by granulation and higher $\beta$ lactose content, less sensitive to moisture	DMV
Roller dried lactose	Roller drying	More surface for bonding, less sensitive to over lubrication	DMV
Ludipress	Co-processed lactose PVP and crospovidone	Improve compression	BASF
Mannitol (Pearlito <sup>®</sup> , various grades)	Spray drying, change of crystal size	Improve compression, flow property, mouth feel	Roquette
Calcium carbonate + starch (10%) (Barcroft CS90)	Co-processing, spray dried	Direct compression	SPI Pharma
Co-processed Sucrose and Maltodextrin (Di-Pac) 96.5% sucrose and 3.0% maltodextrin	Co-processing	Direct compressible sugar with high flow ability, low hygroscopicity	Domino specialty ingredients
Neusulin <sup>®</sup> (magnesium aluminometasilicate)	Amorphous excipient	Direct compression, oil adsorption	Fuji Chemical Industry Co.
Pharmaburst <sup>™</sup> , Pharmafreeze <sup>™</sup>	Co-processing excipients with propriety composition	Rapid disintegration, quick dissolving tablet excipient system	SPI Pharma
Co-dried fructose with starch (5%)	Co-processing	Good flow properties and directly compressible; change of surface morphology	SPI Pharma
Aspirin, various grades	Co-processing, encapsulation, particle size control	Direct compression, improve stability, improve processing capability	Rhodia
Acetaminophen, various grades	Co-processing, granulation, particle size control	Direct compression, improve flow properties	Rhodia
Ibuprofen (DC grade)	Co-processing	Direct compression	BASF

in condensed phase is important in developing these products.

### Development of Amorphous Materials

A functional amorphous drug substance may be considered as a supercooled liquid whose molecular movement is significantly reduced below its glass transition temperature (Fig. 3). Relative to the crystal form, it is metastable with a higher

entropy, enthalpy (Fig. 3), and free energy. These thermodynamic quantities represent the driving forces for phase transition in the amorphous solid but the kinetic stability is controlled by the rate of nucleation and crystallization of the drug in solid phase. The so-called ' $T_g - 50$  K rule' is frequently used for the development of amorphous molecules. This rule suggests that significant crystallization is less likely when the product is stored at 50 K below the glass transition temperature ( $T_g$ ). This simple approach has been substantiated by some



**Figure 3.** Schematic diagram of enthalpy of melting ( $T_m$  = melting point;  $\Delta H_m$  = enthalpy of fusion,  $T_K$  = Kauzmann temperature), glass transition ( $T_g$  = glass transition temperature) and glass annealing ( $T$  = annealing temperature;  $T_{f1}$  = fictive temperature for fresh glass;  $T_{f2}$  = fictive temperature for annealed glass at  $T$ ).

experimental data<sup>93</sup> but its validity has recently been questioned.<sup>94</sup> It is commonly applied in drug form selection when a crystalline material is not available. In addition, Vyazovkin suggested that an amorphous compound will be physically stable if stored at the  $\beta$  relaxation region below  $0.8 T_g$  (below the  $\alpha$  relaxation temperature).<sup>95</sup>

Measurement of thermodynamic properties as well as the determination of molecular mobility by thermal analysis, dielectric relaxation and solid-state NMR spectroscopy above and/or below  $T_g$  have been utilized to determine and predict the physical stability of amorphous pharmaceuticals. Because of the variations of material properties and techniques used, application of nonlinear statistical treatments, extrapolation of thermodynamic parameters, involvement of different assumptions for different models, and the different types of molecular mobility measured, the results reported could vary substantially between methods and between investigators.<sup>96,97</sup> A summary of the models and techniques (with references) for evaluating the physical stability of amorphous drugs is provided in Table 2.

DSC configurational entropy and large  $\Delta C_p$  (heat capacity) at  $T_g$  rather than free energy were

reported to reduce crystallization potential.<sup>99,100</sup> Molecular relaxation time ( $\tau = 1/\text{mobility}$ ) also affords a good measure of nucleation in a condensed phase. Molecular relaxation measurements above or below  $T_g$  are also believed to provide reasonable prediction for crystallization.<sup>96</sup> Unfortunately, molecular mobility and physical stability studies of amorphous drugs are normally performed on model molecules that are unstable in an amorphous state for a minimum product shelf-life (typically 18–24 months). A shelf-life predictive model that correlates the physical stability (crystallization) of an amorphous solid at room temperature has yet to be established.

Zhou et al.<sup>100</sup> indicated that the differences in crystallization potential between nifedipine and ritonavir may be partially explained by the changes of mobility on annealing rather than the initial mobility of fresh glass drug substance. Solid-state NMR data also suggested that the change of  $T_{1\rho}$  relaxation as a function of temperature is related to the crystallization rate.<sup>103</sup> However, it is still difficult to explain why some compounds are more difficult to crystallize in a condensed phase although molecular relaxation characteristics, structural conformation flexibility<sup>28</sup> and higher

**Table 2.** Representative Approaches Used to Study the Physical Stability of a Pharmaceutical Glass

Approach	Model	Technique(s)	Comments
Molecular mobility by thermoanalysis	Kohlrausch–Williams–Watts (KWW) equation $\Phi(t) = \exp\left[-\left(\frac{t}{\tau}\right)^\beta\right]$	Isothermal micro-calorimetry DSC	DSC enthalpy recovery <sup>93</sup> Modified stretched exponential function (MSE) equation used <sup>96,98</sup>
	Vogel–Fulcher–Tammann equation $\tau = \tau_\infty \exp\left(\frac{DT_o}{T - T_o}\right)$	Temperature modulated scanning calorimetry (TMSC)	Capable of measuring below $T_g$ TMSC study used
	Adam–Gibbs–Vogel equation $\tau(T, T_f) = \tau_\infty \exp\left(\frac{DT_o}{T - (T/T_f)T_o}\right)$	MTDSC and DSC	Assume $T_o = T_k$ obtained by extrapolation <sup>99</sup> Adam–Gibbs equation reduced to Vogel–Fulcher–Tammann equation for ideal glass <sup>99</sup>
Configurational entropy and enthalpy	Adam–Gibbs–Vogel equation $\tau(T, T_f) = \tau_\infty \exp\left(\frac{DT_o}{T - (T/T_f)T_o}\right)$	MTDSC	$T_f$ of annealed samples obtained by enthalpy relaxation and heat capacities $D$ and $T_o$ estimated from the heating rate dependence of $T_g$ <sup>101</sup> Modified version by Mao et al. <sup>94</sup>
	$\tau = A \exp\left[\frac{x\Delta h^*}{RT} + \frac{(1-x)\Delta h^*}{RT_f}\right]$	DSC	Data fitting also uses KWW equation <sup>102</sup>
Molecular mobility by dielectric measurements	Configurational enthalpy and entropy determined from melting, heat capacities and free energy are calculated <sup>99,100</sup>	MTDSC	
Molecular mobility and crystallization by solid-state NMR	$\epsilon^* = \epsilon_\infty + \frac{\epsilon_s - \epsilon_\infty}{(1 + i\omega\tau)^\beta} + \frac{\sigma_{dc}}{i\omega\epsilon_s}$	Dielectric relaxation spectroscopy	Measured above $T_g$ <sup>96</sup>
Fragility (m)	$T_1, T_{1p},$ and $T_2$ relaxations, C13 spectral changes	Solid-state NMR	$T_{1p}$ changes with $T$ is a measure of crystallization potential <sup>103</sup>
Activation energy ( $E$ )	$m = \frac{E_a}{2.303RT_g}$	DSC	Activation energy ( $E_a$ ) is calculated by plotting DSC heating rate versus reciprocal $T_g$ <sup>94,104</sup>
	$E = -R \frac{d \ln q}{dT_p^{-1}}$ $E = -R \frac{d \ln f}{dT_p^{-1}}$	DSC Dynamic mechanical analyzer	Activation energy measured after annealing at different temperatures <sup>95,104</sup>
Molecular mobility by thermally stimulated depolarization current	Measure molecular relaxation activated by electric field at specified temperatures	Thermally stimulated depolarization current	Cannot measure $\alpha$ relaxation of raffinose <sup>105</sup> Secondary relaxation for indomethacin <sup>106</sup>

Keys:  $\tau$ , relaxation time;  $\Phi$ , decay function at time  $t$ ;  $\beta$ , stretch power;  $D$ , strength parameter;  $T_o$ , zero mobility temperature;  $\tau_\infty$ , relaxation time at high temperature;  $T_f$ , fictive temperature;  $T_K$ , Kauzmann temperature;  $\Delta h^*$ , activation energy;  $A$ ,  $\tau$  when  $T$  and  $T_f$  at infinity;  $x$ , empirical parameter;  $T_p$ , peak temperature of enthalpy relaxation;  $q$ , heating rate;  $f$ , frequency;  $\epsilon^*$ , complex permittivity;  $\epsilon_s$ , low frequency permittivity limit;  $\epsilon_\infty$ , high frequency permittivity limit;  $\omega$ , frequency;  $\sigma_{dc}$ , dc conductivity contribution.

configurational entropy have been suggested as possible causative factors.<sup>99,100</sup> Nevertheless, recent advances in analytical techniques such as temperature modulated thermal analyses that separate reversible and nonreversible events (e.g., to measure relaxation or annealing) and sensitive isothermal microcalorimetry may help close the knowledge gap. A better understanding of nucleation and growth of drug substance may also provide solutions in other pharmaceutical applications, for example, prediction of minimum particle size in drug/wet milling and Ostwald ripening in suspensions.

Assessment of amorphous drugs should also be based on biopharmaceutical performance and processing capability and their relationship with the solid-state properties. For BCS II or IV compounds,<sup>107</sup> the permeability and aqueous solubility of an amorphous drug candidate should be sufficiently high for the drug to reach the site of action and be absorbed. The rule of 5 by Lipinski et al. may serve as a preliminary guide for permeability prediction. This rule suggests that poor absorption or permeation is more likely when a molecule has more than 5 H-bond donors, a molecular weight over 500, a Clog *P* (calculated) over 5 and more than 10 H-bond acceptors.<sup>66</sup> It should be noted that the excess thermodynamics of an amorphous material (excess entropy, enthalpy, and free energy) determined by calorimetric techniques or solubility measurements may predict several orders of magnitude of improvement in biopharmaceutical behaviors but it is not uncommon that the dissolution or equilibrium solubility (measured) can only be enhanced by several fold<sup>20,108</sup> because of phase transformations upon dissolution in the gastrointestinal tract<sup>109</sup> as well as during manufacture or storage. The biopharmaceutical performance should be checked by dissolution measurements or *in vivo* studies as soon as possible.<sup>110</sup> Amorphous drug substances may not be created equal. The physical and chemical properties of amorphous materials are influenced by the method of preparation and the presence of additives/impurities or excipients. For example, different amorphous and over 20 crystalline forms of atorvastatin displaying different solubility and stability profiles have been reported.<sup>111,112</sup>

### Reduction of Crystallinity: Solid Dispersion

A solid dispersion system was considered as the last resort in oral formulation development

because of its inherent thermodynamic instability. However, there has been a renewed interest in this delivery system as more is known about the crystallization in solid dispersions,<sup>22</sup> roles of modern excipients in the formulations, and capabilities of modern processing technologies.<sup>113</sup> This interest is further fueled by a growing demand for developing low solubility drugs. New knowledge acquired from using traditional (e.g., HPMC for Itraconazole)<sup>114</sup> and newer polymers (e.g., HPMCAS for structurally dissimilar low solubility APIs)<sup>115–117</sup> also facilitates solid dispersion development.

A key formulation goal for an oral solid-dispersion is to prevent or predict nucleation and growth in drug-excipients matrix and dissolution medium. The rate of nucleation ( $r^*$ ) in a condensed phase may be reduced by decreasing both supersaturation (a function of the free energy of nucleus formation,  $\Delta F^*$ ) and mass transport (related to the activation energy for diffusion,  $\Delta f^*$ ) (Eq. 1)<sup>118</sup> and crystal growth may also be limited by controlling the rate of diffusion.

$$r^* \cong \left( \frac{NkT}{h} \right) \exp \left[ - \left( \frac{\Delta f^* + \Delta F^*}{kT} \right) \right] \quad (1)$$

Therefore, preparing a formulation with a high  $T_g$  by using high  $T_g$  excipients such as PVP, HPMC, HPMCAS, and storing it well below the  $T_g$  should slow down the solid-state transformation and prolong product shelf-life. On the contrary, the presence of a powerful plasticizer such as water<sup>119</sup> may destabilize a solid dispersion.

To assure good physical stability, a number of studies have been conducted to predict the influence of excipients on the product  $T_g$ . Several equations such as those of Gordon-Taylor, Fox, Couchman-Karasz, Kwei and Schneider have been used to model the resulting  $T_g$  of drug-polymer compositions. Successful applications of these model equations, for example, Gordon-Taylor equation for a lactose-water system,<sup>119</sup> Fox equation for hydroxypropylmethyl cellulose copolymers<sup>120</sup> and Schneider equation for thiazide diuretics—PVP systems<sup>121</sup> have been reported. Nonlinear regressions with more independent or predictor variables generally yield better correlation coefficients and the identification of the ‘true’ model may be difficult. Modeling the  $T_g$  of amorphous dispersions may be improved by using more in-depth statistical analysis and larger confirmatory data sets from a wider range of formulation compositions.

The initial product  $T_g$  alone may not accurately reflect the physical stability of drug in a solid dispersion. A good understanding of important factors such as temperature dependence of drug solubility (supersaturation; Eq. 1), fragility and relaxation (annealing) (i.e., the influence of temperature on nucleation and growth of crystals in a solid solution) may be required. Shanker reported that the physical stability of drugs in a solid dispersion system for up to approximately 2 years was log-linearly related to the reciprocal of storage temperature at the rubbery state but this log linear relation might not be extrapolatable below  $T_g$ . The log-linear slope also differed significantly from that of the amorphous form.<sup>115</sup> Unlike chemical stability, the physical stability of a solid dispersion system is difficult to predict in a conventional accelerated stability (e.g., 40°C) program. In addition, the temperature dependence of both the molecular mobility and activation energy of nuclei formation needs to be known in order to predict the crystallization rate of amorphous drugs.<sup>101</sup>

The presence of interacting excipients (e.g., PVP) may inhibit or promote crystallization in solid dispersions, and the solid-state interactions may be confirmed by solid-state NMR, FTIR and FT Raman results.<sup>121–125</sup> Unfortunately, the effect of interacting excipients on the physical stability of drugs is frequently observed but not predicted. Use of mechanistic models can reduce cost to feasibility evaluations and facilitate solid dispersion formulation development. For example, the crystal structure may help predict the physical stability of solid dispersion. Matsumoto and Zografi suggested that the inhibition of indomethacin crystal growth in PVP is associated with the inhibition of dimer formation which is required as part of the crystal structure.<sup>125</sup> The solubility of drug in solid dispersion (level of supersaturation) may also help predict physical stability as in the case of griseofulvin-PVP system.<sup>126</sup> Several approaches have been proposed including the use of solubility parameters,<sup>121</sup> and molecular mobility/relaxation measurements by solid-state NMR spectroscopy<sup>124</sup> to predict and elucidate the solid-state behavior of solid dispersions. Techniques such as X-ray diffraction, modulated DSC and microcalorimetry are valuable for molecular mobility and crystallinity assessment.

A solid dispersion is thermodynamically stable if the target dosage does not exceed the drug solubility in the solid matrix. Therefore, the use of

solubilization agents/surfactants (e.g., Gelucire<sup>®</sup> 44/14, PVPs, polyethylene glycols, Vit E TPGS, Solutol<sup>®</sup>, Lutrol<sup>®</sup>, and polysorbate 80), and liquid-filled hard gelatin capsules (filling at elevated temperature if necessary) to produce such a stable solid dispersion is gaining popularity (e.g., ritonavir capsule). Modeling and measuring the solubility of low solubility drugs in solid polymeric matrices at room temperature<sup>126,127</sup> will be valuable for the development of stable and metastable (supersaturation affects stability) solid dispersions.

Most reported solid dispersion studies were performed on samples prepared using bench scale processes that are difficult to reproduce in a manufacturing setting.<sup>128</sup> The material engineering program should include manufacturing procedures that allow the incorporation of drug in high  $T_g$  materials and processes that quench the materials quickly to prevent crystallization. Solid dispersion/solid solution systems can now be produced with good process control on both pilot and industrial scales using a melt quenching (hot-melt extrusion, hot-melt granulation), liquid capsule filling or solvent removal process (freeze drying or spray drying).<sup>129</sup> Hot-melt extrusion (using twin screw extrusion equipment) or hot-melt high-shear granulation equipment allows higher-shear/temperature operations to produce physically more stable (higher  $T_g$ ) products. Spray-drying can be a reliable process to produce the product without subjecting the API to elevated temperatures. A common problem of designing a spray-drying process is to find an environment-friendly solvent for low solubility APIs.

### Excipients with Different Crystallinity

Modern excipients are engineered in many different sizes, shapes, forms and/or degrees of crystallinity. A number of amorphous, partially amorphous or crystalline forms of excipients have been successfully introduced and widely used in the industry. The use of different grades of engineered excipients (e.g., Avicel<sup>®</sup>, Fast Flo<sup>®</sup> lactose, direct compressible calcium carbonates) has provided the required viscoelastic properties, flow, porosity, and bulk density for efficient blending, material transfer and/or direct compression. A list of typical excipients and drug substances together with their crystal engineering approaches and benefits is presented in Table 1. One classic example is the variation of

different lactose isomers ( $\alpha$  and  $\beta$ ) ratios, hydrate levels and degrees of crystallinity to modulate the hygroscopicity (for protecting moisture sensitive drugs but may cause processing issues), compaction and powder flow.<sup>130,131</sup> Despite their wide acceptance, the properties of crystal engineered excipients are generally not included in the specifications and not well characterized by the end users. The development and utilization of these excipients could also be improved through a better understanding of the molecular interactions, manufacture and processing behavior of the 'engineered' solids.

## PARTICLE SIZE REDUCTION

Particle size reduction is a material engineering technology which has been shown to improve bioavailability, reduce dosage strengths (size), optimize compaction behavior, improve content uniformity (mixing), and enhance particle suspendability in suspensions or topical formulations. Milling is by far the most frequently employed size reduction technique in unit processes, for example, postgranulation or fluid bed drying to produce suitable materials for manufacturing.<sup>132</sup> It can also introduce surface and bulk crystal imperfections that may improve tablet compaction.<sup>133</sup> Particle size reduction technology in pharmaceutical industry is generally used as 'rescue tool' when the actives or excipients do not meet the solid-state attributes. Unfortunately, milling often causes flow problems, crystal surface<sup>134</sup> and bulk energetics<sup>135</sup> issues, polymorphic transitions<sup>136</sup> and unwanted Ostwald ripening<sup>137,138</sup> resulting in process and formulation failures. The properties of milled materials including the particle size are also affected by the equipment used.<sup>139</sup> Screening mills (Quadro<sup>®</sup> Comil<sup>®</sup> or oscillating mills) have less impact on crystallinity and work well with more brittle materials. Fitzmill<sup>®</sup> may be more suitable for more plastic materials. Fluid energy mills (e.g., Alpine<sup>®</sup> jet mill) are popular for micronization with inhalation, low solubility suspension or low dosage products. A list of common particle size reduction equipment for pharmaceuticals and their classifications can be found in the addendum of the FDA SUPAC-IR/MR guideline.<sup>140</sup>

The impacts of particle size reduction are often not predictable, not extensively studied and are normally reported postmortem. Typical but often hard-to-detect changes in material properties

such as surface imperfections can be difficult to quantify using conventional quality control techniques, for example, differential scanning calorimetry and X-ray diffraction.<sup>141,142</sup> New technologies such as solid state NMR spectroscopy and microcalorimetry to detect low levels of crystal defects (down to 1% of amorphous content for lactose),<sup>143</sup> as well as inverse gas chromatography (IGC),<sup>144–146</sup> Raman microscopy<sup>147</sup> and atomic force microscopy<sup>148</sup> to study the surface homogeneity may be required to understand and predict the relationship between material processing and resulting properties.

Nanotechnology is one of the few options for developing a high-dosage oral formulation for a virtually insoluble compound. In an ideal situation, dissolution of nanoparticles is improved by an increase of specific surface area, an increase of solubility and a reduction of boundary layer. The solubility ( $S$ ) increase and boundary layer ( $h_H$ ) reduction can be explained by the Kelvin's equation,  $\ln(S/S_b) = 2\gamma v/r$ , where  $S_b$  is the solubility of coarse ( $\geq 100 \mu\text{m}$ ) particles,  $r$  is the radius,  $\gamma$  is the interfacial tension and  $v$  is the molar volume; and by the Prandtl's equation,  $h_H = k\sqrt{(L/V)}$ , where  $k$  is a constant,  $L$  is the length of particle and  $V$  is the relative flow velocity.<sup>149</sup> Reduction of drug particles to a nano-scale holds great promises in improving drug properties such as solubility, dissolution, oral bioavailability, skin absorption (including retention of drugs in hair follicles), targeting delivery,<sup>150</sup> intranasal absorption and bioadhesive on mucus or skin.<sup>151</sup> A number of drug delivery companies, including Dow (BioAqueous<sup>®</sup>), Elan (NanoCrystal<sup>®</sup>), Eurand (Biorise<sup>®</sup>), PharmaSol GMBH (Nanopure<sup>®</sup>), SkypePharma (IDD<sup>®</sup>-P), Ferro and Soliqs (NanoMorph<sup>®</sup>), were established to develop low-solubility drug products. A nano-sized atovaquone suspension manufactured using a Microfluidizer<sup>®</sup> processor has been shown to produce superior bioavailability.<sup>152,153</sup> A micro-fine suspension of this drug (Mepron<sup>®</sup> Suspension) was approved by the US FDA in 1999. A series of oral dosage formulations (Rapamune<sup>®</sup>, TriCor<sup>®</sup>, Emend<sup>®</sup>, Megace<sup>®</sup> ES) have been introduced using the NanoCrystal<sup>®</sup> technology (based on milling) since 2000. Triglide<sup>™</sup> tablets were produced using the SkypePharma IDD<sup>®</sup>-P technology and launched in 2005.

Successful development of a nano-crystal drug delivery system requires the use of suitable process and equipment as well as satisfactory material properties and formulation composition.

A variety of methods, for example, supercritical fluid crystallization, flash evaporation, phase inversion, milling, controlled crystallization, increased nucleation by confined impinging jet reactors, microemulsion templates, and self-assembly from solution, have been studied or developed.<sup>154–156</sup> At present, commercial nanoparticle (oral) delivery systems are often manufactured by high-energy wet milling, which produces smaller particles for more brittle materials.<sup>150,157</sup> Nanosized particles are often prone to Ostwald ripening during wet milling, storage in suspension and dissolution *in vitro* or *in vivo*. Surface modification, carrier mediated, or crystallization inhibition approaches have been used to stabilize nanoparticles.<sup>158</sup> Since the particle size of a nanoparticle suspension is often difficult to maintain,<sup>137</sup> the conversion of the suspension to a solid-dosage form as part of the manufacturing process may allow the product to attain the required physical stability and *in vivo* performance throughout its shelf-life. Nano- or nanostructured particles can be cohesive and difficult to process although high-speed operation on production-scale rotary tableting press was demonstrated.<sup>159</sup> The requirements for developing nanoparticle (as well as milled) formulation are fairly well understood but tools to predict the achievable particles size, physical stability and process requirements are lacking. Feasibility studies are generally conducted by hit or miss approaches, possibly due to a lack of understanding of the molecular interactions of materials (principles of crystal engineering) that influence the mechanical properties of materials (milling), nucleation and growth (Ostwald ripening) in the presence of additives as well as the surface/bulk properties (processability) of pharmaceutical fine solids.

## CRYSTALLIZATION OF ACTIVE PHARMACEUTICAL INGREDIENTS

Batch crystallization from solutions is the typical purification method of pharmaceutical actives employed in pharmaceutical industry. This final synthesis step must produce APIs with defined crystal sizes, habits, structures and degrees of imperfections which are important determinants of bioavailability, mechanical strength and processability. Manufacture of APIs is often conducted following an empirical fashion using a fixed recipe. Lot-to-lot variations in solid-state

properties of APIs are the norm rather than the exception.<sup>160</sup>

Crystal growth is influenced by the chemical potential difference between the dissolved solute and the crystal surface (and the properties of the crystals). Imperfections or inclusions arise from the instability mediated through the combined effects of fluid dynamics, mass transport and growth. The classical model of Burton, Cabrera and Frank (BCF) first described the step motion phenomenon starting with material transport, adsorption and desorption, surface diffusion and deposition in discrete steps on the crystal faces.<sup>161</sup> Depending on the crystallization conditions, pharmaceutical crystals can be fragile and may be prone to erosion, breakage or clumping. Organic crystal lattices generate a higher frequency of ‘amorphism’ than that found in inorganic solids. ‘Oiling out’ of supersaturated solutions is common and these oils may solidify without structure.<sup>162</sup>

Crystallization from a supersaturation environment close to the metastable limit may result in excessive nucleation and poor crystal structure formation; producing mostly small particles of high surface area, low purity, high friability and decreased stability. Slow crystallization by operating close to the solubility curve is used to enhance purity and stabilize crystal structure. However, this approach reduces productivity and produces large particles that require milling resulting in yield loss, noise and dusting and unwanted personnel exposure. Milling may also generate unwanted crystal defects and amorphous materials.

## Development of Industrial Crystallization Process

Bristol Myers Squibb has successfully developed a crystallization process for a proprietary substance that is prone to ‘oil out’ by seeding at low supersaturation to achieve polymorph control and obtain uniform platy crystals.<sup>163</sup> Ultrasound was applied to the crystal slurry just prior to filtration in a recirculating loop to reduce 100–200  $\mu\text{m}$  particles to the 20  $\mu\text{m}$  range for blend homogeneity and bioavailability considerations. Fines and rough edges due to fracture under sonication were removed by post-slurry temperature cycling to accelerate Ostwald ripening in order to obtain a finished API with a narrower particle size distribution, and improved bulk density, flowability and bulk handling.

The introduction of an appropriate anti-solvent into a supersaturated solution, termed reverse addition, is a standard procedure for direct small particle crystallization. The anti-solvent initiates primary nucleation, sometimes with the aid of seeding, and crystal digestion during an aging step. Thorough mixing within the vessel with standard agitators upon introduction of the second fluid is often not possible prior to crystal formation. This gives rise to a heterogeneous environment that impedes optimum crystal structure formation and increases impurity entrainment. Impinging fluid jet streams may be used in a continuous crystallization process to achieve high intensity micromixing of fluids so as to form a homogeneous composition prior to the start of nucleation. This process has been used on smaller scales for the direct crystallization of simvastatin, lovastatin, omeprazole, finasteride, and diltiazem malate to meet the particle size and purity specifications.<sup>164</sup>

Controlling the temperature variation of crystallization in order to maintain supersaturation eliminates the solvent gradient issue but this is a slow process that produces large crystals. Controlled crystallization by following a supersaturation profile in the metastable zone width (MSZW) based on accurate concentration measurements also avoids uncontrolled nucleation. The MSZW represents a controlled nucleation barrier to crystallization and is the concentration-solubility-temperature trajectory bounded by thermodynamic dissolution and kinetic crystallization which is scale, system, reactor and operating condition dependent.<sup>165</sup>

Crystal engineering may also involve the production of spheronized particles (i.e., avoid needle-like crystals) to improve flow properties for tableting and avoid difficulties in washing, filtering and drying during primary manufacturing. A 'radical solution' has been proposed to produce API agglomerates by 'spherical crystallization' to solve lot-to-lot variations and compression problems.<sup>166-168</sup> Another aspect involves improving the ability of crystals to consolidate and bond under pressure and maintain interparticulate bonds upon ejection from tablet presses. This can be achieved by engineering platy particles with greater plasticity,<sup>67</sup> or incorporating additives or inclusions in the crystal structure to increase the crystal free energy and hence the intrinsic dissolution rates.<sup>5</sup>

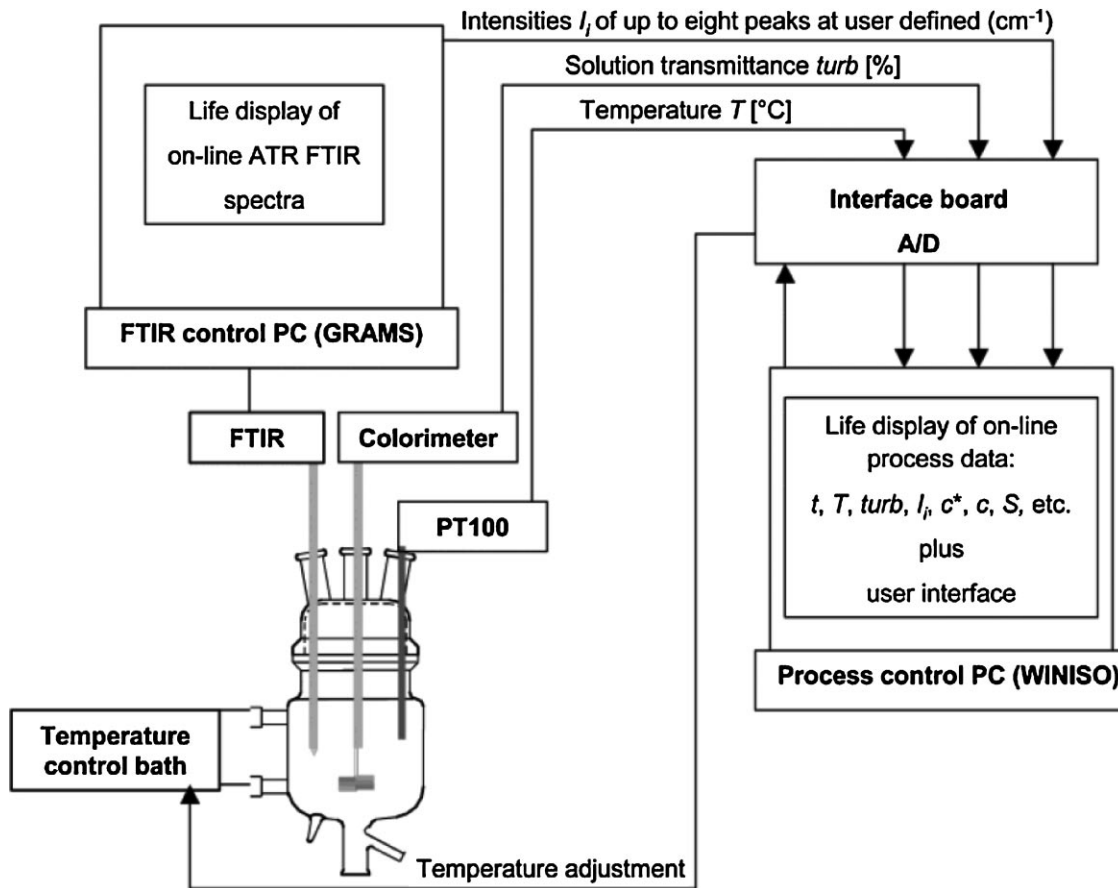
The use of population balance concept to model the particle size distribution in pharmaceutical

crystallization has been studied.<sup>6,7</sup> Commercial software (Fluent<sup>®</sup>) is available for industrial applications. However, satisfactory prediction or modeling of other properties of a drug substance from crystallization at production scale such as particle shape, crystal disorder and polymorphism is not possible due to a lack of sensor technologies and understanding of crystal nucleation and growth.<sup>6</sup>

### Process Analytical Technologies (PAT) for Industrial Crystallization

Recent advances in in-process sensors have enabled the development of measurement-based control of industrial crystallization.<sup>169,170</sup> With fine feedback control as a crystal engineering tool, the resulting crystal size, purity and stability are easier to control. Mathematical modeling of pharmaceutical crystallization using the first-principle approach, for example, use of material and energy balances to optimize particle size distribution, has been reviewed by Fujiwara.<sup>171</sup> Attenuated total reflection (ATR) Fourier transform infrared (FTIR) spectroscopy with advanced chemometrics analysis has been shown to measure solution concentrations within  $\pm 0.1\%$  w/w in dense crystal slurries without interference from the crystals.<sup>172</sup> Representation of a data acquisition and control system is shown in Figure 4. ATR-FTIR could monitor polymorphic transitions, evaluate impurity concentrations as well as detect the metastable zone. The reliability and accuracy of this approach was demonstrated in challenging systems associated with low solubility compounds and polymorphic forms. An undersized seeds and constant supersaturation operation by ATR-FTIR feedback control of supersaturation was used to harvest crystals with a narrow size distribution for multiple solvents and solutes at Merck.<sup>174</sup> MSZW definition employing optical turbidimetry (in-process turbidometric probe) to detect the onset of crystallization and dissolution processes is an alternative to back scattering method; nucleation is an avalanche type process and once nucleation starts, it proceeds with considerable speed.

Control of temperature, solution concentration, and crystal size and shape distribution may be limited by the type of sensors employed. For example, focus beam reflectance measurement (FBRM), assumes *a priori* that all particles are spheres.<sup>6</sup> It may be advantageous to combine



**Figure 4.** Representation of data acquisition and control system utilized for in-process supersaturation control measurements. Reprint with permission from Grön et al.<sup>173</sup> Copyright 2003 American Chemical Society.

measures of particle shape and size for accurate characterization of shape and size distributions. Since the sapphire window can be fouled with adhesion of crystals in dense slurry, the probe should be located in zone with vigorous mixing in the reactor. Advances in imaging fiber optics, cameras and videos allow for high speed *in situ* video microscopy of suspension crystallization processes. Images of 10–30 a second can be collected from crystals as small as 5–15  $\mu\text{m}$ .<sup>172</sup> However, the quality of the images for most dense crystal slurries is often a limitation and multivariate image analysis of data is essential. Pictures can be marred by bubbles in solution, out-of-focus objects and motion of particles, solid concentration, camera focal depth, field of view, hydrodynamics and other sources of noise. Overlapping crystal edges, particle segmentation and size-dependent sampling bias caused by the finite size of the imaging frame must be corrected. On-line digital video microscopy has been used at

GlaxoSmithKline to observe the crystal size, shape and agglomeration, as well as for troubleshooting on benchtop reactions.<sup>6,175,176</sup>

Following a batch recipe, the concentration per temperature trajectory may shift because of changes in kinetics and phase equilibria. More robust *in situ* control strategy of the crystallization process would provide a closed loop feedback control based on solution concentration, and the desired trajectory within the metastable zone and variability in batch time to control product quality.<sup>171</sup> Recent studies have demonstrated the success of using control algorithms and process sensor technologies for the development of batch control of crystallization processes. Nilsen et al. routinely used technologies such as FBRM, and particle vision and measurement (PVM) video microscopy system to monitor the metastable zone width to determine the optimal concentration as a function of temperature profile for seeding. *In situ* measurement technologies

(FBRM, PVM, ATR-FTIR) and automation of batch crystallizers have enabled the determination of metastable limit and solubility curves in cooling crystallization studies as well as tracking of setpoint supersaturation profiles in the metastable zone for antisolvent crystallization. In the former, real time *in situ* crystallization data enables fine temperature feedback to control supersaturation whilst in the latter supersaturation profiles are followed by automated addition of antisolvent.<sup>177</sup> An automated system for the concentration control of antisolvent crystallization was applied to proprietary Merck compounds to enable rapid crystallization following constant relative supersaturation profiles.<sup>178</sup>

Simultaneous multi-in-process measurements for batch automation control on small (500 mL) and large (200 L) scales have also been developed. Specifically, automated batch reactors are equipped with fiber-optic turbidometric probe for crystallization onset detection, platinum resistance thermometer to monitor temperatures, ATR-FTIR to quantify reactant supersaturation, XRD flow through cell for polymorphic form monitoring, stroboscopic video microscope for crystal shape analysis, ultrasonic spectroscopy for particle size characterization and calorimeter to quantify process heat transfer and reaction thermodynamics.<sup>165</sup>

### Control of Polymorphic Forms

The crystal form is defined by thermodynamics if a dimorphic compound is crystallized at a condition sufficiently above or below its transition temperature. Otherwise, the choice of solvent, use of seeds, presence of impurities and conditions of crystallization (supersaturation) becomes important for obtaining the desired polymorph in a pure form<sup>179</sup> during API manufacturing or wet granulation. A metastable form will eventually transform to a stable form and this process will be accelerated if the crystals are immersed in a solvent or kept in a wet state. This phase transition event can be controlled through a better understanding of the solubility-temperature profile, transition temperature and seeding conditions.

The presence and level of impurities or seed crystals also affect the transition of morphic forms. For example, the transformation of abecarnil form B to A occurs more quickly in a system with a low impurity content. This is typical at the late stage development of new chemical entities

and the ability of producing B could be lost.<sup>180</sup> The presence of 1.4 ppm of polymeric additives produces different polymorphs and sizes of calcium carbonate.<sup>181</sup> The use of conformational mimicry with additives was also demonstrated and proposed to stabilize metastable crystals.<sup>182</sup> Common pharmaceutical excipients were found to suppress the growth of the metastable (orthorhombic) form of paracetamol from aqueous solutions. The extent of growth inhibition depends on the property of each excipient. High supersaturation also favours the crystallization of the stable (monoclinic) form.<sup>183</sup>

The selectivity of solvent systems to form stable and metastable polymorphs may largely be kinetic driven involving selective adsorption on crystal faces followed by inhibition of nucleation and growth of the alternative forms. This surface crystallization mechanism is embodied in the empirical Ostwald's law of successive stages, where a less stable form with high free volume energy and low activation energy is crystallized followed by transformation to a lower energy form.<sup>166</sup> Exceptions to the Ostwald's law such as cross-nucleation of more or less thermodynamically stable forms have been reported.<sup>184</sup> Mirmehrabi also suggested that hydrogen bonding played a significant role in the crystallization of specific morphic forms. For example, ranitidine form 2 and stearic acid form C have a stronger tendency to crystallize in solvents capable of forming hydrogen bonds with the solute molecules.<sup>185</sup> At this stage industrial control of polymorphism forms is largely semi-empirical. More research on how solute and solvent molecules interact will allow rational design of reliable API crystallization processes.

### CONCLUSIONS

Crystal engineering is a common element embedded in a number of functions in the drug development process. For example, the intermolecular interactions define the solid-state structure in salt and morphic form (including solvates and cocrystals) development. It also influences how crystals are formed (e.g., in amorphous/solid dispersion systems and drug substance manufacturing) and modified in processing (e.g., in milling). Crystal engineering is a critical component of many pharmaceutical activities. When it is combined with other disciplines, such as computer science for high throughput screening, equipment

engineering for processing and sensor technologies for crystallization control, crystal engineering will bring more effective solutions.

The path to market even for a successful drug candidate is lengthy, costly and inefficient.<sup>186</sup> Empirical approaches alone will unlikely provide the advancement required for the future. The importance of understanding the impact of molecular interactions has been illustrated in this review with specific examples from the design of solid state structure, formulation and manufacturing. It can be envisioned that the concept of crystal engineering will create tremendous opportunities for the development team in industry to formulate more pragmatic strategies for developing new drugs.

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