CRYSTAL ENGINEERING FOR PRODUCT AND PROCESS DESIGN

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Abstract

Particle production and solids processing are essential components of the contemporary process industries. Crystalline organic solids represent a large and important segment of this manufacturing sector. In this paper we discuss the interactions between crystal engineering and process & product design. These interactions lead to new work flow practices during the scientific discovery and conceptual design stages of new business development. We assess the current status of knowledge in this field and identify critical areas for future development.

Keywords

Crystallization, design, crystal growth

Introduction

Crystalline organic solids are ubiquitous as either final products or as intermediates in the specialty chemical, pharmaceutical, and home & personal care industries. Virtually all small molecular weight drugs are isolated as crystalline materials (Gardener et al., 2003), and over 90% of all pharmaceutical products are formulated in particulate, generally crystalline form (Valder and Merrifield, 1996). Crystalline chemical intermediates, such as adipic acid, are produced in large amounts to make polymers and specialty products. Skin creams and other personal care product formulations contain crystalline solids. In most cases the properties of the crystalline solid have a major impact on the functionality of the product as well as the design and operation of the manufacturing process.

Crystal size (or size distribution), shape, enantiomorph, and polymorph all influence product functionality. For example, even a 50 micron particle in a hand cream makes the cream feel gritty (Villadsen, 1997). Size distribution is important in the manufacture of beta-carotene, which is virtually insoluble in water and only sparingly soluble in vegetable oils, and is used as a food colorant. The color shade given to the food is determined by the narrow size distribution which must be in the submicron range (Villadsen, 1997). Crystal shape and polymorph influence solubility, dissolution rate (which influence bioavailability), compressibility (important for tabletting), and stability. The crystal enantiomorph is of vital importance in the manufacture of chiral materials, which has become a $100 billion industry in recent years. The choice of solvent, as well as the design and operation of the manufacturing process determine the crystal properties. Moreover, crystal size distribution, and shape have a major impact on the design of the manufacturing process since small crystals are difficult to separate from solution, and needle-like crystals or plate-like crystals can be difficult to filter and dry.

Many important compounds exhibit polymorphism, the existence of more than one crystal structure. Different polymorphs can have very different physical properties, including color, hardness, and stability. Therefore, control of which polymorph crystallizes in an industrial system is

of vital importance. For example, since bioavailability can vary greatly among polymorphs of the same drug (Aguiar, et al., 1967) the U.S. Food and Drug Administration requires the registration of drug polymorph and the strict production of only that form. It can be difficult to control which polymorph crystallizes, even to the extent that production output can change unexpectedly from one form to another. This can be catastrophic, e.g. halting production until the process can be altered to produce the original polymorph (Chemburkar, et al., 2000). Many in industry, particularly the pharmaceutical industry, are now undertaking exhaustive polymorph screening to identify all possible/likely polymorphs before beginning to scale-up crystallization processes (Desikan, et al., 2000).

The importance of crystal shape to processing and product quality/functionality has been discussed in the context of ibuprofen by Gordon and Amin (1984). The primary interest in this system is the existence of high aspect ratio needles 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. This was discovered by researchers at the Upjohn Company (Gordon and Amin, 1984), who patented the change in solvent as a process improvement.

The structure of this article is as follows. We first highlight some of the advances made in the fundamentals of crystallization during the last decade. This is followed with a brief review of recent improvements in CFD and population balance modeling for crystallizers. We describe new methods for process synthesis of flowsheets containing crystallization steps, and finish with an assessment of how these advances impact modern work practices for process development.

Fundamentals of Crystallization

Crystal Structure

A crystal is an ordered three dimensional array of molecules, and represents one of nature's most remarkable examples of self assembly. This definition contains the concept of periodicity. A solid material that has disordered structure, or that displays no long range order (although it may possess short range order) is called amorphous.

All crystals have translational symmetry, i.e., repetition of motifs by translational displacement in space. Each crystal can be decomposed into a collection of unit cells, which are the smallest structural units that recreate the entire 3-dimensional crystal structure when they are repeated in space by simple translation in every direction. Unit cells are parallelepipeds; the vertices of which constitute a grid of points called a lattice with its own periodicity and symmetry. The unit cell also defines three sets of planes in space, each set being parallel and equally spaced – the distance between the planes in each set is called the interplanar spacing, which is an important concept in crystal growth models. Within the cell, symmetry operations relate the molecules which constitute the contents of the cell. An asymmetric unit is the smallest structural unit (e.g., a non-symmetrical dimer, a single molecule, or part of a molecule) within which no symmetry elements operate. The collection of symmetry elements belonging to a crystal structure is called a space group. Therefore, a space group is the set of geometrical symmetry operations that brings a three dimensional periodic crystal into itself. There are a total of 230 unique space groups. The number of symmetry elements in a space group must be equal to the number of asymmetric units in the cell.

It is important to realize that unit cells do not physically exist in a lattice and the lattice does not physically exist in the solid. These are mental constructs to help us visualize the solid structure. There are several different lattice arrangements and unit cells that can be constructed – but fortunately not too many. In 1848, Bravais showed that there are only 14 possible lattices that fill three dimensional space. These lattices can be further divided into seven crystal systems, each has a fixed relationship between the cell spatial dimensions and angles. The seven systems are: cubic, tetragonal, orthorhombic, hexagonal, trigonal, monoclinic and triclinic. Most organic molecules have uneven molecular shape that leads to low-symmetry crystal systems. The crystallographic systems with uneven unit cell parameters are the monoclinic, triclinic and orthorhombic. The majority of organic structures reported (approximately 95%) belong to these systems.

Molecules arrange themselves in crystals in such a way that the whole spatial arrangement must belong to one of the 14 Bravais lattices. The total number of independent ways in which molecules can decorate these lattices is 230 (corresponding to the total number of independent space groups). Fortunately, only a few of these space groups are important in solid state chemistry. A more in-depth view of crystallography is available from many sources, including Cullity (1978), and the International Tables for X-Ray Crystallography.

Nucleation

Crystals are born by nucleation, which may be defined as the formation of molecular solute clusters in solution which are in dynamic equilibrium with the solute molecules dissolved in the solution. When the clusters reach a critical viable size they become a crystalline particle that grows by the addition of solute material on the crystal faces. Faces may appear or disappear during growth depending on the relative growth velocities of adjacent faces.

Nucleation can be divided into two types: primary and secondary. Primary nucleation is the formation of nuclei in solution whether or not suspended crystals are present. It is further subdivided into homogeneous and heterogeneous. Homogeneous nucleation is the formation of nuclei in previously crystal-free solution. Primary heterogeneous nucleation requires the pre-existence of foreign bodies or catalytic surfaces in the solution. Foreign bodies can be dust particles, nuclei of substances different than the solute, etc. Catalytic surfaces may be roughness on the vessel walls or a surface that was designed specifically for this purpose, such as a compressed surfactant monolayer (Langmuir) film or a

self-assembled monolayer. Secondary nucleation is used to describe any nucleation mechanism that requires the presence of suspended solute crystals. Secondary nucleation may take place by several mechanisms: seeding, breakage, attrition due to collision (collision nucleation), or removal of surface layers through surface shear. Collision nucleation is the dominant mechanism of secondary nucleation, whereby growing crystals collide with the container walls, with a stirrer, or with other crystals.

Homogeneous nucleation from clear solution is of special interest because it is an important pathway in which the crystal polymorph (crystalline packing structure) is created – see the section below on Solution Mediated Polymorphism. The classical view of this process is that it takes place by the solute species clustering together in solution and then adopting the ordered arrangement of the crystalline state to minimize the free energy. The Gibbs-Thomson theory for the critical cluster size, r_c, is also based on free energy minimization. Clusters larger than r_c must grow in order to reduce the free energy of the total system (solute cluster + solution) while clusters smaller than the critical size dissolve in order to reduce the free energy of the system.

In the Gibbs-Thomson theory, it is assumed that only solute transfers from a supersaturated solution (the composition of which is located in the metastable region of the phase diagram) to the nucleus. It is also supposed that the mass of the nucleus phase is so small that the composition of the solution phase is constant during the nucleation event. The total free energy change, ΔG, consists of three terms – a change in bulk free energy of the solution, a change of bulk free energy of the nucleus, and a change of surface free energy of the nucleus. The resulting expression for a spherical nucleus is

$$\Delta G = -\frac{4}{3}\pi r^3 \frac{\Delta\mu_{solute}}{v_{solute}} + 4\pi r^2 \gamma \qquad (1)$$

where $\Delta\mu_{solute}$ is the difference in chemical potential of the solute in the supersaturated solution and in the nucleus, this term is always positive; v_{solute} is the molar volume of pure solute in the nucleus phase. The chemical potential difference can be written

$$\Delta\mu_{solute} = RT \ln(1+\sigma) \qquad (2)$$

where σ represents the relative supersaturation $(C^{supersat} - C^{sat})/C^{sat}$. The major assumption in Eq. (2) is that the activity coefficient of the supersaturated solution is equal to that in the saturated solution – a reasonable approximation in most cases. The leading term in Eq. (1) is always negative and represents the decrease in bulk free energy due to phase change. The second term in this equation contains the quantity γ which is the surface free energy per unit area of nucleus (always a positive quantity) and represents the increase in free energy due to surface formation. The sum of these two terms produces a free energy plot with a single maximum that defines the size of a critical nucleus, as shown in Fig. 1 for the alpha polymorph of the simplest amino acid, glycine, nucleated from aqueous solution at room temperature.

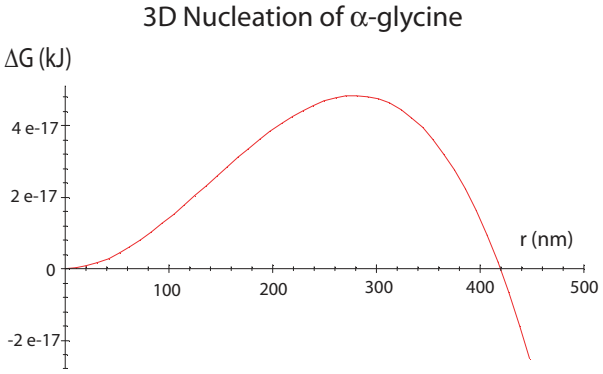

Figure 1. Change in free energy as a function of nucleus size for α – glycine *grown from aqueous solution at room temperature, where* $v_{glycine}$ = 46.71 cm^3/mol, γ = 148.1 erg/cm^2, σ = 0.02, *and RT = 2.5 kJ/mol*

The critical nucleus size is given by

$$r_c = \frac{2\gamma v_{solute}}{\Delta\mu_{solute}} \qquad (3)$$

This theory predicts that typical values for a characteristic length (diameter) of a critical nucleus are in the size range of hundreds of nanometers. For α – glycine the critical diameter is approximately 600nm.

Using atomic force microscopy *in situ* during the crystallization of the protein apoferritin from its aqueous solution, Yau and Vekilov (2000, 2001) have directly measured the crystalline packing structure and critical nucleus size of this material. They found critical nucleus sizes in the range of a few tens of nanometers (depending on the level of supersaturation). A typical value is 40nm for the cluster shown in Fig. 2 - a full order of magnitude smaller than expected from classical nucleation theory. The molecular arrangement within the nuclei were observed to be similar to that in the bulk crystal, indicating that the crystal polymorph is already established at these small length scales. Moreover, the authors state, "Contrary to the general belief, the observed nuclei are not compact molecular clusters, but are planar arrays of several rods of 4-7 molecules set in one or two monomolecular layers. Similarly unexpected nuclei structures might be common, especially for anisotropic molecules. Hence, the nucleus structure should be considered as a variable by advanced theoretical treatments."

Using small angle neutron scattering, Lefebvre et al. (2002) determine the critical length scales in phase separating polymer blends of polymethylbutylene – polyethylbutylene. They obtain results similar to those

reported for proteins, namely, critical diameters in the range 20-50 nm.

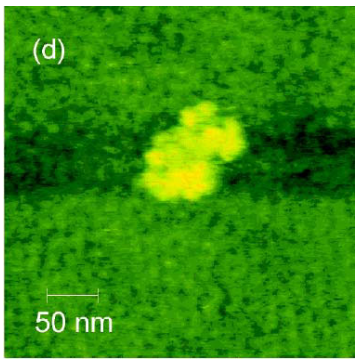

Figure 2. A flat near-critical sized cluster consisting of approximately 20 apoferritin molecules (Yau and Vekilov, 2001)

Therefore, the current status of classical nucleation theory is that it predicts critical nucleus sizes that are about one order of magnitude too high compared to the most recent measurements by Balsara's group at UC Berkeley, and Vekilov's group at the University of Houston. Moreover, classical theory does not provide the molecular arrangement within the nucleus – this is an input to rather than an output from the theory. There are opportunities here for improvements in nucleation theory that could have significant impact on crystal engineering.

Growth Models

Evidence suggests that crystal faces grow by one of three mechanisms: a screw dislocation mechanism, a two-dimensional nucleation mechanism, or by rough growth. It is also known that different faces of a crystal may grow by different mechanisms, according to the solute-solvent interactions at the interface (surface free energy) and the level of supersaturation. At low supersaturation levels, or large surface free energies, the screw dislocation mechanism is normally operative. The original theory, developed by Burton, Cabrera and Frank (BCF) (1951), proposed that screw dislocations, which exist on real crystal faces at all supersaturation levels, provide an infinite source of steps onto which oncoming particles can be incorporated. According to this theory, growth occurs by the flow of steps across the surface, which form a spiral. Spirals have been observed on many faces of many crystals (e.g., Geil, 1963; Land et al., 1996; Paloczi et al., 1998), see Figure 3. At moderate levels of supersaturation, the two-dimensional nucleation mechanism may apply. Above a critical level of supersaturation, the face is roughened and growth proceeds at a high rate.

The BCF expression for the rate of growth normal to a surface is:

$$R_{hkl} = \frac{v_{hkl} h_{hkl}}{y_{hkl}} \qquad (4)$$

where v_{hkl} is the lateral step velocity, h_{hkl} is the step height, which can be approximated by d_{hkl} (the interplanar spacing) for monolayer height, and y_{hkl} is the distance between steps. Since growth occurs at kink sites (vacancies in steps where solute growth units can incorporate – see Fig. 1 in Chen and Vekilov (2002) for a beautiful image of kink sites on a step of crystallized ferritin), the lateral step velocity depends mainly on the density of kink sites. The average distance between the kinks on a step coinciding with a strong bond chain (a so-called periodic bond chain) of molecules is:

$$X^0_{hkl} = a_{hkl}[1 + 0.5\exp(\phi^{kink}_{hkl} / RT)] \qquad (5)$$

where, ϕ^{kink}_{hkl} is the energy required to form a kink per mole, and a_{hkl} is the intermolecular distance in the direction of the step.

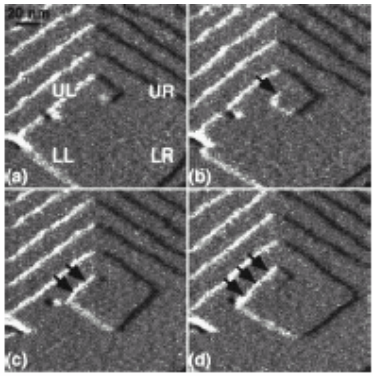

Figure 3. Four consecutive images of a spiral growing from a screw dislocation on a calcite crystal face (Paloczi et al., 1998).

The classical ideas of Kaishev (1962) and Chernov (1984) were incorporated in a model proposed by Winn and Doherty (1998) to predict the shape of organic materials when crystallized from solution. They propose that when the BCF mechanism applies, the lateral velocity of a face can be estimated from the density of kink sites (a_{hkl} / X^0_{hkl}) multiplied by a^p_{hkl}, the distance the step is propagated by adding a monolayer to it:

$$v_{hkl} \propto a^p_{hkl}[1 + 0.5\exp(\phi^{kink}_{hkl} / RT)]^{-1} \qquad (6)$$

The rate of growth of a face is therefore:

$$R_{hkl} \propto \frac{d_{hkl}}{y_{hkl}} a^p_{hkl}[1 + 0.5\exp(\phi^{kink}_{hkl} / RT)]^{-1} \qquad (7)$$

The calculation of y_{hkl}, the distance between steps, and of ϕ^{kink}_{hkl}, the kink free energy, is provided in Winn and Doherty (1998, 2002), and Bisker-Leib and Doherty (2003).

Crystal Shape

It is well-known that crystals grow in a variety of shapes in response to both internal and external factors. Some of these factors can be manipulated (e.g., solvent type, solution temperature and supersaturation, etc) by crystal engineers to steer crystals toward a target shape or away from undesired shapes.

Experiments performed on the growth of crystals from spherical seeds have shown that flat faces appear during growth. Some of the faces that appear eventually disappear, while others grow in size, eventually leading to a fully facetted stationary (steady state) shape. The shape of crystals at thermodynamic equilibrium can be determined using Gibbs' approach of minimality of the total surface free energy per unit volume. This thermodynamic equilibrium condition leads to the Wulff construction to determine crystal shape

$$\frac{\gamma_i}{h_i} = \text{constant}, \quad i = 1, ..., N \qquad (8)$$

where, γ_i is the specific surface free energy of face i, h_i is the perpendicular distance between the origin and face i, and N is the number of faces. Only very small particles (nanoparticles) can undergo rapid shape change to reach equilibrium, during which the size change is not substantial. For larger particles, however, the number of elementary transport processes which have to occur to achieve significant changes in shape is so large compared with the lowering of the surface free energy that the rate of equilibration becomes negligible (Herring, 1953). For crystals grown from seeds, steady state shapes (that have self--similar growth) are therefore observed more often than the equilibrium shapes. Wulff's condition was modified by Chernov (1963) (also see Cahn et al., 1991) to determine the crystal shape at steady state, given as:

$$\frac{R_i}{h_i} = \text{constant}, \quad i = 1, ..., N \qquad (9)$$

where, R_i is the perpendicular growth velocity of face i. As noted in the previous subsection, a number of mechanisms and models are available to estimate the perpendicular growth velocities of facets but in most solution crystallizations only one model, the screw dislocation model (BCF model, eq. (7)) has the proven capability to correctly estimate the relative growth rates of crystals grown from solution. A comprehensive validation of this modeling approach is given by Liu et al. (1995), Winn and Doherty (1998, 2002), and Bisker-Leib and Doherty (2003). The shapes of many organic crystals have been successfully predicted with this approach, e.g., urea grown from aqueous solution, ibuprofen grown from methanol and from hexane, adipic acid grown from water, etc. Fig. 4 compares the experimental and predicted steady state growth shapes of $\alpha-$glycine crystallized from aqueous solution. This is a particularly sensitive test of the approach due to the complex network of hydrogen bonds that are formed in the solid state. Although there are many aspects of this modeling approach that need improvement, such as *a priori* identification of the nature of the growth units that incorporate into the growing crystal faces, the approach is already sufficiently well developed for immediate application to engineering design.

Although significant progress has been made recently on predicting the steady state shapes of organic materials

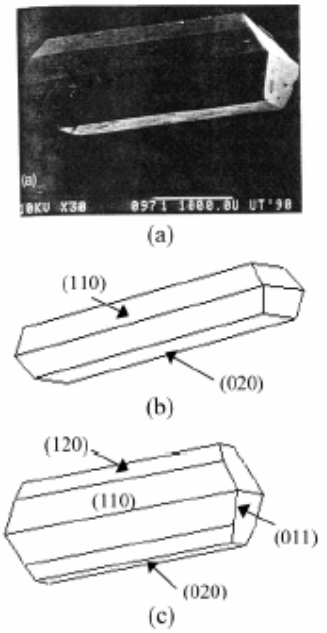

Figure 4. Reported and predicted morphologies for $\alpha-$glycine crystallized from aqueous solution. (a) Experimentally grown crystal from Boek et al. (1991). (b) Predicted shape using the form of the BCF model in eq. (7) with a dimer growth unit. (c) Shape predicted by eq. (7) using a modified monomer growth unit. From Bisker-Leib and Doherty(2003).

crystallized from solution, there is less to report on the important related matter of predicting shape evolution from an initial seed or nucleus shape through to the final steady state shape. The only evolution models reported in the literature are for 2-dimensional crystals, which apply to materials that crystallize in flat plate-like shapes, such as succinic acid grown from water (flat hexagonal crystals), and L-ascorbic acid (vitamin C) grown from water (flat rectangular crystals). The dynamics of shape evolution for 3-dimensional crystals are quite complicated as faces, edges and vertices appear or disappear during growth. The definitive study awaits to be done.

Solution Mediated Polymorphism

The phenomenon of polymorphism - a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements and/or conformations of the molecules of that compound in the solid state - has been known to exist for over two centuries (Bernstein, 2002). Despite this, its prevalence presents

one of the greatest obstacles to the solids processing industries today. To obtain the desired properties of the product, the correct polymorph must be obtained since they have different physical properties: melting points, solubilities, bioavailabilities, enthalpies, color, and many more. Differences between polymorphs are crucial for industries like the pharmaceutical industry, where differences in dissolution rates between two polymorphs may mean that one polymorph is a potential product because of its high dissolution rate (high efficacy) while another is not due to its negligible dissolution.

Paracetamol (acetaminophen) is an analgesic drug that is used worldwide as a pain reliever. Due to its commercial importance, acetaminophen has been subject to many crystallization experiments and in particular, polymorph studies. Paracetamol has three known polymorphs. Monoclinic paracetamol is the thermodynamically stable form at room temperature and, therefore, it is the commercially used form. Unfortunately, it is not suitable for direct compression into tablets, since it lacks slip planes in its structure, which are necessary for the plastic deformation that occurs during compaction. Consequently, it has to be mixed with binding agents, which is costly in both time and material. Crystallization of the orthorhombic polymorph (form II) of paracetamol from solution is more desirable since it undergoes plastic deformation and is therefore suitable for direct compression. In addition, it is believed to be slightly more soluble than form I. Until 1998 there was no reproducible experimental procedure available for the crystallization of form II from solution. The only method that had been reported for bulk preparation of form II was to grow it as polycrystalline material from fused form I.

In 1998, Gary Nichols from Pfizer and Christopher Frampton from Roche described in their paper (Nichols and Frampton, 1998) a laboratory-scale process to crystallize form II from solution. They found that the orthorhombic polymorph of paracetamol could be crystallized from supersaturated solution of industrial methylated spirits (ethanol with approximately 4% methanol) by nucleation with seeds of form II, maintaining crystallization at low temperature 0C and collecting the crystals within one hour after nucleation began. The typical yield achieved was less than 30%, but they proposed that when the process was optimized, a commercial application was possible. By having better control over the crystallization process, they managed to crystallize only the orthorhombic polymorph and to have the desired crystal shape.

Ostwald noted in his Law of Stages describing phase transitions that it is not the most thermodynamically stable state that will appear first but that which is the closest, in free energy, to the current state (Ostwald, 1897, Grant, 1997). In accordance with this law, crystallization of a compound having two polymorphs often will proceed first with the growth of the metastable form until the solution composition achieves the equilibrium solubility of this form. When the saturation concentration of the metastable form is reached it will stop growing. The stable form may have nucleated at any point, determined by relative kinetics, up to and including when the saturation of the metastable form is reached. The stable form will then grow, thus causing the solution to be undersaturated with respect to the metastable form, causing it to begin to dissolve. Once the metastable form has completely dissolved at the expense of the growing stable form, the stable form will grow until the solution reaches its equilibrium solubility with respect to the stable form (Cardew and Davey, 1985). For example, a snapshot of the polymorphic transformation of glycine crystallized from a water/ethanol mixture is shown in Fig. 5. At the beginning of the crystallization, beta-glycine (needles) crystals form first. This is the less stable polymorph. After 10 minutes, the more stable polymorph, alpha-glycine (shaped as a coffin), grows at the expense of the beta-glycine , which dissolves.

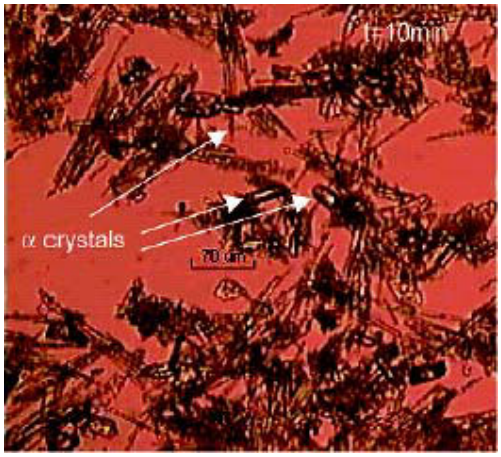

Figure 5. Two polymorphs of glycine in water--ethanol solution; alpha-glycine (shaped as a coffin), beta-glycine (needles). From Ferrari et al. (2003).

A more complete understanding of solution-mediated polymorphism will involve appropriate integration of nucleation, growth, and dissolution, with the thermodynamic equilibrium phase diagram for the polymorphs.

Crystallizer Design

Considering the fundamentals of crystallization , it is tempting to envision crystals growing quietly in a uniform medium. This is an ideal seldom if ever realized in industrial crystallization. In most industrial crystallization processes, crystals grow suspended with a myriad of similar crystals in large, vigorously agitated vessels. Frequently, the solution composition in the vessel is nonuniform both temporally and spatially. Growing crystals are subject to collisions with other crystals, the vessel agitator, wall, and internals. These phenomena have a significant, sometimes profound, effect on the properties of the resulting crystals. Crystallizer and crystallization process design attempt to reconcile and manage these competing effects to produce adequate, even superior crystals.

When the product of a crystallization process is not a single crystal but a suspension of crystals, the particles are essentially never of uniform size for a variety of reasons. Individual crystals nucleate at different times. Because of residence time distribution in crystallizers, crystals are in the growth zone for differing lengths of time. Individual crystals often grow at slightly different rates (growth rate dispersion). Particle aggregation and breakage are stochastic processes. Therefore, we must think of a crystal size *distribution* to characterize the crystals. Since a process may produce polycrystalline particles, we will discuss the general "particle" size distribution (PSD) here. There are several basic mechanisms by which crystalline particles form and grow. These are nucleation, crystal growth, aggregation, attrition, and breakage. The final particle size distribution is the net result of all of these processes. The relative importance of these mechanisms, of course, varies widely. In some cases, it may be possible to neglect one or more because they have little effect.

PSD can be modeled using "dynamic population balances". Each of the mechanisms influencing particle size is modeled as a separate term in a population balance equation. This approach was codified and popularized by Randolph & Larson (1988).

The commonly used expressions to estimate nucleation and growth kinetics are straightforward power-law approximations. Nucleation is often modeled as

$$B = k_B \sigma^n \omega^m M^p \tag{10}$$

where B is the nucleation or "birth" rate; σ is the relative supersaturation defined above, ω is a measure of agitation intensity such as the angular speed of the agitator, and M is the crystal concentration. The parameters k_B, n, m, and p must be determined experimentally for each system of interest. n is typically ≥ 2 for secondary nucleation and >> 2 for homogeneous nucleation.

Crystal growth is often approximated as

$$G = k_G \sigma^q . \tag{11}$$

k_G and q must also be determined experimentally for each system of interest. Usually n > q; therefore, nucleation increases more strongly with supersaturation than growth. These expressions are much simpler than those presented above in the Fundamentals section, and therefore provide much less predictive power. They are meant to correlate experimental data in a form amenable for use in population balance modeling.

It is generally more difficult to incorporate some of the other mechanisms. Aggregation/agglomeration involves both growth of particles and a decrease in number. It is included in the population balance by a volume integral of a nucleation kernel, creating an integrodifferential equation. The kernel is chosen based on the flow conditions of the crystallizer (see Berglund, 2002). Attrition doesn't decrease the size of the original particle significantly, but the resulting fragments create a fines fraction of the PSD. The fragments also grow, contributing to secondary nucleation.

Until recently, application of population balance modeling was usually limited to assuming spatial homogeneity of the crystallizer. This assumption has been labeled "mixed suspension mixed product removal" (MSMPR). This is the equivalent of the CSTR approximation (Levenspiel, 1972) for vessels containing suspension. Not only is the composition of the liquid assumed uniform throughout the vessel and in the vessel effluent, the particle concentration and PSD of the vessel and effluent are uniform and equal through the vessel and effluent as well. This assumption significantly limits the accuracy of predictions. One symptom is that often we find that the nucleation and growth kinetic parameters (k_B, k_G, n,m,p,and q) are not the same at laboratory and full scales, particularly the nucleation parameters. Nonetheless, there have been significant successes using this approach.

It is in general difficult to provide mixing adequate to satisfy the MSMPR criteria for a large vessel, that is, to make the vessel uniform in solute and particle concentration and PSD. A significant limitation on the amount of energy that can be practically used to agitate a vessel is that particle breakage usually increases unacceptably as agitation is increased.

Consider the consequences of inhomogeneity in a crystallizer. Let's say that the zone in the vicinity of a feed injection point has significantly higher supersaturation than the bulk of the vessel contents. By the approximation eq. (10) above, nucleation is very sensitive to supersaturation; therefore, if the feed zone supersaturation is significantly higher than the vessel average, most of the nucleation may actually occur there and not in the bulk. Also, if the particles are not uniformly suspended, collision based processes such as nucleation, aggregation, attrition, and breakage will occur preferentially in zones of higher particle concentration.

Modeling crystallizer flow presents many difficulties, such as concentrated two phase flows, turbulent flow, complicated geometries, and a particle phase that is changing in concentration and properties over time. Despite these challenges, advances in closure modeling, numerical solution techniques, and computational power are beginning to make computational fluid dynamics (CFD) a useful tool for characterizing crystallizer flows.

Approaches to CFD modeling vary greatly. In general, greater fidelity between model and reality comes at the price of higher computational costs. Each stage, however, has something to offer in understanding crystallizer flows, if not in producing very accurate predictions. Single phase, fluid only, models are perhaps the least costly. They say nothing about the distribution of particles and do not include the often significant effect particles have on the fluid motion. They do, however, qualitatively illustrate overall flow patterns. Since it is impossible to see through the concentrated suspension of

most operating crystallizers, the ability to "visualize" crystallizer flow qualitatively with a single-phase model is often valuable. If a turbulence model is included, areas of high turbulent energy dissipation can be identified. This knowledge is important since these are areas that are expected to produce more particle damage and have efficient local mixing. This knowledge is useful, say, in designing agitators that produce less crystal damage, or locating feed points in a zone of high local mixing.

It is currently beyond our capabilities to model turbulence exactly on realistically sized vessels, therefore, an approximation must be used. Reynolds averaged Navier-Stokes models, such as the k-ε model, are used frequently. They are computationally efficient, but invoke some assumptions, such as the homogeneity of turbulence,

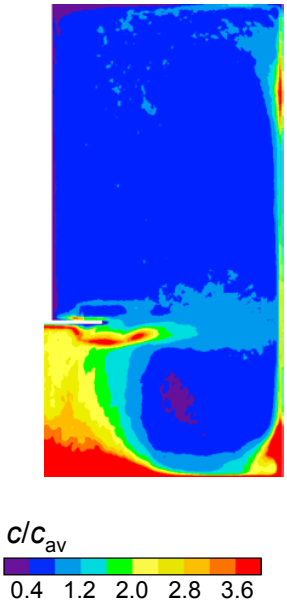

Figure 6. Solids distribution predicted by LES & particle tracking. Rushton turbine in baffled tank, left edge of figure is tank centerline. Slice is taken midway between baffles. From Derksen (2003).

that significantly limit their accuracy. Improved methods, such as Large Eddy Simulation (LES) models, are producing significantly improved model predictions, often at an increased but acceptable computational cost. LES relaxes the assumption that all turbulence is isotropic. Instead, larger eddies are realistically modeled and the isotropic turbulence assumption and corresponding simplification is invoked only for smaller eddy sizes, a much more reasonable approximation (Lu et al., 2002; Derksen and van den Akker, 1999).

Advances have also been made incorporating the effect of the suspended particles on the flow field. Tracking all individual particles and their interactions with the complicated fluid flow field is generally too expensive computationally, although particle-tracking (LaGrangian) techniques are useful to show what typical particle trajectories might look like. This approach does not, in general, track enough particles to model the dense suspensions typical of many crystallizers. However, improvements are being made, and tracking larger numbers of particles and modeling their interactions is now possible. Derksen (2003) recently reported the results of tracking 6.7 million particles in a 10 liter vessel agitated with a Rushton turbine, see Fig. 6. This corresponds to a particle fraction of 0.95 vol% for 0.3mm diameter particles While still considerably lower than the 10-20 vol% typical of many industrial crystallizers, this approach is valuable for low particle concentration systems. This situation is frequently encountered in precipitation processes, or in conventional crystallizers in the nucleation zone.

A proven approach to modeling high particle concentration systems are interpenetrating continua (IC) models, also known as "two-fluid" models (Anderson and Jackson, 1967). In this approach, the particle phase is treated as a continuum that flows through and exchanges momentum with the fluid phase, which is also treated as continuous. Using this approach, we limit the resolution to length scales significantly larger than the particle diameter. In other words, each computational volume element must contain enough particles to appear as a continuum. (This is analogous to treating fluids as continua, even though they are comprised of discrete molecules.) In principle, this modeling approach can be applied to any particle concentration, so modeling high particle concentration systems such as typical industrial crystallizers is possible.

Figure 7 shows the predicted solids distribution in a draft tube vessel with upward flow inside the draft tube, a simplified but typical crystallizer geometry. These predictions qualitatively matched the experimentally measured particle distribution in a similar vessel (Green, et al. 1998).

Lattice Boltzmann techniques simplify the computational treatment of the equations of motion, making numerical solution much more efficient. They are also amenable to including the effect of solids (Seta et al., 2003) and are becoming commonly used. Because they are so much more efficient than traditional solution techniques, significantly more complicated and consequently more realistic problems can now be solved. It remains a challenge to incorporate changing PSD into these models, but this is an area of current research and progress is being made (e.g., Brown, et al., 1995).

The ultimate goal is to combine transport and population balance modeling. Only then will realistic PSD predictions be possible for a wide variety of nonideal systems. Progress has been made, but a model applicable to a wide variety of conditions remains elusive. For example, several teams have been successful modeling precipitation, invoking the simplification that the particles

follow the fluid and do not affect the flow (van Leeuwen, et al., 1996; and Wei and Garside, 1997).

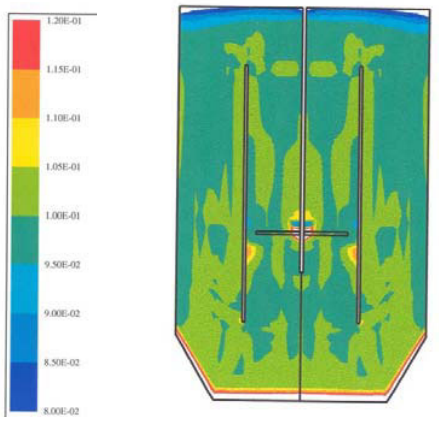

Figure 7: Prediction of particle distribution in a tank with draft tube by interpenetrating continua model. Particles: average 10 vol% 128 μm glass spheres in water, agitator: pitched blade, 500 rpm. From Green et al. (1998).

An interesting way to use the insight provided by fluid flow modeling in a population balance model is through "compartment" models. In these, the crystallizer is divided into a number of zones, or compartments; each zone is assumed to be well mixed, but it can be at a different composition than its neighbors. A population balance is calculated for each compartment. Knowledge of the fluid flow is used in two ways: first, in the selection of compartments. Given the limitation that each compartment is assumed to be well mixed, the modeler makes intelligent choices of compartments. We expect most of the change in solution and suspension composition to occur between and not within compartments. For example, typical choices for compartments include the volume near the feed

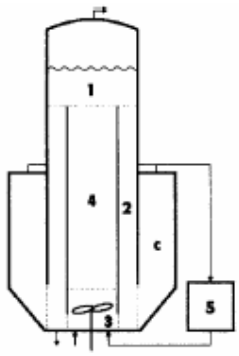

Figure 8. Identification of zones for cell model of 1.1 m^3 DTB crystallizer with fines destruction. Bermingham, et al. (1998).

injection point, the boiling zone of an evaporative crystallizer, inside and outside the draft tube of a draft tube crystallizer, etc. Each compartment communicates with neighboring compartments. Secondly, results of a CFD model (or detailed empirical flow data) are used to specify exchange flows between compartments. Figures 8 and 9 show the identification of compartments in a 1.1 m^3 draft tube baffle (DTB) crystallizer with fines destruction, and the results of a compartment model (for two values of fines removal flow), compared with an MSMPR model. The compartment model settles to a lower steady state median particle size because it is able to model the incomplete particle dissolution in the fines destruction zone, which is typical of actual operation (Bermingham, et al., 1998).

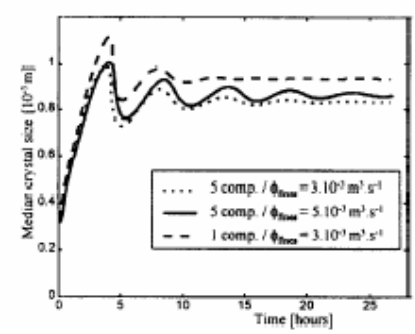

Figure 9. Results of modeling start-up of 1.1 m^3 DTB crystallizer with a 5 compartment cell model at two values of fines flow and an MSMPR (1 compartment) model. Bermingham et al. (1998).

Process Design

Perhaps the first choice for a process designer is whether to build a batch or continuous process. The advantages and disadvantages are much the same as for any other chemical process: continuous processes are more capital efficient, but are generally more costly to implement and less flexible once installed. There are other considerations. Crystallization is a purification process; therefore, impurities are rejected as the product crystallizes. The concentration of these impurities builds in the mother liquor. For a batch process, this occurs over the course of each batch; therefore, the impurity concentration is a function of time during the batch. For continuous processes, however, the impurity concentration builds at process start-up until it reaches a steady state value. Therefore, all crystals crystallized in a continuous process at steady state are formed at essentially the same

impurity concentration. This can affect the purity of the product, as well as the crystal shape and other solid-state properties, particularly if a process is scouted as a batch process and implemented at full scale as a continuous process.

The next choice is the means of generating supersaturation. There are several choices, including cooling, solvent evaporation, chemical reaction, antisolvent addition, and common ion addition. Each scheme has advantages and disadvantages. The choice generally becomes clear once the system properties (e.g. solubility, heat of solvent vaporization, feed stream composition, etc.) are considered. Sometimes, a combination of processes are employed to maximize first pass yield, such as cooling after chemical reaction to increase recovery. A frequent combination is solvent evaporation and cooling, also known as evaporative cooling. The evaporation of solvent removes heat from the suspension, causing cooling. An important consideration for cooling crystallizations is the tendency of the solute to encrust on vessel surfaces, particularly heat transfer surfaces. Evaporative cooling is essentially cooling-surface free, so may be a good choice if encrustation is a problem.

In special cases, special modes of operation may also be considered. One example is clear liquor overflow (CLO), also known as Double Draw-Off (DDO) (Mullin, 1994). Particles are separated from mother liquor, often by settling, and the crystals are kept in the crystallizer or returned to it, while the mother liquor proceeds downstream. The net effect is to give the particles a longer residence time in the process than the liquor; therefore, they have the opportunity to grow significantly larger than they would grow in a conventional MSMPR crystallizer. An example of a successful application is given in Randolph, et al. (1990).

Vessel Design

Crystallizer agitation must be carefully considered. A conventional crystallizer has much the same need for fluid mixing as a liquid-phase chemical reactor, with the added complication of keeping the crystals more-or-less uniformly suspended. In addition (as mentioned above) it is usually beneficial to limit particle breakage by keeping agitator shear to a minimum. Guidelines for suspending solids using efficient impellers and correctly sized equipment should be followed (e.g., see Oldshue, 1983). For continuous crystallizers, it is worthwhile considering a draft tube, which enforces good top to bottom transport of liquid and particles. Draft tubes are usually not a good choice for batch processes because of the changing suspension level. (The draft tube must be submerged to operate.) If needed, multiple impellers can be used on a common shaft to enforce good vertical mixing. To tailor agitation to a particular process, different types of impellers can be used, say an upper axial flow impeller to force top to bottom flow coupled with a radial flow impeller to sweep the bottom of the vessel, as well as perhaps to form a high shear mixing zone into which to inject a feed stream (Green, 2002).

This discussion has centered on agitated tank crystallizers. There are other options. An external pumping loop can be employed. This is known as "forced circulation". Some designs create a fluidized bed of crystals through which mother liquor is pumped (see Larson, 1978 or Bennett, 2002).

As discussed above, areas of locally high supersaturation associated with feed injection can greatly increase crystal nucleation rates. Since this is generally undesirable, feed injection must be carefully considered. Dip tubes or through-wall tubes should be considered to inject feed into a high shear/good local mixing zone. Good local mixing, however, is not sufficient. The mixing zone must be swept by a good macroscopic flow into the rest of the crystallizer (Mersmann and Rennie, 1995). Manifolds of multiple injection points or high velocity jets can further improve feed mixing.

As also discussed above, often selective removal of fines is desired. Crystallizers can be designed with an integral settling zone to separate large from small crystals, so that the fines can be removed. A prominent example of this is the draft-tube baffle (DTB) design (Bennett, 2002). Alternatively, a stream from the crystallizer can be conducted to an external settler, but of course this involves more equipment and piping. The additional expense is offset because the external equipment is usually more flexible.

Process Control

In many cases, it is desired to control the PSD produced by a crystallization process. In batch processes, controlling the ultimate PSD is really an exercise in controlling how many nuclei form during the batch. The average crystal size is determined simply by how much solute precipitates during the batch and the number of nuclei that grow to mature particles. To maximize the average particle size, nucleation should be minimized. The optimum temperature profile for cooling crystallizers has been calculated, maximizing average particle size while minimizing batch time. Such profiles cool the batch slowly through the metastable zone; once nucleation has occurred the cooling rate is increased substantially. See the reviews by Rawlings (1993) and Fujiwara et al. (2004).

Complete control of continuous crystallization processes is limited. First, when one considers the various controllable parameters of a crystallization process, none is obviously the right "knob" to turn to control particle size. For example, we may try to control supersaturation by controlling the feed concentration. The impact on particle size however is complicated. Increasing supersaturation often decreases particle size because the nucleation rate increases faster than the crystal growth rate. (In eqs 10 and 11 above, $n > q$.) The effect is nonlinear and the net result is often not obvious. Fines removal from the crystallizer is often an effective choice

of manipulated variable (Rawlings, 2002). Removing fines tends to increase the average particle size (as long as the accompanying supersaturation increase does not cause additional nucleation). Success has been limited. The dynamics of a continuous process can be improved, but the ability to produce a desired average crystal size at will has not been possible in general. The dynamics of a continuous process can be such that the system rapidly settles to steady state after start-up or a process upset, or the system may undergo damped oscillations, or it may even exhibit limit cycle behavior: oscillating and never settling to a steady state value. Crystallizer control has been successful at minimizing process oscillations upon start-up (Eek, 1995). This is of great value since the amount of off-spec material produced is greatly reduced. Since many continuous processes are continually reacting to minor process upsets (e.g. changes in feed stream composition caused by upstream interruptions), the ability to recover quickly and operate more steadily is very valuable.

Systems Design / Process Synthesis

Normally, large amounts of dissolved solute remain in solution in the effluent stream of a continuous crystallizer, or at the end of a batch crystallization. In either case, the crystals are separated from the solution, and the liquor is recycled. The crystallizer, therefore, is part of a larger flowsheet, which may involve reactors, dissolvers, additional crystallizations, various kinds of separators, heaters & coolers, etc. The structure of the flowsheet, as well as the devices and their operating policies, influence the recycle flow rate and composition, which in turn influence the performance of the crystallizer. Surface active impurities and their buildup in recycle loops can have a major impact (often adverse) on crystallizer performance.

In recent years geometric methods have proved to be useful for the systematic generation of process flowsheets. One such tool, the crystallization path map, is useful for finding feasible flowsheets in which crystallization steps occur. These maps are closely related to residue curve maps for the synthesis of azeotropic distillation systems (Doherty and Malone, 2001). The crystallization paths are trajectories of the liquid composition in a crystallizer as the solid is formed and removed from solution (Ricci, 1951, Slaughter and Doherty, 1995). The presence of eutectics and compounds causes the presence of crystallization boundaries which divide the map into distinct crystallization regions. These regions are non-overlapping and mutually exclusive, that is, a liquid trajectory that starts in one region cannot cross a boundary (except by non-crystallization means) into an adjacent region. Within each region there is one and only one crystal product, which may be a pure component, a eutectic, or a compound.

An example of a crystallization path map is shown in Fig. 10, together with the associated solid-liquid phase diagram, for the ternary mixture of D-mandelic acid, L-mandelic acid, and water (solvent). This example is based on the work of Lorenz and Seidel-Morgenstern (2002). The D- and L- enantiomers are equivalently labelled as (+)- and (-)-, respectively. This map can be used to devise alternative flowsheets for the production of pure D-acid, pure L-acid, or both, starting from mixtures of known composition – usually a racemic (50-50) mixture of the two enantiomers. The map tells us that there are two crystallization boundaries and three crystallization regions for this mixture. Pure L-acid crystals are obtained from liquid feed compositions in the right-hand region, pure D-acid crystals can be produced in the left-hand region, and racemic crystals are obtained from liquid feeds in the middle region (these are single crystals containing both enantiomer molecules in the solid state – they are not a mixture of pure L- and pure D- crystals).

We consider the objective of producing a product consisting of pure D-mandelic acid, starting from a racemic mixture dissolved in water. The first step in the flowsheet must change the ratio of D- to L- enantiomers so that the mixture composition lies in the left-hand crystallization region. One way of achieving this is by asymmetric catalysis (Lorenz and Seidel-Morgenstern, 2002) consider an alternative approach using chromatographic separation, which leads to a different flowsheet). The reactor effluent is crystallized, yielding a solid consisting of pure D- crystals, and a liquid with composition near the crystallization boundary (and by mass balance, on a straight line with the feed composition and the pure D-acid vertex of the map). Solid-liquid separation steps separate the crystals from the liquor, which is recycled to the reactor, see Fig. 11. Not only does this approach generate a flowsheet rapidly, it also shows that the crystallization map actually determines the outlet composition constraints on the reactor design.

Crystallization maps are useful for synthesizing flowsheets for adductive crystallization (where a compound is the desired crystal product), extractive crystallization, and many other embodiments, see Rajagopal et al. (1991), Wibowo et al. (2004), Lashanizadegan et al. (2001).

Summary and Conclusions

During the last decade there have been significant advances made in every aspect of crystal engineering. New experimental techniques, such as atomic force microscopy, allow us to explore crystal surfaces and embryonic nuclei to learn about their formation and growth, infra red and Raman spectroscopy allow us to follow supersaturation changes and polymorphic transformations in situ while crystallization is taking place. New models have been developed to predict the influence of both internal and external factors on crystal polymorph and shape. Molecular templates are being developed to control crystal form and structure. Advances in fluid mechanics and transport phenomena have added greatly to our understanding about mixing patterns and particle trajectories inside crystallizer vessels of realistic geometry. These, and other advances not mentioned or not yet even anticipated, are expected to continue.

However, most of these advances are taking place in isolation, so that we know more and more about less and less. There is a large disconnect, for example, between the microscopic models for growth of individual crystal faces and the macroscopic models for CFD and PSD prediction. While there was/is good reason for this during the development of individual new techniques, the grand engineering challenge for the next decade is to design systems and environments that will integrate across these advances to enable the designer to create processes that meet the desired product functionality and specifications with improved reliability, operability, and cost.

Perhaps the larger question is, "How do we incorporate our rapidly advancing knowledge and modeling capability to make better products?" Industry is faced with ever tightening performance requirements on crystalline products; and the only way of meeting them is to integrate our knowledge (both fundamental and empirical) and our modeling capabilities.

Broadly, there are two approaches to crystallization process development: utilizing knowledge based on fundamental understanding, and developing an empirical database through extensive, efficient experimentation.

Our knowledge base is rooted in our understanding and the ability to predict what occurs at the molecular scale during crystallization. Predictive models – whether intuitive or quantitative - are the means by which we apply this knowledge. As we have discussed, there have been recent significant advances, for example in the prediction of crystal habit. An area of current disconnect is between our treatment of molecular and process scales. To build on our molecular foundation, we need to connect predictive molecular and mesoscale models with process models that will accurately predict crystal properties of interest.

Combinatorial chemistry has revolutionized new compound development. Efficient, rapid means for evaluating a wide variety of crystallization conditions have developed from technology developed originally for combinatorial chemistry screening. Particular examples include standard screens to identify protein crystallization conditions and the extensive polymorph screens currently employed by the pharmaceutical industry to identify as many crystal forms as possible for a particular compound (e.g., see Gardener et al., 2003).

Currently, the link between empiricism and fundamental knowledge is weak. These approaches have almost been viewed as mutually exclusive, when they can actually be complimentary. The knowledge base generated by empiricism leads to advances in fundamental knowledge. Similarly, gaps in fundamental knowledge and predictive capability can be filled effectively by experimentation. For example, our ability to predict crystal polymorphs for wide varieties of compounds remains very limited; therefore, combinatorial polymorph screening is necessary.

In the near future, we anticipate that effective crystallization development teams will be multidisciplinary. They will include scientists and engineers capable of developing molecular understanding and overall process, capable of developing and employing both models and combinatorial screening.

The problems of scale-up perhaps best illustrate this. Because of associated costs, it is generally impossible to generate large data sets (many runs) from even pilot, let alone full-scale equipment. In the past, we have frequently compensated for this by simply producing suboptimized products, or by extensive tuning and troubleshooting at the full scale. By combining knowledge gained both by fundamental and combinatorial science at small scale, and applying it to process-scale predictive models, we should be able to greatly improve scale-up and thereby greatly improve products.

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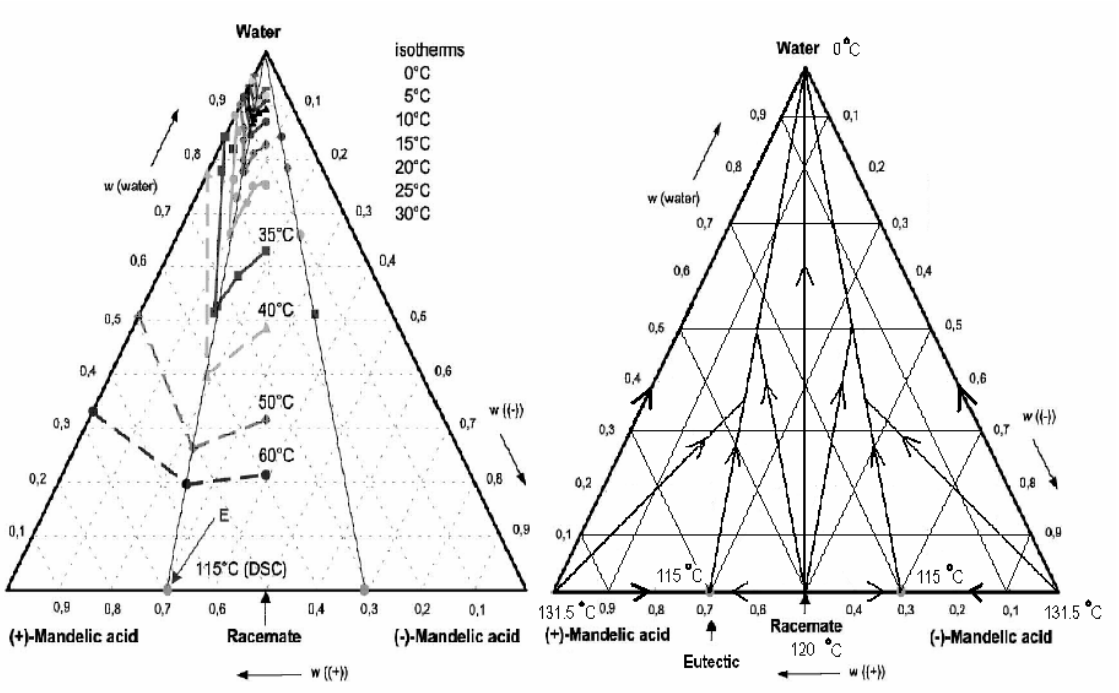

Figure 10. Phase diagram (Lorenz and Seidel-Morgenstern, 2002) and corresponding crystallization path map for the ternary mixture of mandelic acid enantiomers in water.

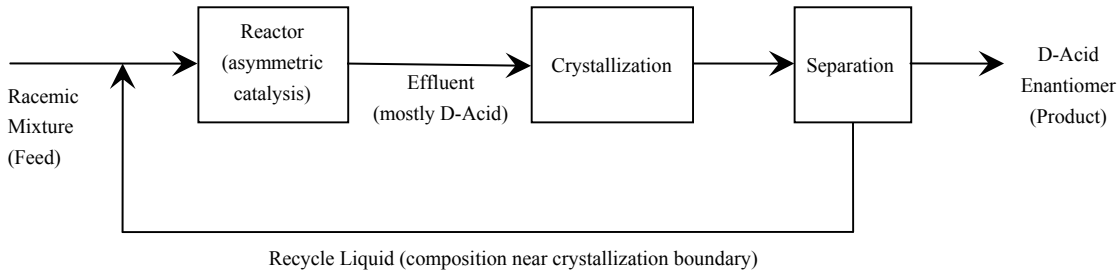

Figure 11. Flowsheet for coupling asymmetric catalysis with crystallization to produce high purity D-mandelic acid.