CRYSTAL ENGINEERING:
From Molecules To Products

Preamble • *According to many contemporary scientists, engineers, policy-makers, and business leaders, the future belongs to biotechnology, nanotechnology, and information technology. Chemical engineering research and teaching are being changed by these fields, as discussed in this series of articles and elsewhere. Change is happening at a measured pace, and biology has joined chemistry, physics, and mathematics as a fourth foundation discipline of the chemical engineering curriculum. I have little to offer that has not already been said about bio, nano, and info. However, there are other subjects that are of vital interest to society that are squarely in the domain of chemical engineering and that have received less attention than their worth. Among these, energy and crystalline solids rank high. I would like to say something about both these topics, but I will confine myself to crystalline solids—particularly organic materials. My goal is to highlight the importance of the solid state and to show how easily it can be incorporated into the chemical engineering curriculum.*

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Crystalline organic solids are ubiquitous as either final products or as intermediates in the specialty chemical, pharmaceutical, and home and personal-care industries. Virtually all small molecular-weight drugs are isolated as crystalline materials,[1] and more than 90% of all pharmaceutical products are formulated in particulate, generally crystalline, form.[2] 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.[3] 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.[3] Crystal shape and polymorph influence solubility, dissolution rate (which influences bioavailability), compressibility (important for tabletting), and stability. The crystal enantiomorph is of vital importance in the manufacture of chiral materials, which has become a $150 billion industry in recent years. The choice of solvent, along with the design and operation of the manufacturing process, determines 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.

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Many important compounds exhibit polymorphism, *i.e.*, 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,[4] the U.S. Food and Drug Administration requires the registration of each 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.[5] 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.[6]

The importance of crystal shape to processing and product quality/functionality has been discussed in the context of ibuprofen.[7] 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 (*i.e.*, low aspect ratio crystals with roughly equal sides) are formed when grown from polar solvents such as methanol or ethanol. This was discovered by researchers at the Upjohn Company,[7] who patented the change in solvent as a process improvement.

The structure of this article is as follows. It begins by highlighting some of the advances made in the fundamentals of crystallization during the last decade, together with recommendations for where these topics can be inserted into the curriculum. Next is a brief review of recent improvements in CFD and population balance modeling for crystallizers. Third are descriptions of new methods for process synthesis of flowsheets containing crystallization steps. Last are some recommendations for incorporating crystal engineering into the core of chemical engineering education and research.

FUNDAMENTALS OF CRYSTAL ENGINEERING

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 re-create the entire three-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 that constitute the contents of the cell. An asymmetric unit is the smallest structural unit (*e.g.*, a nonsymmetrical 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.

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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 visualize the solid structure. There are several different lattice arrangements and unit cells that can be constructed—but 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's 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,[8] Stout and Jensen,[9] and the International Tables for X-Ray Crystallography.

Crystal structure and x-ray crystallography are well suited for inclusion in the undergraduate physical chemistry sequence. Gavezzotti[10] has created an excellent visual introduction to crystal symmetry, written in a tutorial style suitable for undergraduates.

Nucleation

Crystals are born by nucleation, which may be defined as the formation of molecular solute clusters in solution that are in dynamic contact 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 preexistence of foreign bodies or catalytic surfaces in the solution. Foreign bodies can be dust particles, nuclei of substances different from 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 occurs from 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 to the nucleus from a supersaturated solution (the composition of which is located in the metastable region of the phase diagram). 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 Figure 1 for the alpha polymorph of the simplest amino acid, glycine, nucleated from aqueous solution at room temperature.

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 600 nm. Recent computer simulations on small molecules predict critical nucleus sizes of 3-6 nm. The reason for the large discrepancy is currently unknown.

Using atomic-force microscopy *in situ* during the crystallization of the protein apoferritin from its aqueous solution, Yau and Vekilov[11, 12] 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 40 nm for the cluster shown in Figure 2—two orders of magnitude smaller than expected from traditional nucleation theory for large molecules. 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."

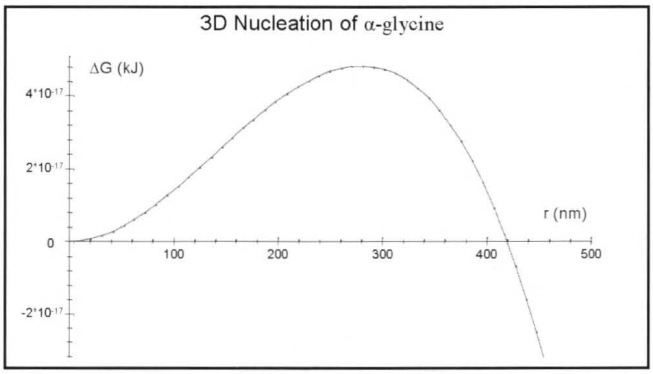

Figure 1. *Change in free energy as a function of nucleus size for* α*-*glycine *grown from aqueous solution at room temperature, where* $\nu_{glycine} = 46.71\ cm^3/mol$, $\gamma = 148.1\ erg/cm^2$, $\sigma = 0.02$, *and* $RT = 2.5\ kJ/mol$.

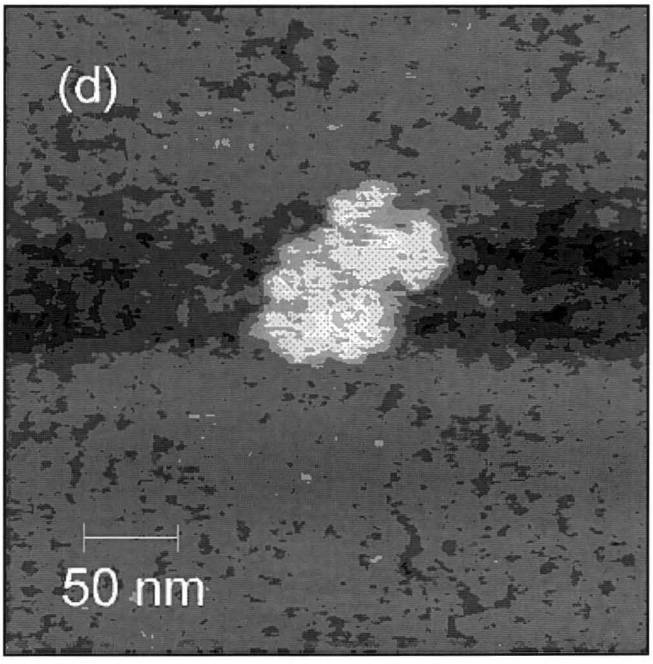

Figure 2. *A flat, near-critical-sized cluster consisting of approximately 20 apoferritin molecules.*[12]

Using small-angle neutron scattering, Lefebvre, *et al.*,[13] determined the critical length scales in phase separating polymer blends of polymethylbutylene-polyethylbutylene. They obtained results similar to those reported for proteins, namely, critical diameters in the range of 20-50 nm.

Therefore, the current status of classical nucleation theory is that it predicts critical nucleus sizes that are about two orders 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 major improvements in nucleation theory that could have significant impact on crystal engineering.

Nucleation is an excellent topic to include in the undergraduate Solution Thermodynamics course. I like to teach the two-dimensional theory in which the solid nucleus is taken to be a rectangular lozenge of fixed thickness with variable length and width (the number of dimensions in the theory is equal to the number of independent lengths that are needed to characterize the shape and size of the nucleus). This model is much richer than the traditional one-dimensional spherical nucleus described above, which is characterized by only one spatial variable: diameter. In the two-dimensional nucleation theory, the critical nucleus corresponds to a *saddle-point* in the Gibbs free energy surface, which is easy to calculate and visualize for undergraduates. Therefore, the expected nucleation path corresponds to a trajectory through the free energy landscape over a saddle-point barrier. This provides a nice analogy to transition state theory and the reaction coordinate over a saddle-point barrier in chemical reaction rate theory. Moreover, it is easy to show that the shape of the critical two-dimensional nucleus satisfies the Wulff construction for a two-dimensional equilibrium shape. That is, the two-dimensional critical nucleus attains a shape that minimizes its total surface energy for the given (faceted) volume. Teaching this material to undergraduates also provides a good vehicle for explaining the difference between surface energy[I] and surface stress.[II] In the case of liquids, all processes of interest

[I] *The reversible work per unit area needed to create a surface—if the variation in surface area does not change the surface density of molecules, then the specific surface work is surface energy.*

[II] *The reversible work per unit area needed to elastically stretch a preexisting surface—if the variation in surface area changes the surface density of molecules, then the specific surface work is surface stress.*

involve variations in area without varying the surface density, and the surface work represents a surface-free energy. The traditional processes involving surface energy are creating a soap bubble and cleaving a solid into two parts, while the traditional example of a process involving surface stress is blowing up a rubber balloon. Both types of energy are expected to play a part in creating a solid nucleus, yet there is no theory that accounts for this. Finally, a good reason for teaching this material to undergraduates is to show them that not all is known, even in traditional areas of science that have been studied for a long time.

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,[14] 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 forms a spiral. Spirals have been observed on many faces of many crystals[15-17] (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 Figure 1 in Chen and Vekilov[18] 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. In the simplest case, molecules along the edges of a spiral are found in one of three microstates: a positive kink site, a negative kink site, and no kink site. The energy for each of these microstates can be calculated, and if we assume that they occur in their most probable configuration, then the probability of finding a kink site along an edge is given by the Boltzman distribution. This

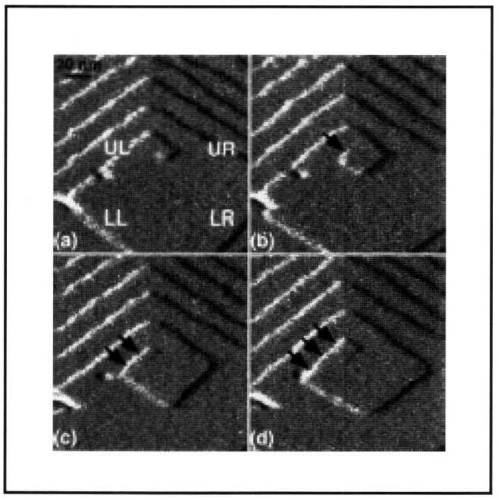

Figure 3. *Four consecutive images of a spiral growing from a screw dislocation on a calcite crystal face.*[17]

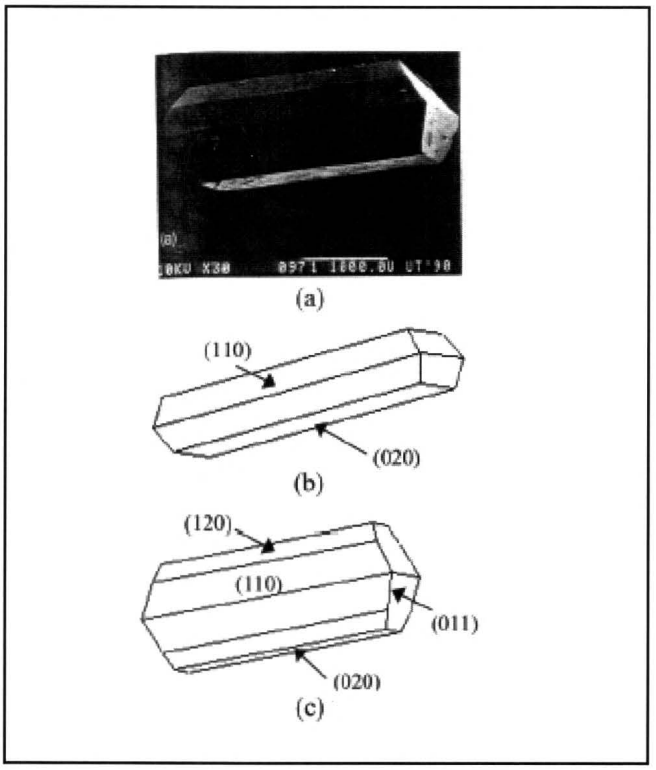

Figure 4. *Reported and predicted morphologies for* α–glycine *crystallized from aqueous solution.* ***(a)*** *Experimentally grown crystal from Boek, et al.*[27] ***(b)*** *Predicted shape using the form of the BCF model in Eq. (4) with a dimer growth unit.* ***(c)*** *Shape predicted by Eq. (4) using a modified monomer growth unit.*[26]

result provides a nice link between elementary statistical mechanics and the kinetics of crystal growth. (In my experience, if you want to teach undergraduates the methods of statistical mechanics so that they understand, use the textbook by Kittel and Kroemer.[19])

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) 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 faceted 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

$$\frac{\gamma_i}{h_i} = \text{constant},\ i = 1,...,N \tag{5}$$

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 that 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.[20] 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[21] (also see Cahn, *et al.*,[22]) to determine the crystal shape at steady state, given as:

$$\frac{R_i}{h_i} = \text{constant},\ i = 1,...,N \tag{6}$$

where R_i is the perpendicular growth velocity of face i. As noted in the previous subsection, many 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. (4)]—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.*,[23] Winn and Doherty,[24, 25] and Bisker-Leib and Doherty.[26] 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. Figure 4 compares the experimental and predicted steady state growth shapes of α-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 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 two-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 three-dimensional crystals are quite complicated as faces, edges, and vertices appear or disappear during growth. The definitive study is yet to be done.

Although some may disagree with me, I think the topic of crystal growth and crystal shape as outlined above is good material for inclusion in an undergraduate transport course.

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.[28] Despite this, its prevalence presents one of the greatest obstacles to the solids-processing industry 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 such as 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. A dramatic example of this phenomenon is provided by the Ritonavir polymorphs.[5]

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[29] described 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 a low temperature of 0 °C 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 Rule of Stages describing phase transitions that it is not the most thermodynamically stable state that will normally appear first but that which is the closest, in free energy, to the current state.[30, 31] In accordance with this rule, crystallization of a compound having two polymorphs will often 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.[32] For example, a snapshot of the polymorphic transformation of glycine crystallized from a water/ethanol mixture is shown in Figure 5. At the beginning of the crystallization, beta-glycine (needle) 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.

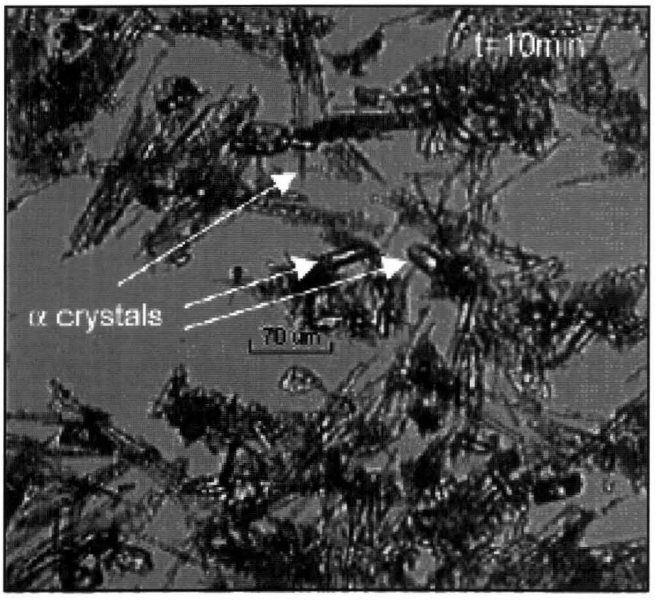

Figure 5. *Two polymorphs of glycine in water-ethanol solution: alpha-glycine (shaped as a coffin) and beta-glycine (needles).*[33]

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.[34]

Crystallizer Design

Crystallization processes are designed to achieve specific material properties in the final solid product, which are normally determined by the crystal purity, polymorph, mean particle size, size distribution, and crystal habit. The design decisions that influence these material characteristics include: choice of solvent, tailor-made surface-active modifiers,[35-37] fines removal system, and the temperature and supersaturation fields inside the crystallizer (which are determined by the solute feed concentration and temperature, crystallizer temperature, vessel volume and geometry, agitation rate, and/or antisolvent feed rate or evaporation rate, as appropriate). Buildup of impurities in the recycle streams also has the potential to significantly influence crystalline material properties.

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 myriad 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.

Modeling crystallizer flows is critically important and 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. Advances have also been made incorporating the effect of the suspended particles on the flow field.

Currently, there is great hope for Lattice Boltzmann techniques to simplify the computational treatment of the equations of motion, making numerical solution much more efficient. The techniques are also amenable to including the effect of solids[38] 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 particle size distribution (PSD) into these models, but this is an area of current research and progress is being made.[39]

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.

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 and coolers, etc. Both the structure of the flowsheet and the devices and their operating

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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 proven 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.[40] The crystallization paths are trajectories of the liquid composition in a crystallizer as the solid is formed and removed from solution.[41, 42] The presence of eutectics and compounds causes the presence of crystallization boundaries, which divide the map into distinct crystallization regions. These regions are nonoverlapping and mutually exclusive; that is, a liquid trajectory that starts in one region cannot cross a boundary (except by noncrystallization 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.

Crystallization maps are useful for synthesizing flowsheets for adductive crystallization (where a compound is the desired crystal product), extractive crystallization, and many other embodiments.[43-45] Although these maps are valuable for laying out process flowsheets, the accumulation of impurities associated with process recycle and the effect on crystal properties both remain difficult to predict. Therefore, integrated pilot-scale testing including all recycle streams is still required for confident system design, but there are significant modeling opportunities here that will enable more reliable and rapid development of process flowsheets.

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, infrared 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 of 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.

Most of these advances are not being made by chemical engineers, however. And moreover, they are taking place in isolation. 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. Perhaps the larger question is, "How do we incorporate our rapidly advancing knowledge and modeling capability to make better products?"

There are major opportunities here for chemical engineers who must be encouraged to take up the challenge. Specific recommendations for incorporating crystal engineering into chemical engineering research and undergraduate education include:

Education

(1) Crystalline solids should be one of the core themes throughout the chemical engineering curriculum. Topics include: *Thermodynamics course-* thermodynamics of solid-liquid phase diagrams and solubility curves, spinodal curve and metastable zone curve, traditional nucleation theory. *Transport course-* diffusion of solute through a solution to a growing crystal surface, estimates of characteristic times for bulk diffusion, surface diffusion and integration of solute at kink sites on a crystal surface, models for flow of steps across crystal surfaces. *Reaction Engineering course-* simultaneous reaction and crystallization (*i.e.*, precipitation). *Separation course-* design of batch and continuous crystallizers. *Design course-* simultaneous product and process design for crystalline products (*e.g.*, a dye, a pigment, or a simple pharmaceutical such as paracetamol—trade name Tylenol).

(2) Solid state chemistry should be part of the undergraduate chemistry sequence. Topics include: crystal structure and crystallography, nucleation (both traditional and statistical mechanics models), solid state bonding and bond chains, and surface growth models—especially the spiral dislocation model.

There are numerous useful monographs and textbooks available on the subject of crystallization that may be used for teaching undergraduates. These include: Randolph and Larson,[46] Mullin,[47] and Davey and Garside.[48] The last of these is short, inexpensive, and extremely well written. Undergraduates should be happy to purchase this book.

Research Topics

(3) New models and experiments for understanding, directing, and controlling nucleation and polymorph selection

(4) Models for understanding and predicting polymorphic phase transitions—both solution mediated and solid state transformations

(5) Models and experiments for predicting the effect of additives and impurities on crystal properties (*e.g.*, crystal shape, size, polymorph)

(6) Improved models for CFD of dense suspensions of crystals that are growing inside a solution crystallizer

(7) Improved procedures for simultaneous product and process design for crystalline particulate products; application and testing of the procedures in such product sectors as: chiral and pharmaceutical products, home and personal care (*e.g.*, skin creams, suntan lotions), food (*e.g.*, margarine, chocolate, ice cream), dyes and pigments, bulk chemicals (*e.g.*, adipic acid), and specialty chemicals

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