7
Process Understanding – Crystallization

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7.1
Introduction

The emergence of molecular-based compounds being developed for applications as advanced materials and pharmaceuticals necessitates an ever more advanced approach to the control and characterization of solid-state properties; one key route to accomplish this goal is by understanding the crystallization of these compounds. Crystalline and solid-form manufacturing is a universal application – more than 80% of pharmaceutical products and 60% of fine and specialty chemical products are made in crystalline form, for example, pharmaceuticals, agrochemicals, fats and oils, foods and confectionary, pigments and inks, consumer products, materials, and metals. This has led to a dramatically increased interest and prominence in crystallization processes, in the discovery of new forms, control of polymorphism, design of morphology for particular modes of delivery, and for formulation and scale-up, in optimizing the crystallization process in batch or flow modes. Further, there has been a general realization that the crystallization process is core to the production of solid-state materials, at a fundamental level, and is set to make an increasing contribution to coatings, especially epitaxially grown layers. Among the issues that require to be addressed in understanding the crystallization process include physical form discovery and screening, particle technology analytical methods for characterizing the synthesized products, backed up by modeling and theory of both microscopic and macroscopic processes.

In more detail, and to set the scope for the discussions introduced below, each of these raise a range of technical and scientific challenges that must be addressed to inform a full understanding of particular crystallization processes geared at the production of selected solid material forms.

- Physical form discovery and screening: Crystallization screening for physical form discovery; crystal structure determination; crystal structure comparison, analysis of three-dimensional structures; polymorphism; effects of solvation; transformations and phase transitions; and physicochemical characterization.

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- Particle technology: Nucleation, crystal growth studies, agglomeration/attrition, morphology control, particle characterization, bulk characterization, crystallizer design, additive synthesis, and processing and scale-up.
- Analytical methods: X-ray diffraction (XRD), single crystal and powder; spectroscopy, Fourier transform infrared (FTIR), Raman, near infrared (NIR), ultra violet (UV), solid-state nuclear magnetic resonance (NMR); thermal analysis/calorimetry; focused beam reflectance microscopy (FBRM); process analytical technologies; chemometrics; optical and scanning electron microscopy (SEM); and surface analysis (atomic force microscopy (AFM)).
- Modeling and theory: Molecular structure, quantum chemistry; intermolecular interactions; crystal structure prediction; morphology prediction; solvation; computational fluid dynamics; molecular dynamics simulations; and chemometrics/design of experiments.

As an example of the importance of control of molecular association in crystallization processes, the following physical and chemical properties can differ enormously among crystal forms and cocrystals of the same material, dramatically affecting their processing, formulation, and delivery modes [1]:

- Physical and chemical properties: Density and refractive index, thermal and electrical conductivity, hygroscopicity, free energy and chemical potential, melting point, heat capacity, vapor pressure, solubility, thermal stability, and chemical and photochemical reactivity.
- Kinetic properties: Rate of dissolution, kinetics of solid-state reactions, and stability.
- Surface properties: Surface free energy, crystal habit, surface area, and particle size distribution.
- Mechanical properties: Hardness, compression, and thermal expansion.

The interplay of some of these effects, and some of the techniques that can be used in their study, are given in Table 7.1; many of these are discussed further in this chapter, which reviews some of the underpinning science and techniques relevant to the crystallization process.

7.1.1 Crystal Definition and Structure – Crystal Defects and Basics of Crystal Growth

Macroscopically, a large single crystal is among the great beauties of nature, with aesthetic properties that pervade many cultures both historically and currently. Microscopically, the crystal retains much of this simplistic beauty. The regularity is retained, although there are microscopic defects even in the most "perfect" of gem-like crystals, as is the simplicity, manifest in the repeated pattern of the units forming the crystal. The regularity of a crystal gives a clear indication of the underlying construction, which is based on a periodic array of lattice points populated by a structural unit that is repeated at the lattice points. The lattice in any crystal is defined by the unit cell, principally by its external dimensions (defining the crystal system) and also by aspects of its internal constitution (defining the lattice type).

Table 7.1 Interplay of crystallization parameters, physical effects, and the techniques used in their study.

Primary physical parameters controllable during crystallization	Secondary effect	Methods of analysis (see Section 7.5)
Particle size	Filterability, dissolution rate/profile, flow of bulk powder	FBRM, DLS
Particle size distribution	Flow of bulk powder, filterability, consistency of processing	FBRM, DLS
Crystal habit	Filterability, mechanical strength, ease of downstream physical processing, flow of bulk powder	XRD, optical microscopy, electron microscopy
Polymorphic form and phase changes	Physical properties, melting point, solubility, availability of active ingredient	XRD, DSC
Solvate formation, desolvation of solid forms	Stability, bioavailability, processing characteristics	DSC/TGA, XRD
Surface effects – roughness, charge characteristics	Flow of bulk powder, ease of formation of agglomerates	–
Cocrystallization	Bioavailability, dissolution rate/profile	DSC/TGA, XRD, chemical analysis

This internal constitution introduces the concept of internal symmetry within the unit cell. There are seven crystal systems, triclinic, monoclinic, orthorhombic, tetragonal, cubic, trigonal, and hexagonal, which are defined on the basis of the external geometry of the unit cell [2], while the introduction of lattice centrings (lattice points not at the corners of the unit cell) leads to the presence of 14 so-called Bravais lattices. Introduction of internal symmetry within the unit cell yields a total of 230 space groups in 3D, with many thousands of space groups possible for >3D systems.

This internal regularity leads to the macroscopic shape of crystals, defined by the crystal faces, whose formation is governed by the minimization of surface energies. In general, these faces tend to be defined by low values of Miller indices (defining the lattice planes forming the faces). Microscopically, this growth mechanism results from the lowest attachment energy of molecules to the growing surface, defined as the interaction energy per molecule between a depositing slice and the crystal face. In this model, crystal faces with the lowest attachment energies tend to dominate the resulting morphology. One simple model directly relates the growth rate of a face to the attachment energy, $R \propto E_{att}$ [3]. The macroscopic shape of a crystal is known as its *morphology*, and is dictated by the rate of crystal growth on each of the binding faces. The morphology is a critical factor in the physical properties of crystalline materials used for applications, affecting important factors such as compaction, flow characteristics, physical properties, anisotropies, and so on.

However, not all crystal faces end up being regular in real crystals, instead containing terraces and steps and, importantly, other forms of defects. The

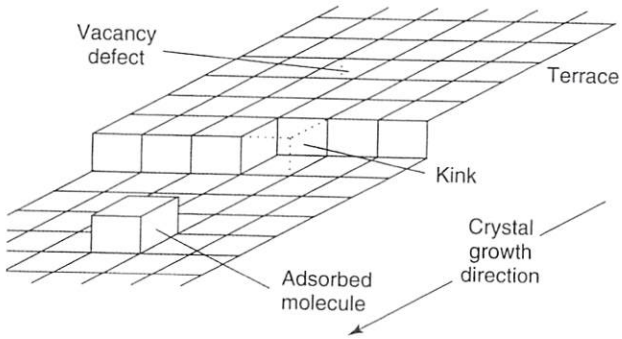

Figure 7.1 Block crystal growth, terraces, and kinks.

attachment discussed above tends to occur at sites where the attachment energy can be minimized. At these kink sites, there are only half the number of neighbors present at the attachment site than would be present in the crystal bulk (Figure 7.1). In addition to minimizing the attachment energy, the kinks are retained following the attachment, this being available for further growth deposition processes. For crystals growing from solution, the density of kinks on the surface tends to be rather low, comprising around 0.1% of all molecular sites on the surface. It is clear from this that the low number of kinks present is likely to be a major factor in controlling the rate of growth of the crystal from solution.

The nature of the growing face significantly affects the mechanism of crystal growth. Broadly speaking, crystal faces can be classified into two categories: atomically rough faces where the growth is diffusion controlled and continuous, with the growth rate depending linearly upon the supersaturation; and flat faces, in which the growth is dependent on the rate of formation of critical nuclei to overcome the energy barriers in the construction of the layer. The need for nuclei formation in the latter case can often be mitigated by the presence of defects, which effectively act as nucleation centers. Crystal morphology can also be tuned by introduction of additives, which can be incorporated in the growth process, and have two distinct potential effects. Once present, some tailor-made additives inhibit the growth of unfavored faces, while others can act as effective nucleation centers and encourage enhanced face growth [4] (Figure 7.2).

7.1.2 Thermodynamics of Crystallization

The equilibrium form of a crystal can be considered to be governed by the Gibbs–Wulff Law, $\sum_n \gamma_n dA_n = 0$, where with reference to the nth face of the crystal, A is the area and γ the surface tension. This takes into account only thermodynamics; in practice, however, kinetic effects can often dominate, particularly as the crystal becomes larger. The interplay of thermodynamic and kinetic effects is one of the real challenges in understanding crystal growth and crystallization

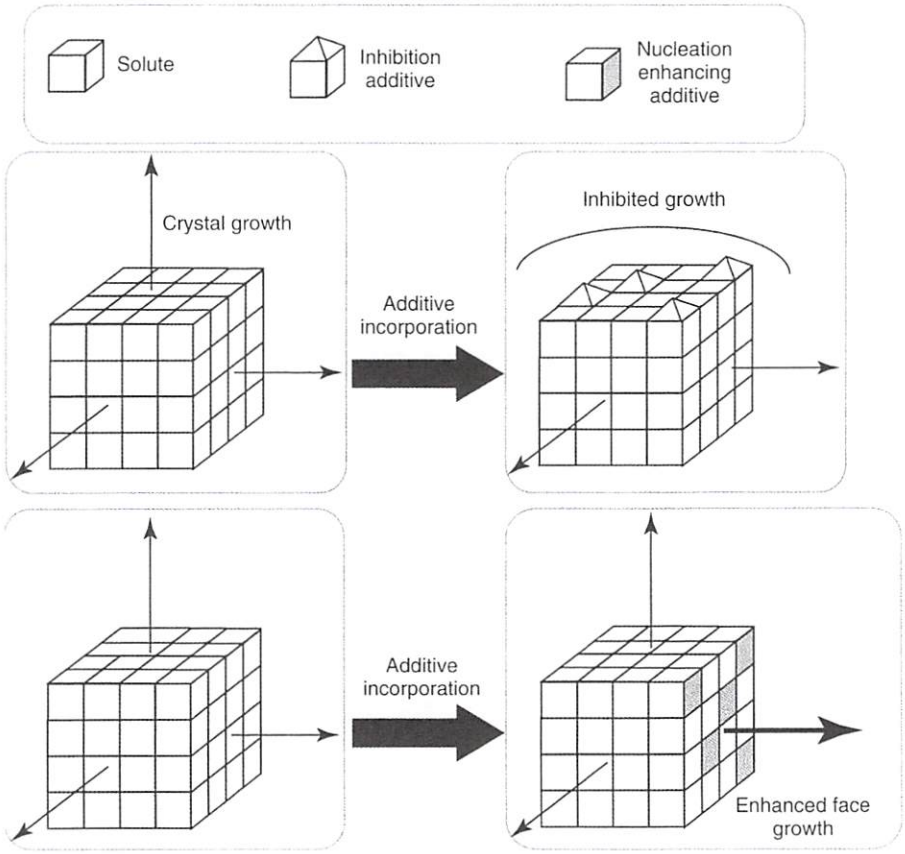

Figure 7.2 Tailor-made additives – inhibition or enhancement of growth on selected faces depending on the nature of the additive.

processes, with factors such as impurity level, mixing regime, vessel design, and cooling profile often having a major impact on the nature of the crystals produced.

In general thermodynamic terms, the crystallization process is a multiphase multicomponent system. For such a general system of C components and P phases, the amount of each component in a single phase, at a given value of temperature (T) and pressure (p), is given by its molar quantity n_i. The Gibbs energy of the phase ϕ, G^ϕ, can then be expressed as a function of temperature, pressure, and these molar quantities of the various components:

$$G^\phi\left(T, p, n_1, n_2 \ldots, n_C\right)$$

with differential form

$$dG^\phi = \left(\frac{\partial G^\phi}{\partial T}\right)_{p,n_i} dT + \left(\frac{\partial G^\phi}{\partial p}\right)_{T,n_i} dp + \left(\frac{\partial G^\phi}{\partial n_1}\right)_{T,p,n_{i\neq 1}} dn_1 + \ldots$$

$$= -S^\phi dT + V^\phi dp + \mu_1^\phi dn_1 + \ldots$$

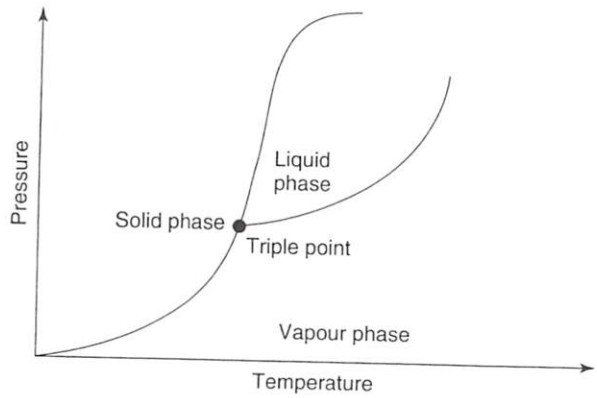

Figure 7.3 Simple phase diagram for a one-component system, showing phase boundaries. The chemical potentials of the relevant phases are equal at these phase boundaries.

where there is a term for each of the C components. The terms μ_i are called the *chemical potentials*, representing the contribution of each component to the Gibbs function, and thermodynamic theory states that the system will attempt to minimize the value of the Gibbs free energy – these chemical potentials thus become the driving force for thermodynamic processes such as, in this case, crystallization. At equilibrium, the chemical potentials of all phases present will be equal.

A one component system is fairly easy to interpret conceptually through use of a simple schematic phase diagram, expressed in terms of thermodynamic variables or chemical potential (Figure 7.3).

The crystal (solid) phase is stable at high p and low T, and at the phase transition point between liquid and solid, the chemical potentials of these two phases will be equal. μ decreases at different rates for solid, liquid, and gas $\left(\left(\frac{\partial \mu}{\partial T}\right)_p = -S\right)$, and the phase transition (in this case crystallization) occurs when $\mu_S = \mu_L$ (and then when $\mu_L = \mu_G$), that is, the chemical potentials are equal (points at which $\Delta G = 0$). From this general framework, the thermodynamics of any specific crystallization process can be developed.

7.1.3 Kinetics of Crystal Growth, Nucleation

We have seen from the above simple consideration of phase diagrams that crystallization is a condensation phase transition process involving the creation of a solid crystalline phase from a parent phase. At the microscopic level, the formation of a new solid phase in this way requires an input of work to create an interfacial region (formation of nuclei). There is thus an energy barrier to the formation of the solid phase, which is related to the surface area of the newly forming phase. Since the nuclei can be very small in the initial stages of crystallization, this surface energy can be correspondingly large. Introduction

of such an energy barrier, or activation energy for the formation of nucleation sites, naturally leads to a chemical kinetic interpretation of the process. In an analogous way to the simple collision theory of gas kinetics, statistical fluctuations in a liquid or solution phase may lead to a locally sufficient energy to overcome the activation energy barrier. Kinetic effects are thus largely bound up with the nucleation process.

Nucleation processes are of two main types: homogeneous nucleation occurs within the single component phase in the system, while heterogeneous nucleation will be induced on a distinct substrate within the system, for example, a surface such as the wall of the crystallization vessel, a mechanical fluctuation, or at the micro and nano positions of particle impurities that are always present in the solution. Following nucleation, the process of crystal growth involves the expansion of these nucleating centers that have achieved a critical size to the macroscopic crystal, once again with energy input required to overcome energy carriers to association of molecules on the growing surface. Thus, the rate of nucleation can be expressed in terms of a two-step process of the formation of a concentration of critical nuclei from the equilibrium system and the subsequent rate at which further molecules accrue upon these nuclei, leading to the growth of the bulk phase.

A simple visual way of depicting the kinetics of crystal growth is presented in Figure 7.4, with particular reference to the production of the final solid phase in a polymorphic system.

In the crystallization process to one of two possible polymorphic crystal structures (I and II), the free energy of the starting liquid phase is given by G_0, and the crystallization can result in the formation of one of two crystalline products (I or II) in which I is more stable ($G_{II} > G_I$). The kinetics of crystallization in this case is complicated by the often complex structure of the activated site. The crucial

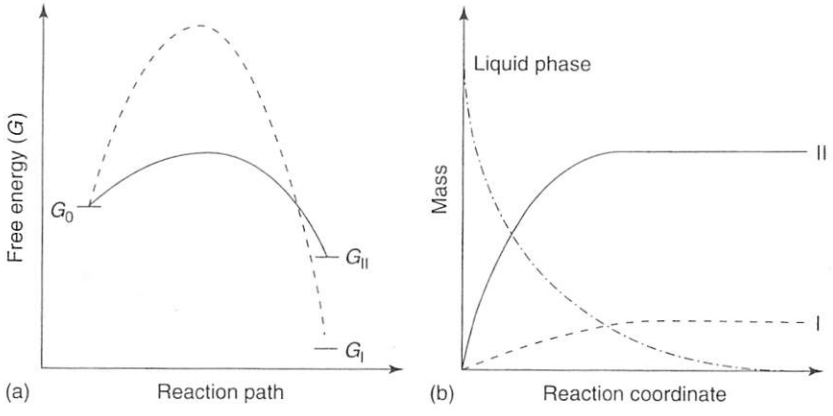

Figure 7.4 Simple schematic representing the kinetic effect in favoring a less stable (metastable) polymorph (II) over a more stable form by the existence of lower activation energy for the production of the less stable form (a). Such situations can lead to coexistence of different polymorphs (b), the composition of the final mixture again being heavily influenced by the kinetics.

factors that result in polymorphism are crystal nucleation and growth, which are under kinetic control as indicated above. Figure 7.4 shows that the final product may result from the less stable but faster growing nuclei, forming a metastable phase, with the transformation to the thermodynamically stable phase forbidden by a considerably higher energy barrier. There is also a substantial energy barrier for possible transformation from the metastable phase to the thermodynamically stable phase.

7.1.3.1 Metastable States

We have seen above that the factors controlling crystallization can often involve a subtle balance between thermodynamic and kinetic factors, and can be dramatically affected by the physical conditions under which the crystallization process occurs. In addition, the occurrence of metastable states can have a significant effect on the outcomes of a crystallization experiment. Metastable thermodynamic states are frequently encountered in a wide range of systems including pharmaceuticals, and can have dramatic effects on the crystallization process. They can, for example, affect the creation of supersaturation conditions, alter the solid-state form produced, and introduce issues with the control of solid-phase conversions during isolation, manufacturing, storage, and dissolution. Since the process of crystallization offers a way of reducing the free energy of metastable thermodynamic states, the occurrence and stability of these states are determined by the crystallization mechanism and kinetics; hence, it is an important factor in the control of many crystallization processes [5].

7.1.4 Nucleation and Crystal Growth

Nucleation has been referred to above several times, as the kinetically controlled first step in the crystallization process. Nucleation remains one of the most challenging aspects of crystal growth to understand, characterize, and control, with many solutions to this based on empirical investigations tuning experimental variables to achieve the desired results reproducibly. The basic process in primary nucleation is the formation of nuclei of sufficient size to be able to sustain growth from solution, thus becoming critical nuclei. We have seen above that the nucleation can be homogeneous or heterogeneous. The nature of homogeneous nucleation is such that the critical nuclei will represent, at the microscopic level, the equilibrium form of the crystal, while this is not true for heterogeneously generated nuclei.

7.1.4.1 Supersaturation and Metastable Zone Width

There are three well-defined regions associated with solution crystallization. The first is a stable, unsaturated zone where crystallization is impossible. The second is the metastable zone between the solubility and supersolubility curves (Figure 7.5), where crystallization is improbable, although growth would occur if seeds were to be planted in a metastable solution to act as heterogeneous nucleation sites. The width of the metastable zone indicates the stability of the solution; the larger the

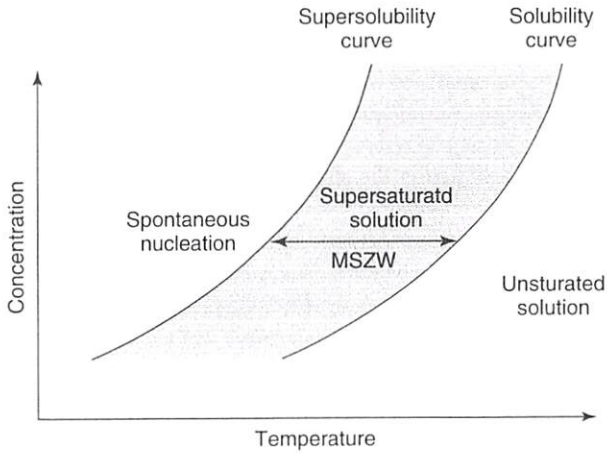

Figure 7.5 The metastable zone between the solubility and supersolubility curves, showing the metastable zone with (MSZW).

zone width, the more stable the solution. This is the preferred region in which to carry out controlled crystallization processes; that is, by adjustment of system parameters, as this helps to prevent any unwanted nucleation from occurring. Crystallization within the metastable zone is not common due to the stability of the solution; beyond this metastable zone, the system is said to be labile, and this is where spontaneous nucleation can occur.

Tuning the cooling rate of a supersaturated solution until the first indications of crystallization can be seen can control the onset of nucleation. This is referred to as the *nucleation point*. A solute is maintained in solution until a sufficiently high level of supersaturation has been developed; this in turn encourages spontaneous nucleation to occur. It is thus important to characterize the metastable zone width (MSZW) under a specific set of operating conditions [6], which relate closely to the conditions of the final-scale crystallization. The polythermal technique involves cooling a saturated solution at a fixed rate until nucleation occurs. This is repeated several times at a variety of cooling rates until a reliable MSZW can be determined. The MSZW can be considered to be characteristic of each unique crystallization system. The *induction period of nucleation* is defined as the time that elapses between the instant when the supersaturated state is generated and the point of time at which solid phase particles become detectable. This includes the time required for the generation of a critical nucleus in supersaturation and the growth to a detectable range, which can be as low as 1 μm in, for example, the FBRM method (see below).

Understanding the MSZW is of fundamental importance to be able to control crystal growth and is thus widely studied. In-depth solubility studies and supersolubility studies of a single compound are needed and temperature control is crucial. Reliable dissolution profiles can be determined and these are fundamental, in particular in the pharmaceutical industry, due to the increase in discovery of new

polymorphic forms and the corresponding changes in their key physical properties such as solubility. For this reason it is vitally important to be able to carry out these experiments in a clean and controlled environment, as even the smallest contaminant such as a speck of dust can initiate nucleation.

In solution crystallization, the strongest reduction of supersaturation takes place during the rate-determining step, which is the slowest step in the crystallization reaction mechanism. The potential processes involved comprise transport to the growth site, overcoming surface energy barriers, and removal of heat of crystallization from the system. For solution crystallization, this tends to be dominated by the first two of these processes, while for the case of melt crystallization, the heat transport tends to be the rate-determining step [7].

Detailed expressions for the thermodynamics of nucleation have been developed. For example, Kachiev *et al.* consider the thermodynamics of the nucleation process and present expressions for the supersaturation, the nucleation work, and the size of the nucleus in homogeneous or heterogeneous nucleation [8]. This leads to the design of experimental methods for the determination of the size of the nuclei. The mechanism and kinetics of nucleation are also considered in this work, with expressions given for the supersaturation dependence of the monomer attachment frequency and the rate of homogeneous or heterogeneous nucleation, together with other kinetic aspects of the process. Methods are also available for estimating the width of the metastable zone from solubility data.

7.2 Crystallization Processes

7.2.1 Crystallization from the Melt

The principles of nucleation and growth control in melt crystallization were initially formulated by Verneuil in 1902, in the work on the growth of synthetic rubies, and are adapted in most later growth methods from melt. This original work established flame-fusion processes, allowing very high temperatures of more than 2000 °C to be reached through designing apparatus that only required a small amount of fine-grained material to be melted using an oxyhydrogen burner. Once the raw material is melted, a seed crystal is used to control the crystal growth [9]. Melt crystallization is still widely used for the production of large single crystals, particularly of metallic or inorganic crystals. Widely used adaptations of the methods introduced by Verneuil include the Bridgeman and Czochralski methods discussed in the following two sections.

7.2.1.1 The Bridgman Method

The Bridgman method, and its closely related variant the Bridgman–Stockbarger method, is an important melt-crystallization technique. As in the original experiments of Verneiul, the polycrystalline sample material is heated above its melting

point, but in this case it is held inside a container and a cooling regime is instigated from one end of this container, where a seed crystal is present. By these means, crystal growth takes place along the container in the form of good quality single crystals that tend to have low concentrations of defects.

7.2.1.2 The Czochralski Method

The Czochralski process is an alternative method for producing single crystals from the melt, which involves pulling a crystal from the melt [10]. Frequently used to produce a range of often large single crystals (at the centimeter level or greater), the Czochralski method is often used to produce single crystals of semiconductors, in cases where a low defect density is not a prerequisite. In addition to large single crystals (that can be up to 2 m long), the technique offers the opportunity for defect engineering, and thereby control of the temperature-dependent properties of crystal defects [11].

7.2.1.3 Crystallization of Organic Materials from the Melt

Although used less frequently, the nucleation and growth of single component and binary organic materials are also susceptible to study using melt-crystallization techniques [12], including growth of crystalline polymer materials [13]. Although these can be used to produce large single crystals as for metallic and inorganic materials, melt conditions have also recently been increasingly shown to be a potential source of new crystal forms, and are now beginning to be used in polymorph screening and discovery. Techniques such as Kofler hot-stage microscopy can allow the growth of new phases to be followed, thereby allowing nucleation and crystal growth kinetics to be followed in these materials.

7.2.2 Crystallization from Solution

Crystallization from solution is the most common technique for producing a wide range of materials, in particular, organic materials such as pharmaceuticals that have driven many investigations into improving crystallization processes in production and manufacturing. The technique is reviewed in several recent publications [14], including consideration of the relevance to large-scale plant crystallization [15].

7.2.2.1 Single Solvent Crystallization

7.2.2.1.1 Temperature-Controlled Crystallization There are many ways to attempt to grow single crystals, from the traditional slow evaporation to more modern apparatus including multiple parallel automatic and robotic crystallizers, and medium-throughput semimanual devices. The characteristics of these systems include the ability to screen crystallization from multiple solvent options, automatic dispensing, and in some cases solid-form characterization, and programmable temperature control. One typical semiautomatic medium throughput instrument

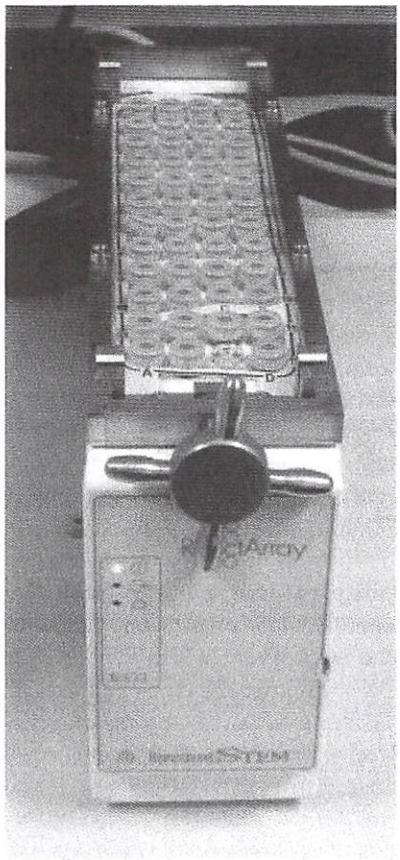

Figure 7.6 A typical parallel laboratory crystallizer, allowing flexible, programmable temperature control for small-scale crystallizations.

is illustrated (Figure 7.6); this device allows 12 separate rows of independently temperature-controlled conditions for crystallization to be trialed simultaneously: with 4 individual vessels in each row this allows for up to 48 different experiments in 12 separate temperature conditions to be carried out simultaneously. These are small-scale vessels, typically containing milligram quantities of material, and can give results in a far shorter period than larger-volume slow-evaporation techniques. The instrument allows ramping and cooling profiles to be set up in each row and can lead to positive identification of the conditions that may lead to the best crystal growth.

7.2.2.1.2 Evaporation-Controlled Crystallization This is amongst the simplest of crystallization methods, and forms the basis of many high-throughput and high-volume processes. On the laboratory scale, the experiment starts with a small amount of the sample being placed in a sample vial (Figure 7.7). Sufficient solvent is added to dissolve the contents of the vial. The vessel is covered, or partially covered, allowing the sample to evaporate slowly and, hopefully, allowing crystals to grow. Evaporation-controlled crystallization will often be carried out under closely

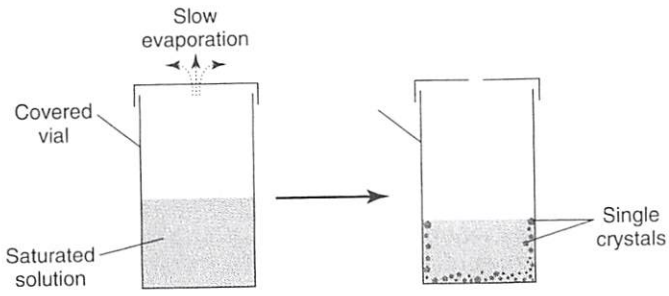

Figure 7.7 Schematic illustrating the principle of simple, slow-evaporation crystallization.

regulated temperature conditions, though for many growth processes accurate temperature control is not required.

7.2.2.2 Multiple Solvent Crystallization

Multiple solvent crystallization techniques can take two main forms: one in which the sample is dissolved in two mutually miscible liquids in both of which it has significant solubility, which are then allowed to evaporate as described above; and the other in which a solvent diffusion process is adopted, involving solvents in which the sample has significantly different solubilities. Solvent diffusion is usually employed if conventional evaporation is unsuccessful. The technique (Figure 7.8) involves dissolving the sample in a solvent in which it is readily soluble (good solvent). Another solvent is then added to this sample vessel, the solvent to be added usually being a solvent in which the sample will not be readily soluble (poor solvent). The two solvents used must be comiscible. The poor solvent is added slowly to ensure that there are two layers present. These two layers will then mix slowly and the crystals will thus be encouraged to grow at the interface. If necessary, cooling of the tube can be done to slow the diffusion rate and to reduce solubility.

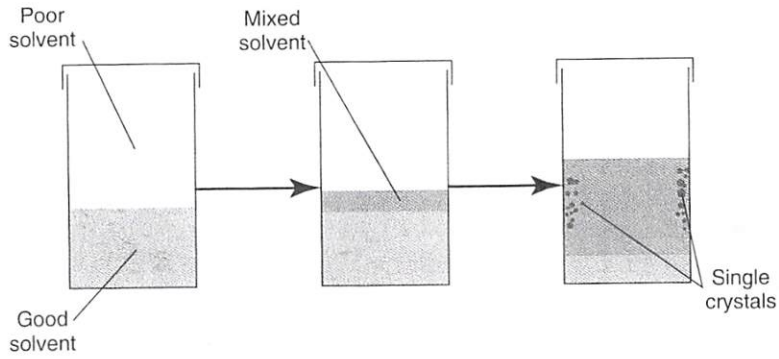

Figure 7.8 Schematic illustrating the principle of solvent diffusion crystallization. The blue solvent is the good solvent, the yellow solvent is the poor solvent, and the green area is the interface.

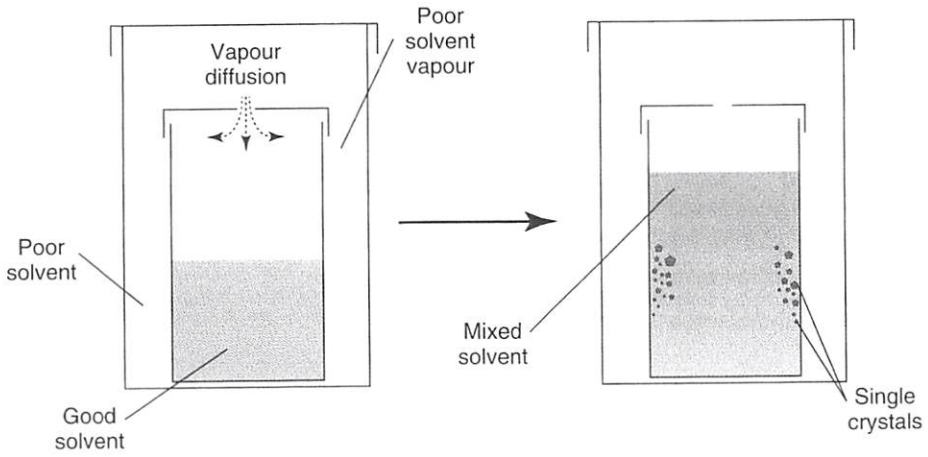

Figure 7.9 Schematic illustrating the principle of vapor diffusion crystallization. Blue represents the good solvent and yellow the poor solvent.

7.2.2.3 Vapor Diffusion

Vapor diffusion is a technique closely related to that of solvent diffusion, and is also known as *isothermal distillation*. The setup is as shown in Figure 7.9, where the good solvent in which the material is dissolved is placed in the crystallization vessel, which is placed in a larger vessel containing the desired poor solvent. The whole system is then covered, and the poor solvent diffuses through the vapor phase into the solution of the target compound in the good solvent, thus reducing the solubility and leading to the precipitation of crystalline material. The main reason for using this technique is that it offers slow rate of diffusion, has high controllability, and is very adaptable.

7.2.3 Crystallization from Vapor

Chemical vapor deposition (CVD) is a further widely used technique for the growth of inorganic or metallic materials, and is often used in the production of, for example, diamond materials [16]. Specific CVD reactors for growth of particular materials have been designed and used. Variants of CVD including pulsed vapor deposition (PVD) have also been developed, and have particular utility in the fabrication of complex-oxide heterostructures, superlattices, and well-controlled interfaces, with deposition methods that approach true layer-by-layer growth [17]. As can be imagined, the understanding of surface chemical processes is vital to the understanding of such crystal growth processes, and approaches such as time-resolved surface XRD can be employed for detailed structural mechanistic studies.

7.3
Batch Crystallization Techniques

In industrial process environments, crystallization would generally be undertaken in a batch crystallizer, allowing for high-volume production. In such environments, the process is usually based on precipitation from a solvent with controllable parameters that allow for phase separation of the deposited solid phases, and, in favorable circumstances, control of important factors such as particle size and morphology. These are vital aspects in producing crystalline materials with appropriate physical properties for the desired application. The control of particle sizes in batch crystallizers is a function of a wide range of factors that include cooling, evaporation, and dilution regimes employed. Modeling of batch crystallizer operation can be undertaken and allows this to be tuned to select appropriate particle sizes [18]. The batch crystallization operation has also been developed into more sophisticated environments for specific applications, for example, in the use of liquid-phase-coupled batch crystallizers enhancing the driving forces for preferential crystallization of enantiomeric forms allowing for enantiomeric separation [19].

The principles of chemical engineering are thus added to the fundamental understanding of crystallization processes in designing and optimizing such batch crystallizers. The rapid expansion of the chemical and other related industries have required increased study of the mechanism and design of the crystallization process, and design of a production plant increasingly takes account of this. The design of industrial crystallizers has reflected the evolution of new crystallization and manufacturing processes. Early designs were based around simple stirred tanks (which have been essentially in existence for hundreds of years) where cooling, evaporation, or pH control were used to induce crystallization, while variants of this design have been implemented for specific applications and have improved product characteristics. Modern approaches to continuous crystallization processes have continued this development, offering various advantages, including substantial improvements in product quality control.

7.3.1
Tank Crystallizers

The simplest cooling crystallizers are tanks provided with a mixer for internal circulation, where temperature decrease is obtained by heat exchange with an intermediate fluid circulating in a jacket. These simple machines are used in batch processes, as in the processing of pharmaceuticals, and are prone to scaling problems. While providing large-volume production capability for crystalline materials, batch processes normally provide a relatively variable quality of product.

There are a series of variants in this approach, which are commonly implemented for bulk crystallization processing. Among these are the following:

- Scraped surface crystallizers. The characteristics of a scraped-surface crystallizer are of a trough within which slow-speed blades rotate, agitating the forming

crystal, and ensuring that any deposits on the walls are returned to the crystallizer body, usually resulting in a wide distribution of crystal sizes. The process of crystallization in a scraped surface system can be complex and considerable investigation is still being carried out to obtain an understanding at the fundamental level of the various factors influencing crystal growth, including fluid flow and heat transfer [20].

- Double-pipe scraped surface crystallizers. These systems are different from the scraped-surface device in having an annular space within which cooling water circulates. This type of device is used in many manufacturing processes including the crystallization of ice cream and plasticizing margarine.
- Circulating-liquid evaporator crystallizer. This device uses carefully designed flow of liquid and vapor phases to induce supersaturation, in a controlled manner, by evaporation processes. The circulating-liquid evaporator crystallizer was one of the earliest batch of crystallizers and is often called the *Oslo crystallizer*, as it was first implemented there.
- Circulating-magma vacuum crystallizer. In this device, a hot suspension or magma of feedstock material is passed through a heater to produce a heated surface liquor that then mixes with the body of the material causing supersaturation, depositing crystals that are then harvested.

7.3.2 Continuous (Flow) Crystallizers

The evolution of crystallization in manufacturing technology for the chemical and other related industries has been rooted in the use of the stirred-tank reactor as the normal approach for manufacture. Although hugely successful, this type of application offers particular challenges around the scale-up of processes, is also expensive, results in wastage of materials, has a large plant footprint, and offers poor control over quality.

In particular, for crystallization, approaches using stirred-batch vessels or through a series of tanks, requires large vessels and offers poor control over crystal form. The industry has therefore begun to move toward leaner and more sustainable forms of manufacturing, with some success (Figure 7.10). However, the real benefit lies in moving toward a fully continuous process, and there are key scientific and technical developments that are required to enable this shift to happen. Indeed, in the area of nanoparticle crystallization, continuous manufacture using crystallization under flow is a new and possible key area [21].

Continuous Crystallization is one approach that overcomes many of these limitations, offering benefits in terms of sustainability, including substantial footprint and capital cost reduction, lower running costs, speed of scale-up of platform technologies, and controllable quality of the crystals formed. There are a range of continuous crystallizer technologies now being adopted in the industry, including devices such as the continuous oscillating baffled crystallizer (COBC; Figure 7.11).

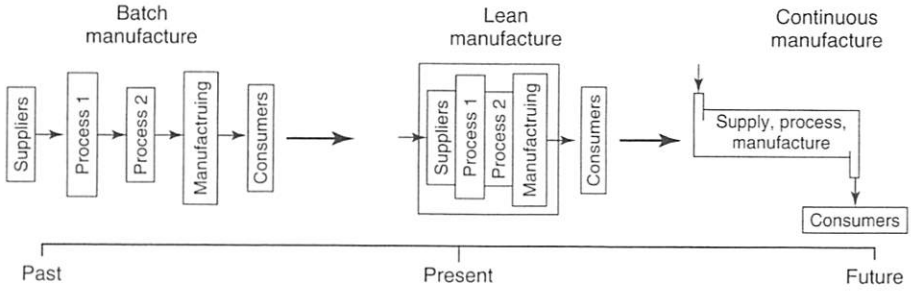

Figure 7.10 The move from batch to continuous manufacturing principles, through leaner methods, offers advantages in terms of cost, efficiency, and sustainability. Major benefits are anticipated in moving from lean to continuous processes, once the technologies are sufficiently developed.

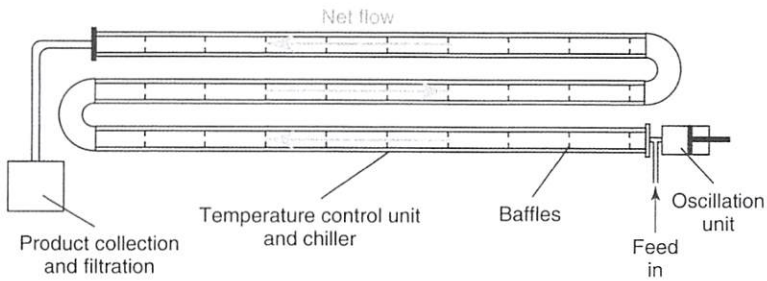

Figure 7.11 Schematic illustrating the construction of industrial-scale COBC devices.

7.3.2.1 Continuous Oscillatory Baffled Crystallizer

The COBC consists of a continuous cylindrical tube or column with baffles periodically spaced along the inside walls. The solution is oscillated axially by means of a diaphragm, bellows, or pistons at one or both ends of the tube. The sharp edges of the baffles are positioned transverse to the oscillating flow of the liquid. On the upstroke the liquid passing through the baffles forms vortex rings and on the downstroke, these rings are swept into the bulk and unraveled (Figure 7.12).

The generation of these eddies in the cells allows for very uniform mixing throughout the column. The mixing can be controlled so that plug flow conditions can be achieved even at low flow rates, that is, radial mixing is uniform and axial dispersion is at a minimum. This also allows for very precise cooling profiles along the length of the reactor. Being able to exercise such precise control over crystal growth conditions therefore allows for the development of processes capable of producing very consistent products in terms of crystal morphology and quality. The quality and consistency of crystals produced in a COBC is enhanced over batch crystallizers, and the particle size can also be altered through altering the oscillation velocity or changing the baffle set-up, that is, the spacing between the baffles or the size of the baffles.

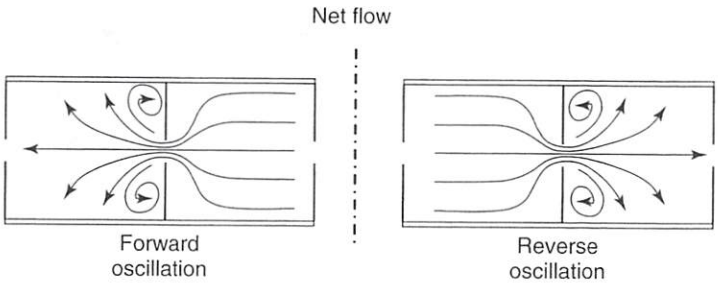

Figure 7.12 Mixing mechanism in an oscillating baffled cell, showing the characteristic eddies generated in the reaction mixture.

Having already highlighted the importance of the relationship between crystal morphology and properties, the benefits of this technology are obvious and it can be used in both cooling crystallization and antisolvent crystallization. Studies of this technology using paracetamol show that the product recrystallized from a COBC is of much better quality than that from conventional methods [22]. Studies of L-glutamic acid have also shown that precise selective polymorph formation can be achieved by altering the solution concentration, and the crystal size can also be varied by altering the cooling rate [23]. These studies emphasize the value of the technology in developing processes for precise morphology control of active pharmaceutical ingredients (API s) and other materials, and in offering significant advantages in terms of process, operation, and cost [24].

7.4 Process Control of Crystallization

Despite the important role that crystallization has in process control and in determining solid-phase outcomes, until recently, understanding and controlling crystallization phenomena has often been neglected in the pharmaceutical industry (and others), only becoming a significant consideration when problems in manufacturing or processing were encountered [5]. Now, however, the realization that understanding and control of this critical phenomenon is vital, has led to a dramatic increase in awareness and the development of advanced techniques for crystallization process monitoring and control.

There has been significant development of *in situ* techniques for monitoring crystallization processes that do not require sampling and give real-time data analysis, such as attenuated total reflectance – ultra violet (ATR-UV), FBRMs and attenuated total reflectance – Fourier transform infrared (ATR-FTIR), and techniques such as dynamic light scattering (DLS) to allow particle sizing during the crystallization process. These techniques are discussed in Section 7.6 below; here we discuss the parameters that are often essential to control during crystallization processing.

7.4.1
Crystal Growth Rate and Morphology Control

Modifying crystal growth processes using additives is a well-established approach, with additives of two forms – the predominant inhibitors and the lesser known promoters of crystal growth. The principles of additives are very well established, with many naturally occurring materials being constructed in this way; for example, the area of biomineralization where inorganic structures are controlled by organic materials. The additive design allows the control of crystal growth rates and the control of morphology by selective inhibition (or enhancement) of growth of selected faces. These techniques can, of course, also often result in interesting hybrid materials that are of less interest in a process environment [25].

The solvent also has a strong influence on the habit of crystalline materials, with an important role played by the surface chemistry; models describing the effect of solvent–surface interactions in enhancing or inhibiting crystal growth have been developed [26–30]. This surface chemistry also has, of course, implications on the effects of "tailor-made" additives as discussed above [31]. The interplay between solvent–surface interactions, additives, and their implications for the effect of solvent on crystal growth and morphology have been discussed [32].

7.4.2
Particle and Crystal Size

Crystal growth is based on the principles of precipitation, and control and monitoring of the shape and size of the growing particles is vital in controlling the properties of the resultant product. Consideration of particle morphology and size distributions is important both in laboratory and industrial environments, and in considering the implications for process control, understanding these factors in industrial reactor environments is important [33].

During crystallization processes, it is possible to manipulate the growth of individual microscopic particles to exercise control over the overall dimension to which these are likely to grow under set crystallization conditions, and also the morphology of these, for example, through the introduction of tailor-made additives. As mentioned above, these alter molecular recognition and can reduce the growth rate of a specific face, offering control over of both shape and size of the final crystalline product. Particle sizing is frequently carried out using DLS (see below), while recent developments in on-line methods for characterizing particle shape and size during crystallization process allow the design and optimization of crystal shape control within crystallizers [34]. In a similar vein, the principles of crystal engineering, including multicomponent crystallization, can also be effective in offering routes to the control of crystal habit and particle morphology and ultimately an improved solubility and dissolution rate [35].

In addition to the usual thermodynamic variables discussed above, and together with effects such as rector design (affecting flow conditions, agitation, etc.), ultrasound has also been found to be an effective way of controlling particle and crystal size in "sono-crystallization" processes [36].

7.4.3 Crystal Purity

In many cases, the phase compositional purity of a single crystal – and its mechanical perfection – can be important for applications. However, in many other situations, impurities at the microscopic level can be vital to allow the material to function. Introduction of these so-called defects into crystalline materials is an important aspect of materials design that is most often carried out under carefully controlled crystallization conditions. However, the incorporation of impurities, whether by intent or not, can also be discussed in the context of process crystallizers, with, for example, the effect of crystal surface roughness on adsorption of impurities during the crystallization of sucrose in a fluidized bed crystallizer and in a batch crystallizer [37]. In situations such as these, the impurity adsorption is growth rate dependent and is strongly influenced by the crystal surface properties, with high surface roughness correlating with lower impurity adsorption.

7.4.4 Composition Control (Cocrystallization)

Cocrystallization is a method for controlling crystallization that has gained increasing interest recently. The technique offers the potential for control of the physical properties of crystalline products that is of great interest. For example, in the pharmaceutical industry, favorable physical properties of a pharmaceutical cocrystalline material, such as solubility, can be designed to be more favorable for drug products than the pure material. In addition, cocrystallization – multiple component crystallization – can drastically affect both the thermodynamics and kinetics of crystallization processes, and offers a further dimension to the variables to be optimized during the process of obtaining a desired crystallization product, on which systematic investigations have been carried out in a range of studies [38].

These considerations are important, as the increasing prevalence of poorly soluble drugs in development can cause problems with bioavailability, particularly for orally administered drugs. Although a range of methods has been implemented for enhancing the bioavailability of drugs with low aqueous solubility, these do not guarantee success [35]. Techniques such as cocrystallization – an example of an application of the growing field of "Crystal Engineering" – offer an alternative route to addressing these issues. A further potential advantage of cocrystallization methods is that derivatization of APIs (or indeed materials in general) through noncovalent interactions is considered a greener approach than making and breaking covalent bonds as it minimizes the formation of by-products. The potential number of true cocrystals for a given API also far exceeds that of salts due to the

relatively low number of acceptable counterions when compared with the large number of cocrystal counter molecules that would be acceptable. Pharmaceutical cocrystals therefore represent a broad patent space and have broad scope for "noncovalent derivatization" without compromising the structural integrity of the API and thus, possibly, the bioactivity.

7.4.5
Polymorphism Control

Many organic molecules are emerging as having many crystalline forms, including polymorphs and solvates, as more techniques are being used to generate and characterize the organic solid state. The fundamental scientific and industrial interest in controlling crystallization and polymorph formation has inspired a very substantial research effort on this area, which has at its heart experimental methods for comprehensive polymorph screening, involving crystallization and characterization methods outlined above. Most new solid-form materials are now subjected to full polymorph, salt and solvate screening, for reasons both of ensuring sample purity, selecting the most effective formulation, and allowing for patent protection of discovered materials. Computational methods are also under development as an intended complement to these experimental investigations [39].

The identification of polymorphs is critical, but once discovered, and with a given polymorph being desired for a particular application of the molecular material in the solid state, the ability to control polymorph formation becomes vital. This control can take the form of careful choice of solvent, temperature, crystallization regime, and the judicious choice of additives in appropriate cases. Seeding is also regularly employed, particularly for high-volume polymorph selection in batch crystallization processes [40].

7.5
Analytical Techniques for Product Characterization

As outlined above, increasing in-line "*in situ*" analytical techniques are being implemented in the monitoring of crystallization processes, allowing real-time intervention and control over the process. These include methods based on ATR and DLS. The analytical techniques discussed here can often be used both on-line and off-line, and methods for implementing more on-line solutions are being developed continuously. In any case, following recrystallization to produce a solid, often polycrystalline, sample, it is vital for product control and for the understanding of the process involved to undertake a series of characterization experiments using a wide range of analytical techniques, including thermal methods such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), various spectroscopies including infrared spectroscopy (IR), X-ray powder diffraction (XRPD),

SEM, and a range of light scattering and optical methods including DLS and low angle laser light scattering (LALLS). Some of these are also outlined here.

7.5.1 Focused Beam Reflectance Measurements and Attenuated Total Reflectance Ultra Violet

The theory of ATR is based on light passing from a material of high refractive index, for example, a crystal, to a material of lower refractive index, for example, a solution. Light travels to the reflection surface and can be partially absorbed by the solute before being reflected back to the probe. The reflected light is therefore attenuated, causing a measurable reduction in the output signal dependent on the absorbance of the solution [41]. Each probe has two fiber optic cables, one for transmission of the light from the light source to the measuring head of the immersion probe, and the other for conducting the signal, which is the light that has passed through the sample and back to the spectrophotometer. ATR-UV probes are suitable for the direct measurement of strongly absorbing solutions in which the UV absorption of the solvent does not mark the solute absorption.

The main advantage of using an ATR-UV probe for measuring solubility and crystallization in solution is that no sampling is required and that this is a real-time process. Other advantages are that the probe is relatively insensitive to the presence of particles in solution as the probe is based on surface measurements and it is suitable for an easy setup. However, in deciding to use the ATR-UV probe, it must also be considered whether the solute has a significant UV absorption compared to the solvent in which the process is carried out so that it can be measured in the presence of the solvent. The UV absorption of the solute is directly proportional to the concentration of the solution according to the Beer–Lambert law and therefore provides a convenient method for accurate *in situ* real-time measurement of solute concentration when compared to other techniques. This process comes into its own during cooling crystallization processes, enabling a significant solubility profile to be compiled from solubility to crystallization.

ATR-UV can also be used in connection with FBRM. FBRM uses a highly focused laser beam projected through the sapphire window of the FBRM probe to rapidly scan over a small region. The beam is rotated at a fixed high velocity, allowing rapid scans across particles flowing across the path of the beam. This high-speed scanning movement of the beam is significant as this means that the motion of the particles is insignificant. A particle entering the beam path produces back-scattered light, which is picked up by a stereoscopic system. The crystal continues to backscatter light until the beam reaches the other edge of the crystal. The time period of backscattering is recorded and multiplied by the scan speed of the beam to give the distance between one edge of the crystal and the other; this is known as the *chord length*. These chord lengths that are measured are profiled in a chord length distribution (CLD) plot. FBRM has been used to measure solubility and MSZW for potash alum using a ramping method.

7.5.2 Dynamic Light Scattering

DLS can be used for measuring the size and size distribution of molecules and particles in the submicron region, down to ~1 nm, with obvious applications in the understanding of the particle formation and association that underpins crystallization processes. The technique is based on the interaction of an incident beam of laser light with particles that are intrinsically in motion through the Brownian motion indices by their collisions with solvent molecules that are moving due to their thermal energy. In such a situation, the fluctuation in the light scattered from the particles changes depending on the amount of motion of these particles, and hence on their size, since smaller particles will be affected more by the Brownian motion of the surrounding solvent. The particle size is extracted from such experiments using the Einstein–Stokes relationship for the diffusion constant:

$$D = \frac{k_B T}{6\pi\eta r}$$

where η is the viscosity, and r the radius of the spherical particle, which is valid in regions of low Reynolds number, where the viscous forces dominate over the inertial forces.

The particle dimension measured in DLS experiments is the hydrodynamic diameter as it refers to particle diffusion in a fluid. As can be seen from the above equation, the dimension obtained is that of a sphere with the same translational diffusion coefficient as the particle being measured. This interpretation is thus an approximation, as the diffusion coefficient will depend not only on the diameter of the scattering particle but also on other effects such as surface structure, charge, and so on. The particle sizes extracted from DLS experiment, however, are extremely useful in many contexts and are widely applied.

7.5.3 Ultrasound Methods

High-frequency ultrasound has a wide range of applications in science, medicine, and industry, including in crystallization and materials processing. Waves of high-intensity ultrasound generating cavitation effects in liquids locally – the formation of small vacuum bubbles or voids in the liquid – leads to extreme nonuniform effects in temperature and pressure, and also mechanical effects due to acoustic cavitation. These effects can be used in processing, where their influence on particle surfaces and collisions and local mixing and milling effects can be used in the control of crystallization [42].

7.5.4 X-Ray Methods

XRD is the definitive method for determining the structural characteristics of the materials formed during crystallization processes. XRD techniques are based on

the fact that when a beam of X rays is passed through a crystalline material, the beam is scattered by the electrons of the atoms in definite directions with varying intensities. This process is called *diffraction* and the scattered rays can be recorded with a detector giving a pattern reflective of the symmetry of the unit cell of the crystalline material or materials present, their atomic composition, and the positions of the atoms and molecules in the unit cell. There are two major techniques used in XRD studies in crystallization science, powder X-ray diffraction (PXRD) and single-crystal XRD.

When a crystalline material is produced from a crystallization process, it is frequently in the form of polycrystalline material. These so-called powder materials consist of a large collection of very small crystallites, which lead to diffraction patterns that are ideally suited to rapid identification. PXRD is primarily used for identification of new cocrystals and/or phases, although full structure determination is possible in some cases. In this method, the polycrystalline sample is loaded into a thin capillary or on a flat plate. The sample holder is placed in the X-ray beam on a powder diffractometer and the diffraction pattern collected as a function of scattering angle 2θ. In the case of a capillary mounted sample, the holder is rotated to minimize preferred orientation effects. The polycrystalline nature of the sample material means that, instead of a pattern of discrete spots, as is produced with a single crystal, a pattern of concentric rings is produced. As the powder contains randomly orientated polycrystallites, each individual crystal generates each Bragg reflection at the same Bragg angle but is diffracted in a different direction. The diffracted beams are measured by a detector and the intensity is recorded as a function of angle for each reflection, that is, a cross section through the rings. Figure 7.13 shows how the powder diffraction pattern (Figure 7.14) is built up.

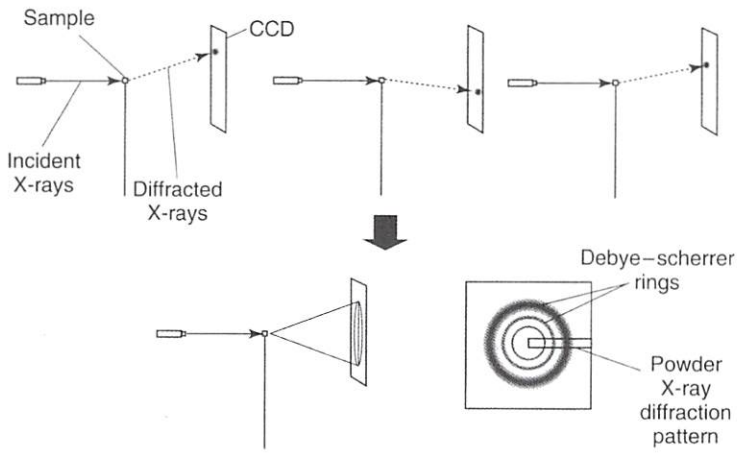

Figure 7.13 The principles of powder diffraction and the construction of Debye–Scherrer rings from a polycrystalline sample containing many tiny crystallites in random orientations.

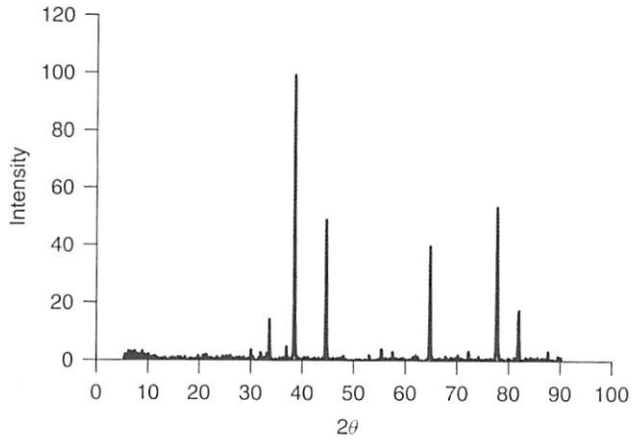

Figure 7.14 Typical X-ray powder diffraction pattern of intensity versus 2θ.

This technique is ideally suited to the rapid identification of crystalline phases present in the product sample, and modern high-throughput PXRD techniques, including instrumentation to allow automated multiple sample data collections, such as the Bruker General Area Detector Diffraction System (GADDS) system, that allow tens to hundreds of samples to be analyzed in a day. The technique is nowadays utilized together with sophisticated software for phase analysis including powder profile analysis software (Rietveld), extensive database of powder patterns International Centre for Diffraction Data Powder Diffraction File (ICDD-PDF), and multiple sample recognition software (PolySNAP). It allows almost on-line analysis of outputs including identification of new phases, polymorph identification, detailed quantitative analysis of crystalline and possible amorphous phases present, and subsequent analysis of any new phases synthesized in the crystallization process.

In the more specialist cases, particularly in the discovery aspects of crystallization process development, full characterization of new phases depends on the determination of crystal structures. For this, although high-resolution PXRD is sometimes able to allow for full structure determination, single-crystal XRD is the technique of choice. Provided that a single crystal of sufficient size can be obtained (for modern CCD-based diffractometers, this is typically 0.1 mm sized crystals), a full 3D diffraction pattern can be measured and, from measurements of the intensities of the reflections, the molecular and crystal structure can be routinely obtained, allowing full definition of molecular geometry and analysis of the interactions controlling the formation of the crystal structure.

7.5.5 DSC/TGA

DSC is a thermoanalytical technique, which is routinely used in the identification and characterization of crystalline materials, including multiple-component crystals and polymorphs of materials. The method is based on the principle that a change

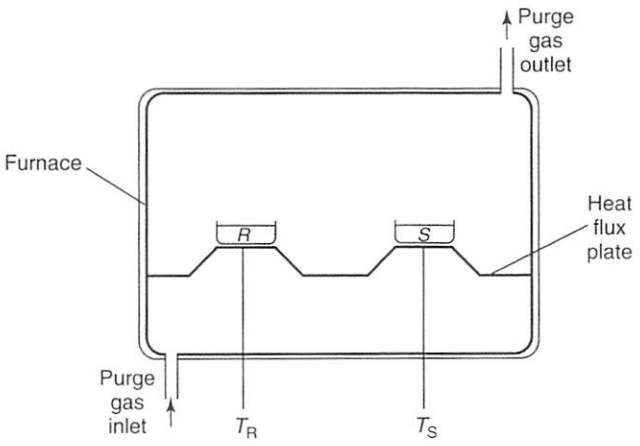

Figure 7.15 Schematic view of the setup for carrying out differential scanning calorimetry (DSC).

in the physical state of a material is accompanied by the liberation or absorption of heat. In practice, it is used to measure the heat energy necessary to establish a near-zero temperature difference between a substance and an inert reference material, as the two specimens are subjected to identical temperature regimes in an environment heated or cooled at a controlled rate. One of the common analysis methods used in DSC is heat flux DSC, in which the sample and reference are enclosed in a single furnace and connected by a low-resistance heat-flow path (Figure 7.15) with a purge gas flow for efficient heat transfer and removal of volatiles.

As the temperature is changed in a linear manner, any heat changes in the sample result in a difference in the energy needed to maintain the sample and reference at the same temperature. As they are in good thermal contact, any excess heat energy will flow into the metallic disc and this heat flow is measured as it is directly proportional to the small temperature difference between the sample and the reference. This technique is used to observe phase transitions, polymorphs, and new phases in the materials resulting from crystallization processes as they undergo heating or cooling, as endothermic processes such as melting will result in a negative heat flow, whereas exothermic processes such as crystallization will result in a positive heat flow (Figure 7.16).

TGA can be used to monitor weight changes as the sample is heated up toward the melting point. The TGA instrument typically consists of a high-precision balance with a typically platinum pan. Once loaded with the sample, the balance is placed in an oven with thermocouples allowing for accurate temperature reading. On heating, the weight of the sample is recorded as a function of the temperature, with weight loss correlated with change in sample composition, for example, a dehydration step in which solvent water was vaporized would result in large weight loss. In many cases, combined DSC/TGA is used for sample analysis, the complementary information available from the two techniques offering further insights into sample behavior.

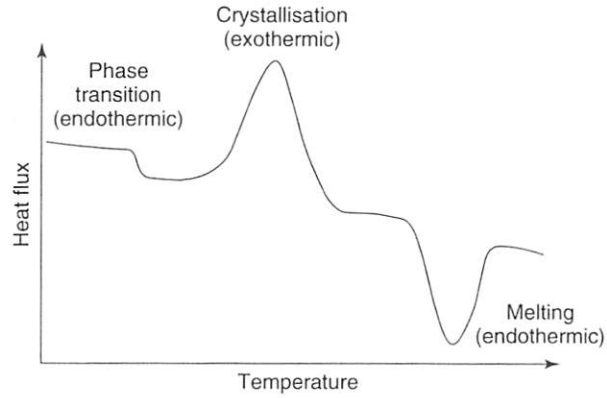

Figure 7.16 Example of a DSC trace exhibiting endothermic and exothermic processes.

7.6 Conclusions

It is clear that the importance of crystallization in manufacturing and processing is set to increase in the next few years, traditional batch crystallization methods being joined by a much enhanced emphasis on continuous and flow processing, facilitated by technological developments especially in automated control systems with multiple feedback routes from sensor arrays. Such moves to more dynamic crystallization environments make it still more important that both the fundamentals of the crystallization process and the translation of these into scaled-up environments are fully understood. A battery of process technologies and analytical techniques are available to the researcher, process engineer, or manufacturer in this area, and with the help of these techniques and the associated understanding of the fundamentals, a rational and rewarding approach can be taken to developments in this area.

Acknowledgments

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