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Organic crystallization processes

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Abstract

Crystallization has been the most important separation and purification process in the pharmaceutical industry throughout its history. Many parallels exist in the fine chemicals industry also. Over the past several decades the study of crystallization operations has taken on increasing levels of importance because of several factors that require effective control of crystallization processes. These levels of control require better understanding of the complex interactions of nucleation and growth as well as the operating characteristics of crystallization equipment including the critical issue of scale-up.

In the pharmaceutical industry, the issue of better control, desirable in and of itself, is reinforced by the need to satisfy both company internal and governmental regulatory authorities on the consistency of chemical and physical properties of active pharmaceutical ingredients (APIs). Control of crystallization operations and choice of equipment both for pilot plant and manufacturing are thereby critical. The objective of this paper is to summarize the critical issues that must be addressed in order to achieve this level of control.

Keywords: Crystallization; Nucleation; Growth

1. Introduction

Crystallization has been arguably the most important separation and purification process operation in the pharmaceutical industry throughout its history. Many parallels exist in the fine chemicals industry as well. In the past one to two decades, the study of crystallizer operation has taken on even higher levels of importance because of several critical factors that require increased control of crystallization processes. These higher levels of control cannot be achieved without increased levels of understanding of the fundamentals as well as the operating characteristics of crystallization equipment, including the critical issue of scale-up.

The issues that require increased control include the following: (1) purification of final bulk drug substances to lower impurity levels than were historically measurable, (2) increased control of the physical attributes of the bulk drug substance to meet formulation needs for reproducibility and bioavailability, (3) achievement and maintenance of chirality, (4) achievement and maintenance of morphology, (5) processing of increasingly complex molecular structures with higher molecular weights, (6) achievement of bulk drug solid stability by control of crystal growth, and (7) precipitation of macromolecules in the biotechnology sector.

Added to this list is the assertion, based on operating experience, that crystallization is difficult to scale-up without experiencing changes in physical attributes and impurity rejection. When scaling from pilot plant to manufacturing, it is now necessary to meet the regulatory requirement that final bulk drug substance at both scales must now duplicate several physical attributes, including particle size distribution, bulk density, and/or surface area within narrow ranges. This places great demands on the development of the crystallization process and the design of equipment at all scales of operation.

2. Nucleation versus growth

Control of crystallization processes requires control of either nucleation or growth, or, as is most often the case,

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both modes of crystal development simultaneously. Each operation must be evaluated to determine which of the process objectives is the most critical, to determine whether nucleation or growth should be the dominant phase. Much of the literature is focused on nucleation, for the obvious reason that the number and size of nuclei initially formed can dominate the remainder of the operation. However, it is generally agreed that nucleation can be difficult to control, since there are several factors that can play a role in the conditions for nucleation onset, nucleation rate, and number of crystals generated before growth predominates.

The demand for increasing control of physical attributes for final bulk pharmaceuticals has necessitated a shift in emphasis from control of nucleation to control of growth. This trend is also finding application for control of purity in both intermediates and final bulk products. The obvious critical factors then become seeding and control of supersaturation, where supersturation (S)=actual concentration/solubility=(C)/C*.

Quantitative evaluation of these factors is essential for development of a scaleable process. Much of the discussion to follow is focused on the growth process and methods to minimize nucleation.

3. Nucleation

In the absence of control of supersaturation, nucleation will usually predominate. When nucleation does predominate, the outcome is dependent on the number of crystals formed. As discussed below, this control may be exceedingly difficult to achieve at any scale, and particularly difficult to reproduce upon scale-up, often because of mixing issues.

A specific crystallization can be dominated by either nucleation or growth, depending on how the critical variables are controlled, the amount of seed, the size distribution and surface qualities of the seed, and the environment in which supersaturation is created. Both nucleation and growth virtually always proceed simultaneously. In general, nucleation will dominate when supersaturation, either local or global, is near to or greater than the upper limit of the metastable region (Fig. 1). Growth

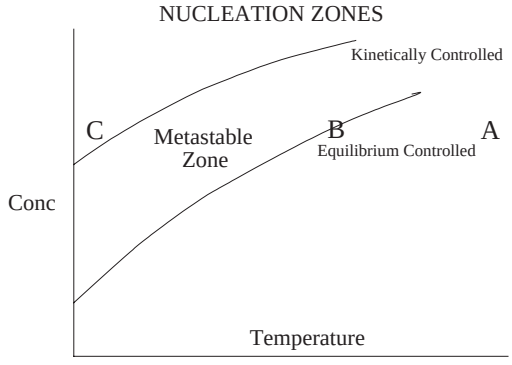

Fig. 1. Metastable zone.

can dominate at low supersaturation and in the presence of sufficient crystal surface area. Both inherent nucleation rate and growth rate of the specific compound also play a major role in determining the dominant mechanism.

In some cases, a process that is dominated by nucleation can result in an acceptable process outcome. The process may appear satisfactory in laboratory scale operation. However, there are several potential problems with a nucleation-driven process upon scale-up, including:

fine crystals and/or wide particle size distribution (PSD);
high surface area;
low bulk density;
the risk of large batch-to-batch variation;
occlusion of solvent and impurities;
agglomeration/aggregation; and
lack of control of hydrates, solvates, and polymorphs.

In addition, scale-up of a nucleation dominated process is difficult to predict unless the generation of supersaturation is well controlled. The difficulties associated with stirred-batch crystallization scale-up relying on nucleation were highlighted by Nyvlt [1, p. 111] and discussed in Myerson [2, p. 239], the latter in a section describing why external seeding might be preferable. As noted by Nyvlt,

"Its difficulties are the comparatively large amount of manual labour involved, and as a rule, a not very high degree of reproducibility of product quality. The product quality suffers mainly because the rate of supersaturating in the stage following introduction of a new batch is excessive, so that a large number of nuclei form in a rather uncontrolled manner. These cannot subsequently grow into large crystals. The product is, therefore, fine-grained, with the attendant difficulties of filtering, centrifuging, and washing. It retains an appreciable amount of impure mother liquor, dries badly, and tends to cake in storage."

In the case of extremely high nucleation rate, the degree of control required to prevent formation of the large number of nuclei, as noted by Nyvlt above, may not be achievable in a stirred vessel, in part because of the inherent properties of the compound and/or because of mixing scale-up issues. Extreme examples of this are found in ionic reactions to precipitate inorganic salts. Organic acid–base reactions can also generate nuclei at high rates. An in-line type crystallization may be required for anti-solvent and/or reactive crystallization both of which may be dominated by nucleation in the absence of strategies to promote growth.

Nucleation must also be minimized by tight control of supersaturation in processes involving resolution of optical isomers and, in some cases, of polymorph formation depending on the zone of stability of the operation.

4. Nucleation rate

The nucleation rate is both species specific and a function of supersaturation ratio. The relation between nucleation rate, growth rate, and particle size is a function of supersaturation ratio. The actual rate and supersaturation characteristics are system specific and can vary over exceedingly wide ranges.

In addition, for a specific compound, the nucleation rate is also dependent on the solvent(s) system, impurity levels, and mixing. These factors combine to cause the extreme difficulties that are often encountered in controlling a nucleation based crystallization process, especially on scale-up.

5. Growth

When crystal growth is desired, tight control of several variables may be required. The outcome is species dependent, however, and in some cases growth may not be achievable because of the inherent growth rate or morphology. Nucleation followed by growth on a large number of nuclei may then predominate thereby limiting the ultimate particle size as discussed below in the section on seeding. The type of crystallization equipment selected plays a key role.

Benefits from operation under conditions in which growth predominates include:

large, three-dimensional crystal product for facile downstream operations: filtration, washing, drying;
predictable dry solid flow characteristics;
control of polymorphs; and
resolution of optical isomers.

6. Growth issues

A growth dominated process may have several advantages, including:

improved control of PSD;
larger average particle size;
lower surface area;
higher bulk density;
improved solvent/impurity rejection;
improved control of hydration, solvation and polymorphs;
decreased sensitivity to mixing;
improved reproducibility on scale-up; and
adaptability to continuous operation.

Control of supersaturation is the key to successful crystallizer operation. The local and global supersaturation ratios that are experienced over the course of a crystallization operation are critical because they determine the balance between nucleation and growth not only at the onset of crystallization but throughout the course of a batch or semi-batch operation. This balance, in turn, determines the resulting physical properties and, in many cases, the distribution of chemical impurities between the crystals and the liquors.

7. Growth rate

The factors influencing the crystal growth rate of a specific compound are discussed by Myerson (2002, p. 80ff). In addition to molecular structure and the solvent system, the growth rate can be greatly modified by the presence of dissolved impurities that may either compete for growth sites or block these sites. As with nucleation rate, these differences can be so extreme as to make growth impracticably slow, or in the opposite extreme, the rate may be sufficient to achieve an essentially all growth process with careful control of supersaturation and growth area.

Supersaturation has an important effect on growth rate. However, if an essentially all growth process is desired, the increased growth rate that can be achieved at higher supersaturation may come at the expense of increased nucleation, leading to broader PSD and possibly bimodal distribution.

In design of a crystallization process, therefore, the balance that is achieved between nucleation and growth rates is critical to particle size. Supersaturation ratio can be controlled to limit nucleation in order for growth to predominate. This becomes increasingly difficult at lower inherent growth rates.

Impurities can have a large effect on growth and can dominate the course of a crystallization in the following ways:

They can retard nucleation rate leading to high supersaturation before ‘oiling out’ and/or ‘crashing out’.
They can retard or stop growth.
They can co-crystallize and/or form solid solutions.

Experimentation is required to evaluate these affects. One useful technique is to spike with known impurities when they can be isolated for this purpose. However, as is often the case, the number and possibly low concentration of impurities often make this impractical. An experimentally simpler method is to re-crystallize the compound with and without spiking of the mother liquors obtained from the process isolation.

Differences in nucleation and growth may be observed by such techniques as in-line particle size/particle count and concentration measurement, but if these are not available, much can be deduced by comparing photomicrographs of the resulting crystals. Both size and shape can be expected to be affected. If no significant differences are observed, the impurities from the process may not cause any nucleation or growth changes and the inherent properties of the compound may be assumed to prevail.

8. Agglomeration and aggregation

One mechanism for agglomerate growth is attributed to growing nuclei colliding and becoming 'cemented' together by continuing growth between two or more crystals. Although simultaneous collision of more than two particles is not statistically important, the addition of a large number of nuclei to an original two-crystal agglomerate can readily occur by ongoing collisions leading to very large agglomerates.

Several investigators have developed models for the effectiveness of collisions that lead to agglomeration. This complex interaction of hydrodynamics and surface chemistry is difficult to predict or describe but can be critical to the successful operation and scale-up of a crystallization process. In particular, for reactive crystallization in which high supersaturation levels are inherently present, agglomeration is very likely to occur as the precipitate forms. Careful control may be necessary to avoid extensive agglomeration.

The difficulties that can result from agglomeration include:

entrapment of solvent and/or impurities in the crystal mass;
reduced effective surface area for true growth;
subsequent break-up of agglomerates into small crystals that were captured during nucleation without opportunity for growth;
difficulties in downstream processing because of these small crystals; and
friability during dry processing (drying, solids transfer) leading to changes in PSD.

For these reasons, agglomeration is generally to be avoided. The use of additives (Myerson, 2002, p. 255ff) may be considered for suppressing agglomeration. However, the use of additives in the pharmaceutical industry–particularly for final products–is generally not considered for regulatory reasons, barring extreme need.

There are operations, however, which may intentionally generate agglomerates for a particular purpose (example: granulation processes for pharmaceuticals). These phenomena are also described as flocculation and/or coagulation. However, purposeful generation of these clusters is beyond the scope of this discussion.

9. Minimization of agglomeration

The primary process variables that can be manipulated to minimize agglomeration include:

operation within the metastable region;
controlled rate of supersaturation generation;
removal of crystallization inhibitors from the feed stream;
appropriately high seed levels;
solvent selection; and
mixing conditions.

Both the formation and disruption of agglomerates are functions of mixing conditions and local shear. The reader is referred to the detailed treatment by Mersmann and Braun [3, p. 235ff] in their chapter on 'Agglomeration' for a comprehensive analysis of the forces involved in these phenomena. This discussion includes the distinction between attrition and disruption that are both functions of mixing. Disruption refers to break-up of agglomerates that formed under conditions of low supersaturation that can be broken because the binding forces are small. Agglomerates that are formed under conditions of high supersaturation are much stronger and not as subject to disruption by typical mixing conditions. Attrition refers to break-up of large primary crystals that were formed by growth at low supersaturation and is a function of local shear and crystal shape.

10. Seeding

The influence of seeding on crystallization is often critical to control of a process and the importance of a well developed seeding strategy cannot be over-emphasized. While some systems will and do nucleate spontaneously, control of a process, especially on scale-up, that depends on spontaneous nucleation can be subject to extreme process variation (discussed previously) for several reasons including:

presence or absence of seed particles and/or foreign particles from a previous batch;
differences in concentration of impurities from batch to batch that can affect nucleation rate;
differences in the rate of generation of supersaturation from batch to batch;
differences in concentration of solute from batch to batch;
differences in mixing scale-up; and
local conditions in the crystallizer such as wall temperature, anti-solvent addition point, and evaporation rate.

The importance of seeding has been underscored by several authors, including Mersmann [3, p. 410ff], Mullin[4, p. 197ff], and Myerson (2002, p. 256ff). Mullin, in particular, discusses the many ways it is possible to unintentionally seed a crystallization process, with (usually) undesirable effect on the operation.

The effectiveness of intentional seeding is dependent on size and number. In some cases with low level seeding, larger particles can be more effective than small ones. The reason is that low level seeding requires subsequent secondary nucleation, and large particles can generate more secondary nuclei because of greater contact probabilities

and collision energies. Small crystals generally follow the streamlines within the turbulent eddies and have little contact with other crystals. In addition, when smaller than 10 μm, their growth rate may be slower than larger crystals.

Unintentional seeding can result from dust and foreign solid particles in the crystallizer and can occur both in the laboratory and in manufacturing. A particularly uncontrollable form of unintentional seeding can be caused by seeds in the dust around operations. Many stories may be found in the literature about crystallization of new polymorphs, hydrates, or solvates after long periods of operation in which only one form had been obtained. Companies in the pharmaceutical industry are now exerting considerable effort up-front to screen for polymorphs to reduce the risk of finding new forms late in development.

Although providing no guarantee of successfully avoiding these issues, the methods of using large amounts of intentional seeds and at low supersaturation can provide the most protection against unintentional seeding by providing a growth on seed environment. Additional safeguards can be provided by 'clean-room' type environment in closed systems.

11. Determination of seed quantity and size

At the conclusion of a crystallization operation, the number and size of the product crystals will be primarily determined by the number and size of the following:

nuclei generated initially;
nuclei generated during the course of the operation (e.g. by energy input of mixing, local regions of high supersaturation);
fragments of crystals generated by attrition during the operation;
Ostwald ripening, growth dispersion, and size dependent growth; and
seed added at the outset.

Of these critical factors, the one that is most subject to pre-determination and control is the seed added at the outset. The following offers guidelines on effective seeding strategy and methods.

Methods for calculation of an adequate amount of seed are presented below starting with general guidelines and followed by more quantitative approaches.

12. Seeding guidelines

Four levels of seeding can be categorized depending on the purpose of seed addition as follows:

'Pinch', to hopefully avoid 'oiling out' and/or uncontrolled nucleation, 'crashing or snowing out'. May be satisfactory in the laboratory but rarely effective or reliable on scale-up. This level of seeding is employed by necessity early in development when material is limited.
Small (<1%), to hopefully aid in more controlled nucleation but not adequate to achieve primarily growth on scale-up. Subject to additional nucleation and bimodal distribution of the product.
Large (5–10%), to improve the probability of growth with the possibility of preventing further nucleation and bimodal distribution.
Massive (the seed is the product in a continuous or semi-continuous operation), to provide maximum opportunity for all growth. Seeding with "heel" (usually conditioned) from the previous batch is generally in this category.
The amount of seed can be critical in control of enantiomer separation and selection between polymorphs and hydrates/solvates. In these applications, nucleation must be prevented to achieve growth of the desired product under conditions in which the undesired isomer/polymorph/hydrate/solvate could nucleate.
It is best to provide seed particles which are unagglomerated and are already wetted by the liquid. Feeding as a slurry or previous batch "heel" is more desirable than dried/milled solid for this reason.

13. Estimation of seed quantity

Necessary seed quantities to achieve specific amounts of particle size increase in an all-growth process can be calculated by a simple algebraic relationship relating seed and product size to the amount and particle size of seed to be added.

i.e. if using 10% seed, 10 μm, all three-dimensional growth, will yield 21.5 μm product, or
if using 1% seed, 10 μm, all three-dimensional growth, will get yield 46.4 μm product.

The 1% seed sounds great but may not provide enough growth surface to prevent secondary nucleation as crystallization proceeds and will then get smaller average d_p and larger PSD.

Perhaps worse yet, can get bimodal distribution. Microscopic examination of the crystals dictates whether growth is predominantly linear (thin needles), surface (plates) or volume (crystals with significant thickness). Since the validity of this calculation depends on an all-growth process, simultaneous nucleation–that is virtually always present to some degree–will result in a reduction in the actual particle size of the product, as well as in an increase in the PSD. This increase often comes in the form of a bimodal distribution made up of growth on seed and nucleated smaller crystals. This relationship can be useful, in predicting a minimum amount of seed to be required.

Seed quality (unmilled, milled, otherwise preconditioned) can play a role in seeding effectiveness, although stressed

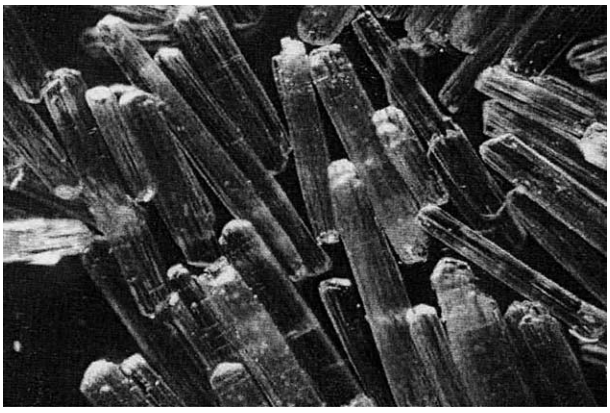

Fig. 2. Large (20×100 micron) crsytals grown from needles (5×75 micron).

particles (from milling) are often well shaped after a brief initial growth period.

In some cases, seeding may not be necessary because the nucleation rate is very slow and the growth rate relatively high thereby allowing growth on a few nuclei without continued excess nucleation. Reliance on this balance of rates on scale-up, however, is extremely risky primarily because the necessary dependence on spontaneous nucleation to start the process is subject to the batch-to-batch variables discussed above.

Figs. 2 and 3 illustrate development of large three-dimensional crystals that can be used as seeds to achieve essentially all-growth processes. In both cases, the initial crystals are long, thin needles (~5×75 μm) that are grown initially in the laboratory and then used for seed in manufacturing operations.

14. Effectiveness of seeding

The effectiveness of seeding is linked to several key factors including the following:

timing of seed addition;
condition of the seed surface;
method of seed addition; and
the rate of generation of supersaturation.

15. Timing of seed addition

The obvious problem of adding the seed before reaching saturation is that dissolution of some or all of the seed may occur. Conversely, adding after reaching saturation may induce nucleation. These difficulties are greatly exaggerated in cooling crystallizations where steep solubility dependency on temperature exists.

This problem can also be severe in evaporative methods, particularly at reduced pressure. For these and other reasons, evaporative methods are considered to be the most difficult for predictable control of final average particle size and PSD on scale-up.

For anti-solvent addition methods, the seed can be added to a small part of the anti-solvent. Seed is added as a slurry as the saturation point is approached. Although some of the seed may dissolve, this technique is considered to be more reliable than adding the seed all at once.

For reactive crystallization, the solubility of the product is usually low, and seed can be added before the operation is initiated without concern for dissolution. However, since this method generally produces the smallest particles and is subject to agglomeration, the effectiveness of seeding is critically dependent on providing sufficient surface area for growth at the outset to prevent nucleation at the high local supersaturation conditions at the point of addition.

16. Mixing and crystallization

The interactions between mixing and crystallization are often ignored, but should not be.

In many cases, these interactions can affect every aspect of a crystallization operation including nucleation, growth, and maintenance of a crystal slurry. To further complicate the problem, mixing optimization for one aspect of an operation may require different parameters than for another aspect even though both requirements must be satisfied simultaneously. In addition, these operations are intrinsically scale dependent.

For these and other reasons to be discussed below, the following statement may be made:

Crystallization may be the most difficult operation to scale-up—successfully.

Successful scale-up implies that both physical and chemical properties have been duplicated between pilot plant and plant operations. These rigid criteria are particularly applicable to final bulk active pharmaceutical products (APIs). In these cases, the width of the PSD, the average particle size, the bulk density, and the surface area may all be required to fall within specified ranges. In all

Fig. 3. Large crystals (b) on right after growth from needles (a) on left.

cases, however, it is prudent to monitor these variables in the developmental stages in order to reduce the risk of a dramatic failure. Examples of failures that could result from scale-up issues are: (1) increased impurity levels, (2) small crystal size causing drastically reduced filtration rates, large PSD including bimodal distribution, and (3) poor washing and slow-drying product.

For final bulk active pharmaceutical compounds, failures could also include physical and chemical properties that result in downstream problems in pharmaceutical processing (e.g. content uniformity, tablet hardness, sticking).

17. Mixing considerations

The following is a brief discussion of mixing issues that can be expected to influence crystallization processes. Extended discussion of these and other mixing topics may be found in several references including Baldgya and Bourne [5], Harnby et al. [6], and Paul et al. [7], as well as the crystallization texts of Mersmann [3], Myerson (2002), Söhnel and Garside [8], and Mullin [4].

Although many variations of mixing systems have been used for crystallization processes, the three primary types are the stirred vessel, fluidized bed, and impinging jet. Each of these utilizes a different mixing environment to achieve the desired local and global conditions.

The predominant system in the pharmaceutical industry is the stirred vessel. Fluid beds and impinging jets fill specific mixing requirements.

Mixing requirements for crystallizers involve the complete range of issues in blending and solid–liquid mixing including:

blending of solution and anti-solvent components to the molecular level to achieve supersaturation;
blending or reagents to the molecular level to achieve reactive crystallization/precipitation;
maintenance of a crystal slurry of the required solid/liquid ratio;
avoidance of entrainment of gas/vapor from the head space;
avoidance of encrustation—solid scale on walls and baffles;
rate of heat transfer;
minimization of secondary nucleation through impact;
avoidance of shear damage to crystals;
effect on agglomerate formation/break-up;
maintenance of crystal slurry for satisfactory discharge of the slurry without excess retention of product crystals; and
possible operation over a wide volume range.

The initial blending of components to the molecular level while avoiding regions of high supersaturation requires consideration of the mesomixing and micromixing environments of the contactor. Other requirements involve the macromixing capabilities of the crystallizer. Extensive discussions of these fundamentals of mixing may be found in the references cited above.

18. Mixing effects on nucleation and growth

The aspects of crystallization that may be affected by mixing are discussed in the following sections.

18.1. Primary nucleation

The effects of mixing on primary nucleation are exceedingly complex. The overall result is a reduction in the width of the metastable region when this width for a static solution is compared to that for an agitated solution. Therefore, an unagitated solution can in general be cooled further before the onset of nucleation than an agitated solution. Since an industrial system with few exceptions will always be agitated, this is of theoretical interest only.

In a mixed solution without crystals present, mixing intensity can change the induction time—the time elapsed after mixing to create supersaturation to the time crystals first appear. The induction time has been reported to decrease with increased mixing up to a critical speed after which it remains unchanged (Myerson, 2002, p. 145).

18.2. Secondary nucleation

Since secondary nucleation is dominant as soon as nuclei appear, the nucleation mechanisms become virtually impossible to characterize in an industrial operation. In addition, any seeded crystallization is by definition secondary even though some nuclei may simultaneously form by a primary or other secondary mode mechanism. Therefore, the major part of this discussion will be on secondary nucleation.

Secondary nucleation is mixing dependent as follows:

Crystal–crystal impact: a function of both the local micromixing environment and the overall macromixing circulation.
Crystal–impeller and crystal–wall impact: functions of the impeller speed, shape of blade, and material of construction.

These factors, along with the other intrinsic nucleation properties of the crystallizing substrate, affect the rate of nucleation, which in turn determines the number of nuclei formed and their size. This complex relationship is extremely dependent on the specific system characteristics but, in general, the nucleation rate increases rapidly with increasing energy input. This high dependence is especially true for reaction crystallization with fast reactions.

The effect of agitation on secondary nucleation has been reported in the literature and several references are discussed by Mullin [4]. The following discussion highlights the complex nature and unpredictability of these interactions.

18.3. Scale-up of nucleation based processes

Nucleation events can dominate the entire crystallization operation with respect to both physical and chemical purity attributes. Since the nucleation rate can often increase on scale-up because all key parameters of mixing cannot be held constant, the resulting average particle size on scale-up could be reduced because there are more particles to grow on but growth will be limited by the amount of substrate remaining after nucleation. In addition, other mixing factors that affect growth could increase the size distribution further as discussed in the section on growth below.

The critical nature of these interactions is the key factor in causing difficulty in scale-up of nucleation based crystallization processes—even with small quantities of seed.

The critical mixing factors are impeller speed and type and their influence on local turbulence and overall circulation. Since all aspects of these factors cannot be maintained constant on scale-up, either locally or globally, the extent to which changes in the crystallizing environment will affect nucleation are difficult to predict. To the mixing issue must be added the uncertainties caused by soluble and insoluble impurities that may be present in sufficiently different concentrations from batch to batch to cause variation in induction time and nucleation rate.

The problems associated with nucleation based operations, some of which are directly caused by mixing issues, leads to the conclusion that dependence on nucleation can only rarely be relied on to achieve reproducible results on scale-up and/or in ongoing production.

If no process alternative exists such that dependence on nucleation can be avoided, mixing scale-up can be based on equal power per unit volume, assuming the same impeller type is used. In most cases, however, this approach will result in changes in PSD on scale-up that may or may not be acceptable. In general, the PSD will be broader and the average particle size will be smaller if this scale-up criterion is used, as suggested by Nyvlt [1]. A further generalization may be proposed that fast nucleating systems tend toward the smaller size distribution on scale-up whereas slow nucleation can give the opposite result.

19. Growth

Mixing can affect crystal growth in several ways as summarized below:

Mass transfer rate in the diffusion film around growing crystals.
Bulk turnover rate and local shear and their affect on minimizing differences in supersaturation ratio throughout the vessel.
Heat transfer rate and wall film thickness.
The effect of shear on crystal breakage.
Dispersion of an anti-solvent or reagent.
Growth rate dispersion.
Maintenance of slurry uniformity.

Mixing can obviously have a large effect on the mass transfer rate to growing crystals through its effect on the film thickness. This influence is dependent on both the size of the crystals and the mixing intensity. As mixing intensity increases, mass transfer rate increases and film thickness decreases up to a limit beyond which the effects approach limiting values.

Large crystals (>100 μm) will be more subject to these film mixing issues than smaller crystals because the crystals less than 10–20 μm are approximating the Kolmogoroff eddy size and tend to follow these eddies with limited mass transfer rates. These differences in crystal size can change the limiting growth rate from film control in large crystals to intrinsic growth rate control in small crystals leading to bimodal distribution. Because of these complex effects of mixing on films, the overall effect of this aspect of mixing is difficult to predict.

20. Conflicting mixing effects

Factors that improve with greater mixing intensity are (1) heat transfer, (2) bulk turnover, (3) dispersion of an additive such as an anti-solvent or reagent, (4) uniformity of crystal suspension, (5) avoidance of settling and minimization of wall scale, and (6) minimization of impurity concentration at the crystallizing surface. Since small-scale experiments inevitably operate with reduced turnover time and thus more passes by the impeller, these runs can sometimes achieve better results than would be expected on scale-up. An effort should be made in small scale to establish mixing sensitivity of the crystallization process.

However, these needs must be balanced against the possibly negative results of over-mixing that can result in crystal breakage and/or shedding of nuclei as well as increased secondary nucleation and growth rate dispersion as discussed above.

These concerns lead to the conclusion referred to above, that it is often necessary to choose a mixing condition (impeller speed, type, etc.) that may not be optimal for every aspect of the crystallization and may actually not be optimal for any of them. In many cases, however, one end result (i.e. PSD, bulk density, uniformity of suspension, approach to equilibrium solubility (yield)) may dictate the choice of mixing conditions. In this case, it becomes essential todetermine if the negative effects can be tolerated.

21. Reactive crystallization

21.1. Introduction

When supersaturation of a crystallizing compound is created by its formation by chemical reaction, the operation is termed reactive crystallization. These operations are also known as precipitation. The products of reactive crystallization are crystalline. The products of the more general term 'precipitation' may be amorphous or crystalline.

The reaction may either be between two complex organic compounds or a neutralization by acid or base to form a complex organic salt. These reactions can be very fast compared to both the mass transfer rates to the crystals and the growth rate of the crystals thereby leading to high local supersaturations and, therefore, extensive nucleation.

In some cases, the fine crystals or precipitates resulting from high supersaturation (often in the range from 0.1 to 10 μm) are desired in order to meet specific needs for downstream processing or formulation. In most cases, however, these fine particles are not desired since they can be very difficult to handle in downstream processing—notably filtration, washing, and drying.

22. Control of particle size

Control of particle size in reactive crystallization is difficult because there is usually no method to significantly slow down the reaction that generates the supersaturation. Traditional methods such as reduced concentration and temperature may help, but the range of improvement may not be significant. The rate of addition of the reagents, however, does provide a means to control supersaturation globally in the reactor but not locally since the reaction may be complete near the point of addition. Successful operation depends, therefore, upon a careful balance between addition rate of the reagent(s), local supersaturation, global supersaturation, mass transfer, and crystal growth surface area.

Controlled supersaturation at the initiation of the addition of the reagent(s) requires an initial charge of seed to prevent uncontrolled nucleation and the resulting creation of an excess number of particles. The seed must be developed in a separate operation because the intrinsic reaction may only generate crystals that are too small to be used as seed if a growth dominated process is required. This issue, and suggested operating strategies, are discussed below.

23. Controlling for growth

23.1. Supersaturation control

Control of both local (point of addition) and global supersaturation is essential, as in all crystallizations, if a satisfactory balance between nucleation and growth is to be achieved. This is particularly relevant to reactive crystallization because of the creation of local high supersaturation of these low solubility compounds that is unavoidable at the point of reaction. In addition to the mixing issues outlined above, the critical variables in minimizing supersaturation are as follows:

Addition time of the reagent—must be long enough to maintain the global supersaturation in the metastable region.
Sufficient initial seed area—to avoid or minimize nucleation at the outset of addition and prevent formation of an excessive number of nuclei which would limit overall growth.
Continuing balance between addition rate and growth surface area—to promote growth and avoid continuing nucleation which would result in bimodal distribution.

24. Seeding

Seeding is the key to achieving control of a reactive crystallization process.

Without seeding, excessive nucleation can be expected in most systems thereby resulting in limitation on the final crystal size by creating an excessive number of particles.

The number, surface area, and surface condition of seed crystals are critical to successful minimization of nucleation and realization of growth.

Recommended seed mean particle size is approximately 1/2 that expected for the final product.

Recommended seed amount is 10–15% (the amount necessary to maximize growth by providing sufficient initial surface area to minimize nucleation).

Recommended method to add seed is in a slurry or as a heel from a previous batch. As noted in the earlier discussion on seeding, drying and milling are not recommended, in large part because of static clumping effects and occasional wetting problems. Wet milling or sonication is recommended between batches to maintain desired seed size as necessary.

Recommended initial seed preparation is by recrystallization from a suitable solvent(s). (Initial preparation by reactive crystallization without seed will typically give seeds that are too small for significant growth in successive use.)

Note: Seed growth by heat/cool temperature cycling is an effective means of growing seeds for initial use. This method is also useful in determining the potential for a particular compound to grow.

The requirement for increased amounts of seed for reactive crystallization compared with the cooling, evaporation, and anti-solvent methods is discussed by Mullin [4, p. 339]. Amounts of seed up to 50% (this is difficult in practise) are indicated to be necessary in recycle systems 'to provide the seed area necessary'. This requirement for this

increased amount is the direct result of the rapid development of supersaturation by reaction and the need to have sufficient surface area for growth throughout the operation and especially at the start of reagent addition.

25. Crystal growth

The first issue with regard to growth is to determine if the compound in question has potential for growth. Growth potential may be very difficult to determine definitively, because of (a) large dependence on impurities, and (b) lack of patience

Once established, growth can be used for initial seed preparation.
Once seed is grown, all crystallizations are started with proper seeds.

Agglomeration and/or aggregation are common in reactive crystallization and should not to be confused with true growth. Secondary growth phenomena can also be expected such as growth rate dispersion and size dependent growth.

26. Addition strategies for growth

For increasing the probability of achieving and maintaining a primarily growth process, the entire operation must be maintained in the metastable region. The three critical factors that can achieve this condition are (1) mixing to minimize local supersaturation at the point of addition, (2) limiting addition rate to prevent buildup of bulk concentration of the reaction product, and (3) sufficient seed surface area. The rates of mass transport through the film surrounding each crystal and the incorporation into the crystal lattice by surface integration reach a balance so that they are essentially equal. The key to successful operation is to maintain the bulk concentration sufficiently low to allow the rate of surface integration to control so that transport through the film does not create a region of high concentration at the surface that could result in local nucleation.

27. Instrumentation

Development programs and plant operations can benefit from instrumentation that is now available for in situ measurement of PSD and imaging of crystals. Focused Beam Reflectance Measurement (FBRM) and Particle Visualization Measurement (PVM) devices (Lasentec) are finding increased use at all scales of operation to follow crystal growth (size measurement) and nucleation effects (particle counts), and other companies are developing systems to make similar measurements.

28. Creation of fine particles—in-line reactive crystallization

In-line methods are applicable to reactive crystallization in systems with relatively fast reaction rate and nucleation induction time. Two in-line devices that have potential for these applications are impinging jets (Fig. 4) and vortex mixers. The application to reactive crystallization is similar—creation of high supersaturation in a short time. One limitation is in the range of flow rate ratios of the reacting feed streams to balance momentum of impact. Although some adjustments in feed tube diameter can be helpful in maintaining the momentum balance by equalizing velocities, the ratio of feed streams may be limited to ~65/35. This limit may be an issue in reactive crystallization applications because the feed streams may have volume ratios of 80/20 or more.

Impinging jets have been studied experimentally for the reactive crystallization of calcium oxalate by Condon [9]. A primary objective of this study was the to determine the capability of this system to produce fine particles. Particles with a mean particle size of 2 μm and particle size distribution of 1–3 μm were obtained. In addition, the effect of jet velocity on mean and PSD was studied, and a correlation in the expected direction of smaller d_p with increased velocity was obtained. This system is complicated by the appearance of two hydrate forms, mono- and di-hydrate. The di-hydrate is favored at higher excess oxalate local concentration while the mono-hydrate is favored at higher excess calcium local concentration. Local concentrations within the device were shown to be possible and to cause a shift in hydrate ratio.

Johnson and Prud'homme [10] have studied the manufacture of nanoparticles stabilized by block copolymers in confined impinging jets. Different geometric parameters and operating conditions were examined.

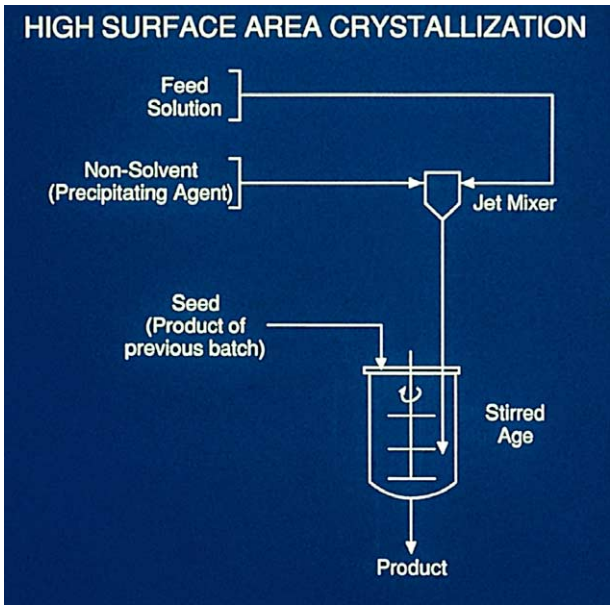

Fig. 4. Impinging jet schematic.

29. Summary and conclusions

Successful control of crystallization processes in the laboratory and on scale-up requires understanding of the key properties of the molecule in question with regard to several system specific properties including nucleation and growth rates, induction time, width of metastable region, and morphology. These system properties are in turn dependent on operating variables including impurities, mixing, solvent systems, and supersaturation.

A crystallization process can be dominated by nucleation or growth. The choice can, to some extent, be directed by manipulation of the key variables—supersaturation, seeding, and crystal surface area depending on the desired outcome in terms of particle size, PSD, chemical purity, etc. This choice can determine the preferred crystallization equipment, method of crystallization, and procedure.

Understanding and control of these interdependent factors are key to successful development and scale-up to achieve the desired chemical and physical attributes of the product.

References

[1] J. Nyvlt, Industrial crystallization from solutions, Butterworth, London, 1971.
[2] A.S. Myerson (Ed.), Handbook of industrial crystallization, 2nd ed., Butterworth-Heinemann, Newton, MA, 2002.
[3] A. Mersmann (Ed.), Crystallization technology handbook, Marcel Dekker, New York, 2001.
[4] J.W. Mullin, Crystallization, 4th ed., Butterworth-Heinemann, Oxford, 2001.
[5] J. Baldyga, J.R. Bourne, Turbulent mixing and chemical reactions, John Wiley and Sons, Chichester, 1999.
[6] N. Harnby, M.F. Edwards, A.W. Nienow (Eds.), Mixing in the process industries, 2nd ed., Butterworth, Stoneham, MA, 1992.
[7] E.L. Paul, V. Atiemo-Obeng, S.M. Kresta (Eds.), Handbook of industrial mixing: science and practice, John Wiley and Sons, New York, 2003.
[8] O. Söhnel, J. Garside, Precipitation, Butterworth-Heinemann, Oxford, UK, 1992.
[9] Condon, J.M., Investigation of impinging jet crystallization for a calcium oxalate model system, PhD thesis, Rutgers University, New Brunswick, NJ (2001).
[10] B.K. Johnson, R.K. Prud'homme, AIChE J. (2003) (in press).