Second Edition

Crystallization of Organic Compounds

An Industrial Perspective

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Edward L. Paul
Michael Midler
James A. McCauley

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Preface

With the supporting feedback received over these years after the first edition, the goal of the second edition of this book inherits the same as the first edition. The first is to facilitate the understanding of crystallization fundamental properties and the impact of these properties on crystallization process development. The second is to improve problem solving ability through actual industrial examples under real process constraints.

In the second edition, the fundamental knowledges and key examples from the first edition are retained. New learnings are incorporated to reflect the current practice and potential future direction. These include a deeper knowledge on the phase behavior between drugs and solvents/excipients and in silico solubility prediction and screening (Chapter 2); formation of stable/metastable polymorphs via equilibrium and kinetic factors and conformer screening of salt/cocrystal and chiral resolution (Chapter 3); in situ seed generation via wet mill, model-based crystal growth/nucleation parameter estimation, and process optimization (Chapter 4); CFD simulation, mixing scale-up, and quality-by-design/process control strategy (Chapters 5 and 6); updated examples of anti-solvent/evaporation/reactive crystallization (Chapters 8, 9, and 10); and API/excipient coprocessing of amorphous and crystalline solid dispersion composite (Chapter 13). Additionally, in the second edition, new chapters on filtration and drying downstream operations (Chapters 11 and 12) are added to address the final isolation aspects of solid properties after the crystallization.

During the period in preparing the second edition, two of our authors, Drs. Ed Paul and Mike Midler, passed away. However, their passion and dedication will continue to stay through this book.

Finally, as cited in the first edition, Matthew: 12:33, "Either declare the tree good and its fruit is good, or declare the tree rotten and its fruit is rotten, for a tree is known by its fruit." It continues to be our hope that you, as readers, will find the second edition of this book useful for your works. If so, this will be the nicest reward for us.

Hsien-Hsin Tung,
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Chapter 1

Introduction to Crystallization

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 as well. Over the past several decades, the study of crystallization operations has taken on even higher levels of importance, because of several critical factors that require increased control of the crystallization process. These levels of control require better understanding of the fundamentals as well as of 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 the regulatory authorities that a continuing supply of active pharmaceutical ingredients (APIs) of high and reproducible quality and bioavailability can be delivered for formulation and finally to the patient. The "product image" (properties, purity, etc.) of this medicine must be the same as that used in the clinical testing carried out to prove the product's place in the therapeutic marketplace. Some additional comments on critical issues, quality-by-design, and regulatory issues are included later in this chapter (Section 1.4).

The issues noted above that require increased control, relative to previous practice, include the following:

- Final bulk drug substances must be purified to high levels that are increasingly quantifiable by new and/or improved analytical methods.
- Many drugs now require high levels of achievement and maintenance of chirality.
- Physical attributes of the bulk drug substance, i.e. crystallinity, amorphism, crystal forms, and particle size distribution (PSD), must be better controlled to meet formulation needs for bioavailability, stability, and reproducibility needs.
- Increased demands are being made for achievement and maintenance of crystal morphology.
- Increasingly complex molecular structures with higher molecular weights are being processed.
- The biotechnology sector has increased the use of precipitation of macromolecules for purification and isolation of noncrystalline materials.

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Added to this list is the assertion, based on operating experience, that crystallization and its downstream operations including filtration and drying can be difficult to scale-up without experiencing changes in physical attributes and impurity rejection. Regulatory requirements for final bulk drug substances, as noted above, now include the necessity for duplication of physical attributes including PSD, bulk density, and surface area within narrow ranges when scaling from pilot plant to manufacturing scale.

When compared to the development of models and methods for other unit operations, it is obvious that crystallization and its downstream operations have not been generalized to the degree that has been accomplished for distillation, extraction, adsorption, etc. This situation is changing rapidly, however, with increasing research now being carried out at academic and industrial centers on crystallization fundamentals to model and predict solubility, polymorph, nucleation, growth rates, and mixing as well as other key properties, such as hydration, dehydration, particle attrition, and agglomeration in drying.

Control of crystallization processes requires modulation of either nucleation or growth, or, as is most often the case, both modes of crystal development simultaneously. Each operation must be evaluated to determine which of the process objectives is the most critical from the point of view of overall outcome, in order to determine whether nucleation or growth should be the dominant phase. The number and size of nuclei initially formed, or equivalently seeded, can dominate the remainder of the operation. However, it is generally agreed that nucleation can be trickier 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 an integration in emphasis from control of initial nucleation as seed to control of growth for the rest of crystallization. This trend is also finding application for control of purity and improved downstream handling for both intermediates and final bulk products. The obvious critical factors then become *seeding and control of supersaturation*. Quantification of these factors for each process is essential for development of a scalable process.

For downstream filtration/washing and drying, it would require control of both equilibrium and kinetic variables. If mixture of solvents is used for cake washing, fractionation of residual solvent in the wet cake during drying can lead to solvent entrapment in the final dry cake. Improper humidity level during drying of hydrate can also induce dehydration risk. Simultaneous particle attrition and agglomeration would also require a good balance among process operating parameters, cake wetness, particle physical properties, etc. Cake homogeneity has always been a challenge upon scale-up. Again, a sound knowledge of these factors is essential for development of a scalable process.

The purpose of this book is to outline the challenges that must be met and the methods that have been and continue to be developed to meet these requirements to develop reproducible operations and to design equipment in which these goals can be realized.

The four conventional crystallization operations (Chapters 7, 8, 9, and 10) and downstream operations (Chapters 11 and 12) will be discussed in terms of their strengths and weaknesses in achieving specific process objectives. In addition, methods of augmenting the conventional processing methods will be included with emphasis on the enhanced control that is often necessary to achieve the specific objectives.

This book also includes chapters on the properties of organic compounds (Chapter 2), polymorphism (Chapter 3), the kinetics of crystallization (Chapter 4), mixing and scale-up in crystallization (Chapter 5), and critical issues and quality by design (Chapter 6). Selected

Topics (Chapter 13) contain areas of current crystallization research and development we thought worth mentioning and also some unique crystallization processes that have special features to be considered in process development. To assist in the thought process for organization of a new crystallization process, and to address the quality-by-design and control strategy topics, Chapter 6 specifically contains a suggested protocol for development and scale-up of a crystallization operation.

1.1 CRYSTAL PROPERTIES AND POLYMORPHS (CHAPTERS 2 AND 3)

Basic crystal properties include solubility, supersaturation, metastable zone width, induction time, oil, amorphous solid, polymorphism, solvate, occlusion, morphology and PSD, and so on. Clearly, in order to properly design and optimize crystallization processes, along with downstream operations to generate desired solids, it is essential to have a sound understanding of these properties.

For pharmaceuticals and special organic chemicals, solution crystallization, in which solvents are used, is the primary method of crystallization compared to other crystallization techniques such as melt and supercritical crystallization. Therefore, the goal of these chapters is to introduce basic properties of solution and crystals related to solution crystallization and subsequent downstream operations. The relevance of these basic properties to crystal qualities and crystallization operations will be highlighted with specific examples.

Some properties are more clearly defined than others. For example, solubility is defined as the amount of solid in equilibrium with the solvent. Solubility can affect the capacity of the crystallization process, and its ability to reject undesired compounds and minimize loss in the mother liquor. In addition, solubility varies widely from compound to compound or solvent to solvent. On the other hand, there are properties that are much less characterized or understood. For example, the mechanism and condition for the formation of oil or amorphous solid remain less clear. The composition of oil and amorphous solid can be variable, and certainly can contain a much higher level of impurities than that in the crystalline solid, which leads to a real purification challenge. In addition, oil or amorphous solid generally is less stable and can create critical issues in drug formulation and storage stability. In recent years, some amorphous organic compounds are formulated using amorphous solid dispersion technique which contains polymeric or other non-active ingredients to maintain the amorphous state of the organic compounds over sufficient shelf life. The amorphous state of compounds can improve the bioavailability over that of the corresponding crystalline compounds. But special attentions are required on design and processing to ensure both chemical and physical stability of the compounds.

One property of a crystalline compound is its ability to form polymorphs, that is, more than one crystal form for the same molecular entity. The phenomenon of polymorphism plays a critical role in the pharmaceutical industry. It affects every phase of drug development, from initial drug discovery to final clinical evaluation, including patent protection and competition in the market. A critical challenge is the early identification of possible polymorphs. A relevant property of a crystalline compound is the possibility to form salts or cocrystals with the same active ingredient. Similar to the case of polymorph, salt and cocrystals can have different physical and chemical properties from the original compound. Chapters 2 and 3 will address these key issues.

1.2 NUCLEATION AND GROWTH KINETICS (CHAPTER 4)

Meeting crystal product specifications with a robust, repeatable process requires careful control and balancing of nucleation and growth kinetics. Careful structuring of the environment can dictate the fundamental mechanisms of nucleation and crystal growth and their resultant kinetics. Undesired polymorphs can be often minimized or eliminated by suitable control of rate processes.

One important industrial implication of nucleation is generation of wet seed. Under high mixing condition and supersaturation, the resulting nuclei via primary nucleation and/or secondary nucleation can serve as seed and act as a wet-seed generation platform. This wet seed possesses theoretical and practical advantages over dry seed generated by dry milling techniques. The wet seed can contain less defects than that of the dry (milled) seed, due to simultaneous seed annealing in wet condition. The concern about long-term storage stability of seed is nonexistent. The size of nuclei can be manipulated by controlling the mixing environment and supersaturation. Also, the amount of seed can be a control variable. Interestingly through actual industrial observation of applying wet-seed generation platform, the likelihood of discovering and generating the most stable crystal form in the early phase of drug development seems to improve drastically. It is hypothesized that the kinetics of metastable form conversion to stable form is much accelerated under the high mixing intensity environment versus the typical crystallization environment in the laboratory which is under low mixing intensity.

Understanding of the possible nucleation and crystal growth kinetics for desired (and undesired) compounds can lead the process development effort on a considerably shorter path to success. Applying fundamental models and determining these kinetic factors through design of experiment (DOE) approach enable in silico simulation for what-if scenarios quickly. It can greatly improve the process understanding, reduce the process development efforts, and ensure success upon scale-up and commercialization. Alternatively, applying process analytical technology to monitor the nucleation and crystal growth kinetics without the modeling can also be applied. The PAT measurement determines the crystallization kinetics in real time and adjusts the operating parameter through selected feedback control algorithm. A reliable PAT instrument would be very beneficial for the model-free approach.

1.3 MIXING AND SCALE-UP (CHAPTER 5)

While many crystallization processes, including downstream filtration and drying, can tolerate a wide range in mixing quality and intensity, many engaged in development do not examine the effect of mixing on their process until forced to do so by problems in scale-up, or even possibly at lab scale. The result is, at best, loss of time and effort.

Transport of momentum, mass, and energy, all affected by mixing can be critical for success in many crystallization processes, especially so with complex organic compounds. Momentum transport can influence slurry homogeneity, impact nucleation, shear damage, agglomerate formation, and discharge of slurry. Mass transport can affect the uniformity of supersaturation (micro-, meso-, and macro-mixing), and in reactive crystallization can affect, even at the molecular level, the resultant reaction and subsequent supersaturation pattern. Energy transport has a direct effect on heat transfer, for example drying, and proper mixing can minimize or avoid encrustation on the heat transfer surfaces.

From the industrial perspective, mixing would be considered to be the sole critical factor upon scale-up. Since mixing affects multiple variables simultaneously, it can be complex to evaluate the mixing impact on the scale-up due to potentially nonlinear and/or conflicting trends from different considerations. It can be beneficial to consider different mixing criteria separately, i.e. mixing time, mixing intensity, and mixing pattern/distribution, then evaluate the overall impact of mixing on the process performance.

An adaptation of the Damkoehler number (Da) is a useful concept for evaluating the impact of mixing time. It is the ratio of the characteristic mixing time to its corresponding process time (nucleation induction time, crystal growth/supersaturation release time, reaction time, etc.). Studies of these times and the resulting predicted Damkoehler number in a laboratory setting can provide evidence of possible scale-up problems.

The effects of mixing intensity on, for example surface films in crystal growth, and micro-mixing time (local homogeneity) when adding antisolvent or reagent, are examined in Chapter 5. The mixing pattern of varying options (impeller design, vessel geometry—e.g. fluidized bed, contoured bottom), external re-circulation loops, etc. are also discussed. Computational fluid dynamics (CFD) is increasingly being utilized to analyze mixing systems, particularly the stirred vessels commonly used for crystallizer operation. Case of CFD simulation is presented in Chapter 5.

1.4 CRITICAL ISSUES AND QUALITY BY DESIGN (CHAPTER 6)

1.4.1 Critical Issues

Difficulty in control of crystallization processes and downstream operations in general can be exacerbated when working with complex organic compounds. The solids of these complex organic compounds can have complex behavior, for example amorphous solid, polymorphs, solvate/hydrate, humidity, and temperature environment. This can be even worse when attempting to develop a nucleation-dominated kinetic-driven process, which even in the best of circumstances can potentially operate over a very wide range of supersaturation, depending on small changes such as varying amounts of very low level impurities.

Organic compounds are subject to agglomeration/aggregation effects and even worse, to "oiling out." All of these can potentially result in undesired trapping of solvent and/or impurities in the final crystal. Oiling out, of course, can completely inhibit the formation of a crystalline phase thereby resulting in a gum or amorphous solid. Agglomeration or aggregation (as well as attrition) can occur not only during the crystallization but also during the drying. These phenomena are discussed qualitatively in Chapter 6.

Crystalline processes often provide initially a seed bed for crystal growth. The wet-seed generation approach, as mentioned in Section 1.2 and Chapter 4, possesses many advantages over dry seeding. Seed crystals directly affect final crystal form and purity, particularly in avoiding formation of "undesired" crystals, such as chiral resolution. Seed particle size and amount directly affects final product particle size. For a growth-dominant crystallization process, it would be straightforward to estimate the final product particle size and shape based upon the seed size, amount, and shape. When attempting to control particle size and shape of final product, an excessive number of seed nuclei can limit the upper range of achievable product particle size or morphology. For case like that, optimal processes with externally or internally generated wet seed often requires some level of seed conditioning for modifications of seed size and morphology. Principles for such conditioning are discussed in Chapter 6 and in some of the examples.

1.4.2 Design of Experiment

The need for controlled crystallization methods and equipment is required not only to meet internal standards, as indicated by consistency for intermediates and particularly for APIs, but also to meet regulatory requirements. These requirements include controls on both chemical purity and physical attributes.

For APIs, critical quality attributes (CQAs) are set by the "biobatch" model for clinical evaluation. The specifications can include chemical purity, mean particle size, PSD, and other appropriate physical attributes. The term "biobatch" refers to the regulatory requirement of identifying a particular batch, normally a pilot scale batch used in clinical trials, as the defining standard for physical and chemical attributes that must be reproduced at the manufacturing scale to be acceptable for sale. The critical process controls (CPCs) for the process, which includes critical process parameters (CPPs) and critical in-process controls or analysis (IPCs or IPAs), are defined to ensure that the process can consistently manufacture APIs meeting the specifications. The CPCs, once established, must be met on scale-up to the manufacturing facility. In addition, the process must be operated within the range of design space established. Development of a crystallization and downstream process must include determination of realistic and reproducible ranges for both the CPPs and the IPCs.

With the advancement of online measurement techniques such as focused beam reflective measurement (FBRM) and Fourier transform infrared (FTIR), it is possible to obtain hundreds of data points of PSD and solution concentration (i.e. supersaturation) information during one single crystallization experiment. Applying design of experiment principle with focus on nucleation and crystal growth phenomena, respectively, just a few model-based experiments can reliably estimate these crystallization parameters, which in return afford rapid in silico screening of various crystallization scenarios. This model-based QbD approach offers deep fundamental understanding and significant savings on experimental effort and time for the development and optimization of crystallization processes. Examples will be given in Chapter 4.

Based upon a similar concept, using simple PAT tool such as liquid refractive index, vapor phase humid meter, the model-based QbD can also provide deeper knowledge and control of downstream filtration/washing and drying performance. Some cases are provided in Chapters 12 and 13.

It can be asserted that one of the most difficult processes to scale-up successfully is crystallization. Methods to achieve control of nucleation and growth are keys to development, and the degree to which they are successfully applied can determine the difference between success and failure on scale-up. It is to this fundamental problem that this book is addressed, combining critically important teachings from the literature with personal experience of the authors and their colleagues in a variety of crystallization and downstream operations.

1.5 CRYSTALLIZATION PROCESS OPTIONS (CHAPTERS 7–10)

The following is a qualitative discussion of several of the procedures that are used to create and maintain conditions under which crystallization can be carried out. These procedures create supersaturation by different methods and utilize seeding to varying degrees. The procedures are classified by the manner in which supersaturation is generated.

The equally critical issues of when to seed and how much seed to use are introduced in each classification. The amount of seed can vary from the extremes of none to "massive" and include the familiar classifications of "pinch" to hopefully avoid complete nucleation, "small" (<1%) to hopefully achieve some growth, "large" (5–10%) to improve the probability of growth, and "massive" (the seed is the product in a continuous or semicontinuous operation) to provide maximum opportunity for all growth. The amount of seed can also be critical in control of polymorphs and hydration/solvation.

The important and developing methods of online measurement of solution concentration and particle size and count are adding powerful tools to aid in control of crystallization operations both in experimentation and manufacturing operations. These methods will also be discussed in the context of their utilization.

1.5.1 Cooling (Chapter 7)

1.5.1.1 Batch Operation

Cooling a solution from above its solubility temperature can be performed in a variety of ways depending on the system and the criticality of the desired result. Natural cooling as determined by the heat transfer capability of the crystallizer is the simplest method but results in varying supersaturation as the cooling proceeds. This may or may not be detrimental to the process, depending on the nucleation and growth rate characteristics of the particular system. Natural uncontrolled cooling has the potential to decrease the temperature rapidly enough to pass through the metastable region and reach the spontaneous nucleation region before seeding can be effective. Spontaneous nucleation can be non-predictive from batch to batch; a major problem with potential to cause "oiling out," agglomeration and/or fine particles; a larger PSD; and occlusion of solvent and impurities. A secondary disadvantage to uncontrolled cooling can be accumulation of crystal scale on the cooling surface caused by low temperatures at the wall. Accumulation of a scale layer can be triggered by nucleation on the cold surface followed by growth on the thickening scale. This encrustation can severely limit the cooling rate, as well as cause major issues of nonuniformity in the product.

When high supersaturation is not acceptable, temperature cooling strategies can be utilized to match the cooling rate with the increasing surface area. These rates were derived by Mullin and Nyvlt (1971) and further derived by Mullin (1993) and are very useful in control of supersaturation. They prescribe cooling rates that are much slower at the outset than natural cooling in order to maintain supersaturation in or close to the growth region when the crystal surface area for growth is low. Cooling rate can be increased as the surface area increases. An added benefit of this method is the potential to reduce encrustation by limiting temperature differences across the jacket. In theory, encrustation can be eliminated if the temperature difference between the cooling fluid and the crystallizing mixture is less than the width of the metastable zone (Mersmann 2001, pp.437 ff).

A further refinement of this strategy is described by Jones and Mullin (1974), in which a seed age is added as a further aid in limiting the development of supersaturation thereby reducing nucleation and promoting growth.

As with all crystallization options, the most critical factor is seeding. One issue is determining the seed point. If the seed is added at a temperature above the solubility, some or all of it can dissolve. If the seed is added at a temperature too far below saturation, the product may have already nucleated. This issue, determining the point of seeding, is common to crystallization by cooling, solvent removal by concentration, and by anti-solvent

addition. The application of in situ seed generation approach greatly removes the sensitivity of seeding supersaturation via primary and secondary nucleation. To control the nucleation event consistently, a portion of (or all) the batch can be subject to a high mixing intensity environment under supersaturation. The resulting nuclei serve as slurry seed for the remaining batch for crystallization. The rate of nucleation and size of nuclei can be manipulated via controlling mixing intensity environment as an independent variable, as well as supersaturation. As a result, the nucleation event can be controlled with a much higher degree of certainty in comparison to the conventional "non-predictable" primary nucleation event.

Online, in situ instrumentation to measure product composition has been developed to successfully determine the seed point, and is being utilized in increasing number of crystallization operations. Image analysis or photographic methods may be useful in determining the presence of nuclei >5 microns but would be too late to determine the point of seeding. These methods can be used, however, to determine if seeding was successful and to observe whether or not excessive nucleation has occurred. Incorporation of an age period at constant temperature after seeding can also help normalize the nucleation/growth ratio.

Heat/cool temperature cycling is a common and powerful technique for improvement of crystal morphology in cooling crystallization. It can be easily adopted into evaporative, anti-solvent, and reactive crystallization as well. As per authors' experience, this technique has a higher impact in improving the final crystal morphology, if applied at the seed generation stage instead of at the end of crystallization stage. At the end of each cooling cycle, an additional wet-milling operation such as sonification or homogenizer can be applied to break the longest dimension of crystals and reduce the aspect ratio. Cases will be presented throughout the book.

Crystallization by cooling may not be feasible when polymorphs are stable at different temperatures within the cooling range. Cooling through these regions of stability can result in mixed morphologies or a change from one polymorph to another. Uncontrolled nucleation can also be a major issue in achieving a uniform product when polymorphs are possible. A constant temperature process with either a high level of seed or "massive" seed may be required to achieve selection of the desired polymorph. Hydrates and solvates may also be subject to these considerations in crystallization processes. Polymorphism is the subject of Chapter 3.

1.5.1.2 Continuous Operation

The difficulties in batch-to-batch variation discussed above for batch cooling methods can be largely overcome by utilizing continuous operation to achieve both control of low levels of supersaturation and operation with "massive" amounts of seed. This technology is widely practiced for high volume products but finds less application in the pharmaceutical industry because of lower volumes and campaigned operations in which continuous operations are more difficult to justify. However, in some examples discussed below, there is no alternative to continuous operation to achieve the separation and purification required.

A primary example is the resolution of optical isomers by continuous crystallization in fluid beds. Control of low supersaturation by control of the temperature difference between the continuous feed and the seed bed is critical to maintaining an essentially all-growth regime in which the individual isomers grow on their respective seeds in separate crystallizers. The seed beds in both crystallizers are "massive" in relation to the amount of racemic solution passing through in order to present sufficient seed area to maintain low supersaturation. Uncrystallized isomers in the overhead streams are recycled to dissolve

additional racemic feed. Crystal size is maintained by sonication. See Examples 7.6 and 13.6 for a discussion of resolution of optical isomers by continuous crystallization.

This special case illustrates the power of continuous cooling processes with "massive" seed to reject impurities that have the potential to crystallize at equilibrium. Batch cooling to achieve this separation of optical isomers is not a practical alternative because the resolution is not based on equilibrium solubility. The time required for batch cooling would result in the nucleation of the undesired isomer when any practical amount of product is to be harvested in each cycle.

High degree of control can also be achieved in continuous stirred tank crystallizers. Temperature differences between feed and crystallizer can be regulated as necessary. The "seed" is the product and will normally be present at the slurry concentration as determined by the feed rate, concentration, and solubility differences achieved. However, in cases in which this amount of "seed" is not sufficient, cross-flow filtration on the discharge of the crystallizer(s) can be used to increase the slurry density. See Example 7.4 for a discussion of the resolution of ibuprofen lysinate.

1.5.2 Evaporation Solvent (Chapter 8)

1.5.2.1 Semibatch Operation

Increase in concentration by removal of solvent by evaporation (semi-batch operation) is widely practiced but can have several nucleation and growth control problems. These problems can be sufficiently severe to make this method unsuitable in some cases, e.g. for final bulk drug substances (API) that may require tighter control of mean particle size and PSD than can be achieved on scale-up.

Evaporation rate is analogous to cooling rate in creating supersaturation and may be controlled by similar methods of control to match evaporation rate with surface area available for growth. The point of seeding is also an issue since it is difficult to determine when the saturation line is being crossed as concentration proceeds. Adding the seed as slurry in the evaporation solvent, as the concentration passes through saturation, can be useful in this regard.

Local variation in supersaturation is the most significant control issue that can cause non-reproducibility in PSD and other physical attributes, as well as solvent and impurity occlusion. These local variations occur both at the heating surface and at the boiling liquid/vapor interface.

At the heating and solvent evaporation/boiling surface, local high temperatures and vaporization rate result in uncontrollable local supersaturation environments in which uncontrolled nucleation can be excessive, particularly in these regions of poor bulk mixing. Foaming can also be a significant issue. Wall scale above the heated surface can also lead to significant product quality issues. Decomposition on the surface above the liquid–vapor interface can be excessive because of direct exposure to the higher temperature of the heating fluid. Product scale from this area could also drop into the product slurry and result in unacceptable physical properties for a final bulk drug substance as well as handling difficulties in any system. Finally, over-concentration can lead to safety issues if the concentrated mass is thermally unstable. Although this is not a crystallization issue, it is mentioned as a possible serious consequence of the evaporative type of crystallization operation.

These sources of variability all contribute to potentially severe scale-up problems with evaporative crystallization. Control of distillation rate by control of jacket temperature may require higher wall temperatures thereby making supersaturation variation more severe.

The decrease in bulk circulation and increase in mixing time will further exacerbate this issue. In some cases, these problems can result in unacceptable results, thereby requiring development of an alternative crystallization method. See Example 8.2 for a discussion of an application in which adequate PSD control could not be achieved.

1.5.2.2 Semicontinuous and Continuous Evaporation

Although widely practiced for industrial chemicals, continuous evaporation for crystallization is rarely, if ever, used in pharmaceutical operations. Although continuous operation has the advantage of the use of "massive" seeding and increased control of supersaturation and crystal surface area, the throughput necessary for its application is rarely, if ever, met for final bulk drug substances. In addition, continuous operation to achieve the conditions for crystallization (as discussed above for resolution of optical isomers) is often not applicable or achievable. Local supersaturation at the liquid–vapor–solid interfaces is the primary cause of uncontrolled nucleation.

A semicontinuous feed and bleed evaporation approach is a common technique to change the solvent composition. Utilizing the difference of boiling point and drug solubility difference among solvents, it can be a useful process technique. One approach is to distill off the initial crystallization solvent system, which has a lower-boiling point but with a higher solubility, and replace it with a secondary solvent system, which has a higher boiling point but with a lower solubility. The secondary solvent system can be partially or totally immiscible with the first solvent system. Examples are presented in Chapter 8 to illustrate this approach.

1.5.3 Antisolvent Addition (Chapter 9)

1.5.3.1 Semibatch Operation

This widely practiced option has many inherent potential advantages over both batch cooling and concentration in terms of crystallization control. It does, however, have the obvious disadvantage of creating solvent mixtures requiring separation for recovery.

Control of both supersaturation and crystal growth area is readily achievable by control of antisolvent addition rate. This control requires consideration of both the change in solubility as addition proceeds as well as the crystal growth area and is, therefore, potentially more complex than for the single solvent processes of cooling and concentration. Rates of anti-solvent addition can vary from constant in noncritical cases to "cubic" (as in cooling operations) depending on the slope of the saturation curve with concentration. Solubility curves of unusual shape, possibly including a maximum over the range of addition, may require a more complex addition scheme if maintenance of essentially constant supersaturation in the metastable region is necessary.

Determination of the seed point is again the key to consistent operation. Addition of the anti-solvent containing seed during the segment in which the saturation line is crossed is a good method of seed control. "Massive" seeding is also possible by utilizing a significant portion of the previous batch as the seed. Wet-seed generation under high mixing intensity environment can be very easily implemented here.

Scale-up of these processes requires careful consideration of the mixing of the antisolvent, both at the point of addition and in circulation of the bulk. Insufficient control of local mixing at the point of addition can result in local supersaturation and excessive nucleation. Subsurface addition of the anti-solvent is a good precaution to minimize this risk and

is, in some cases, essential for successful scale-up. Micro- and macro-mixing issues in crystallization have been analyzed by Mersmann and Kind (1988) and Mersmann (2001, pp. 418). Overmixing is also an issue since shear can break crystals and create nuclei by secondary nucleation. Torbacke and Rusmason (2001) has devised a loop reactor/crystallizer for separately evaluating the effects of macro-, micro-, and meso-mixing. Designed for reactive crystallization, this loop design can also be used to assist in scale-up of anti-solvent crystallization processes. These issues are further discussed in Chapter 5 on mixing effects.

1.5.3.2 Semicontinuous Antisolvent Addition

Excellent control of crystallization conditions can be achieved by semicontinuous methods in which the supersaturation is controlled locally at the point of mixing in an in-line device. Both once-through and recycle operations can be carried out with and without seeding. In the case of unseeded operation, an in-line device with a controlled mixing time can create a high supersaturation ratio in a very short time and provide a method of control of nucleation with a controlled mixing intensity that is difficult or impossible to achieve in conventional crystallization vessels.

1.5.3.3 Impinging Jet and In-line Mixer Crystallization

The rapid blending of two steams that is achieved by impinging jet technology, as developed for reaction injection molding (Lee et al. 1980) was adapted for crystallization by Midler et al. (1994) and further developed by others [examples: Mahajan and Kirwan (1996), Lindrud et al. (2001), Johnson and Prud'homme (2003)]. With proper design, mixing to the molecular level can be accomplished in shorter times than the nucleation time, thereby achieving a primarily nucleation based process for the production of uniform, fine particles. After leaving the mixing zone, additional crystallization continues in a standard agitated vessel on a well-defined initial number of nuclei with well-defined size and shape.

This technology can produce narrow PSDs with controlled surface area and is finding utilization for final bulk drug substances. Control of particle size can result in the added benefit of the elimination of the need for milling for particle size reduction and control. In addition, scale-up can be achieved in production scale by operation at the same local conditions in the same (or only 2× or so larger) size jets that are run for longer times. See Examples 9.5–9.6.

Besides impinging jet mixing, a rapid blending of two streams can also be achieved with different types of mixers, including rotor–stator type homogenizer, high pressure flow cavitation homogenizer or ultrasonicator, etc. With a proper control of mixing, for example mixing time, mixing intensity, and mixing distribution, and the supersaturation, the resulting particle size can be adjusted to meet specific project needs. See examples in Chapter 9.

1.5.4 Reactive Crystallization (Chapter 10)

When supersaturation of a crystallizing compound is created by its formation by chemical reaction, the operation is characterized as reactive crystallization. The reaction may be between two complex organic compounds or be neutralization by acid or base to form a salt of a complex compound. 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 supersaturation and nucleation. These operations are also known as precipitations because of the rapid inherent kinetics.

Control of particle size in reactive crystallization can be difficult because there is usually no method to slow down the reaction that generates the supersaturation. The rate of addition of the reagents, however, does provide a means to control this critical parameter globally in the reactor but not locally since the reaction may be complete near the point of addition. Successful operation depends, therefore, on 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 basic growth process is required.

Wet-seed generation under high mixing intensity environment can be equally applicable here as in the case of cooling, evaporative, or anti-solvent crystallization. See example in Chapter 10.

1.6 DOWNSTREAM OPERATIONS (CHAPTERS 11 AND 12)

To remove the impurities in the mother liquor, the crystalline slurry would need to be filtered and washed. Without properly filtering and washing the cake, it could result in a product of poor quality failing the specifications. Compressible cake can not only slow down the filtration rate, but also affect the effectiveness of the cake wash and rejection of impurity. A real concern is cake cracking upon scale-up which leads to preferential bypass of the wash and nonuniform removal of impurities. Similar to crystallization operation, the filtration performance can be affected by PSD, particle morphology, filter media, process equipment, filtration procedures and corresponding operational parameters, etc. A sound understanding of fundamentals would be desirable to accomplish the required performance, in particular upon scale-up.

Following the filtration and washing operations, the wet cake needs to be dried to remove the residual solvent. In addition, for the case of solvates or hydrates, drying operation can induce desirable or undesirable crystal form conversion, for example, forming the desolvate from solvate or hydrate under controlled humidity. Also, it is not uncommon to form amorphous compound from initial crystalline wet cake via melt-back or desolvation (or dehydration) phenomena. A good knowledge of thermodynamic equilibrium properties, including solubility in the wash solvents, would be essential to define the suitable operation ranges.

Blending or agitation during drying can cause particle agglomeration and particle attrition. Depending upon multiple factors varying from solubility, particle mechanical strength, and PSD to cake wetness, dryer design, cake blending pattern and blending uniformity, etc., the degree of agglomeration or attrition can vary significantly. From the particle size control perspective, neither change is desirable as the PSD is altered from the final PSD at the end of crystallization.

After drying, to remove the potential lumps (agglomerates) and ensure cake homogeneity, an additional delumping operation would normally be conducted. Delumping is considered to be a gentle milling operation which only breaks up the potential agglomerates, but does not break up the individual particles. More energetic dry mills, such as pin or jet mill, can be used to break up individual crystal and reduce its size. Upon breaking up the individual crystal, it inevitably induces crystal defects which could cause chemical and physical stability problems. Impinging jet crystallization as mentioned in earlier chapters

serves as good examples to avoid the need for dry milling and overcome the stability problem. In terms of cost, dry milling can be the most expensive step among all steps in the entire synthesis of pharmaceuticals. Authors strongly recommend dry milling to be the last resource to meet the desired PSD for the compounds.

Examples are provided in these chapters to highlight these issues.

1.7 SPECIAL APPLICATIONS (CHAPTER 13)

This chapter includes discussion of several special topics of crystallization, including ultrasound for crystallization, crystallization using supercritical fluids, and crystalline/amorphous solid dispersion, and also contains examples of crystallization operations that were developed to meet special requirements.

The use of ultrasound in crystallization can be unique and very helpful in certain applications. In Examples 7.3 (heel/sonication), 7.6, and 13.6 (stereoisomer resolution), ultrasound was used to break up crystals and generate fresh surface area for subsequent crystal growth. In these cases, the crystals were snapped into shorter crystals along the long axis. Therefore, the aspect ratio is effectively reduced. Improving the crystal aspect ratio by either breaking up crystals along the longer axis and/or facilitating growth on the slowest growing surface can be very useful in applications involving needles.

One key driver for supercritical crystallization is generation of nanoparticles for improvement of drug dissolution rate. Fundamentally, this approach bears much similarity to the impinging jet crystallization shown in Example 9.5, in which high supersaturation is generated by mixing two streams rapidly. Several types of supercritical crystallization operation have been developed successfully to multi-kilogram scale.

CFD is increasingly being utilized to analyze mixing systems, particularly the stirred vessels commonly used for crystallizer operation. The problem of modeling fluid dynamics in the presence of a solid phase is not trivial, but some workers are starting to make headway in this field. In addition to discussion in Chapter 4, some additional reference to these efforts is made in Chapter 13.

Examples in this chapter include sterile crystallization of a labile compound, yield enhancement by crystallization, yield and selectivity enhancement, removal of low level impurities via crystallization from the melt, crystal formation in vials in a freeze drier, and nonequilibrium resolution of stereoisomers by crystallization and formation of crystalline/amorphous solid dispersion. These examples represent unique crystallization processes designed specifically to meet specific goals. One lesson to be learned from examination of these unique applications is that understanding of principles can lead to inventive solutions to problems. For instance, in Examples 13.2 and 13.3, advantage is taken of the solubility difference between starting material and desired product to optimize the reaction yield/selectivity by crystallizing the product and "protecting" it from over-reaction.

The crystalline and amorphous solid dispersion represents a new theme in material science and particle engineering of drug compounds. The drug compound is tentatively dispersed with non-APIs to form the "solid dispersion." The solid dispersion material shows much better solubility for bioavailability and/or better mechanical properties for formulation. The solid dispersion material also suffers certain limitation such as physical and chemical stability, drug loading, and manufacturing complexity. A side-by-side comparison of a unique hybrid solid dispersion, consisting of amorphous and crystalline API, with the amorphous solid dispersion is presented to address these issues.

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Crystallization of Organic Compounds: An Industrial Perspective, Second Edition. Hsien-Hsin Tung, Edward L. Paul, Michael Midler, and James A. McCauley.

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