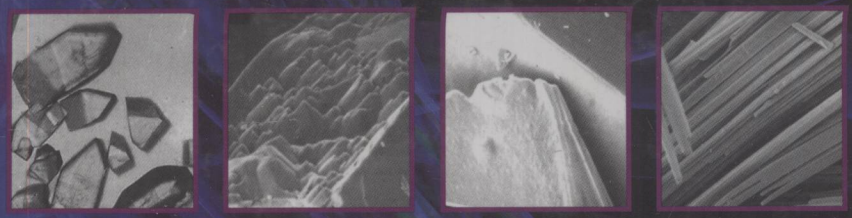

Crystallization of Organic Compounds

An Industrial Perspective

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Crystallization of Organic Compounds

Preface

Crystallization is an essential operation in pharmaceutical manufacturing because the majority of active pharmaceutical ingredients (APIs) are produced in solid form. Yet, this subject is much less a part of the academic curriculum compared to other topics such as distillation, extraction, and reaction. Very often engineers will learn crystallization process development on the job through trial and error, and it is not surprising that wheels are reinvented from time to time, despite hard work and effort. In terms of resource utilization, this approach is certainly inefficient. Added to this deficiency is the lack of a mechanism to pass on the knowledge and expertise developed from previous efforts. Over the years, one way to accomplish this has been via memos and process reports. But memos are generally project specific. Therefore, it is not a trivial task to uncover the technical knowledge and know-how buried in various memos and reports. Combining a summary of relevant theory and illustrative examples in a book to fill this gap seems to be a good mechanism for the transfer of information on principles and suggested practice.

The idea of writing a book on crystallization to fulfill this need was first conceived in mid-1990. At that time, few books were available which dealt with crystallization development. These books appeared to overemphasize theory, and the majority of examples concerned crystallization of inorganic compounds. Over the past 10 years, several new crystallization books have been published which provide wider applications and richer information for development scientists and engineers. Unfortunately, the practical aspects of crystallization in our industries and actual industrial examples have not been adequately described.

This book has two goals. One is to facilitate the understanding of the fundamental properties of crystallization and the impact of these properties on crystallization process development. The second is to aid practitioners in problem-solving using actual industrial examples under real process constraints. This book begins with fundamental thermodynamic properties (Chapters 2 and 3), nucleation and crystal growth kinetics (Chapter 4), and process dynamics and scale-up considerations (Chapters 5 and 6). Subsequent chapters cover modes of crystallization operation: cooling (Chapter 7), evaporation (Chapter 8), antisolvent (Chapter 9), reaction (Chapter 10), and special cases of crystallization (Chapter 11). As mentioned, real industrial examples are provided in each chapter.

We would like to express our sincere thanks to the late Omar Davidson for his diligent support throughout the preparation of this book. We also want to thank our colleagues, Lou Crocker, Albert Epstein, Brian Johnson, Mamoud Kaba, Joe Kukura, Amar Mahajan, Jim Meyer, Russ Lander, Karen Larson, Chuck Orella, Cindy Starbuck, Jose Tabora, and Mike Thien, who have graciously spent their time in reviewing individual chapters of this book (and in several cases, more than that). Their recommendations have significantly enriched the content of this book. Needless to say, we are truly grateful to our spouses

and family members for their understanding and support during the long period of preparation.

Our goal is to help reader develop the crystallization process. 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 is our hope that you, as readers, will find this book useful for your work. If so, this will be the nicest reward for us.

Contents

Chapter 1

Introduction to Crystallization Issues

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 itself, is reinforced by the need to assure 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 regulatory issues are included later in this chapter (Section 1.7).

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.
- Physical attributes of the bulk drug substance must be better controlled to meet formulation needs for reproducibility and bioavailability.
- Many APIs now require high levels of chirality.
- Increased demands are being made for achievement and maintenance of morphology.
- Increasingly complex molecular structures with higher molecular weights are being processed.
- Bulk drug solid stability is increasingly being achieved by improved control of crystal growth.
- The biotechnology sector has increased the use of precipitation of macromolecules for purification and isolation of noncrystalline materials.

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

Crystallization of Organic Compounds: An Industrial Perspective. By H.-H. Tung, E. L. Paul, M. Midler, and J. A. McCauley

rejection. Regulatory requirements for final bulk drug substances, as noted above, now include the necessity for duplication of physical attributes including particle size distribution, 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 has 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 nucleation and/or growth rates as well as other key properties, including polymorph formation.

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 these process objectives is most critical, from the point of view of overall outcome, 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 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 growth process is essential for development of a scalable process. Much of the discussion to follow focuses on the growth process and methods to minimize nucleation.

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 crystallization operations and to design equipment with which these goals can be achieved.

The four conventional crystallization operations (see Chapters 7, 8, 9, 10) 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 considered, 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) and the kinetics of crystallization (Chapter 4), critical issues (Chapter 5), and mixing effects in crystallization (Chapter 6). Chapter 11 includes 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, Chapter 11 also contains a suggested protocol for development and scale-up of a crystallization operation.

1.1 CRYSTAL PROPERTIES AND POLYMORPHISM (CHAPTERS 2 AND 3)

Basic crystal properties include solubility, supersaturation, metastable zone width, oil, amorphous solid, polymorphism, occlusion, morphology, and particle size distribution. Clearly.

in order to properly design and optimize crystallization processes, 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 or supercritical crystallization. Therefore, the goal of these chapters is to introduce basic properties of solution and crystals related to solution crystallization. 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, as well as 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 well characterized or understood. For example, the mechanism and condition for the formation of oil or amorphous solid remain unclear. 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.

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 because 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. Chapters 2 and 3 will address this key issue.

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.

Understanding of the possible nucleation and crystal growth kinetics for desired (and undesired) compounds can place the process development effort on a considerably shorter path to success. Reference will be made to examples in the other chapters in this book.

1.3 CRITICAL ISSUES (CHAPTER 5)

Difficulty in controlling crystallization processes in general can be exacerbated when working with complex organic compounds. This problem can be even worse when attempting to develop a nucleation-dominated process, which, even in the best 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 problems 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, resulting in a gum or an amorphous solid. These phenomena are discussed qualitatively in Chapter 5.

Crystalline processes often provide a seed bed for crystal growth with an initial nucleation step. When attempting to control particle size and shape, an excessive number of nuclei can effectively make it impossible to achieve the desired size or morphology. Optimal processes with externally or internally (heel) added seed often require some level of seed conditioning. Principles for such conditioning are discussed in Chapter 5 and in some of the examples.

Instrumentation for control of seed point and growth/nucleation processing is discussed.

1.4 MIXING AND CRYSTALLIZATION (CHAPTER 6)

While many crystallization processes can tolerate a wide range of 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 laboratory 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 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 macromixing), 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, and proper mixing can minimize or avoid encrustation on the heat transfer surfaces.

An adaptation of the Damkoehler number (Da) is a useful concept for evaluation of mixing effects in crystallization. It is the ratio of the characteristic mixing time to its corresponding process time (nucleation induction time, crystal growth/supersaturation release time, or reaction time). 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 on surface films in crystal growth, and on mixing/local homogeneity when adding antisolvent or reagent, are examined in Chapter 6. Low-shear options (impeller design, vessel geometry—e.g. fluidized bed, contoured bottom) are also discussed.

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 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 the 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 the control of

crystallization operations both in experimentation and manufacturing operations (Nagy et al. 2007). 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 cooling has the potential to decrease the temperature rapidly enough to pass through the metastable region and reach the uncontrolled nucleation region before seeding can be effective. Uncontrolled nucleation can be a major problem with the potential to cause oiling out, agglomeration and/or fine particles, a larger particle size distribution (PSD), and occlusion of solvent and impurities. A secondary disadvantage of 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, 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. The 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.

Another key variable in batch cooling is seeding. The difficulty is in determining the seed point, which is ideally when the batch temperature first crosses the saturation curve. However, this temperature can be affected by batch-to-batch variations in several factors, including the actual concentration of the material to be crystallized, as well as by impurities that can affect the solubility. If the seed is added at a temperature above the solubility temperature, some or all of it can dissolve, resulting in uncontrolled nucleation. If the seed is added at a temperature too far below saturation, the product may have already nucleated. In either case, the increase in nucleation could result in a decrease in impurity rejection and/or a change in particle size distribution and other physical attributes.

This issue, determining the point of seeding, is common to crystallization by cooling, as well as solvent removal by concentration, and by antisolvent addition. As such, seed point determination merits discussion of various methods.

Online, in-situ instrumentation to measure product composition has been developed to successfully determine the seed point, and is being utilized in an 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.

Adding the seed as slurry in the proper solvent composition is one of the best methods to control a batch cooled crystallizer. The slurry addition is started before reaching saturation and is continued until it can be determined that the seed is no longer dissolving. Although this method can increase the probability that seed will be present at the start of crystallization, the amount of seed actually remaining may be subject to excessive variation.

Crystallization by cooling may not be feasible when polymorphs are stable at different temperatures within the cooling range (Saranteas et al. 2005). 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 select the desired polymorph. Hydrates and solvates may also be subject to these factors in crystallization processes. Polymorphism is the subject of Chapter 3.

1.5.1.2 Continuous Operation

The 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 supersturation and operation with massive amounts of seed. This technology is widely used 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 11-6 for a discussion of resolution of optical isomers by continuous crystallization.

This special case illustrates the power of continuous cooling processes with massive amounts of 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.

A high degree of control can also be achieved in continuously 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 Concentration of Solvent (Chapter 8)

1.5.2.1 Semibatch Operation

Increasing the concentration by removing solvent by evaporation (semibatch operation) is widely practiced but has several nucleation and growth control problems. These problems can be sufficiently severe to make this method unsuitable in some cases, such as 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 the 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 increases. 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 surface, local high temperatures and a high vaporization rate result in uncontrollable local supersaturation environments in which uncontrolled nucleation can be excessive, particularly in those regions of poor bulk mixing. 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, overconcentration 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 an evaporative crystallization operation.

At the boiling surface, vapor disengagement can lead to very high local supersaturation as well as nucleation induced by vapor–liquid interfaces. Foaming can also be a significant issue. In addition, throughout the bulk, vapor bubbles can cause local nucleation.

These sources of variability all contribute to potentially severe scale-up problems with evaporative crystallization. Control of the distillation rate by control of the jacket temperature may require higher wall temperatures, thereby making supersaturation variation more severe. The decrease in bulk circulation and the increase in mixing time will further exacerbate this problem. In some cases, these problems can produce unacceptable results, 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 Continuous Evaporation

Although widely practiced for production of industrial chemicals, continuous evaporation for crystallization is rarely if ever used in pharmaceutical operations. Although continuous operation has the advantages of using massive seeding and increased control of supersaturation and the crystal surface area, the throughput necessary for its application is rarely, if ever, achieved 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.

1.5.3 Addition of Antisolvent (Chapter 9)

1.5.3.1 Semibatch Operation

This widely used procedure 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 the antisolvent addition rate. This control requires consideration of both the change in solubility as addition proceeds and 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.

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 antisolvent is a good precaution to minimize this risk and is, in some cases, essential for successful scale-up. Micro- and macromixing issues in crystallization have been analyzed by Mersmann and Kind (1988) and Mersmann (2001, p. 418). Overmixing is also an issue since shear can break crystals and create nuclei by secondary nucleation. Rasmussen (2001) has devised a loop reactor/crystallizer for separately evaluating the effects of macro-, micro-, and mesomixing. Designed for reactive crystallization, this loop design can also be used to assist in scale-up of antisolvent crystallization processes. These issues are further discussed in Chapter 6 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 can create a high supersaturation ratio in a very short time and provide a method of control of nucleation that is difficult or impossible to achieve in conventional crystallization vessels.

1.5.3.3 Impinging Jet Crystallization

The rapid blending of two steams that is achieved by impinging jet technology, as developed for reaction injection molding by Edwards (1984) was adapted for crystallization by Midler et al. (1994) and further developed by others [examples: Mahajan and Kirwan (1996),