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A Review of the Use of Process Analytical Technology for the Understanding and Optimization of Production Batch Crystallization Processes

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Abstract:

Crystallization at production scale is typically a poorly understood unit operation, with little implementation of the first principles aspect of crystallization in its design, optimization, and control. Problems with production crystallizers include the following: (1) inconsistencies of batch-to-batch in terms of the size and number of crystals produced and (2) the purity profile (residual impurities in crystals, or wrong polymorph or chiral purity). This can have a significant impact both on product quality and downstream process unit operations including filtration, drying, milling, and product formulation. This contribution reviews typical problems encountered in production crystallization, with case studies, advice, and strategies to understand and avoid these problems through the use of in situ crystallization characterization tools.

1. Introduction

Crystallization from solution is a widely applied unit operation in both the pharmaceutical and bulk chemical industries for solid−liquid separations. Its extensive use is based on the fact that this single operation is both a separation and a purification process whereby a solid crystalline product can be isolated with high purity and with relatively low capital and operating costs. The production of a solid-phase material provides a unique opportunity to control both the size and number of crystals produced. Typically for a pharmaceutical crystallization, the size and shape of the crystals are very important parameters. Product quality and efficacy are often contingent on adequate control of particle size and shape in the crystallizer. The size of material produced in a crystallizer can have a detrimental impact on downstream unit operations such as the filtration rate,[1−3] drying and formulation operations.[4]

Therefore, it is often desirable to design a crystallization process to avoid excessive fines generation, which can help minimize downstream processing problems. In the laboratory, the optimum rate of supersaturation generation can be calculated using the population balance[5] coupled with knowledge of the nucleation and growth kinetics and the prevailing supersaturation level.[6,7] The population balance approach plays a large role in crystallization and other particulate processes.[8] Modeling a crystallization process can also give insight into the optimum operating conditions.[9,10] However, mixing plays an important role in the size of the particles produced and distributions of solids in the crystallizer,[11,12] particularly when the scale of the crystallization process is increased or the crystallizer configuration changes. A poor mixing environment can promote concentration and temperature gradients within the vessel, and this can result in different nucleation rates than those encountered in a laboratory environment.[13] A compartmental computational fluid dynamics approach has been shown to give a good indication of the size of material produced in a large crystallizer.[14] Simulations have also been usefully applied to demonstrate the effect of the cycling of the contents of an industrial crystallizer[15] and the effect of attrition in a continuous crystallizer.[16]

While simulations can play an important role in characterizing a crystallization process, from a practical perspective experiments are often vital to help characterize physical mechanisms such as attrition/breakage and aggregation/agglomeration. A scale-down protocol would seem a logical route to investigate, particularly for pharmaceutical manufacturing processes, as ultimately the process will be performed in large-batch crystallizers, often with little scope to modify or optimize the geometry of the production vessel. The goal of scaling a process down would be to try and mimic the conditions of shear, heat transfer, and mass transfer associated with a large production vessel. Some researchers have attempted to mimic attrition phenomena encountered

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in the plant in laboratory vessels.[17,18] There has also been some success with using a loop reactor as a practical method to simulate the long circulation times associated with a large, stirred-tank crystallizer.[19] Laboratory experiments, while not mirroring exactly the conditions of a full-scale production process, can be used to highlight the weaknesses of a production process and, in this sense, can be utilized to help in process optimization.[20]

Tracking the supersaturation of the solution can also aid in understanding and optimizing a crystallization process. This has been made easier by the recent advent of sensors that can monitor the supersaturation level in situ.[21−24] Some recent publications have also used in situ tools for monitoring and controlling the supersaturation level during a crystallization.[25,26] However, monitoring the supersaturation alone is not enough to assess how the crystals are changing in size and number over time. To give an experimental insight into the influence of operating variables on the actual size and number of crystals produced, a technique is required to size the material.

The sieve has long been the technique of choice for particle sizing, but with the advent of modern computers and more reliable electronics and laser sources, there is now a vast variety of techniques available for particle size analysis.[27] However, for crystallization applications, few sizing techniques offer the ability to size material in situ.[28] Off-line sizing techniques typically rely on good sampling, but with a large-scale production process sampling is often hazardous and nonrepresentative. In addition, with many organic crystalline materials forming needles or platelets, shape can influence the results of many sizing techniques.[29] If these issues can be overcome, an off-line measurement can provide useful information about a point in time of the process. However, measuring the crystals off-line gives no insight into the rate and degree of change of the size of the material over time. Without knowledge of the process dynamics, it is often difficult to assess the impact of key process variables on the size and number of crystals produced.

In recent years, Lasentec focused beam reflectance measurement (FBRM) has emerged as a widely used technique for the in situ characterization of high-concentration particulate slurries. FBRM is a probe-based measurement tool, which is installed directly in the crystallizer without the need for sample dilution or manipulation. FBRM measures a chord length distribution (CLD), which is a function of the number, size, and shape of particles under investigation.[30] A more detailed description of the operation of the FBRM probe is provided in the literature.[31,32] FBRM has been successfully applied as a useful tool for detecting a nucleation event and characterizing the metastable zone width.[33,34] It also offers the advantage that it can characterize crystal behavior after the nucleation event,[35] giving an indication, for instance, of growth or agglomeration,[36] or the complex effects of micro- and meso-mixing on a precipitation process.[37] FBRM is widely used as a tool for batch and continuous crystallization development and scale-up,[38,39] crystallization control,[40] and the troubleshooting and optimization of downstream processing problems.[41−43] FBRM has become popular in the pharmaceutical industry for identifying and helping to solve a variety of crystallization processing problems.[44−47] From a crystallization research and development perspective, FBRM has been implemented to aid in the optimization of an enantiomer separation problem,[48] in monitoring and understanding polymorphic behaviour,[38,49] and identifying and understanding process irregularities such as phase separation.[50] Other researchers have modeled how particle shape affects the chord length distribution,[51] and more recently this has been used, under certain ideal conditions, to predict the actual size distribution of nonspherical crystals in a crystallizer.[52] Rather than convert the FBRM chord length distribution to a size distribution, other researchers have utilized the FBRM data to directly

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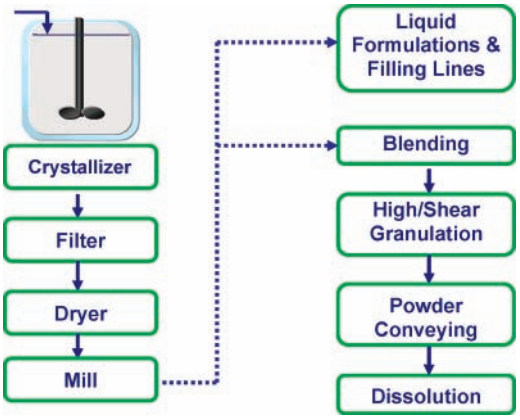

Figure 1. **Pharmaceutical manufacturing: where particles play a role.**

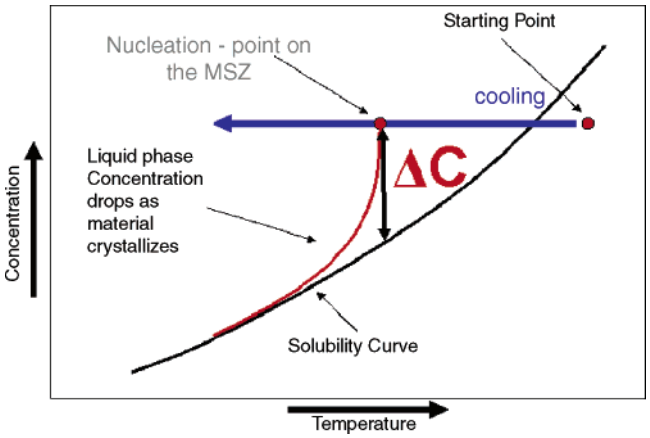

Figure 2. **Illustration of solubility curve and metastable zone (MSZ).**

estimate the crystallization kinetics, both from batch processes[53] and continuous processes.[54] This approach should hold great promise for future crystallization research and development work.

2. Fundamentals of Crystallization in Production

As discussed above, the characteristics of the material produced in the crystallizer can have a significant influence on subsequent downstream processing operations such as filtration, drying, milling, blending, granulation, and tableting. Figure 1 shows a typical schematic of some of the solids-handling steps encountered post crystallization in pharmaceutical manufacture. For instance, variability in filtration and drying performance can typically be attributed to variability in the amount of "fines" produced in the crystallization. Clearly understanding and optimizing the production crystallization step offers the opportunity to minimize and potentially prevent any downstream solids-handling bottlenecks. However, within the pharmaceutical industry, there are often significant regulatory hurdles when making changes to a production process. We recognize this fact, but characterizing the process and its behavior (for discussion in this article) can highlight the critical process variables and their impact on the product formed, thereby providing an opportunity to improve the production process.

2.1. Solubility, Metastability and Supersaturation. First and foremost, knowledge of the solubility curve in a given solvent (or solvent system) is required. It is worth noting that for a given solute in a given solvent, the solubility curve is fixed thermodynamically; however, impurities can have an impact on the solubility, and as impurities' profiles and levels can change during process development or as process feedstock change from plant-to-plant, it is quite possible that the solubility could change. Additionally, given that the material being crystallized is coming from a chemical reaction step—where it is possible to get variable yield—it is therefore possible that each batch could be starting from a different part of the solubility curve. Hence, it is worth assessing the solubility of your material in the mother liquor from which it is crystallized. A variety of techniques exist for measuring the solubility curve including HPLC and gravimetric analysis. Recent publications have described the use of the polythermal method[34] or the use of attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR) in combination with automated reactors.[25]

To complement the solubility information, it is also useful to have knowledge of when the solute will crystallize. A solute will remain in solution until a sufficiently high level of supersaturation has been generated to induce spontaneous nucleation. The extent of this supersaturation is referred to as the metastable zone width. It will typically be influenced by a variety of process parameters including saturation temperature, rate of supersaturation generation, impurity level, mixing, and solution history. It is therefore important to characterize the metastable zone width under a specific set of operating conditions, which relate closely to the conditions of the final scale crystallization. An excellent overview of published metastable zone width experiments is available in the literature.[55] The polythermal technique is perhaps the most widely used technique for determining the metastable zone width. This methodology involves cooling a saturated solution at a fixed rate until nucleation occurs. This process is repeated for a variety of cooling rates and saturation temperatures, with the recorded nucleation temperature allowing the calculation of the metastable zone width for a given cooling rate. It is important to note that the nucleation kinetics, and hence location of the metastable zones, are very sensitive to process variables such as mixing. This makes information on the metastable zone measured in the lab difficult to use and scale reliably to the plant. However, knowledge of the metastable zone in the laboratory will certainly give a helpful indication of the likely performance of the process at production scale, and the laboratory experiments could be repeated under different agitation conditions to assess the impact of different mixing conditions on the nucleation temperature.

Figure 2 can be utilized to explain and define supersaturation. Supersaturation can be defined as the difference between the liquid-phase concentration and the equilibrium solubility concentration at a given temperature. Clearly, in

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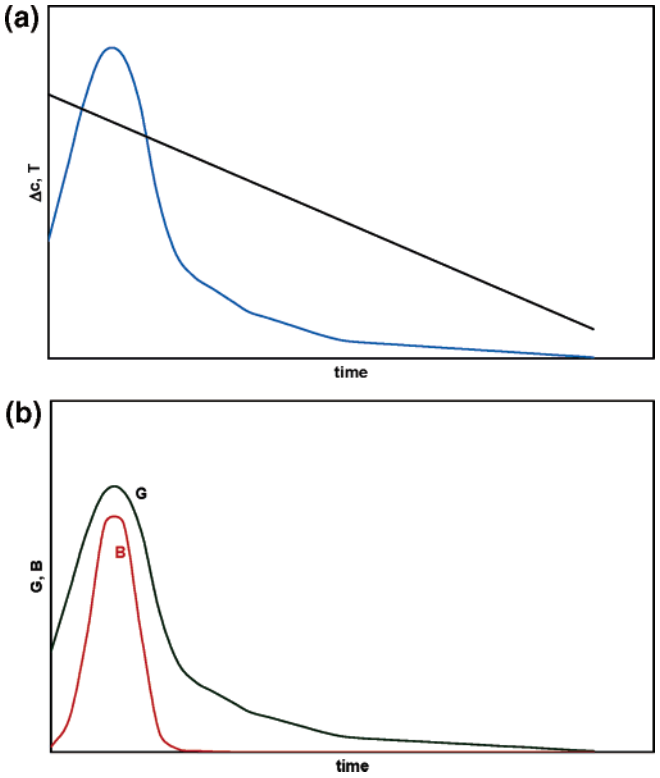

Figure 3. **(a) Schematic of supersaturation level during cooling crystallization. (b) Schematic of growth and nucleation levels.**

Figure 2 the supersaturation is changing over time. Supersaturation levels drive the kinetic mechanisms of a crystallization process. There is a tremendous amount of research on the fundamentals of these processes,[56,57] but the prime components of these kinetics can be distilled down to simple equations.

Crystal growth rate (typically termed *G* and expressed in terms of micrometers per unit time) is a function of supersaturation—the higher the supersaturation, the higher the growth rate. Additionally, nucleation or formation of fine crystals (typically termed *B*, in terms of birth of new crystals per unit time) is also driven by the supersaturation. Therefore, controlling the supersaturation level over time can aid control of the levels of growth and nucleation achieved, hence presenting the opportunity to control the size of the crystals produced. Certainly for a production process, having high levels of both growth and nucleation will result in a very broad crystal size distribution, which is undesirable from a downstream handling perspective. Figure 3b shows schematically the supersaturation and relative growth and nucleation levels encountered in the cooling and nucleation example shown in Figure 3a.

Measuring the supersaturation levels offers significant insight into understanding the driving force and dynamics of the production crystallization. Many techniques exist for measuring concentration, but few offer the potential for in-line measurement. In-line is essential for supersaturation measurement, as the "crystallization" will continue to occur in a sample from a crystallizer, which may result in misleading information.

Measuring and quantifying the supersaturation can be an important tool for optimizing the crystallization. Spectroscopic techniques such at ATR-FTIR have become important in the characterization and control of crystallization processes. ATR-FTIR allows the user to measure and characterize the solution phase of the mixture with only minimal interference by the solids present in the mixture. This is due to the limited penetration depth of the light into the solution, resulting in a measurement of the wetted ATR surface. On occasion, the nucleation process can be observed if the nuclei are smaller than a few micrometers, but often the mid-IR spectrum of the particles is only weak compared to the spectrum of the dissolved species.

Supersaturation measurements are more difficult when cooling crystallization experiments are performed. MIR spectra are significantly affected by the change in temperature, mostly caused by changes in hydrogen bonding. To build an accurate quantitative model, these changes have to be taken into account in the calibration model. Band ratioing procedures or chemometric techniques such as partial least squares (PLS) often provide robust quantitative models as described in the work of Feng and Berglund[26] and Togkalidou et al.[58] Band ratioing procedures simplify the calibration and supersaturation measurement, an important requirement for process development. In the work of Feng et al.[26] this method is described and applied in the batch crystallization of succinic acid. The concentration profiles that are measured can be used for feedback control to determine the optimal cooling curve by keeping the supersaturation level close to the solubility curve, resulting in crystal growth rather than nucleation. Togkalidou et al.[58] uses principal component regression (PCR) and partial least square (PLS) for modeling the concentrations in a multiple-component system of different drugs in a mixture of solvents and antisolvents. They demonstrate that the concentrations of the different components can be measured with high accuracy, enabling control of the crystallization.

These techniques have been applied by Liotta et al.[25] to carefully control the crystal size of an active pharmaceutical ingredient (API). Liotta et al.[25] describe a stepwise approach to optimize the crystallization. First, they apply FBRM to determine the metastable zone. Characterizing the metastable zone provides the working range for controlled crystallizations. Next, they determine the calibration model of the dissolved compound using ATR-FTIR and PLS. They use the concentration data to study the effects of seeding and cooling rates on the final crystal size and shape. Finally, they use the concentration data as measured with ATR-FTIR to control the supersaturation close to the solubility curve for optimal crystal growth conditions.

From a production perspective, knowledge of the liquid-phase concentration helps determine the starting concentration for the process. This can be particularly useful if there is variable yield coming from a previous reaction step or if

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a distillation is needed. Also, tracking liquid-phase concentration within the solubility map helps highlight when the batch is over (i.e., maximum yield) and what that yield level is expected to be.

2.2. Seeding. A technique widely used in production crystallization to help control the size and number of crystals produced, as well as the polymorphic form, is "seeding". Seed crystals, added to a crystallizer before nucleation occurs, provide surface area for crystal growth and nucleation, hence offering the advantage of being able to control the onset of crystallization. Unseeded batches tend to exhibit batch-to-batch point of nucleation consistency problems (this is process dependent), which can have a dramatic influence on the size and number of crystals produced.

From a production perspective, some of the key components to take into consideration are ensuring the seeds (if added) are added before nucleation occurs and that they are not added too early (and hence to the right of the solubility curve as shown in Figure 2). This information is basic but important in terms of production performance. This highlights why knowledge of the solubility curve and metastable zone are vital.

Also, key variables in seeding include seed loading (i.e. wt % of seed), seed size, and how they are added. Typically, the smaller the seeds, the higher the surface area per unit mass, and hence the more opportunity for a growth-dominated process. Large crystals, relative to smaller ones, will provide less surface for growth and may result in secondary nucleation being the dominant crystallization mechanism during the process. It is difficult to generalize these areas specifically, but typically the smaller the seed size and the higher the seed loading, the easier it is to "control" a crystallization process with the minimum of process upsets throughout all process development and production.

Seeds can be added dry or in slurry form. Adding the seed in slurry form (either in antisolvent or mother liquor) may help the seeds disperse to their primary crystal size. Adding dry seeds may induce unwanted solvent entrapment and agglomeration, as the dry seeds may have aggregated during storage/preparation.

2.3. Cooling. The most dominant technique for performing a batch crystallization in the plant is through cooling. Cooling the batch reduces the solubility of material in solution, thereby forcing material out of solution. As discussed above, the material driven out of solution will result in nucleation and/or growth.

Obviously, there is a variety of cooling rates and curves that can be implemented in the production plant. So which one is best? In general, the rule of thumb for "optimum" cooling of a crystallization process would be to cool slowly at first, while the concentration of solids, and hence surface area for growth, is low. As the concentration of solids increases and the surface area is increased, supersaturation can be generated faster and still be consumed by the growing crystals. Thus, an increase in cooling rate is appropriate. This results in a nonlinear cooling curve. Parts a and b of Figure 4 show schematically a nonlinear cooling curve and the

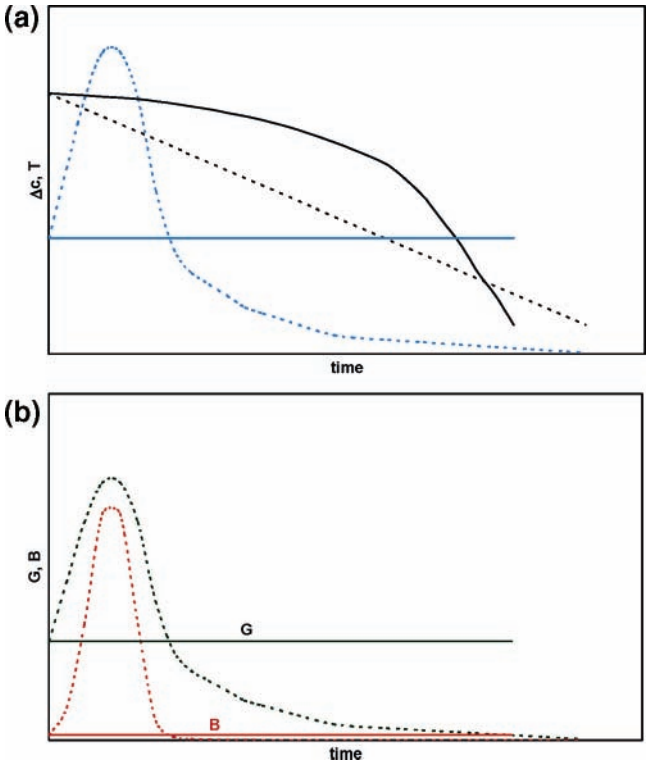

Figure 4. **(a) Schematic of supersaturation level during optimum cooling crystallization. Dotted lines represent cooling profile and supersaturation shown in Figure 3a. (b) Schematic of the growth and nucleation levels encounters during optimum cooling.**

relative growth and nucleation rate encountered during this cooling process. Cooling in this manner helps keep the supersaturation constant while simultaneously maintaining the operation of the process well within the metastable zone and close to the solubility curve.

Seeding and optimum cooling are illustrated schematically in Figure 5, with FBRM data utilized to highlight what is occurring and why.

Step A: Seeds are added and FBRM is utilized to track the seed addition and growth.

Step B: The batch is held isothermally, allowing the seed bed to grow and increase in mass. As the solution-phase concentration drops back to the solubility curve, the FBRM particle counts stop changing, highlighting that there is little dynamics in the crystal size distribution occurring.

Step C: As cooling is started, an FBRM statistic can be utilized to track the rapid rise in large material ($>100\ \mu$m), highlighting the growth-dominated nature of the process.

The technique described in Figure 5 can similarly be applied to all aspects of crystallization understanding and optimization. One of the key components of understanding and utilizing FBRM data in a production environment is to take advantage of knowledge of information about the process variables. For most production processes the dominant process variables (in terms of impact on the dimension of the crystals produced) include temperature, stirrer speed, and addition rate. Knowledge of these variables in addition to FBRM data provides an understanding for when a change has occurred and what is driving it. This is the key to the

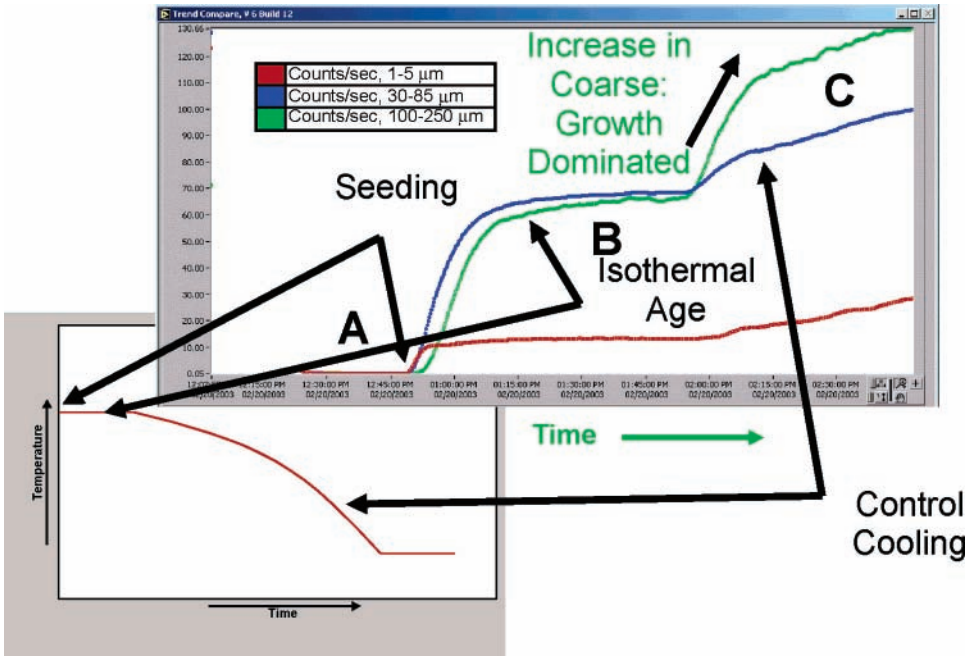

Figure 5. **FBRM data during a seeded crystallization with seed aging and subsequent cooling.**

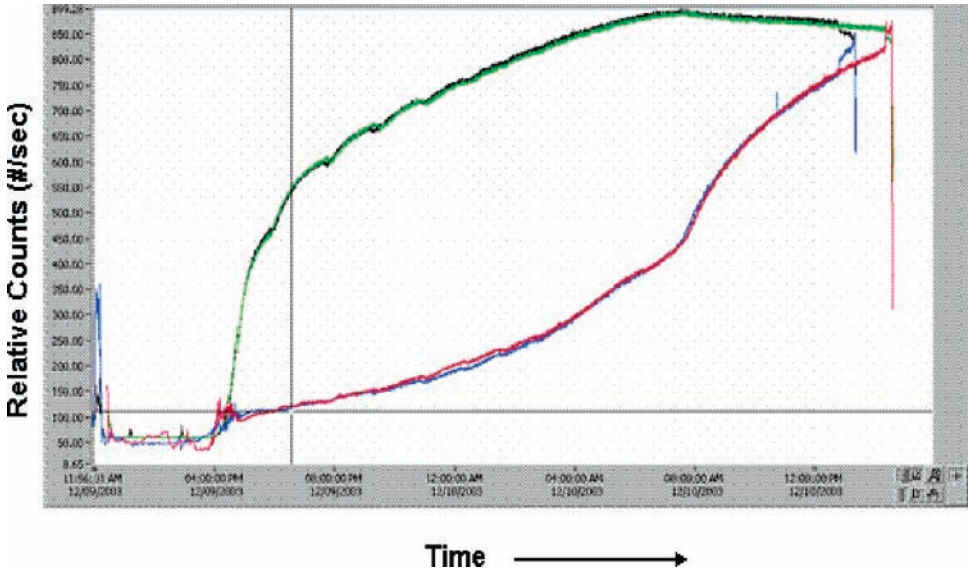

Figure 6. **Comparison of batch-to-batch aging.**

use of Process Analytical Technology (PAT) in crystallization processes—knowledge of the data as it relates to the process variables. With this understanding in place it may be possible to come up with ways to improve the robustness of the process.

As shown in Figure 5, hold time following seeding can be a very simple way of increasing the surface area of the seed bed before cooling. Additionally, hold time or age time at the end of the batch can be another process variable to play with. Knowledge of where you are within the solubility map should help highlight the batch yield. However, it is important to examine the behavior of the crystals, as this can indicate whether excessive breakage/attrition is occurring, particularly during an age period where the batch may be agitated for an extended period.

Figure 6 shows FBRM data from a laboratory-scale process that has variable batch aging time. One is aged for 2 h, the other for 4. The trend in particle counts indicates that the batches are almost identical in terms of size and number of crystals produced. However, when comparing the trend, one can observe that the batches are still changing right up to the point of being emptied from the vessel for filtration. This type of change would be indicative that the crystallization is not complete, and additional age time would be required to ensure the maximum yield. In other words, when the FBRM data reaches a steady state, it is a signal that no additional crystallization is occurring.

In many cases the formation of an unwanted amount of fines crystals, given the crystallization kinetics of the system, can be unavoidable. A useful technique for getting rid of

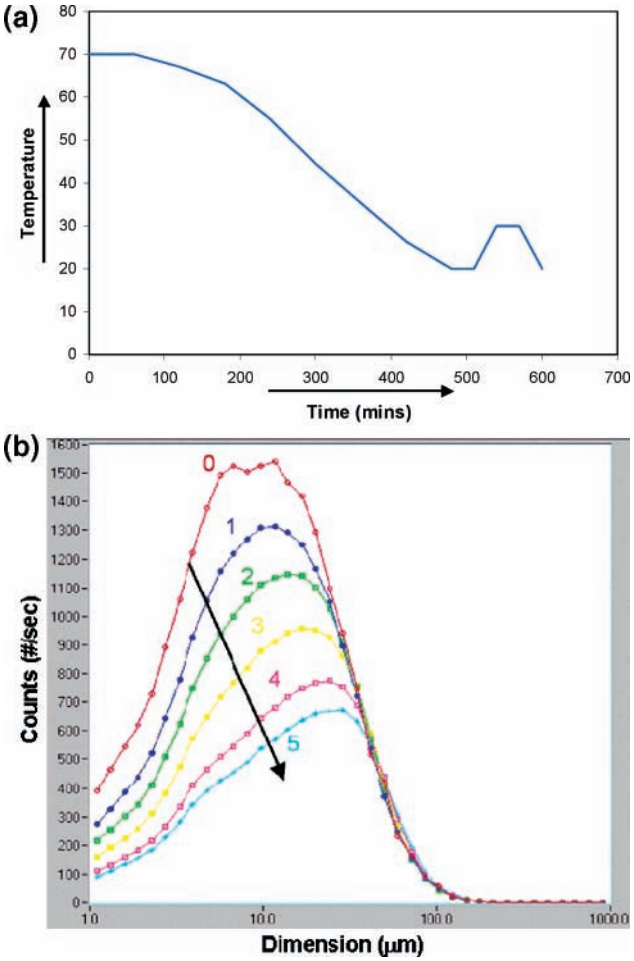

Figure 7. **(a) Temperature profile with temperature cycling. (b) FBRM distributions tracking fines dissolution during temperature cycling.**

unwanted fines crystals without losing yield is temperature cycling. The Gibbs−Thompson effect describes thermodynamically that smaller particles have a slightly higher solubility than larger ones. In effect, if you heat a slurry of crystals, the fines particles will dissolve at a faster rate relative to the coarse particles. Therefore, in a production process, if you warm the slurry (typically by an additional 5−20°C—depending on the solubility curve of the material and the quantity of fines needed to dissolve), the fines will preferentially dissolve; subsequently, cooling back down to the same temperature, the yield will be the same, but crystal size distribution will shift to the coarse end. Figure 7a shows a typical schematic of a temperature profile that may be used, and Figure 7b shows the resulting FBRM data.

This temperature cycling effect can also be implemented earlier on in the batch, perhaps even after nucleation, to optimize the size of the seed bed for subsequent cooling.

Additionally, if dendritic growth has occurred (Figure 8), it may be desirable to perform a temperature cycling step to remove these dendrites before they break off in the dryer.

2.4. Antisolvent Addition. An antisolvent is by definition a poor solvent—i.e. the solute will have relatively low solubility in it. Adding an antisolvent to a crystallization will further reduce the solubility of the solute in solution, forcing additional material out of solution. Similar to cooling rate,

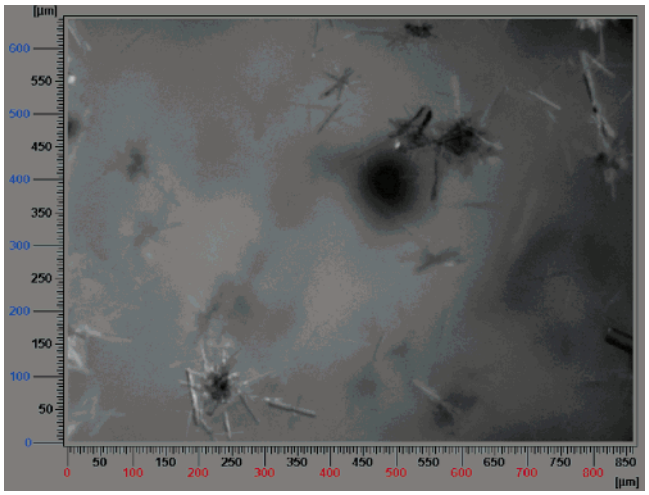

Figure 8. **PVM image of dendritc growth.**

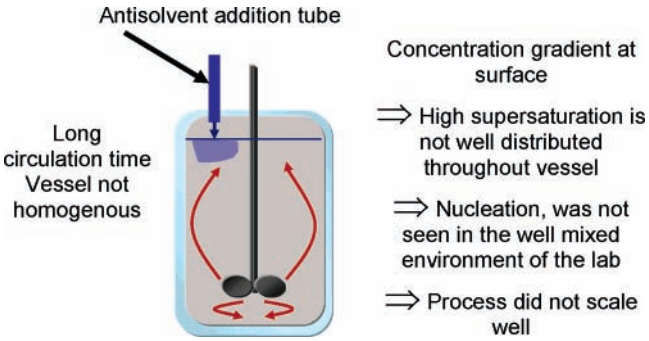

Figure 9. **Schematic of addition in the plant.**

careful control of the addition rate is important to control the rate of supersaturation generation and hence the size and number of crystals produced. There is a variety of ways of performing an antisolvent addition—adding it at the beginning of a process to help induce nucleation or adding it at the end of a cooling period to help enhance yield. Alternatively, a reverse addition process could be performed where seeds are in an antisolvent suspension and the saturated solution of the solute in a good solvent is added to the antisolvent.

In all cases, careful knowledge about the amount of antisolvent to be utilized is important. This relates to the desired yield and the relationship with the solubility curve. Additionally, mixing plays a significant role with regard to antisolvent addition rates in production crystallization processes.

In a laboratory environment, it is possible to get a very homogeneous concentration level throughout the vessel as the antisolvent is added. However, in the plant, there can be very localized concentration gradients (Figure 9) around the addition location, resulting in localized levels of supersaturation, and hence nucleation, that were not encountered in the lab.

Clearly, from a mixing perspective it can be desirable to add the antisolvent in the vicinity of the agitator, but in many cases, encrustation on the impeller can occur. Additionally, care should not only be taken with the addition rate but also the pipe diameter. In other words, considering the same flow rate, a pipe with a smaller diameter will have a higher linear velocity of the antisolvent added, hence giving better

penetration and dispersion of the antisolvent below the surface. This would become more and more important when considering reactive-type crystallizations with fast kinetics.

2.5. Filtration. Filtration in a production environment has a variety of factors influencing it. Some are outside the realm of crystallization influence—such as solids build up ("heel") on the filter cloth. Additionally, the type of filter used can have an effect on filtration rate. From a PAT perspective, there has been a tremendous amount of emphasis on the use of NIR for monitoring the solvent content in drying but less emphasis on the root cause or variability within the dryer—variability in the size and solids loading coming from the crystallizer.

In general, the rate of filtration will be governed by the specific cake resistance of the filter cake that is formed. The driving force within this cake resistance term is the "particle size and number". For instance, a process that generates many small particles (fines) will have a high specific cake resistance. As FBRM measures a function of the size and number of crystals produced, it is possible to correlate FBRM data in the crystallizer directly to the filtration rate. This can be done by using certain FBRM statistics or nonlinear regression of a combination of statistics. Additionally, laboratory experiments can be utilized to assess the cake compressibility, which is particularly relevant if a centrifuge is utilized.

3. Conclusions

Production crystallizations can be difficult processes to characterize and improve. The advance and use of in situ tools offers a unique opportunity to understand and optimize production crystallization processes. Monitoring the liquid-phase concentration (and hence the prevailing supersaturation level) in production highlights the starting point and potential yield of the process, as well as areas where problems could occur (i.e. high levels of supersaturation). Monitoring the solid phase in production highlights the process kinetics (nucleation and growth levels) as well as a route to understanding how the process variables impact the process. These technologies are well established in production for process monitoring and troubleshooting of crystallization processes, but they also open up the possibility of control of production crystallization processes.

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