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Crystallization Process Development of an Active Pharmaceutical Ingredient and Particle Engineering via the Use of Ultrasonics and Temperature Cycling

Soojin Kim,* Chenkou Wei, and San Kiang

Process Research and Development, Bristol-Myers Squibb Company, New Brunswick, New Jersey 08903, U.S.A.

Abstract:

Process development of a Bristol-Myers Squibb drug substance candidate involved the development of crystallization and particle engineering protocols to address polymorphism, oiling out, and particle size control issues. Two monotropic polymorphs were evaluated, and one was determined to be thermodynamically more stable. The oiling problem was solved by adjusting the polarity of the solvent system and conducting controlled nucleation at low supersaturation. Two protocols were developed to produce the desired form consistently in high quality and yield with a short processing time. Slow crystallization was required to ensure product quality since the final crystallization served as an important purification step, but slower crystallization led to larger crystals. To avoid dry milling, ultrasound was used for particle size reduction in the crystal slurry post-crystallization. Temperature cycling followed for particle size uniformity. The scale-up involved use of an ultrasonic tube through which the crystal slurry was passed continuously. The protocol was successfully executed in multikilogram-scale GMP batches.

Introduction

Crystallization is a critical operation in the manufacture of active pharmaceutical ingredients (APIs). The development of a chemical process for the API final step may face many challenges related to crystallization and particle characteristics. Commonly encountered challenges include purity, yield, oiling-out/amorphism, polymorph control, and compound stability during processing. Other issues related to particle formation are particle size and distribution, crystal habit, filterability, crystal attrition or agglomeration, and the bulk powder properties related to formulation, such as flowability, bulk density, and compactibility. Other important considerations are the scalability and reproducibility/robustness of the process to yield consistent product.

Many of the problems can be addressed by the development of crystallization protocols with careful process control and optimized process conditions, such as solvent/antisolvent choice, temperature, agitation, and seeding.[1−3] The other issues related to particle and bulk properties may be addressed by the development of specialized crystallization techniques, using an approach to "engineer" particles during crystal formation to manipulate the particle size or habit through the control of nucleation and growth mechanism.

A Bristol-Myers Squibb (BMS) drug substance candidate, Compound A, faced a number of challenges during the early development of the final step crystallization. The first problem was the tendency of the compound to "oil-out" or to form a partly amorphous solid. Although in most cases the crystallization gave largely crystalline material, the crystallization required a long processing time and had a serious problem with scalability. In addition, on many occasions an undesired polymorph was generated. Thus, it was important to develop a more controlled crystallization process to achieve reliable polymorph control and a consistently high product quality.

The other major issue with Compound A crystallization was particle size and uniformity. The API was being developed for a low-dose formulation, and thus small, uniform particle size was essential for blend/dosage uniformity. A dry-milling operation was highly undesirable for this compound due to concerns about the physical instability of the crystals under the stresses applied during milling. Moreover, dry milling in general is undesirable in the large-scale manufacture of APIs due to safety concerns related to the potential for dust explosion. There are also possibilities of reduced yield, personnel exposure to a pharmaceutically active compound, noise, extra costs related to special equipment for safety, as well as capacity and productivity issues.[4]

There are widely used techniques for obtaining small particles directly by crystallization. These largely involve fast nucleation under high supersaturation conditions to produce a large number of small particles.[5] However, when fast crystallization is caused by rapid cooling or antisolvent mixing, the potential for solvent or impurity entrapment is large,[6] and thus adverse effects on product purity may result. In addition, fast crystallization is also generally undesirable for polymorph control. For Compound A, purification was an important function of the final step crystallization. Therefore, the crystallization had to take place slowly to ensure cleanup of process impurities, but slow crystallization would cause the crystals to grow bigger. Hence, we needed

* Author for correspondence. Mailing address: Bristol-Myers Squibb, 1 Squibb Dr., New Brunswick, NJ 08903, U.S.A. Phone: (732) 227-7025. Fax: (732) 227-3942. E-mail: soojin.kim@bms.com.

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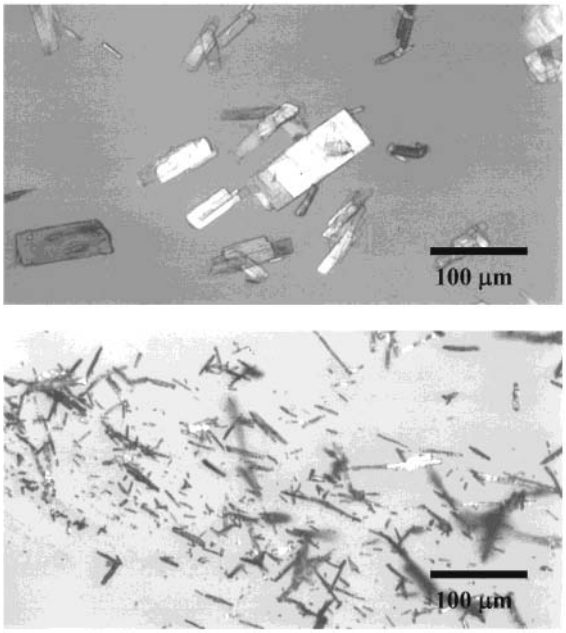

Figure 1. **Optical microscope images of crystals of Form I (plates) and Form II (needles).**

to find an alternative method of obtaining small particles other than the fast crystallization method or dry milling.

In the process development for Compound A, the combination of the compound's innate characteristics and the product requirements posed difficulties for crystallization and led to the use of unconventional techniques for particle engineering. This report describes the unique challenges and goals faced during the crystallization development and provides illustrative findings and solutions that successfully resulted in a robust crystallization process for API with the desired particles properties.

Polymorphism

During the early lab development, two polymophic forms were discovered. The two forms had similar melting points (75 and 72 °C), but each had a unique powder X-ray diffraction (PXRD) pattern and habit. Form I was known as "plates," and Form II was known as "needles." Figure 1 shows the optical microscope images of Form I and Form II crystals. Although many lab batches were of Form I, occasionally Form II was obtained.

The two polymorphs were evaluated for their relative thermodynamic stability in the process solution. For quick evaluation, a slurry of the polymorph mixture (1:1 weight ratio) was aged in the process solvent (ethyl acetate/cyclohexane) at 30 °C for several hours. Form II completely converted to Form I as confirmed by PXRD and optical microscopy. When the crystallization was forced to occur faster by rapid cooling or evaporation, Form II crystallized out initially and slowly converted to Form I. On the basis of these observations, it was confirmed that Form I was thermodynamically more stable and Form II was a metastable and kinetically faster forming polymorph. It was also further corroborated, by aqueous solubility and heat of solution results, that Form I was thermodynamically more stable than Form II. This kind of phenomenon has been widely observed

Table 1. **Solubility of Compound A (Form I) at 20 °C**

solvent	solubility (g/mL)
ethanol	0.55
acetone	0.46
isopropyl alcohol	0.39
ethyl acetate	0.22
isopropyl acetate	0.26
methyl *tert*-butyl ether	0.028
toluene	0.15
cyclohexane	<0.001
heptane	<0.001
water	<0.001

and sometimes referred to as "Ostwald rule of stages".[7] Often in crystallization processes, a metastable phase crystallizes out first and transforms to a more stable phase at a rate specific to the compound, depending on the relative solubility of the two phases in the solvent. For Compound A the transformation from Form II to Form I was irreversible (monotropic) over the temperature range of 0−60 °C, and the transformation rate was in the order of several hours. Therefore, to isolate Form I it was important to ensure that crystallization occurred slowly and in a controlled manner. In addition, seeding with the desired form prior to crystallization was helpful to control the form.

Crystallization Process Development

Compound A exhibited high solubility in most solvents with the exception of water, heptane, and cyclohexane. Table 1 lists the solubility of Compound A in several common solvents. The earliest small-scale attempts thus used a mixture of a small amount of solvent and a larger amount of antisolvent. Using ethyl acetate/cyclohexane at 1:5 volume ratio (0.18 ethyl acetate mass fraction), the compound was induced to crystallize under high supersaturation. The crystallization occurred through initial "oiling-out," followed by seeding the oily suspension and cooling, effecting crystal growth over 20 h. The resulting crystals were highly inhomogeneous, containing hard agglomerates and partially amorphous materials. The process was considered not scalable.

Development of a new crystallization protocol involved an investigation of the polarity of the solvent system. The polarity index of ethyl acetate being 4.4 and that of cyclohexane being 0.2, in the old protocol the initial polarity of the solution in ethyl acetate was shifted drastically to a nonpolar environment by the abrupt addition of a large amount of cyclohexane. In this case, the oiling-out appeared to be related to the incongruity of the compound's and solvent system's polarities. We could avoid oiling-out by using an initial solvent composition of 2:1 volume ratio (ethyl acetate:cyclohexane; 0.69 ethyl acetate mass fraction), keeping the overall polarity in the mid-region while inducing nucleation from seeds by slow cooling. Once the nucleation started, cooling was stopped to allow the crystallization to progress at low supersaturation. Hence, the crystallization

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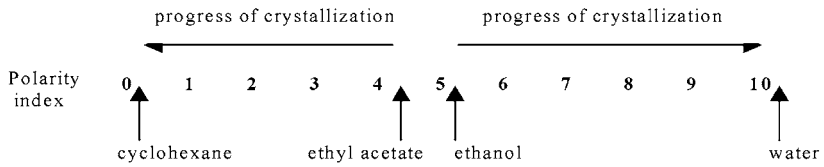

Figure 2. **Polarity of solvent systems and the change of polarity during crystallization.**

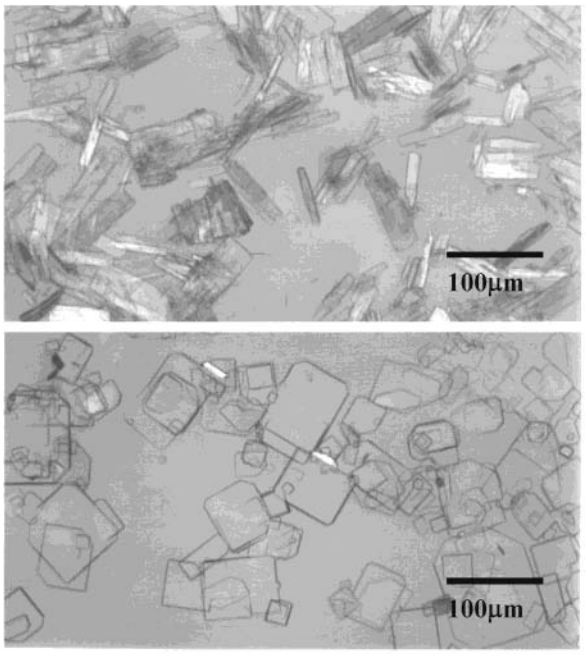

Figure 3. **Optical microscope images of crystals produced from ethyl acetate/cyclohexane process (top) and from ethanol/water process (bottom).**

occurred in an initially lower solvent volume but under a more controlled environment. As the crystallization proceeded well and more crystals were generated to provide enough surface areas for further growth, an additional amount of antisolvent (cyclohexane) was added gradually to increase the yield. This new process produced consistently uniform "plate-like" crystals of the desired form in a shorter process time (3 h) in 95% yield.

On the basis of the success of the ethyl acetate/cyclohexane protocol, we investigated the use of the more "green" solvent system, ethanol/water, on the other side of the polarity index spectrum (Figure 2). Similarly, the nucleation was initiated in the mid polarity region by seeding the solution at low supersaturation (2:1 volume ratio of ethanol/water; 0.67 ethanol mass fraction), and the overall polarity was allowed to change more gradually toward the high end by the slow addition of water. The crystallization proceeded under good control, and crystals of the desired form were produced in high quality and yield (95%) in a short processing time (3 h). The particles from the ethanol/water process also had "plate" morphology, but they were more "square-like" when compared to the morphology from ethyl acetate/cyclohexane (Figure 3). The crystal structure of solids obtained from both processes was identical as determined by PXRD.

Figure 4 shows the solubility of Form I at 20 °C as functions of solvent composition in ethanol/water and ethyl acetate/cyclohexane systems. Figure 5 shows the schematic

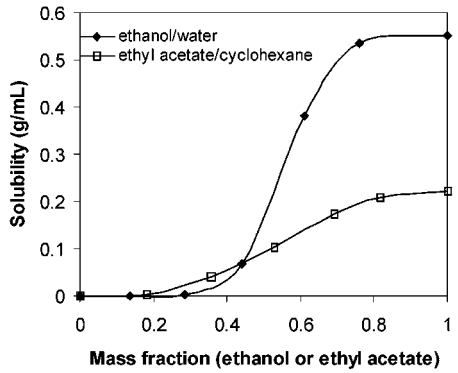

Figure 4. **Solubility of Form I at 20 °C in ethanol/water and ethyl acetate/cyclohexane.**

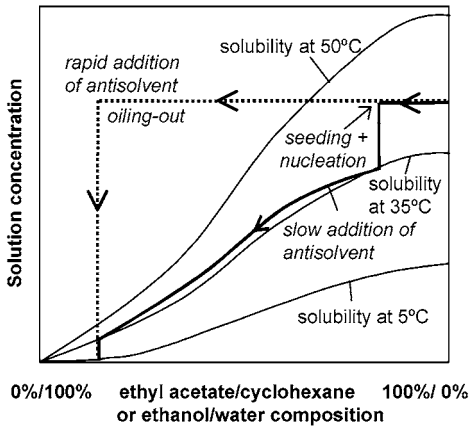

Figure 5. **Schematic solution phase diagram representing the crystallization processes.**

phase diagram illustrating the crystallization courses. The extent of crystallization is represented by the decrease of the solution concentration as a function of solvent composition. The figure depicts the two crystallization processes, one from the early protocol involving oiling and high supersaturation (dotted line), and the other involving low supersaturation and more controlled crystal growth (solid line).

The crystallization played an important role in the removal of many process impurities generated in the final step chemistry. Hence, the protocols required slow crystallization to ensure product purity as well as the correct polymorph. The ethanol/water process was demonstrated to provide better purification capacity with respect to a particular process impurity that was difficult to purge. The ethanol/water process also proved to be more robust for polymorph control, in that the process was unable to produce the undesired polymorph no matter how fast the crystallization was forced to take place.

Particle Engineering

As the process chemistry continued to develop, the impurity profile of the final step chemistry improved. Not

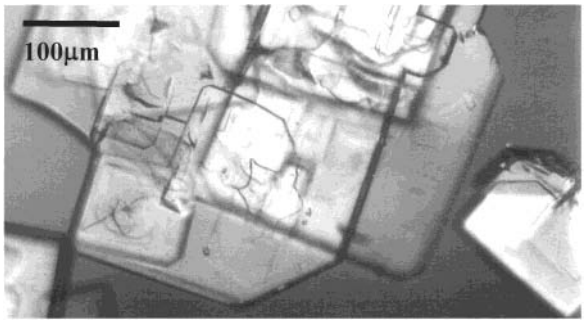

Figure 6. **Large crystals obtained in ethanol/water system from high purity material.**

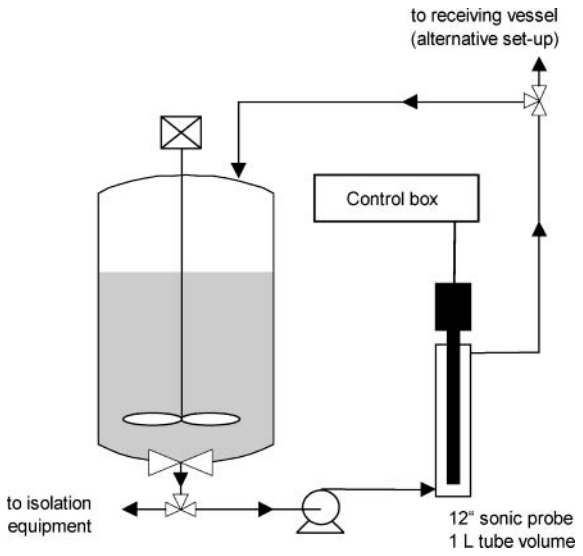

Figure 7. **Schematic diagram of the in-line sonication setup in the scale-up process (not to scale).**

unexpectedly, the crystal size became larger as the system became cleaner. This indicated that the presence of some process impurities at significant levels in the crystallization system had aided particle size control by inhibiting crystal growth beyond a certain extent.[8] In some very clean systems, particles as big as 250 μm were observed from the ethanol/water system (Figure 6). The desired mean particle size was <30 μm for the dissolution rate requirement and content uniformity in the small dosage form.

Commonly used methods of forming small crystals from high supersaturation systems, such as by rapid cooling or rapid mixing with antisolvent (e.g. impinging jet crystallization[9]), could not be considered due both to the propensity of the compound to oil out and the likelihood of impurity entrapment. In addition, dry milling for particle size reduction could negatively affect the crystal quality due to the low melting point and soft texture of the crystals. There was a serious potential for the crystals to partially lose crystallinity under stresses generated on crystal surfaces during milling.

Circumventing the need for dry milling or the fast nucleation method, we obtained small particles by the application of ultrasound in the crystal slurry after normal

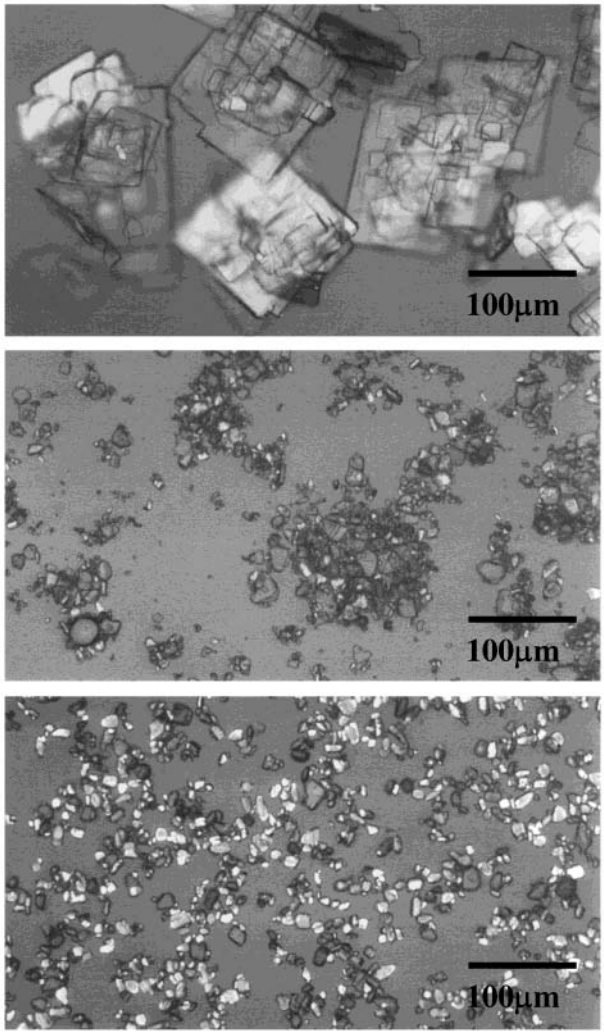

Figure 8. **Large crystals as produced from ethanol/water (top) were size-reduced by ultrasonic treatment in the crystal slurry (middle), and subsequent temperature cycling removed fines and rough edges to produce more uniform small particles (bottom).**

crystallization and before filtration. Thin platelike crystals broke up easily by ultrasound without any adverse effects on the crystal quality. The product purity and crystal form were maintained since the sonication process did not interfere with the crystallization process. In the laboratory development, the process was demonstrated in a batch mode with an ultrasonic probe operating at 20 kHz frequency with the effective energy input of 100−200 W for 10 g of the material. Crystals with initial particle size of 100−200 μm were reduced to particles smaller than 20 μm.

The scaled-up process involved passing the crystal slurry through a sonic tube with the internal volume of 1 L, frequency of 20 kHz, and power input of 1000 W. The crystallization and particle engineering protocols were successfully carried out in GMP batches of 1- and 15-kg scales. In the scale-up runs, the slurry was processed through a recirculating loop containing the in-line sonic tube as illustrated in Figure 7. Alternatively, the slurry could be processed through the sonic tube from one vessel to another. The throughput and processing time would be determined by optimization of the slurry flow-rate, power input, and

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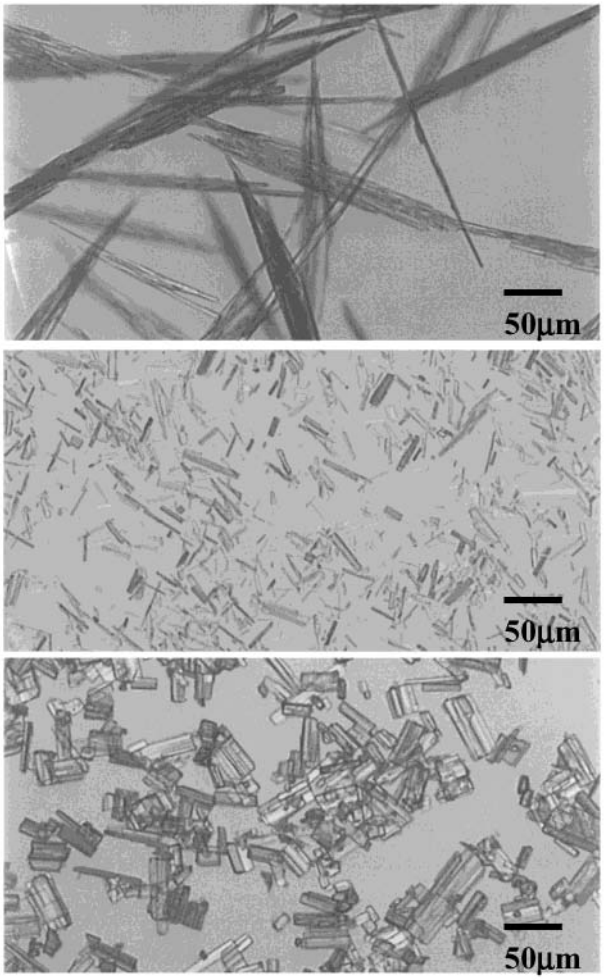

Figure 9. **Needlelike crystals of another BMS compound as crystallized (top); the particle length of the needles were reduced by application of ultrasound in the crystal slurry (middle); subsequent series of temperature cycling and ultrasonic treatment produced "brick-like" morphology (bottom).**

pressure, which in turn would determine the final particle size. Multiple ultrasonic units could be used in parallel for higher throughput.

The fines and rough edges generated due to the crystal fracture by ultrasound were removed by a subsequent temperature oscillation protocol[10] applied to the sonicated slurry, which was used to accelerate the effect of Ostwald ripening. For a single cycle, the slurry was subjected to a temperature fluctuation of 35 °C over a 4.5-h period. This process produced changes of solubility during the cycle and effected faster dissolution of the fine particles and rough edges during the heating period followed by their recrystallization onto the existing crystals during the cooling period. A few repeat cycles helped achieve a much narrower particle size distribution. Figure 8 shows the crystals before and after sonication and after temperature cycles for particles uniformity.

This ultrasound technique was also used on another BMS compound to reduce the particle length of "needle-like" crystals (Figure 9). The needlelike crystals exhibited fluffy, fiberlike bulk property, posing a difficult handling problem. Breaking up the long needles into shorter rods helped increase bulk density as well as meet the particle size specification required for this drug substance. Subsequent temperature cycling applied to the ultrasound-treated crystal slurry helped grow the shorter needle segments into thicker rods. A series of combined sonication and temperature cycling produced "brick-like" crystals with much improved bulk density, flowability, and bulk handling of the API. This technique of crystal habit modification from "needles" to "bricks" had been previously developed for a BMS drug substance and reported elsewhere.[11]

Although ultrasound has been well-known as a useful tool for reaction, nucleation, crystal growth, or deagglomeration,[12−14] its application for particle-size reduction has been seldom reported. The previously reported use of ultrasound to increase bulk density of irregular or needlelike crystals is described in an European patent.[15] In our studies, the ultrasound technique has been demonstrated to be highly effective for particle-size reduction of APIs with platelike or needlelike crystal habits.

Conclusions

Crystallization process development of active pharmaceutical ingredients often needs to address issues of polymorphism, oiling out, and particle size/habit modification. Proper development of well-controlled crystallization processes is critical for product quality, uniformity, and efficiency. Screening of polymorphs early in the development allows selection of the thermodynamically more stable form, thereby minimizing chances of form conversion during API manufacturing. Effective crystallization protocol development may involve consideration of solvent/antisolvent ratio and polarity, supersaturation degree, and seeding point. Proper control of supersaturation during crystallization is essential for obtaining the desired polymorph, high product purity, and good crystal quality. Ultrasound was demonstrated as a useful tool for particle size reduction, especially for crystals with platelike or needlelike habits, and a subsequent temperature cycling protocol was shown to be highly effective for particle uniformity and crystal habit modification.

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