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Crystal Product Engineering in the Seeded Cooling Crystallization of Adipic Acid from Aqueous Solution

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ABSTRACT: The effects of seed preparation method and operating conditions during the batch cooling crystallization of adipic acid in aqueous solution are reported. Seeds were prepared by cooling crystallization with and without ultrasound and by grinding commercial crystals. The effects of cooling rate, initial concentration, seeding load, and supersaturation at the point of seeding on the crystal size distribution and crystal habit of the final product were studied to characterize the conditions for the achievement of a growth-dominated operation. A seed loading at 10% of the total mass of dissolved material ensured a near unimodal distribution of product crystal particles for any type of seed source investigated. Higher values of initial concentration/temperature led to larger particles; however the nucleation rates increased as well, requiring slower cooling rates to maintain the growth predominantly within the metastable zone. A slow cooling (0.1 K/min) applied exclusively during the first 10 °C subcooling, followed by a higher rate (0.5 K/min) provided large product crystal particles with reduced secondary nucleation, shortening the operation times. Seeding with round crystals obtained from a continuously insonated crystallization resulted in a product of more regular crystal habit with increased thickness than seeding with conventionally ground material.

1. INTRODUCTION

Crystallization processes in the pharmaceutical industry are mainly carried out in a batch-wise manner for greater flexibility and shorter process development times.[1] In unseeded crystallization systems, the spontaneous formation of crystals usually occurs at high supersaturation with consequent high nucleation and poor reproducibility in the product as a result.[2]

Inoculation of seeds in supersaturated solutions is commonly employed to control the final product characteristics by acting on the nucleation process and circumventing uncontrolled spontaneous primary nucleation. Furthermore, adding seeds is an appropriate way to operate under reproducible conditions. Four major circumstances can be identified as candidates for seeding: (i) to initiate crystallization if the system crystallizes with difficulty, (ii) to control the crystal size distribution, in most cases to produce large crystals with a narrow size distribution and to avoid fines, (iii) to achieve a "single-crystal-growth", where seeding is necessary to obtain crystals of high purity, (iv) to avoid encrustation through spontaneous nucleation, and the control of the polymorphic crystal form.[2]

In the case of adipic acid crystallization from water, where the system does not crystallize with particular difficulty and is reported to exhibit different polymorphic forms below 136 K,[3,4] seeding policies can be directed to the production of large-size product crystals of unimodal distribution, to improve downstream processing efficiency and total separation economics.[1]

The efficacy of seeding depends on the growth propensity of the seed crystals. Origins, purity, temperature, and amount of seeds are all influencing parameters. Seed crystals should have a large surface area, so that the use of fines is often preferred, for example in the form of milled material, and the amount of seeds should be the smallest possible, so as to ensure predominance of growth and narrow size distributions in the final product.[2] However, small particles tend to agglomerate, decreasing their effective surface area, while grinding processes can introduce impurities, with negative consequences in sterile operations required for pharmaceutical applications.

In the case of seeding targeted to yield only grown seed crystals in the product with no new nuclei, the final crystal size is given by McCabe's ΔL law.[5] The seed loading can be defined as the ratio of inoculated seeds' mass, W_s, to the amount of solute dissolved in the nurturing solution before inoculation. However, the concentration of seeds is often referred to as ratio between the mass of inoculated seeds and the mass theoretical yield, Y_t,[2,6,7] calculated from mass solubility data at initial and final temperature; the mass concentration of seeds C_{seed} can be expressed as

$$C_{seed} = W_s/Y_t \quad (1)$$

where W_s is the amount of added seed .

The final mass of crystals produced, W_f, includes the contribution of the mass of seeds (W_s) and the total mass of dissolved solute turned into crystals, defined as Y_t:

$$W_f = W_s + Y_t \quad (2)$$

Under the assumption of pure growth of seeds, with virtually no nucleation, and spherical particles, the number (N) of seed crystals is assumed to be conserved. Defining a characteristic size L_s for original seeds and L_{sp} for product crystals, the ratio

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between the final mass of crystals and the mass of inoculated seeds becomes

$$\frac{W_f}{W_s} = \frac{N\rho_s L_{sp}^3}{N\rho_s L_s^3} = \left(\frac{L_{sp}}{L_s}\right)^3 = \frac{Y_t + W_s}{W_s}$$
$$= \frac{Y_t(1 + C_{seed})}{Y_t C_{seed}} = \frac{1 + C_{seed}}{C_{seed}} \quad (3)$$

where ρ_s is the density of solids. Therefore, eq 3 can be rearranged as

$$\frac{L_{sp}}{L_s} = \left(\frac{1 + C_{seed}}{C_{seed}}\right)^{1/3} \quad (3.1)$$

L_s can be chosen as the mean mass size of the original seeds and L_{sp} as expected mean mass size of grown seeds, that can be evaluated from this equation and compared with the effective mean mass size of product crystals L_{wp} measured experimentally.[6,7] A good agreement between L_{wp} and L_s validates the assumption of pure growth of seed, while $L_{wp} > L_{sp}$ can be attributed to agglomerative phenomena with consequent decrease in the number of seed crystals during crystallization. In the latter case, agglomeration among seed crystals can be reduced by selection of a large seed size.[6]

At a low seed concentration the transient supersaturation profile is expected to have an initial high peak; reduced (total) surface of the seeds will cause low deposition rates of solute, and a massive production of nuclei. On the other hand, at high seed concentration, the transient supersaturation profile should present a lower supersaturation peak at the beginning, corresponding to fewer nuclei produced.

The amount and the effectiveness of seeding are directly correlated to the rate of cooling. Two opposing effects are involved; the added seeds cause a flux of mass out of the solution, hence decrease the supersaturation via their growth, which is directly proportional to the amount of surface of seeds, while the cooling increases the supersaturation. These processes have to be balanced in such a way that supersaturation does not reach or cross the limit of the metastable zone and no spontaneous nucleation occurs.[1,2,5] Typical values for the amount of seed are given as $C_s \approx 10\%$.[2]

As the cooling rate affects the increase in supersaturation, the higher the cooling rate, the greater the amount of seeds is required to avoid spontaneous nucleation. Slow cooling rates, such as 0.1 K/min, offer the use of a smaller amount of seeds but are not economically attractive due to the longer time required for cooling.[8] A convex cooling program may be used to optimize this aspect, while a linear rate at the cost of more seeds can be a simpler compromise.[9]

Finally, inoculation of seeds has to be operated at a correct time during the development of the supersaturation profile, within the metastable limits, to avoid uncontrolled conditions. Early inoculation, viz. when the solution is still undersaturated, will result in at least partial dissolution of seeds, while a late operated seeding, when the metastable limit has been crossed, will be ineffective as the solute material may already have crystallized at high nucleation rates (because of high supersaturation levels), with consequent prolific and uncontrolled nucleation, giving a product of inferior physical characteristics.[2,10] Besides, the border of the metastable zone is not a physical constant but depends on a number of parameters, including the degree of purity of the investigated compound, cooling rate and presence of foreign entities in solution.[2]

This present work concerns an experimental investigation on the effect of cooling rate combined with seeding load, initial concentration and supersaturation at seeding on the production of large crystals in the cooling crystallization of adipic acid from aqueous solution. Two different sources of seeds have been used: commercial adipic acid after grinding treatment and rounded shaped adipic acid particles from batch insonated experiments. The metastable zone limits are measured in first instance to determine the operating limits for an effective seeding. A comparison with unseeded experiments at the same values of initial concentration and cooling rates is proposed to highlight the benefits of seeding. A review is provided on the effect of each parameter on the final habit and particle size distribution, with discussion of challenges and strategies.

2. EXPERIMENTAL SECTION

2.1. Materials. Adipic acid (>99.5% pure) was supplied by Sigma Aldrich. Deionized water was used as solvent.

2.2. Apparatus and Operating Procedure. Lasentec FBRM and Mettler Toledo Multimax 50 mL crystallizers were used to determine both solubility of adipic acid in aqueous solution and the metastable zone limit. Lasentec technology allows in situ monitoring of particle chord length counts throughout the experiment. To estimate the solubility conditions, a batch of defined composition was heated up at 0.1 K/min: the temperature of full dissolution was established as indicative of the solubility temperature. The metastable zone limit was instead characterized by determining the temperature value at which spontaneous nucleation occurred in cooling experiments of solution of defined compositions. For this purpose, two different cooling rates were selected, 0.1 and 0.5 K/min.

Batch crystallization experiments were mainly performed in Mettler Multimax vessels (ID = 32 mm) equipped with a three-blade marine-type glass stirrer. Stirrer speed was set at just suspension speed of 500 rpm to ensure well-mixed crystal suspension avoiding both vortexing and bubble formation. Experiments with the highest initial composition investigated were carried in a jacketed 500-mL flat bottomed reactor with HEL automate platform as explained in the following section.

Typically, an aqueous undersaturated solution of adipic acid was cooled down to 20 °C by linear cooling and aged for at least one hour to ensure achievement of stable conditions, in terms of particle counts. At the end of the run the suspension was drawn from the crystallizer, and product crystals were separated by filtration under suction and dried in an oven overnight. Malvern Mastersizer 2000 was used to measure the volumetric particle size distribution (PSD), but also the volumetric mean diameter L_{43} and the uniformity U, defined as the absolute deviation from the median of the distribution. The instrument provides particle size measurements referring to spherical particles with equivalent volume as the measured ones, that makes convenient to use eq 3 valid for spherical shapes. Each sample was analysed three times at least. Measurements were made on wet material to ensure an adequate obscuration value, and all particles were detected.

The shape of crystals was investigated using a Nikon ECLIPSE E600 POL optical microscope. Images were recorded by means of an Olympus video camera module attached to the microscope. Further morphologic investigation was carried out using a

scanning electron microscope (SEM), using magnifications up to 1000.

Seeds used for the experiment were mainly derived by grinding raw material from the supplier to reduce size and narrow the PSD of the seeds. However, a number of experiments were carried out using the seeds from the crop of batch experiments continuously insonated with a nominal ultrasonic power of 8.47 W/100 g of slurry.

Three values were selected for the amount of seeds, corresponding to 1%, 5%, and 10% of the total amount adipic acid dissolved at the beginning of the experiment.

3. RESULTS AND DISCUSSION

3.1. Operating Challenges. Dry seed crystals were used in the initial experiments. Under these conditions, seeds tended to float on the liquid surface. Crystal formed and aggregated on the liquid surface in the form of an encrustation on the top of a clear solution, with greater visible segregation. For effective seeding experiments, seeds were added as wet crystals, using a saturated solution at room temperature as carrier liquid; this procedure ensured that seeds were added close to the stirrer and easily dispersed.

It is suggested[2] that the surface of seeds can be activated by preparing a slurry in which dissolution of the outer layer causes the surface activation. Furthermore, slurry is easier to handle than powder and does not create dust. However, as the carrier mother liquor is introduced in hot solution, it is expected that its temperature increase causes partial dissolution of the seeds. This procedure induces activation of seeds, and it is expected that the fines, characterized by higher dissolution rates, are eliminated. The amount of seeds added, W_s, was increased by a quantity corresponding to the expected dissolved mass (estimated as the difference of solubility values at the temperature before and after the inoculation).

Finally, when a Multimax vessel was filled with 50 mL of solution and the initial concentration was chosen higher than 9 g of solute/100 g of solvent, the stirring visibly appeared inefficient with crystals forming an encrustation layer on the top of a clear mother liquor. The phenomenon was ascribed to the high ratio H_{50} /ID (= 1.9), where H_{50} is the height of liquid for 50 mL of solvent and ID represents the internal diameter of the vessel, coupled with rotational speed of 200 rpm. Adequate stirring, without visible segregation of crystals, was achieved by increasing the rotational speed to 500 rpm and reducing the content of the vessel to 40 mL of solvent (H_{40}/ID = 1.5). However, in the case of highest initial composition investigated, the encrustation on the top of the liquid was often observed even at increased rotational speed and reduced ratio H/ID; therefore, the experiments at 18 g solute/100 g solvent were carried out in a crystallizer with comparable values of height of liquid and internal vessel diameter and 500 mL volume. In scaling up agitated tanks, mixer speed generally decreases and tip speed increases, resulting in lower average shear and maximum shear rate at the blade tip, with a wider distribution of shear rates on scale-up. For crystallization, the average size can be larger and the size distribution wider in the large tank. However, at high Reynolds numbers, the concepts of shear, mean shear, and the impeller rotational speed become unimportant relative to the impeller tip velocity as viscosity is no longer the mechanism by which momentum is transferred.[11] Size distribution measurement from the different scales adopted, at the same operating conditions, revealed comparable values of mass mean diameter L_{43} (difference up to 0.6%) and difference in the uniformity not greater than 7%. For this reason, the comparison in size distribution results based on the different scales adopted is deemed to be consistent.

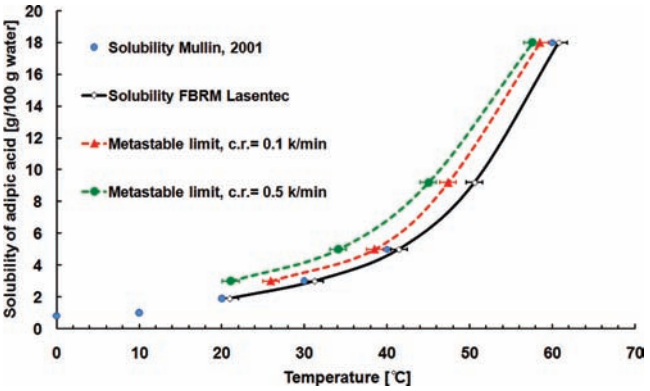

Figure 1. Solubility and metastable limit of adipic acid in water with standard error bars.

3.2. Solubility and Metastable Zone Width. Measured solubility concentration data were compared with the literature.[5] The units used are mass of solute on a solvent basis, and the results are presented as a function of the temperature in Figure 1. The nucleation temperature corresponds to a sharp increase in the particle count per unit time, in the chord size range 1−1000 μm, monitored by Lasentec FBRM. Measured values present a good agreement with the literature ones, with differences in solubility temperatures with literature data provided by Mullin (2001) lower than 1.5 °C within the investigated range of concentrations.

The onset of crystallization was also detected from the trend of the difference between the reactor temperature, T_r, and the coolant temperature in the vessel jacket, T_j, as the exothermicity of the nucleation process is compensated by an increased temperature difference $T_r - T_j$ (Figure 2). The temperature gradient between reactor and jacket presents a peak when crystallization starts. The method provided data in agreement with FBRM results, but only for the highest (absolute) values of cooling rate.

The global trend of results revealed that spontaneous nucleation occurred at low subcoolings, varying between 3 K at the highest concentration investigated (18 g of solute/100 g of solvent), and 10 K for the lowest one (3 g of solute/100 g of solvent). The narrow width of the metastable region could be correlated with the high purity level of adipic acid (>99.6%). Impurities in the solute can hinder the nucleation considerably, thus increasing the width of metastability while the MZW decreases when using material with high purity degree.[2]

3.3. Unseeded Batch Crystallization. The influence of cooling rate and initial concentration on the final crystal size distribution and crystal habit was first evaluated in an unseeded crystallization operation. Three different values were chosen for both parameters with cooling rates set at 0.1, 0.3, and 0.5 K/min and initial concentration at 5, 9.2, and 18 g of solute/100 g of purified water. Figure 3 illustrates the results in terms of volumetric particle size distribution of the final product of crystallization.

Higher cooling rates lead to smaller particles and lower uniformity in sizes for every value of initial concentration; in fact, faster cooling induces high supersaturations inducing high

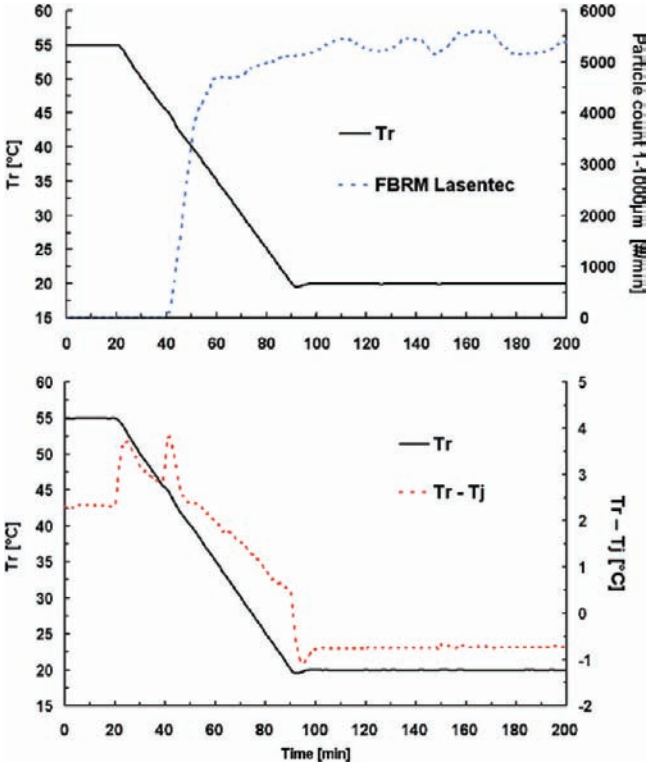

Figure 2. Measurement of metastable limit with Lasentec FBRM (top) and Mettler Multimax (bottom) technology.

nucleation rates and, hence, a wide spread of the particle size distribution.

Larger particles are produced for 9.2 and 18 g of solute/100 g of water with a bimodal particle size distribution that could be ascribed to the agglomeration of smaller flat-shaped crystals with hexagonal geometry, shown by SEM photomicrographs in Figure 4. The extreme cases of 5 g of adipic acid/100 g of water cooled from 40 to 20 °C at 0.5 K/min and 18 g of adipic acid/100 g of water cooled from 60 to 20 °C at 0.1 K/min are shown in Figure 5. Faster cooling combined with low initial concentration produced more elongated crystals with faceted edges whilst higher inlet concentration and slower cooling rates produced a more regular shape with rounded edges, with presence of fragments indicating the occurrence of breakage phenomena favored by the massive presence of large particles.

3.4. Seeded Batch Crystallization: Effect of Seeding Load and Cooling Rate. Figure 6 compares the product particle size distributions at three different values of seeding load from ground row material. The plots refer to the cooling crystallization from 40 to 20 °C at 0.5 K/min, and seeding operated as the reactor temperature reached 39 °C; at this point the temperature was held constant for 60 min before resuming the cooling. Crystals produced with low values of seed concentration (1% and 5%) present widespread and bimodal PSD. The smaller part of the distribution is inferred to be crystals generated by secondary nucleation mechanisms, while the larger part may be classified as grown seed crystals and agglomerates. The results indicate that at the highest seed concentration considered for this study, corresponding to C_{seed} = 11%, the PSD was unimodal and narrower. The values of volumetric mean diameter and uniformity were smaller in the last case, with $L_{43} = L_{sp}$ = 238 μm and U = 34%. Largest particles are produced in the case of 1% of seeds load

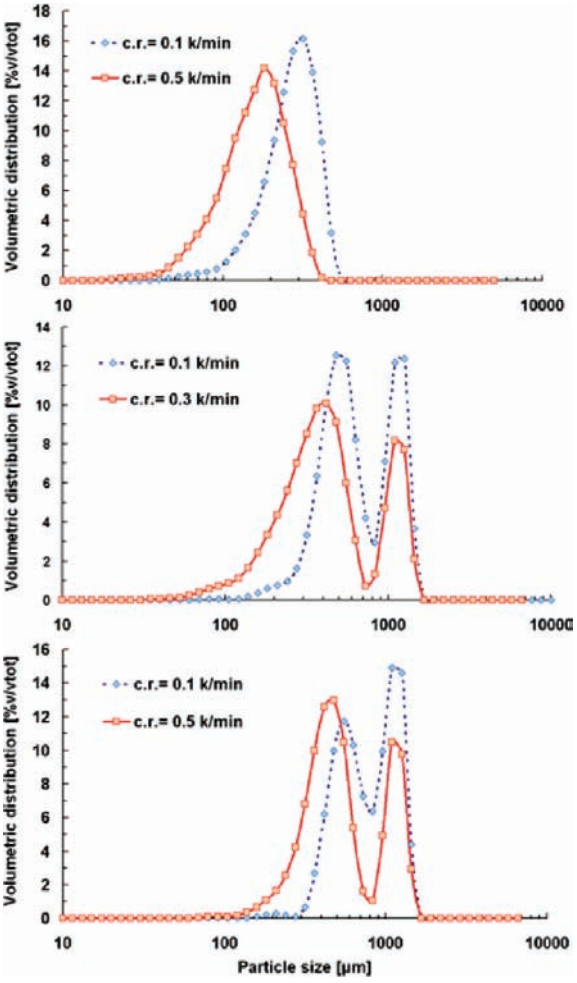

Figure 3. Effect of initial concentration and cooling rate on the final crystal size distribution. Concentration values: 5 g of AA/100 g of water (top), 9.2 g of AA/100 g of water (center), 18 g of AA/100 g of water (bottom).

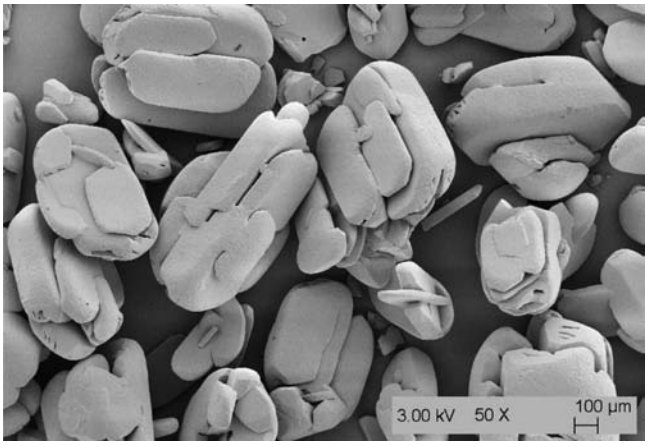

Figure 4. SEM photomicrograph of agglomerated adipic acid crystals from unseeded cooling crystallization.

($L_{43} = L_{sp} = 336\,\mu$m), while a wider uniformity (39%) is obtained in the case of unseeded crystallization. C_{seed} = 11% corresponds to L_{sp}/L_s = 2.16 that shows results similar to L_{wp}/L_s = 2.14,

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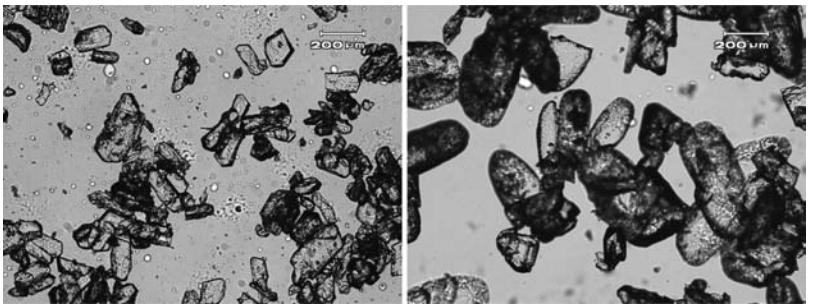

Figure 5. Optical micrographs of adipic acid crystals from unseeded cooling crystallization. Operating conditions: cooling 5 g of AA/100 g of water from 45 to 20 °C, at 0.5 K/min (left); cooling 18 g of AA/100 g of water from 65 to 20 °C, at 0.1 K/min (right).

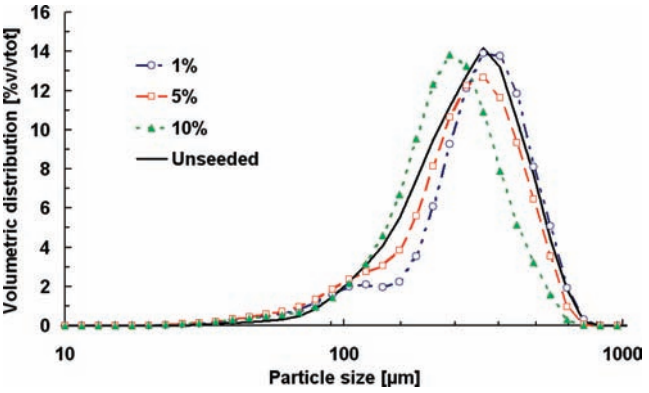

Figure 6. Effect of the amount of seeds on the final particle size distribution. Operating conditions: cooling 5 g AA/100 g water from 45 to 20 °C, at 0.5 K/min.

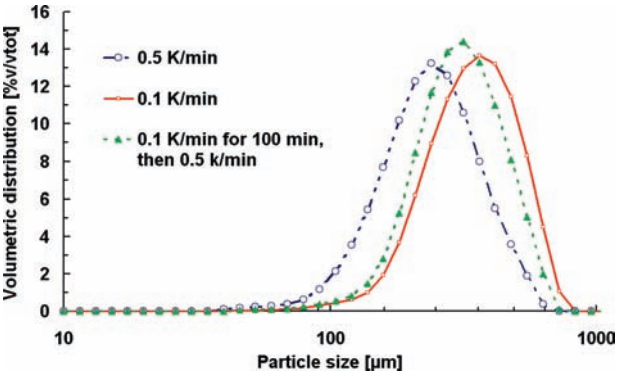

Figure 7. Effect of cooling rate on the final particle size distribution. Operating conditions: cooling 18 g AA/100 g water from 65 to 20 °C, 10% of seed loading.

indicating a growth-dominated process. When the amount of seeds was set at 5% of dissolved material, Malvern Mastersizer measurements indicated a high presence of fines (from the PSD plot) and provided L_{wp}/L_s = 2.44, slightly higher than L_{sp}/L_s = 2.38 (C_{seed} = 8%), suggesting some agglomerative phenomena of fine particles. The experiment with 1% of seed load produced a bimodal size distribution and gave L_{wp}/L_s = 2.64, lower than L_{sp}/L_s = 3.98 (C_{seed} = 8%), suggesting the occurrence of secondary nucleation phenomena.

Figure 7 shows the PSD after seeded crystallization of 18 g of adipic acid from 100 g of purified water. The amount of seeds corresponds to 10% of the total mass of adipic acid dissolved before seeding, and seeded crystals have been produced under continuously insonated unseeded batch cooling crystallization from the same composition/temperature. Seeding temperatures were reached by cooling at 0.5 or 0.7 K/min to ensure a wider metastable zone; the temperature was then held for 60 min before resuming the cooling down to 20 °C at linear rate. Two different cooling rates have been chosen after seeding: 0.1 K/min and 0.5 K/min. It can be seen that the higher cooling rate gives smaller particles with wider PSD (uniformity of 34.4%), whereas larger particles are produced for the linear cooling rate of 0.1 K/min, with narrowed PSD. In a third case the system is cooled first at 0.1 K/min for 100 min, and then at 0.5 K/min; the resulting PSD lies between the two previous cases, and results in the narrowest produced (uniformity of 30.5%).

Figure 8 illustrates temperature and Lasentec FBRM data over processing time for cooling crystallization of 5 g of adipic acid from 100 g of purified water from 40 to 20 °C at 0.1 K/min, with

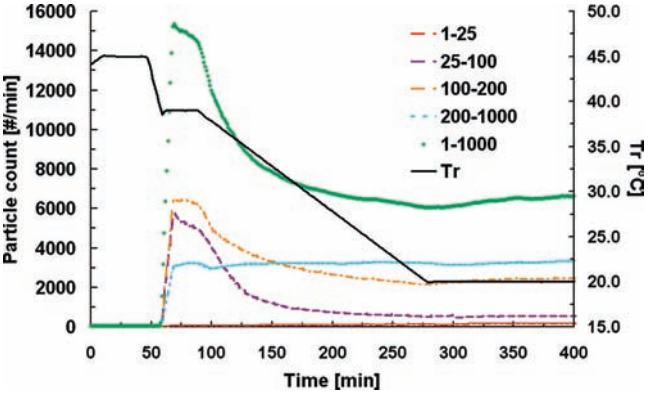

Figure 8. Particle count evolution over time in seeded batch cooling crystallization of 5 g of solute/100 g of water from 40 to 20 °C at 0.1 K/min, with 10% of seed loading.

10% of seeding load at a supersaturation ratio of 1.05. A continuous decrease in the total count of particles can be seen, with a slight increase in the number of larger particles (200−1000 μm) during cooling. The normalized product mean volumetric size ($L_w/L_s \geq$ 2.5, with L_{wp}/L_s = 2.5 without dissolution of seeds) is higher than the expected value in the case of pure growth of seeds crystal (L_{sp}/L_s = 1.93) indicating the occurrence of agglomeration of small nuclei.

3.5. Effect of Initial Concentration and Origin of Seeds. Figure 9 shows the PSD for the lowest and the highest values

chosen for the initial concentration of adipic acid. The trends refer to a 10% of seeds loading (from ground raw material), to avoid bimodality in the size distribution, and a cooling rate of 0.5 K/min. As in the unseeded cooling crystallization, higher initial compositions lead to larger particles with narrow PSD (uniformity reduced from 34.3 to 30.3%). However, the increase of inlet concentration favors secondary nuclei formation by attrition due to the narrower metastable zone, and the likelihood of breakage due to the larger sizes and the longer times involved.

The volumetric distributions of both kinds of seeds used for the present investigation show comparable results, as shown in Figure 10; however, the habits revealed by the SEM photomicrographs

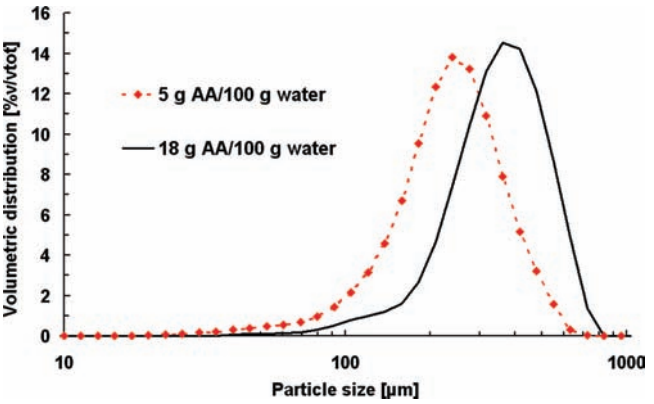

Figure 9. Effect of initial concentration/temperature on the final particle size distribution. Operating conditions: 10% of seed loading, cooling rate of 0.5 K/min.

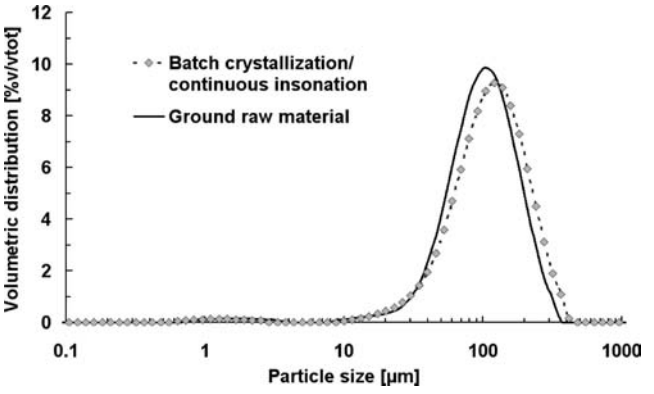

Figure 10. Particle size distributions of seed particles.

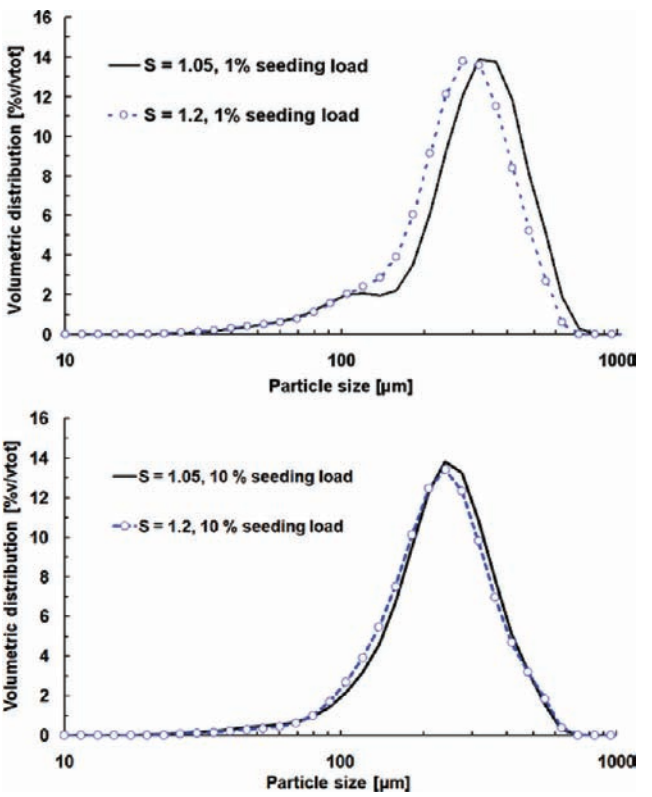

Figure 12. Effect of supersaturation at seeding on the final particle size distribution. Operating conditions: cooling 5 g of AA/100 g of water from 45 to 20 °C, at 0.5 K/min.

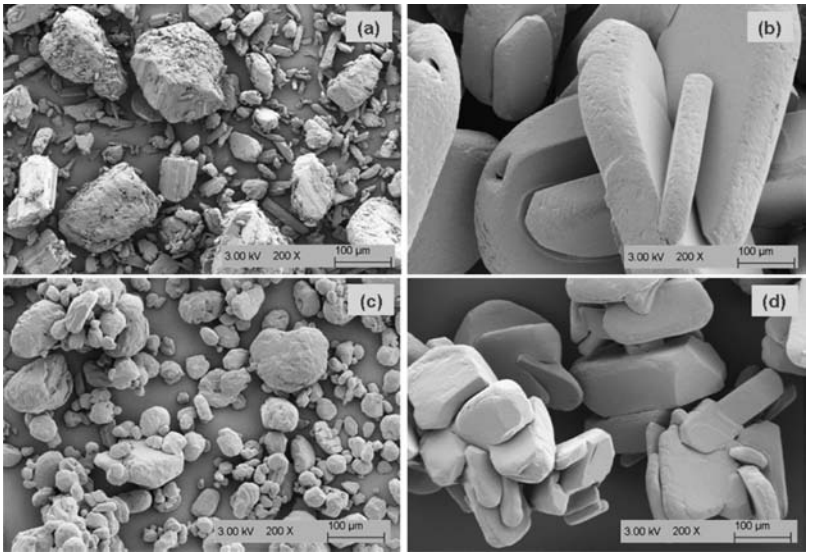

Figure 11. SEM photomicrographs of (a) raw material after grinding, (b) final crystals after seeding with (a), (c) round-shaped particles from batch sonocrystallization, (d) final crystals after seeding with (c).

in a and c of Figure 11 appear significantly different. Seeds produced by grinding the raw commercial material present an elongated shape in the smallest particles, while crystals produced in batch-cooling experiments under continuous insonation present a rounded shape due to the continuous pitting caused by cavitational effects.

Crystals produced from both kinds of selected seeds yield particles grown into one another; small particles tend to agglomerate, decreasing the effective surface area for crystal growth. However, in the first case elongated and flat particles were produced, while the product of the latter case presented reduced elongation and increased thickness, with a more symmetric habit (Figure 11 right-hand side). The surfaces of the latter crystals appeared smooth, without the pitting effect as in the originating seeds.

3.6. Effect of Supersaturation at Seeding. In a cooling crystallization, as mentioned above, seeds have to be added under supersaturated conditions and before the limit of the metastable zone is crossed. The metastability limit is not an exactly defined quantity but depends on a number of parameters, and keeping well within the value estimated experimentally is advisable. For this reason, the seeding point should be fixed near the solubility line and to a maximum of one-fourth to one-half into the metastable zone.[2]

The effect of supersaturation at seeding was investigated at the initial composition of 5 g of solute/100 g of water, corresponding to a wider metastable zone, at the cooling rate of 0.5 K/min, and at supersaturation ratio at seeding of 1.05 (39 °C), and 1.2 (37.5 °C). The results are depicted in Figure 12. For a low seeding amount, where spontaneous nucleation appears more likely to occur, the difference between two different supersaturations at seeding is more evident, with a more pronounced nucleation for the highest supersaturation value at seeding and a higher peak for fine particles at reduced supersaturation. For the highest levels of seeding load, a less marked difference appears between the final product crystal size distributions after seeding at different levels of supersaturation, since the growth of seeds is the dominant process.

4. CONCLUSIONS

Seeded batch cooling crystallization of adipic acid from aqueous solution was investigated to determine the effects of the method used to produce seeds, seeding load, cooling rate, initial concentration, and supersaturation at seeding on the final crystal product habit and size distribution. Seeds were inoculated as a slurry of adipic acid crystals in deionized water to ensure they were efficiently dispersed and their surfaces activated.

An effective seed loading of 10% ensures unimodal distribution of product crystal particles, while the largest sizes are achieved by cooling at 0.1 K/min. Increasing the inlet concentration, thus the temperature, also favors the achievement of larger crystals, but a narrow metastable zone increases the probability of nucleation, thereby requiring slow cooling. An initial cooling rate of 0.1 K/min for 10 °C, followed by 0.5 K/min provides large product crystal particles and reduces nucleation with shorter operation times. Seeding with ground commercial material gives elongated and flat particles, while seeding crystals with a regular rounded habit obtained from batch sonocrystallization provides reduced elongation and increased the thickness in the final crystal product.

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NOMENCLATURE

C_{seed}	mass fraction of seeds (mass of seeds/total mass of dissolved adipic acid before seeding), %
H_{40}	liquid level for 40 mL solvent, mm
H_{50}	liquid level for 50 mL solvent, mm
ID	internal diameter of the vessel, mm
L_{43}	particle's volume mean diameter, μm
L_s	characteristic size of seeds, μm
L_{sp}	characteristic size of final particles, μm
L_{wp}	effective mean mass size of final particles, μm
T_j	temperature in the jacket, °C
T_r	temperature in the reactor, °C
U	uniformity, %
W_f	mass of produced crystals, g
W_s	mass of seeded crystals, g
Y_t	mass theoretical yield, g
ρ_s	solid crystal density, g/cc

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