CRYSTAL GROWTH & DESIGN

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Indirect Ultrasonication in Continuous Slug-Flow Crystallization

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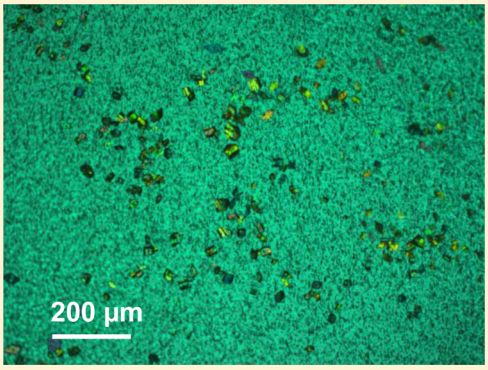
Supporting Information

ABSTRACT: Continuous-flow solution crystallization is an approach to manufacture pharmaceutical crystals with improved control of product characteristics, simplified postcrystallization operations, higher production rate flexibility, and reduced capital costs and footprint. An indirect ultrasonication-assisted nucleation process is designed to vary the seed generation rate during operation independent of mass flow rate, by varying the ultrasonication power. The ultrasonication probe is pressed against a tube to generate a spatially localized zone within the tube inside of a temperature bath for the generation of crystal nuclei without heating or contaminating the supersaturated solution. This nucleation design is integrated into a continuous slug-flow crystallization process to generate uniform-sized product crystals within each slug at a high supersaturation level and a short residence time of ~8.5 min, without inducing significant secondary nucleation. By increasing size uniformity, the indirect ultrasonication-assisted slug-flow crystallizer has potential as a final crystallization step to produce crystals for direct compression tableting without having any possibility of metal contamination.



1. INTRODUCTION

In the pharmaceutical industry, the continuous generation of crystals of target size distribution has the potential to simplify and/or reduce postcrystallization operations.[1,2] Crystal growth can be effectively controlled in a segmented/slug flow[3−6] that can be operated at low enough supersaturation to remove or greatly suppress secondary nucleation,[7] but the control of primary nucleation to generate the initial seed crystals is more limited.[8] The joining of two streams in dual impinging jet, coaxial, or radial micromixers has been demonstrated to produce seed crystals of uniform crystal size distribution (CSD)[7,9] but with a nucleation rate that depends on the liquid flow rate.[7,9−11] In addition, the primary nucleation rate in many micromixer designs is very sensitive to inlet flow alignment, and clogging can potentially occur in low velocity regions of the micromixers.

Ultrasonication is a technology for facilitating primary nucleation that has been useful in various industrial and academic studies.[12−16] The nucleation rate is a function of ultrasonication parameters rather than just liquid flow rate, which provides extra degrees of freedom for controlling the CSD. Ultrasonication-assisted crystallization seldom has clogging problems and actually has the opposite effect and is commonly used to remove particles from containers for cleaning purposes.[13] Ultrasonication facilitates primary nucleation by inducing acoustic cavitation in the liquid solution using high-frequency mechanical vibrations from converters (connected sonication generator).[17]

The effect of ultrasonication operation parameters on crystallization process and crystal size has been widely studied (e.g., see refs 13, 17−20, and citations therein), which indicates that the primary nucleation rate is sensitive to the power amplitude. This observation suggests that the power amplitude is a good choice for control of the primary nucleation rate in a continuous crystallization, which is the approach taken in this article.

In most studies of sonocrystallization, an ultrasonication probe (or horn) is in direct contact with the liquid solution, which may induce secondary nucleation from metal contact or contaminate the solution with metal after a long time of use.[13,21] The closer the liquid solution is to the probe tip, the more ultrasonication energy per unit volume is transferred to the solution, which is more spatially localized than when a sonication bath is used. This article uses an ultrasonication horn and so has spatial localization of ultrasonication energy but does not directly contact the horn with the liquid solution. The ultrasonication probe tip is placed close enough to the liquid solution so as to transfer significant power and induce primary

Received: February 22, 2015
Revised: April 6, 2015
Published: April 7, 2015

DOI: 10.1021/acs.cgd.5b00263
Cryst. Growth Des. 2015, 15, 2486−2492

nucleation, but the tip and liquid solution are separated by a thin wall of plastic.

This article describes the implementation of this indirect ultrasonication-assisted primary nucleation into a slug-flow cooling crystallizer to demonstrate rapid generation of a large amount of crystals of larger size than the nuclei. The most closely related study is described in a high-quality paper published by Khinast and co-workers[3] that also employs indirect ultrasonication and crystal nucleation and growth in a liquid solution flowing through plastic tubing. The main differences compared to ref 3 (and relevant work in a very recent paper[22]) is that this article (i) uses an ultrasonic probe focused on a small spatial location instead of placing a long tube in a sonication bath, (ii) has more than an order of magnitude less time in which the solution is in contact with ultrasonication, and (iii) uses a simpler experimental system. The pros and cons of the different configurations are discussed at the end of the Results and Discussion section.

2. EXPERIMENTAL MATERIALS AND METHODS

2.1. Materials. The solute is L-asparagine monohydrate (LAM, purity ≥99%, from Sigma-Aldrich), which forms crystals in the solvent, deionized (DI) water, that have a strong tendency to aggregate.[9]

2.2. Equipment. A slug-flow cooling crystallizer that decouples crystal nucleation, slug formation, and crystal growth to allow control of the individual processes is shown in Figure 1. The main differences with past similar experimental systems are described in the Introduction section.

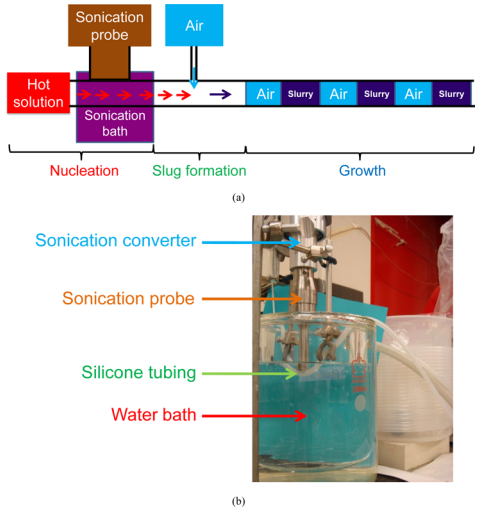


Figure 1. (a) Schematic of the slug-flow cooling crystallizer with ultrasonication-assisted nucleation. (b) Photograph of the experimental setup for ultrasonication. For maximum acoustic energy transmitted from the ultrasonication probe to the solution inside silicone tubing, the probe was placed in direct contact with the outer wall of silicone tubing, in water whose temperature was kept constant. The water outside the tubing is used to draw thermal energy generated by the ultrasonication away from the ultrasonication zone. The right background shows downstream tubing whose temperature can be controlled by placement in a temperature-controlled water bath.[7]

The ultrasonication equipment for nucleation (Sonics VCX 750, Figure 1b) is composed of a generator, a converter, and a probe. Its generator has a working frequency of 20 kHz (widely used for sonocrystallization studies[13,17,18,20,23]) and an input electric power of 750 W. The generator's output power to the probe (Sonics 630-0597) increases as the amplitude increases (Table 1). Different amplitude values are set on the control panel of the generator keypad. The probe tip diameter is 13 mm, which is large enough for the center of the tip to cover the outer diameter (6 mm) of the silicone tubing.

A T-mixer of 2.7 mm inner diameter was employed for slug generation with its two inlets connected to the slurry and air. A peristaltic pump (Masterflex pump drive 7521-40, Easy Load II pump head with model no. 77200-50) was used to transfer hot slurry to the T-mixer through a silicone tube (Masterflex BioPharm Plus platinum-cured silicone tubing, 3.1 mm inner diameter). Filtered air at room temperature (20 °C) was transferred to the T-mixer through the same peristaltic pump with dual pump heads (their rollers were offset to suppress flow oscillation). Downstream of the T-mixer was 15.2 m of silicone tubing (Dow Corning Pharma-80 tubing, 3.1 mm inner diameter) in room-temperature air used for downstream crystal growth.[7] The solubility of LAM in DI water is 0.023 g/g at room temperature. Product crystals were characterized using a stereomicroscope (microscope model no. XV331AC20C from Cyber Scientific Corporation and camera model no. DFK 22BUC03 from The Imaging Source, LLC).

2.3. Procedure. Nucleation from a supersaturated liquid solution is induced by the ultrasonication probe, which is followed by the formation of alternating slugs of air and slurry. The inlet air and liquid flow rates are selected so that the slugs form spontaneously as the hydrodynamically stable multiphase flow.[7] The supersaturated liquid solution was generated by slowly cooling a solution of 0.09 g LAM/g DI from 52 to 45 °C, which was the temperature of the bath in which the ultrasonication probe tip was placed (Figure 1b). (The slow cooling was the result of heat loss from the tube to its surroundings during transit from the 52 °C feed tank through the peristaltic pump to the 45 °C tank. The temperature of the solution in the tube right at the probe was also measured to be 45 °C in separate experiments using the same setup, same solvent (DI water), and same temperature—with the only difference being with no solute present.) It is well established that ultrasonication reduces the width of the metastable zone,[12] and the resulting absolute supersaturation of 0.015 g LAM/g DI at 45 °C was selected to be lower than but close to the unseeded metastable limit of cooling nucleation observed in past experiments[9] so that primary nucleation is induced in the solution in front of the ultrasonication probe only when the probe is in operation. The mass flow rate of the inlet liquid solution was 4.03 g/min with a linear velocity of 0.89 cm/s, and the ultrasonication residence time, that is, the time in which the liquid solution experiences cavitation as observed by eye, is 3 s.

LAM nuclei generated from ultrasonication of supersaturated LAM solution traversed the tubing for 0.7 m before slug formation, with the tubing in room-temperature air. The distance of 0.7 m was selected to be long enough that the presence of air downstream in the tube does not significantly dampen the energy transferred to the liquid by the ultrasonication probe. The slug generation experimental setup is the same as in a previous slug-flow experiment that used a radial mixer,[7] except this article also uses slugs of water before and after the LAM-containing slugs so that the pressure drops from the inlets to the tube outlet are nearly constant. This procedure results in constant slug velocities throughout the entire experiment instead of having time periods during startup and shutdown with higher slug velocities. The crystals grow in the slugs of slurry while traversing through the tubing, for a residence time of ~8.5 min between slug formation and outlet. At the outlet of the tubing, slurry slugs were collected into polystyrene wells (1.5 cm in diameter) for off-line imaging under the stereomicroscope.[7]

3. RESULTS AND DISCUSSION

The nuclei from indirect ultrasonication-assisted cooling nucleation at different amplitudes are compared in section 3.1 to determine good values for subsequent crystal growth in the slug-flow crystallization process in section 3.2.

3.1. Sonication-Assisted Continuous Seed Generation by Cooling Crystallization. For the same experimental system, inlet streams, and operating conditions, more nuclei were formed with ultrasonication than without (see Figure 2),

DOI: 10.1021/acs.cgd.5b00263
Cryst. Growth Des. 2015, 15, 2486−2492

Table 1. Experimental Conditions and Size and Shape Statistics for the Ultrasonication-Assisted Nucleation of Seed Crystals[a]

experiment number	1	2	3	4	5	6
ultrasonication amplitude set point (% maximum)	0	20	40	50	60	80
ultrasonication power output (Watts)	0	9	26	39	45	68
image of generated seed crystals	Figure 2a	Figure 2b	Figure 2c	Figure 2d	Figure 2e	Figure 2f
mean length (μm)	34	53	42	24	20	20
standard deviation, length (μm)	20	25	20	8	12	11
standard error, length (μm)	2.3	1.6	1.3	0.5	0.8	0.9
mean width (μm)	23	33	27	15	12	13
standard deviation, width (μm)	18	18	16	6	8	8
standard error, width (μm)	2.1	1.2	1.0	0.4	0.5	0.7
coefficient of variation in length	0.60	0.46	0.47	0.32	0.59	0.54
coefficient of variation in width	0.79	0.54	0.56	0.41	0.65	0.65
mean aspect ratio	1.87	1.84	1.69	1.83	1.82	1.66

[a]The ultrasonicator vendor recommended that the ultrasonication be operated at or below a set point of 80% maximum amplitude (the power reading takes a few seconds to reach stable counts) continuously for our experimental time of 7 min or longer, thus continuous ultrasonication at 100% maximum amplitude was not carried out. The power output was calculated, as suggested by the vendor, to be the difference in power reading from the generator screen between when probe is in solution and in air at the same amplitude. The mean length and width are on a number basis. The standard errors are estimates of the uncertainties in the mean width and length measurements determined using Monte Carlo sampling.[28]

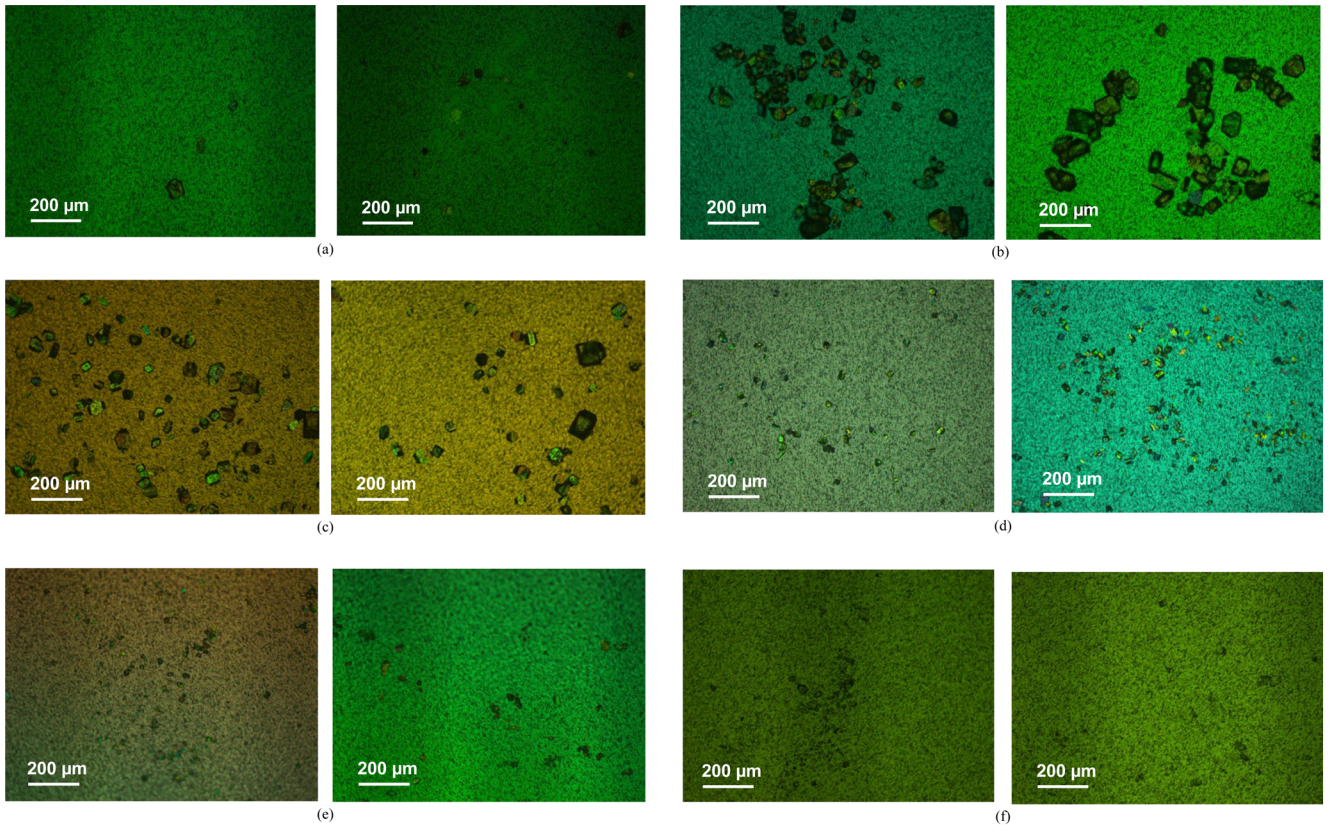


Figure 2. Microscope (with polarizers) images of seed crystals generated by cooling nucleation with ultrasonication (before slug formation in Figure 1a) at different ultrasonication amplitude set points (values listed in Table 1): (a) experiment no. 1, (b) experiment no. 2, (c) experiment no. 3, (d) experiment no. 4, (e) experiment no. 5, and (f) experiment no. 6. The background of each figure is a membrane filter with a pore size of 2 μm. Images at two different spots on the membrane are shown for each experiment. The images for experiment no. 1 with zero ultrasonication power were selected among the few that showed any crystals on the membrane filter. The images for the experiments with nonzero ultrasonication power contained crystals, with representative images shown in parts b–f. The ultrasonication setup, excluding the slug-flow section, is shown in Figure 1b. The seed crystal size and shape statistics are reported in Table 1

which is consistent with past studies that indicate a shortened induction time with ultrasonication.[14] For experiment no. 1 at zero ultrasonication power (Table 1), most of the membrane filter contained no crystals, which is consistent with the average supersaturation of 0.015 g of LAM/g DI being below the metastable limit for this experimental system under these operating conditions (i.e., at 45 °C).[9] Figure 2a shows the few images that contained any crystals, with the seed crystals that were obtained having over an order of magnitude variation in crystal size. Crystals were consistently nucleated for the experiments with ultrasonication (Figure 2b–f), with the crystals becoming smaller with increasing ultrasonication

DOI: 10.1021/acs.cgd.5b00263
Cryst. Growth Des. 2015, 15, 2486–2492

power (Table 1, Figure S1 in the Supporting Information). Some abnormally large crystals were observed for an ultrasonication power amplitude set point of 40% and less (Figure 2a–c) but not for 50% and higher ultrasonication power (Figure 2d–f), indicating that the higher power should be used in this experimental system if the objective is to manufacture uniformly sized crystals.

Ultrasonication increased the nuclei number and size uniformity (compare coefficient of variations for experiments 1 with 2–6 in Table 1). In the range of ultrasonication power amplitude set points from 20% to 50%, higher ultrasonication power reduced the size of the seed crystals (Figure 2d–f, Table 1), which is consistent with sonocrystallization results published for other compounds.[17−20,23] This observation is consistent with a higher ultrasonication power generating more bubbles that can act as direct or indirect sites for nucleation, so that the solute crystallizes on a larger number of nuclei. Increased ultrasonication power would be expected to increase the nucleation rate as long as the fluid inside and outside of the tubing has a high enough mass flow rate and heat capacity to draw enough thermal energy away from the ultrasonication zone. No clear trend was observed in the mean aspect ratio with varying ultrasonication power (Table 1). The lowest coefficient of variations for the mean and length of crystals occurred for the ultrasonication power amplitude set point of 50%.

When the amplitude was 60% or 80% of the maximum (Figures 2e,f), no evident increases in the size uniformity were observed (Table 1). A possible explanation is that the mass flow rate and heat capacity of the water were insufficient to draw enough thermal energy away from the ultrasonication zone, so the local temperature increased, which increased the solubility and lowered the supersaturation and nucleation rate per nucleation site, which counteracted the increasing number of nucleation sites generated by the larger power input. The images showed more aggregation for the 60% or 80% power amplitude, which could be associated with increased particle–particle contacts resulting from increased cavitation. On the basis of having the lowest coefficient of variation and low aggregation (Table 1), the ultrasonication power amplitude set point of 50% was selected to provide seeds in subsequent slug-flow crystallization experiments to manufacture product crystals.

3.2. Product Crystals Obtained after Growth in Slugs.

The product crystals generated without ultrasonication showed a high variability in size (see Figure 3), which is consistent with the large variability in the size of crystals observed immediately before the slug formation zone (Figure 2a and associated caption). In contrast, crystals from ultrasonication-assisted nucleation are much more uniform in size, while also having a small degree of aggregation (Figure 4), which is consistent with the higher size uniformity of seed crystals continuously generated by ultrasonication (Figure 2d). The unimodal character of the crystal size distribution within each slug (Figure 4) indicates that secondary nucleation was small in the slug growth zone (Figure 1), which is consistent with a past observation[7] that recirculation within each slug provides sufficient mixing without requiring the use of any mixing blade that would induce secondary nucleation.[24] This operation allows the slug-flow crystallization to occur at orders of magnitude higher supersaturation and shorter residence times than traditional crystallizers, without inducing significant secondary nucleation.[7]

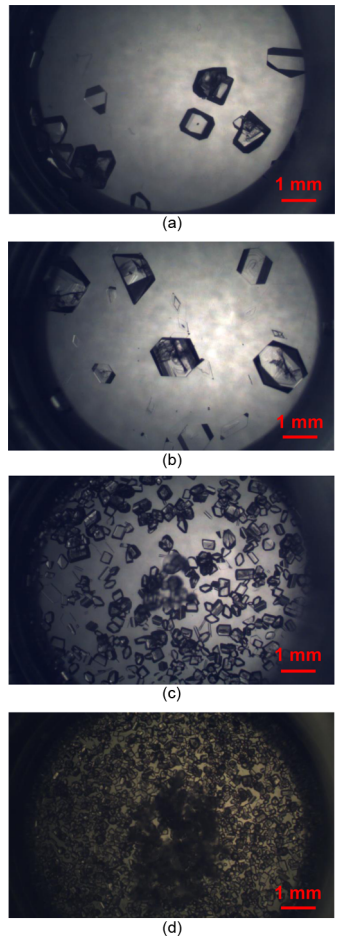


Figure 3. Stereomicroscope images of product crystals obtained by cooling nucleation without ultrasonication followed by slug flow in a 15.2 m long tube (experiment no. 1, with conditions in Table 1) for slug numbers (a) 106–109, (b) 170–173, (c) 234–237, and (d) 298–301. The detailed data collection procedure is described in section 2.3.

While there is relatively low variation in crystal sizes within each well, there is variation in the mean crystal size from well to well (Figure 4), which could be caused by fluctuating flow from peristaltic pumps.[7] A recent joint academia-industry white paper[25] points out that no continuous-flow process can ever actually operate at steady state due to disturbances and also discusses the common misconception that steady-state operation is the main objective of continuous operation. Actually, it is impossible to drive fluctuations from steady-state operation to zero, which is not an issue because what is important is that the product crystals collectively meet operational specifications or bioavailability specifications when incorporated into the drug product.

By first selecting the ultrasonication power amplitude for nucleation and then combining with slug flow for crystal growth, product crystals were obtained with high size uniformity, comparable with the best results from past experiments that combined ultrasonication with subsequent growth in slugs.[3] Compared to a past study,[3] this design requires simpler experimental configuration for the slug-flow section, with no fines dissolution equipment, by instead generating tunable seed size with spatially localized ultrasonication. The one ultrasonic probe can be replaced by two ultrasonic probes in series along the tubing with only one probe in ultrasonic mode and the other in rest mode, alternating

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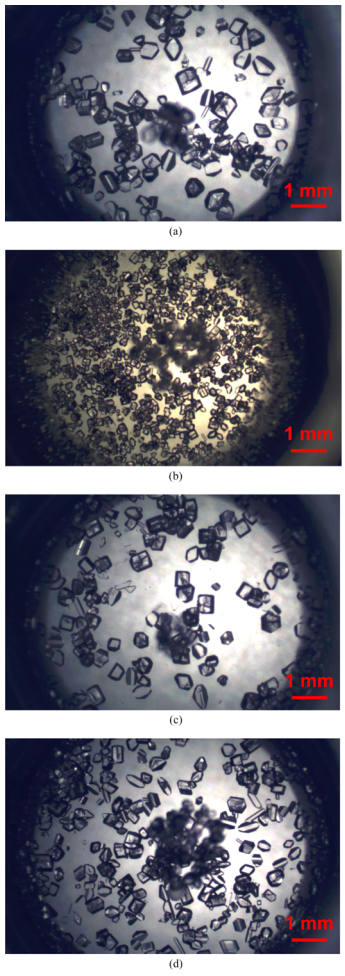

Figure 4. Stereomicroscope images of product crystals obtained at an ultrasonication power amplitude set point of 50% followed by slug flow in a 15.2 m long tube (experiment no. 4, with conditions in Table 1) for slug numbers (a) 108−110, (b) 180−182, (c) 252−254, and (d) 324−326. The product crystal size and shape statistics are reported in Table 1. The detailed data collection procedure is described in section 2.3.

between the modes of the two probes, to extend their lifetime. This two-probe design does not significantly increase the complexity of operation while facilitating scale-up, which is a typical problem in ultrasonication-associated research.[16]

Table 2 compares the product crystals obtained from seeds generated by spatially localized ultrasonication with product crystals obtained from seeds generated using a radial micromixer for the same conditions as experiment 4. The product crystals generated by spatially localized ultrasonication are about 28%−35% smaller in mean length and width and have 15%−23% narrower crystal size distributions based on smaller coefficients of variation. The mean aspect ratios are similar.

An advantage of using ultrasonication to generate nuclei is that the nucleation rate can be manipulated by the ultrasonication power, which is a control variable that can be changed independently from the mass flow rate through the tubular crystallizer. The nuclei generation rate produced by a micromixer cannot be varied independently from the mass flow rates of the inlet streams, regardless of whether the micromixer is radial, coaxial, or dual-impinging-jet type. In a crystallizer that uses a micromixer, any operating variable that affects the nuclei generation rate also affects the crystal production rate. The

Table 2. Comparison of Product Crystals Obtained Using the Nucleation Conditions in Experiment No. 4 of Table 1, with Representative Images of Crystals in Figure 4d, with Product Crystals Reported in ref 7[a]

nucleation method for slug flow crystallization	micromixer (radial mixer)	spatially localized ultrasonication
crystal image	Figure 11 in ref 7	Figure 4d
mean length (μm)	444	321
standard deviation, length (μm)	152	92
standard error, length (μm)	13.0	6.4
mean width (μm)	326	211
standard deviation, width (μm)	142	69
standard error, width (μm)	12.0	4.8
coefficient of variation in length	0.34	0.29
coefficient of variation in width	0.43	0.33
mean aspect ratio	1.46	1.60

[a]The mean width and length are on a number basis.

nuclei generation rate can be affected by changing the design of the micromixer, but such equipment design parameters are then fixed during operation.

The measured process yield (mass of product crystals/total inlet mass of solute) for the slug-flow crystallizer with ultrasonication nucleation (73.8%) was close to the theoretical maximum yield of a batch cooling crystallizer of the same initial concentrations and final supersaturation of zero (74.4%). In contrast to employing micromixers that combine hot and cold inlet solutions, applying ultrasonication to a single hot inlet solution in a continuous crystallizer can better approach the maximum yield obtainable in a batch cooling crystallizer. For the slug-flow crystallizer, the maximum yield is obtained by having a sufficiently long tube for maximum consumption of supersaturation.

Another advantage of employing ultrasonication over micromixers is that the former is less likely to clog. By using a consistent inner diameter of tubing in the slug-flow crystallizer, as in Figure 1, there are no constrictions available to induce clogging. Although the potential for clogging in micromixers can be reduced by employing computational fluid dynamics simulations to improve the micromixer design,[26] a surer approach to avoid clogging is to replace the micromixer by employing ultrasonication instead.

In a past study[3] that also employed indirect ultrasonication and crystal nucleation and growth in a liquid solution flowing through a plastic tubing, primary nucleation occurs within 3 m of plastic tubing placed inside of a sonication bath. The ultrasonication power per unit volume varies widely with spatial position inside of a sonication bath, and having crystals nucleate throughout a long tubing length means that the crystals leaving the sonication bath have widely varying residence time and sizes. In particular, crystals that nucleate near the inlet of the tubing enters the sonication bath have much more time to grow in size than crystals that nucleate near the tubing outlet. This article uses a sonication probe tip focused in a small spatial location, which enables primary nucleation to occur within a small section of tubing. The much narrower size distribution that results is shown in Figure 5, which compares product crystal size distributions (CSDs) obtained in ref 3 with the product CSD obtained in this study.

Another difference with a past study[3] is that the experimental system in this article uses a simpler single solution stream instead of two streams and so has one less pump and less

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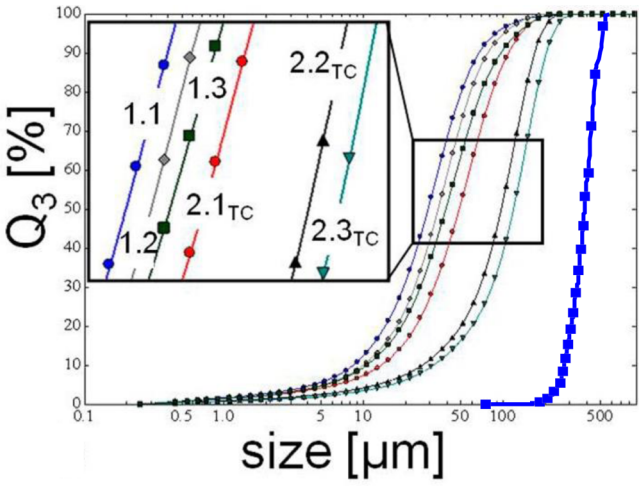

Figure 5. Comparison of the cumulative product crystal size distribution on a mass basis (labeled as Q_3) obtained using the nucleation conditions in experiment no. 4 of Table 1 (blue square, with representative images of crystals in Figure 4d) with product crystals reported in Figure 4b of ref 3. A mass basis was used to allow a direct comparison with the results of this manuscript with Figure 4b of ref 3. The CSD for the product crystals in this manuscript is much narrower even though the crystals are grown much larger and have a greater opportunity to be affected by growth dispersion.

tubing and does not require a mixer to combine two liquid streams. The experimental apparatus in ref 3 has higher flexibility of operation but also has higher complexity. Instead of applying ultrasonication to liquid solution for a half minute or more as in past studies,[13] this article exposes the liquid solution to ultrasonication for a much shorter time (e.g., a few seconds), to reduce heating of the solution and widening of the CSD.

4. CONCLUSIONS

This article presents a slug-flow crystallizer that employs indirect ultrasonication to continuously generate seed crystals. The ultrasonication probe is pressed up against a tube to generate a localized ultrasonication zone within supersaturated solution in the tube for the generation of crystal nuclei (Figure 1). The ultrasonication design with an intermediate power amplitude (Figure 2d) continuously generated a larger number of uniform-sized seed crystals than using micromixers or direct cooling in a past study,[7] with minimal aggregation for a solute–solvent combination known to have a high tendency toward aggregation. The ultrasonication design also enables the seed generation rate to be varied in real time independently of the production rate, providing an additional degree of freedom that can be used in feedforward and/or feedback control design.

The ultrasonication-assisted nucleation design was implemented into a continuous slug-flow crystallization process to generate uniform-sized product crystals within each slug (Figure 4). The ultrasonication-assisted slug-flow crystallizer was operated at sufficiently high supersaturation for the entire crystallization to have a residence time of only ~8.5 min, without inducing significant secondary nucleation. The overall production rate can be increased by operating at a higher inlet mass flow rate while using a longer tube for crystal growth. The crystallizer can be operated continuously for a long time period with equipment of similar complexity, such as by placing two ultrasonic probes in series along the tubing with only one probe in ultrasonic mode and the other in rest mode, alternating between the modes of the two probes, so as to extend the probe lifetimes.

By increasing size uniformity, the indirect ultrasonication-assisted slug-flow crystallizer has potential as a final crystallization step to produce crystals for use in direct compression tableting,[27] which would remove the need for milling and/or granulation steps from the drug product manufacturing process chain. The use of indirect ultrasonication, as demonstrated for segmented-flow crystallization in a past study,[3] avoids the potential for sample contamination from metals detaching from the ultrasonication equipment,[6,21] which can be a significant concern in pharmaceutical applications. The use of an ultrasonication probe, in contrast to an ultrasonication bath used in a past study,[3] allows the ultrasonication zone to be more spatially localized, which can produce a narrower size distribution of seed crystals (Figure S1 in the Supporting Information, Table 2), and hence narrower product crystal size distribution (Figure 5, Table 2).

■ ASSOCIATED CONTENT

Supporting Information

Plot of mean crystal length (blue circle) and width (red square) of seed crystals at various ultrasonication power amplitudes. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Takeda Pharmaceuticals International Co. is acknowledged for financial support; Mark Molaro, You Peng, Yuan Gao, Yunzhi Gao, Steve Wetzel, Lucas Foguth, Tan Li, and Liang Su for helpful technical discussion and support; and Yanyang Wu, Bruce Green, and Michael Donaty for the ultrasonication commercial equipment purchase and its technical support.

■ REFERENCES

(1) McCormick, D. Evolutions in direct compression. *Pharm. Technol.* **2005**, *29* (4), 52–62.

(2) Sun, Z.; Ya, N.; Adams, R. C.; Fang, F. S. Particle size specifications for solid oral dosage forms: A regulatory perspective. *Am. Pharm. Rev.* **2010**, *13* (4), 68–73.

(3) Eder, R. J. P.; Schrank, S.; Besenhard, M. O.; Roblegg, E.; Gruber-Woelfler, H.; Khinast, J. G. Continuous sonocrystallization of acetylsalicylic acid (ASA): Control of crystal size. *Cryst. Growth Des.* **2012**, *12* (10), 4733–4738.

(4) Eder, R. J. P.; Schmitt, E. K.; Grill, J.; Radl, S.; Gruber-Woelfler, H.; Khinast, J. G. Seed loading effects on the mean crystal size of acetylsalicylic acid in a continuous-flow crystallization device. *Cryst. Res. Technol.* **2011**, *46* (3), 227–237.

(5) Gerdts, C. J.; Tereshko, V.; Yadav, M. K.; Dementieva, I.; Collart, F.; Joachimiak, A.; Stevens, R. C.; Kuhn, P.; Kossiakoff, A.; Ismagilov, R. F. Time-controlled microfluidic seeding in nl-volume droplets to separate nucleation and growth stages of protein crystallization. *Angew. Chem., Int. Ed.* **2006**, *45* (48), 8156–8160.

(6) Schiewe, J.; Zierenberg, B. *Process and apparatus for producing inhalable medicaments.* U.S. Patent 20030015194 A1, January 23, 2003.

DOI: 10.1021/acs.cgd.5b00263
Cryst. Growth Des. 2015, 15, 2486–2492

(7) Jiang, M.; Zhu, Z.; Jimenez, E.; Papageorgiou, C. D.; Waetzig, J.; Hardy, A.; Langston, M.; Braatz, R. D. Continuous-flow tubular crystallization in slugs spontaneously induced by hydrodynamics. *Cryst. Growth Des.* **2014**, *14* (2), 851−860.
(8) Myerson, A. S.; Trout, B. L. Nucleation from Solution. *Science* **2013**, *341* (6148), 855−856.
(9) Jiang, M.; Wong, M. H.; Zhu, Z.; Zhang, J.; Zhou, L.; Wang, K.; Ford Versypt, A. N.; Si, T.; Hasenberg, L. M.; Li, Y. E.; Braatz, R. D. Towards achieving a flattop crystal size distribution by continuous seeding and controlled growth. *Chem. Eng. Sci.* **2012**, *77*, 2−9.
(10) Mahajan, A. J.; Kirwan, D. J. Micromixing effects in a two-impinging-jets precipitator. *AIChE J.* **1996**, *42* (7), 1801−1814.
(11) Midler, M., Jr.; Paul, E. L.; Whittington, E. F.; Futran, M.; Liu, P. D.; Hsu, J.; Pan, S. H. *Crystallization method to improve crystal structure and size*. U.S. Patent 5,314,506, May 24, 1994.
(12) Deora, N. S.; Misra, N. N.; Deswal, A.; Mishra, H. N.; Cullen, P. J.; Tiwari, B. K. Ultrasound for improved crystallisation in food processing. *Food Eng. Rev.* **2013**, *5* (1), 36−44.
(13) Sander, J. R. G.; Zeiger, B. W.; Suslick, K. S. Sonocrystallization and sonofragmentation. *Ultrason. Sonochem.* **2014**, *21* (6), 1908−1915.
(14) Ruecroft, G.; Hipkiss, D.; Ly, T.; Maxted, N.; Cains, P. W. Sonocrystallization: The use of ultrasound for improved industrial crystallization. *Org. Process Res. Dev.* **2005**, *9* (6), 923−932.
(15) Lindrud, M. D.; Kim, S.; Wei, C. *Sonic impinging jet crystallization apparatus and process*. U.S. Patent 6,302,958, October 16, 2001.
(16) Ensminger, D.; Bond, L. J. Applications of high-intensity ultrasonics: Basic mechanisms and effects. In *Ultrasonics: Fundamentals, Technologies, and Applications*; CRC Press: New York, 2011.
(17) Miyasaka, E.; Ebihara, S.; Hirasawa, I. Investigation of primary nucleation phenomena of acetylsalicylic acid crystals induced by ultrasonic irradiation-ultrasonic energy needed to activate primary nucleation. *J. Cryst. Growth* **2006**, *295* (1), 97−101.
(18) Devarakonda, S.; Evans, J. M. B.; Myerson, A. S. Impact of ultrasonic energy on the crystallization of dextrose monohydrate. *Cryst. Growth Des.* **2003**, *3* (5), 741−746.
(19) Nishida, I. Precipitation of calcium carbonate by ultrasonic irradiation. *Ultrason. Sonochem.* **2004**, *11* (6), 423−428.
(20) Luque de Castro, M. D.; Priego-Capote, F. Ultrasound-assisted crystallization (sonocrystallization). *Ultrason. Sonochem.* **2007**, *14* (6), 717−724.
(21) Santos, H. M.; Lodeiro, C.; Capelo-Martínez, J.-L. The power of ultrasound. In *Ultrasound in Chemistry: Analytical Applications*; Capelo-Martínez, J.-L., Ed.; Wiley: KGaA, Weinheim, Germany, 2008.
(22) Besenhard, M. O.; Neugebauer, P.; Da-Ho, C.; Khinast, J. G. Crystal size control in a continuous tubular crystallizer. *Cryst. Growth Des.* **2015**, *15* (4), 1683−1691.
(23) Amara, N.; Ratsimba, B.; Wilhelm, A. M.; Delmas, H. Crystallization of potash alum: Effect of power ultrasound. *Ultrason. Sonochem.* **2001**, *8* (3), 265−270.
(24) Bermingham, S. K. *A Design Procedure and Predictive Models for Solution Crystallisation Processes*, Ph.D. Thesis, Delft University of Technology, The Netherlands, 2003.
(25) Myerson, A. S.; Krumme, M.; Nasr, M.; Thomas, H.; Braatz, R. D. Control systems engineering in continuous pharmaceutical processing. *J. Pharm. Sci.* **2015**, *104* (3), 832−839.
(26) Woo, X. Y.; Tan, R. B. H.; Braatz, R. D. Modeling and computational fluid dynamics−population balance equation−micromixing simulation of impinging jet crystallizers. *Cryst. Growth Des.* **2009**, *9* (1), 156−164.
(27) Sun, C.; Grant, D. J. W. Effects of initial particle size on the tableting properties of L-lysine monohydrochloride dihydrate powder. *Int. J. Pharm.* **2001**, *215* (1−2), 221−228.
(28) Bohm, G.; Zech, G. *Introduction to Statistics and Data Analysis for Physicists*; Verlag Deutsches Elektronen-Synchrotron: Hamburg, Germany, 2010.

DOI: 10.1021/acs.cgd.5b00263
Cryst. Growth Des. 2015, 15, 2486−2492