

Ultrasound-assisted solution crystallization of fotaliptin benzoate: Process intensification and crystal product optimization

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ABSTRACT

The ultrasound-assisted crystallization process has promising potentials for improving process efficiency and modifying crystalline product properties. In this work, the crystallization process of fotaliptin benzoate methanol solvate (FBMS) was investigated to improve powder properties and downstream desolvation/drying performance. The direct cooling/antisolvent crystallization process was conducted and then optimized with the assistance of ultrasonic irradiation and seeding strategy. Direct cooling/antisolvent crystallization and seeding crystallization processes resulted in needle-like crystals which are undesirable for downstream processing. In contrast, the ultrasound-assisted crystallization process produced rod-like crystals and reduced the crystal size to facilitate the desolvation of FBMS. The metastable zone width (MSZW), induction time, crystal size, morphology, and process yield were studied comprehensively. The results showed that both the seeding and ultrasound-assisted crystallization process (without seeds) can improve the process yield and the ultrasound could effectively reduce the crystal size, narrow the MSZW, and shorten the induction time. Through comparing the drying dynamics of the FBMS, the small rod-shaped crystals with a mean size of 9.6 μm produced by ultrasonic irradiation can be completely desolvated within 20 h, while the desolvation time of long needle crystals with an average size of about 157 μm obtained by direct cooling/antisolvent crystallization and seeding crystallization processes is more than 80 h. Thus the crystal size and morphology were found to be the key factors affecting the desolvation kinetics and the smaller size produced by using ultrasound can benefit the intensification of the drying process. Overall, the ultrasound-assisted crystallization showed a full improvement including crystal properties and process efficiency during the preparation of fotaliptin benzoate desolvated crystals.

1. Introduction

Solution crystallization is one of the widely used technologies to separate and purify solid products from solution, and nowadays attracts much attention in engineering crystalline product properties and optimizing process robustness and efficiency [1–3]. The performance of the final product is reflected in the crystal polymorphic outcome, crystal size, crystal size distribution (CSD), morphology, flowability, and tap density [4,5]. The crystallization process efficiency can be evaluated by the process parameters such as operation period, metastable zone width (MSZW), yield, and induction time for nucleation. Generally, in a solution crystallization process, the process parameters such as solvent type, cooling rate, antisolvent addition rate, and operation temperature can

be optimized to tune the crystallization process as well as the properties of the final crystal products [6,7]. In recent years, besides the mentioned parameters above, seeding techniques [8–10] and external fields, e.g. ultrasound irradiation [11–13], magnetic field [14], electric field [15], microwave [16] were heavily studied for the process and product optimization. Among these approaches, sonication has been proven to be an intensification technology in the crystallization process, in which both process and product quality can be improved significantly [13,17]. Sonocrystallization is an effective way to enhance the nucleation process, narrow crystal size distribution, improve crystal purity and product homogeneity, shorten crystallization time, preferential polymorph formation, and process repeatability [18–22].

The drying process of crystal products obtained by solution

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crystallization is considered as a time and energy-consuming step which is an essential element in the design of a production process for a new solid-state pharmaceutical product [23,24]. Drying kinetics are affected by several parameters including temperature [25], particle size and morphology [26,27], structure [26], moisture [28], pressure [29], mixing intensity (stirrer speed), etc. [30,31]. Drying of solvates consumes more energy for the removal of bound solvent, resulting in incomplete desolvation in industrial production, and may turn out to be a bottleneck in the overall process cycle time [34]. The wide crystal size distribution and needle like crystals are easy to cause agglomeration during stirring drying [32,33]. Especially, the needle-shaped crystals are easy to cause the mother liquor residue, which will cause the dissolution of the sample during high-temperature drying [34]. In the conventional API manufacturing process, the crystal size distribution and morphology of APIs are mainly controlled by crystallization and milling. However, the traditional methods of reducing particle size (such as grinding, shearing, and compression) causes problems such as higher energy-consuming, the crystal form transformation, and obtaining uneven particle size [35]. Therefore, several alternative processes for the modification of crystal size distribution and morphology of APIs by crystallization have been developed. In literature, the ultrasonic-assisted crystallization method has been shown to change the crystal size and morphology in many compounds such as paracetamol [36], roxithromycin [37], benzoic acid [38], griseofulvin [39], phenacetin [40], L-glutamic acid [41], and salicylic acid [17]. In addition, seeding as one of the most widely used techniques in industrial batch crystallization was used to induce secondary nucleation and control the crystal size distribution. However, in a batch process, it is hard to control the precise timing and seed loading amount during the development of the supersaturation profile to achieve effective results [9,10,42].

Fotagliptin benzoate is a novel dipeptidyl peptidase IV inhibitor [43]. In the solution crystallization process, the FBMS can be obtained in the methanol system. The solvent types were studied in the solution crystallization process of Fotagliptin benzoate and methanol was selected as the solvent, in which the FBMS formed as intermediate firstly. The FBMS can desolvate to form the commercial desolvated crystalline product. For the crystallization process, the solubility of Fotagliptin benzoate in other solvents except methanol is too large to get a satisfying yield and crystalline product. For example, the concentration of Fotagliptin benzoate in ethanol, tetrahydrofuran, isopropanol, n-propanol, n-butanol, acetonitrile, ethyl acetate, acetone, and dichloromethane solvents can reach 400 mg/ml. If the solute was added to the solution continuously, it will still be dissolved until the solution separates oil. In addition, the solvates can also be formed in other solvent systems, such as DMF solvate, acetonitrile solvate, acetone solvate, which are hard to desolvate in downstream processing. Due to the toxicity of the solvent, the desolvated crystal is preferred. Among these solvent systems, methanol is a relatively friendly solvent that has a low boiling point that is benefit to the solid-state desolvation of solvates. Thus the drying operation is a key step in the downstream processing. The desolvation or drying performance can be affected by powder properties such as crystal size, morphology, tap density, which can be tuned in the solution crystallization process. In the actual production, the FBMS shows a needle-like shape that needs a long time for desolvation in the downstream drying process. In addition, in the solution crystallization process, the induction time for the nucleation of FBMS is hard to control, which brings instability to the unit operation and reduces the process efficiency. The potential instability of the crystallization process and the needle like crystal shape render the downstream process inefficient and result in a poor quality of the crystalline product.

In this study, the solution crystallization was investigated by direct cooling/antisolvent crystallization approach. Subsequently, the seeding technique and ultrasonic irradiation were introduced into the crystallization process for the intensification of the crystallization process and modification of the crystalline product properties for the first time. The crystallization process robustness and efficiency including the reduction

of the induction time, narrowing the MSZW, and increasing the yield were studied quantitatively as a function of the power of ultrasound irradiation. The seeding strategy was also studied to optimize the crystallization process, especially for the improvement of process efficiency and product yield. At last, the desolvation process of FBMS was tested, which showed its close relation to the size and morphology of crystals. The ultrasound-assisted crystallization process proved to be an efficient technique in process intensification and crystalline product modification.

2. Experimental section

2.1. Materials

FBMS was provided by Shenzhen Xinlitai Pharmaceutical Co., Ltd., China. Methanol and methyl *tert*-butyl ether (MTBE) were purchased from Ailan (Shanghai) Chemical Technology Co., Ltd., China. All of the chemicals were analytical reagent grade and used without further purification.

2.2. Solubility measurement

The solubilities of FBMS in the mixture of methanol and MTBE with different mass ratios ranging from 0 g MTBE/g solvent mixture to 0.9 g MTBE/g solvent mixture were measured by the laser dynamic method at 303.15 K. The laser-based dynamic method (He-Ne laser, light intensity digital display, Beijing Haikesirui Photoelectric Instrument Co., Ltd., China) is widely used in solubility measurement, and the details of the procedure can be referred to in our previous report [44]. The mass of methanol is 30 g, and the mass of anti-solvent MTBE is between 0 and 270 g according to the MTBE: solvent mixture mass ratio (0–0.9). The mass of FBMS ranges from 0.1014 to 3.4092 g. When starting the experiment, a certain amount of binary solvent and solute were weighed (ML204T/02 of Mettler-Toledo, Switzerland) and then dissolved in a jacketed crystallizer. The solution was continuously stirred by a magnetic stirrer, and the temperature was maintained at 303.15 K by using a constant temperature water bath (Julabo, CF41). The laser beam passing through the solution is scattered due to the presence of solute particles, and the transmission intensity is reduced accordingly. When the solute was completely dissolved in the solution, the intensity of the laser beam passing through the crystallizer would reach its maximum. Then, 10 mg FBMS was added to the crystallizer. The procedure was repeated until the final added solute did not completely dissolve. Therefore, the solubility of FBMS in different solvent mixture mass ratios could be determined at 303.15 K.

2.3. The MSZW and induction time measurement

The MSZW was measured using the apparatus as shown in Fig. 1. Two grams of FBMS were completely dissolved in methanol. The used volume of methanol ranges from 11 to 25 ml to obtain different initial concentrations at 318.15 K. The solubility of FBMS in methanol at 318.15 K and 303.15 K is 0.190 g/g methanol and 0.114 g/g methanol respectively. In order to ensure the initial methanol solution of a certain concentration is completely dissolved, the temperature is increased to 318.15 K, then the solution was cooled down to 303.15 K to obtain a certain degree of supersaturation and kept at the constant temperature (Julabo, CF41). The anti-solvent MTBE was accurately added to the solution by using a peristaltic pump (Longer, BT-100-1F) at a rate of 1 ml/min. When MTBE was added, the appearance of the turbid liquid was marked and the amount of MTBE added was recorded to determine the MSZW.

In the induction time measurement experiment, for the ultrasonic-assisted crystallization process, the supersaturation ratio $S = c/c^*$ is set in the range of 3.9 to 6.3, and for the experiment without ultrasonic crystallization, the supersaturation S is in the range of 5.8 to 6.8 at

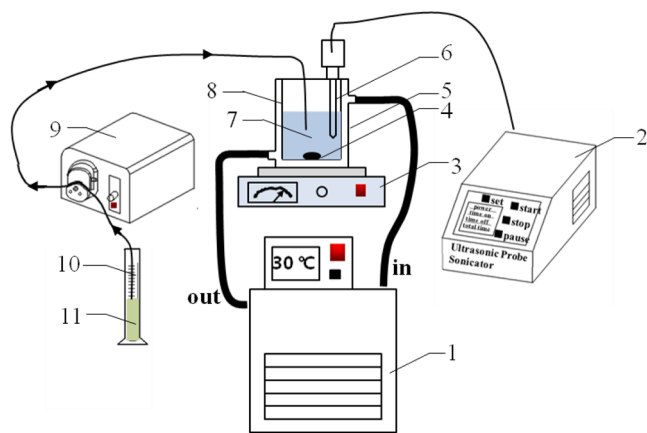


Fig. 1. Schematic diagram for the measurement of the metastable zone width and crystallization experiments: (1) thermostat, (2) ultrasonic power supply, (3) magnetic stirrer, (4) magnetic bar, (5) jacketed crystallizer, (6) ultrasonic probe, (7) the solution of FBMS, (8) cooling water, (9) peristaltic pump, (10) measuring cylinder, (11) anti-solvent MTBE.

303.15 K. The mass ratio of the anti-solvent MTBE was 0.6 g MTBE/g solvent mixture, at which point the equilibrium concentration c^* was 0.0206 g/g methanol. Two grams FBMS was completely dissolved in a certain amount of methanol ranging from 24.89 g to 15.41 g for the ultrasonic-assisted crystallization process and 16.74 g to 14.28 g for the process without ultrasound conditions at 318.15 K. Then, the clear solution was cooled down to 303.15 K immediately for the induction time measurement. Different amounts of the MTBE in the range 37.34 g to 23.11 g for the ultrasonic-assisted crystallization process and 25.11 g to 21.42 g for the process without ultrasound conditions were added (within one minute) to reach the required supersaturation ratios. The solution was mixed by a magnetic stirrer at a stirring speed of 300 rpm. The induction time was measured as the first appearance of cloudy particles.

In the ultrasound-assisted crystallization process, the frequency was fixed at 20 kHz using an ultrasonic homogenizer workstation (Ningbo, China JY92-IIN). The horn depth (2 cm) and the tip diameters (6 mm) were used in this work. The power of ultrasound was set to 80 W, and the ultrasound was operated at the mode of 2 s pulse on and 4 s pulse off. The pulse on was the time that ultrasonic irradiated while pulse off was the interval time between the pulsing periods. The crystallizer was sealed during all the experiments to prevent the evaporation of the solvent. Each experiment was conducted three times to minimize the error and ensure measurement accuracy.

2.4. Crystallization experiments

The crystallization experiments used the experimental apparatus as shown in Fig. 1. The experiments were devised to study the effect of intentional seeding and ultrasonic irradiation on process yield, crystal morphology, and size. The experiments were carried out in three protocols, viz. (1) the direct cooling/antisolvent crystallization process, (2) seeding crystallization, and (3) the ultrasound-assisted crystallization process (without seeds). A 200 ml double jacketed crystallizer coupled with a magnetic stirring (300 rpm) was used to carry out the crystallization processes. At the beginning of crystallization, 5 g of FBMS was dissolved in 35 ml methanol and maintained at 318.15 K for 1 h to ensure that all particles were dissolved, and then cooled the solution down to 303.15 K at the rate of 3 K/min as the direct crystallization (protocol 1). For seeding crystallization, the seeds were dry-milled powder. After the temperature drops to 303.15 K, a certain amount of seeds (5 wt%) were fed to trigger nucleation (protocol 2). And then 105 ml MTBE was added through the peristaltic pump (Longer, BT-100-1F) at the rate of 1 ml/min. For protocol 3, ultrasonic irradiation was

applied during the addition of MTBE.

For protocol 3, the ultrasound power should be calibrated in order to avoid the lack of efficiency of the treatment. The calorimetric power was calculated using water in the crystallizer and measuring the change of temperature, which under the condition of continuous sonication (without pulsing) and without a cooling jacket at 80 W and 20 kHz. The net calorimetric power is calculated which was 0.228 W/ml for the lowest volume of 35 ml and 0.079 W/ml for the highest volume of 140 ml. The equation used is given below where m is mass of water, c_p is specific heat (4.2 kJ/kg.K) and ΔT is the temperature difference, V is the volume of water, t is the time of ultrasound on duration [45,46].

$$Q = \frac{m \times c_p \times \Delta T}{t \times V} \quad (1)$$

To monitor the crystallization process, the suspension was sampled at intervals of half an hour to one hour, and the crystallization period was studied over ten hours. The samples were first observed under an optical microscope (Olympus, CKX53) with a digital camera (Olympus, SC180) to study morphology. Then, the mean size and crystal size distribution were determined on the basis of analysis of more than 800 crystals from the images using the Nano Measurer software (Department of Chemistry, Fudan University). Then, 1 ml of the turbid suspension was immediately filtered with a 0.22 μ m filter membrane (Jinteng, Nylon), and the solute concentration of the filtrate was determined based on the peak area at 225 nm by using an HPLC instrument (Waters e2695, 2489 UV/Vis Detector). The crystal yield was calculated based on the difference in FBMS concentration between the initial feed solution and the final solute concentration in the filtrate mother liquor. Every measurement was repeated three times to minimize the error.

2.5. Drying experiments

The drying experiments were conducted in a vacuum drying oven (DZ24T, Tianjin Taisite Instrument Co., Ltd., China). The samples were placed on the tray and the temperature was maintained at 313.15 K. The experiment lasted 84 h, and samples were weighed during the drying process to monitor the weight loss. The initial and final crystal forms were characterized by using the powder X-ray diffraction (PXRD) (Japan Rigaku D/MAX-2500) to determine the change in crystal forms.

3. Results and discussion

3.1. Ultrasound-assisted crystallization process intensification

3.1.1. Effect of ultrasound on MSZW

The solubility of FBMS in the mixture of methanol and MTBE with different mass ratios was measured. As shown in Fig. 2, the black triangle curve shows the FBMS solubility as a function of the mass ratio of MTBE /mixture solvent ranging from 0 to 0.9. The MSZW was calculated as the amount of antisolvent added until the appearance of the cloudy particles. As shown in Fig. 2, the blue curve indicates the occurrence of nucleation without the application of ultrasound irradiation, which shows a wide range of the metastable zone between the solubility (black) and the limit of the metastable zone (blue) curves. Without ultrasound, when the initial concentration is lower than 0.14 g/g methanol, it requires a long time (more than a week) to crystallize even if a large amount of anti-solvent (anti-solvent ratio up to 0.9) is dropped. So in the supersolubility measurement without ultrasound, the initial concentration is higher than 0.14 g/g methanol. With the application of ultrasound, the nucleation was enhanced and the crystals could precipitate at lower initial concentrations of FBMS. The MSZW was narrowed down (between the black and red curves) with the assistance of ultrasound. For example, when the concentration of FBMS was 0.154 g/g methanol, the mass ratio of MTBE used to produce crystals in the absence of ultrasound was 0.71/mixture solvent, and correspondingly, in the presence of ultrasound, the MTBE mass ratio of 0.42/mixture

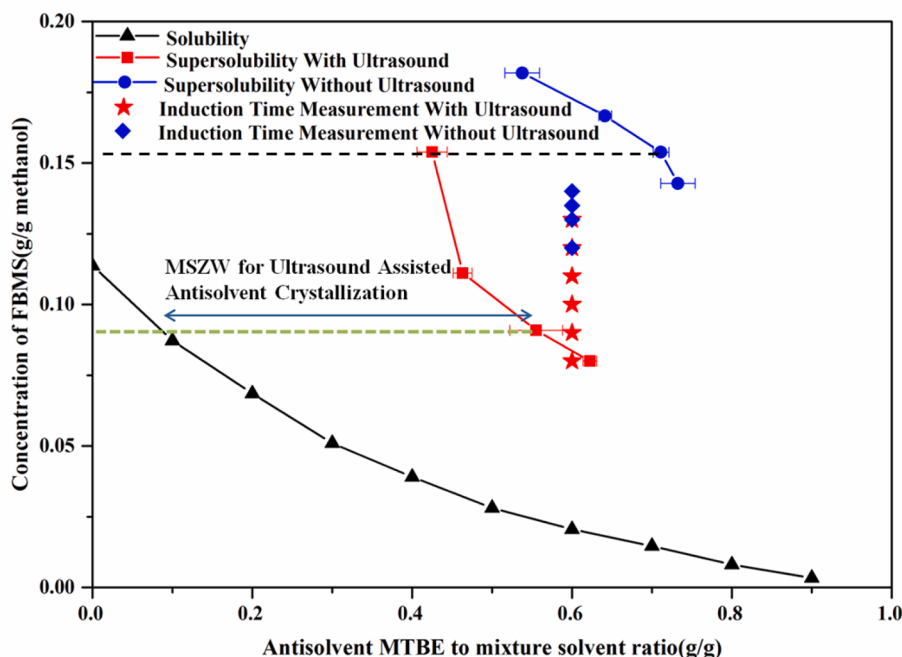


Fig. 2. The solubility curve of FBMS in the mixture of methanol and MTBE with different mass ratios showing the MSZWs for antisolvent crystallization and ultrasound assisted antisolvent crystallization at 303.15 K.

solvent can generate the nuclei for the following crystallization process, as shown in the upper black dotted line in Fig. 2.

The mechanism of the crystallization process enhancement by ultrasonic irradiation has attracted much attention. Ultrasonic waves propagate in the solution in the form of compression and rarefaction cycles, resulting in the formation, growth, and implosion of bubbles in the solution. This phenomenon is termed acoustic cavitation. The symmetric or asymmetric collapse of bubbles results in shockwaves or the formation of microjets in the solution. The shock wave generated by cavitation bubbles induces the increase of local free energy in the solution, on the other side, the shock waves increased collisions among solute molecules and accelerated the rate of mass transfer. These could help in creating a tiny cluster of solute molecules from the mother phase [13,18,47]. Moreover, according to the classical nucleation theory, the existence of cavitation bubbles provides heterogeneous nucleation sites, and the shock wave causes the crystal to break which induced the secondary nucleation to occur in the solution [48,49]. In this way, the nucleation barrier around the bubble is greatly reduced. It's easier for these clusters to grow up and become crystal nuclei around the acoustic cavitation. In addition, the local cooling or evaporation around the bubble due to its expansion is also a means of ultrasound-induced nucleation [50–52]. During the growth of the cavitation bubble, the solvent can evaporate to the interior of the cavitation bubble. This may not only induce cooling at the bubble surface but may also produce a depletion layer of solvent near the bubble wall. As a result, the solute concentration, and hence supersaturation, is thought to increase locally at this bubble wall [52–54]. Thereby, cavitation bubbles and shock waves created due to ultrasound can promote nucleation [13,55,56]. The enhancement of nucleation could effectively improve the robustness of the crystallization.

3.1.2. Effect of ultrasound on induction time and solid–liquid interfacial tension (γ)

The duration of the induction time was studied with and without ultrasonic irradiation. As shown in Fig. 3, the induction time in the absence of ultrasound varied between 13 min and 190 min at supersaturation levels of 6.80 and 5.82, respectively. While in the presence of ultrasound, the induction time varied between 14 min and 170 min at

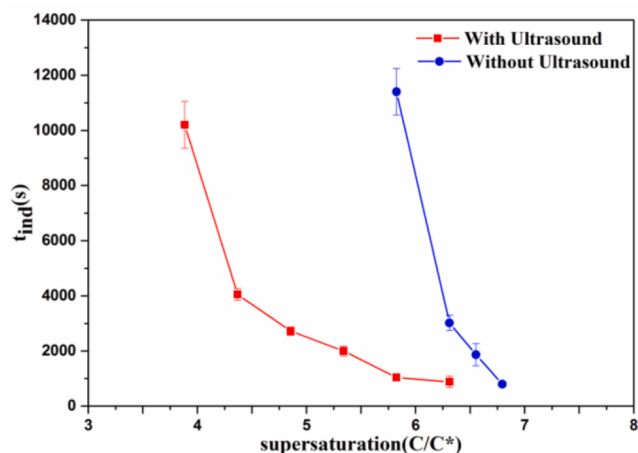


Fig. 3. Nucleation induction time vs. supersaturation with or without ultrasonic irradiation at 303.15 K.

supersaturation levels of 6.31 and 3.88, respectively. In the absence of ultrasound, it is difficult to nucleate when supersaturation is lower than 5.8 at a low initial concentration (pure methanol). Therefore, a cooling–anti-solvent coupling crystallization method is designed to obtain a higher degree of supersaturation when cooled to 303.15 K. The induction time increased exponentially as the concentration of FBMS decreased in the absence of ultrasound. When the ultrasonic irradiation was applied, the induction time decreased significantly. As shown in Fig. 3, at the same supersaturation, $S = 5.83$, the induction time with the ultrasound treatment experiment was 1040 s, which was significantly shorter than the induction time without ultrasound (11400 s). Ultrasound assisted crystallization can crystallize at low initial concentration and low supersaturation. When the supersaturation is at 6.31, the induction time is only 14 min. Therefore, only the induction time with a supersaturation degree of less than 6.31 was measured in the presence of ultrasound. All of this indicates that irradiating the solution with ultrasonic waves can promote nucleation, thereby shortening the

induction time, especially at low supersaturation.

When nucleation happens at the bubble-liquid interface, the contact angle (θ) between a crystalline particle and the external surface changes due to the change in interfacial tension [13,56]. The interfacial tension between solid and liquid phases can be estimated by crystallization induction time measurements. The nucleation rate can be calculated from the classic nucleation theory:

$$J = A \exp\left(\frac{-16\pi\gamma^3\omega^2}{3k^3T^3(\ln S)^2}\right) \quad (2)$$

$$S = \frac{C}{C^*} \quad (3)$$

Where A is the pre-exponential factor, k is the Boltzmann constant, T is the absolute temperature, γ is the interfacial tension, ω is the molecular volume, and S is the supersaturation, C is the actual concentration and C^* is the equilibrium concentration of FBMS. Assuming that the induction time t_{ind} is mainly composed of the true nucleation time t_n , which is inversely proportional to the nucleation rate J , Eq. (2) can be rearranged as:

$$\ln t_{ind} = K + \frac{B}{\ln^2 S} \quad (4)$$

Plotting the $\ln t_{ind}$ vs. $(\ln S)^{-2}$ yields a straight line with the slope of B . And the solid-liquid interfacial tension γ can then be estimated as [57,58]:

$$\gamma = \left(\frac{3Bk^3T^3}{16\pi\omega^2}\right)^{\frac{1}{3}} \quad (5)$$

As shown in Fig. 4, for the relationship of $\ln t_{ind}$ and $(\ln S)^{-2}$ with and without ultrasonic irradiation, the induction times can be linearly fitted using the formula derived from Eq. (4) as below:

$$\ln(t_{ind}) = 10.1521(\ln S)^{-2} + 3.7143; R^2 = 0.983 \quad (6)$$

In the absence of ultrasound:

$$\ln(t_{ind}) = 52.1709(\ln S)^{-2} - 7.4335; R^2 = 0.992 \quad (7)$$

Combine the Eq. (5)-(7), we can obtain:

$$\frac{\gamma_2}{\gamma_1} = 0.579 \quad (8)$$

Where γ_1 and γ_2 are the interfacial tension in the absence and presence of ultrasound, respectively. The interfacial tension of ultrasound-

assisted crystallization is only 0.579 of that without ultrasonic irradiation. Low surface tension facilitates nucleation. Thus, the use of ultrasound in the crystallization process can lower the nucleation energy barrier and promote nucleation effectively [56].

The shock wave generated by the collapse of cavitation bubbles in the solution can accelerate the diffusibility of solute molecules and increase the collision frequency, which can facilitate the occurrence of nucleation, reduce the induction time and significantly increase the robustness of the crystallization process [13,18,59]. Besides, cavitation bubbles due to ultrasound can promote nucleation by providing an external interfacial surface area for heterogeneous nucleation. The nucleation was enhanced and occurred at the bubble-solution interface, which can be explained by the ultrasound-induced interfacial tension decrease between the solid crystalline phase and cavitation bubble surface or the liquid and cavitation bubble [13,56].

3.1.3. Effect of ultrasound on yield

To increase the yield of the crystallization process, the experiments were conducted to evaluate the effects of direct cooling /antisolvent, seeding, and ultrasonic irradiation on the process yield. Table 1 lists the initial FBMS concentration c_0 , the average final FBMS concentration c_f , final supersaturation S_f and yield y for all the experiments. The crystallization theoretical yield y is defined as:

$$y = \frac{c_0 - c_f}{c_0} \quad (9)$$

From Fig. 5 and Table 1, it can be concluded that the direct cooling/antisolvent crystallization process required a longer crystallization time to nucleate due to a larger induction time (180 min), and it took a long time (600 min) to reach the maximum yield 39.86%. The addition of seed crystals can facilitate the nucleation and increase the final yield to 46.07%, compared to 39.86% in the direct crystallization within 600 min. The addition of ultrasound showed an obvious process intensification effect compared with the seeding crystallization experiment. It only took 90 min to reach the same yield of 39.82% as in the direct crystallization group, and the crystallization time shortened by more than six times. And the yield of the process reached the maximum level of 54.92% in 200 min, rapidly. Within 600 min, the yield increased by 1.4 times compared to that of the direct crystallization. The improvement of yield and the faster crystallization time of the ultrasound-assisted crystallization can be explained by the enhancement of the mixing performance on one hand. And on the other hand, the microbubbles produced by ultrasonic cavitation provide heterogeneous nucleation sites for crystal growth. These factors could make the ultrasound crystallization experiment fast and efficient, and achieve a relatively high yield in a short time.

3.2. Effect of ultrasound on crystal properties

3.2.1. Effect of ultrasound on morphology and size distribution

The morphologies and size distribution of the FBMS crystals obtained in three crystallization conditions are shown in Fig. 6. Particle size distribution is based on the maximum ferret diameter calculation. The crystal products obtained in the direct and seeding crystallization experiment were long needle-like with a mean size 155–157 μm . The long needle-like crystal habit is undesirable as it adversely affects the efficiency of downstream processing (e.g., filtering/drying), as well as the storage and stability performance. Using ultrasonic irradiation, small (mean size 9.6 μm) and uniformly sized crystals were obtained, and the aspect ratio was significantly shortened. The rod-like crystal habit promoted by the application of ultrasound, as shown in Fig. 6(c), provided better powder flowability and is more favorable for the downstream processes. In addition, Table 1 shows that the bulk density of the crystals obtained in the ultrasound group was 0.3943 g/cm^3 , which was much higher than that of the other two groups of direct cooling/antisolvent (0.2241 g/cm^3) and seeding (0.2791 g/cm^3)

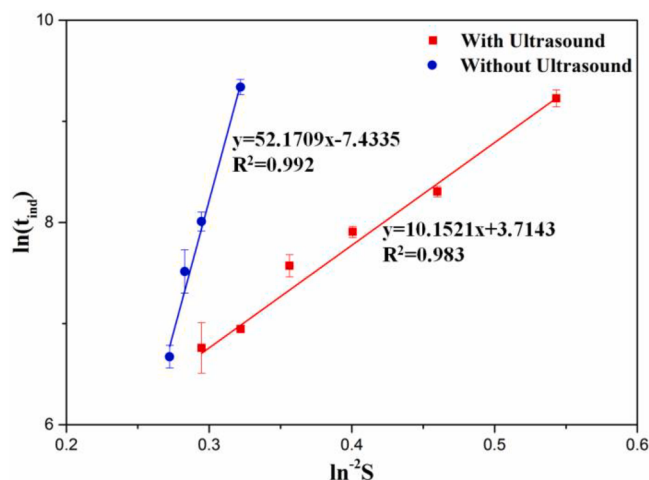


Fig. 4. The effect of ultrasonic irradiation on interfacial tension, $\ln(t_{ind})$ plotted vs. $(\ln S)^{-2}$ with or without ultrasound at 303.15 K.

Table 1

The final FBMS concentration, supersaturation, yield, and bulk density for (1) direct cooling/antisolvent, (2) seeding, and (3) ultrasound-assisted crystallization experiments.

Protocol no.	Ultrasonic field or seeding	$c_0(\text{g/g})$	S_0	$c_f(\text{g/g})$	S_f	y	Bulk density g/cm^3
1	N/A	0.143	12.32	0.086	7.41	39.86%	0.2241
2	seeding	0.143	12.32	0.077	6.64	46.07%	0.2791
3	Ultrasonic field	0.143	12.32	0.064	5.52	54.92%	0.3943

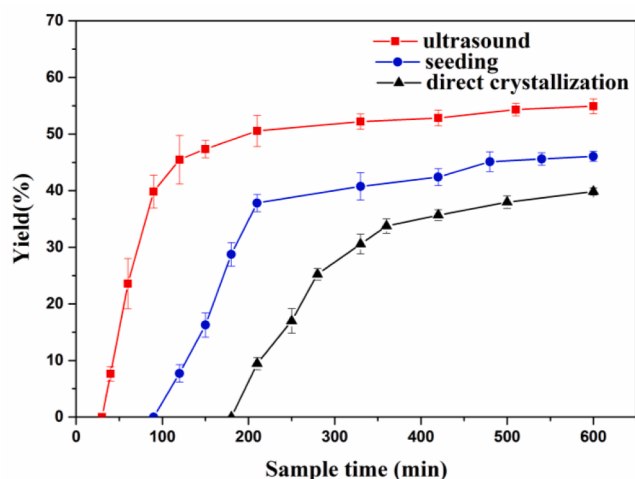


Fig. 5. The yields along with the time in the experiments of direct cooling/antisolvent crystallization process, seeding, and ultrasonic groups.

crystallization processes.

The bubbles produced by ultrasonic cavitation provide heterogeneous nucleation sites and increase the nucleation rate [13,21]. The size and size distribution would be mainly affected by the number of nuclei and the crystal growth rate [36,50,60]. Moholkar et al. reported the ultrasound-assisted crystallization process of KCl in the methanol–water system. The results showed that, compared with the mechanical stirring system, the nucleation rate increased with an order of magnitude, and the growth rate decreased significantly with the application of ultrasonic irradiation [50]. For the ultrasound-assisted crystallization process, the increase in the number of crystal nuclei quickly consumed supersaturation and reduced the amount of solute available for the

crystal growth, resulting in smaller crystal size and narrower size distribution [36,39,50].

3.2.2. Relationship between particle size and drying efficiency

It is well known that the downstream efficiency is significantly affected by crystal properties such as size, size distribution, and morphology. Fig. 7 shows the drying performance of the crystals produced by three different crystallization processes. The red square curve shows that the drying process of the crystals with a rod-like shape produced with the assistance of ultrasonic irradiation could reach equilibrium within 20 h. The solvent adsorbed on the surface of the crystals and the solvent in the crystal lattice could be removed with high efficiency. However, the needle-like shape crystals shown in Fig. 6(a) and 6(b) had a serious occlusion of mother liquor during the drying process. On the other hand, as a solvate crystal, the relatively large crystal size made it difficult to remove the solvent in the crystal lattice. As shown by the black and blue curves in Fig. 7, in the latter case, the drying process could not reach equilibrium until 84 h. That is, the crystal products produced by direct crystallization and seeding crystallization had low efficiency in the drying process.

The crystal products were characterized by the PXRD spectrum at the beginning and end of the drying process. The initial sample was methanol solvate. As shown in Fig. 8, the crystals obtained by the assistance of ultrasonic irradiation were devoid of the solvent completely and turned into desolvated crystal polymorphism. While the crystals obtained in the direct or seeding cooling/antisolvent crystallization experiments still had characteristic peaks of methanol solvate crystal after 84 h drying. It can be concluded that, by comparing the drying dynamics of FBMS, crystal size and morphology are the key factors affecting the kinetics of the evaporation and desolvation of solvent. The addition of ultrasound in the crystallization process significantly changes the morphology and reduces the crystal size, which can greatly shorten the time required for drying and improve the process efficiency.

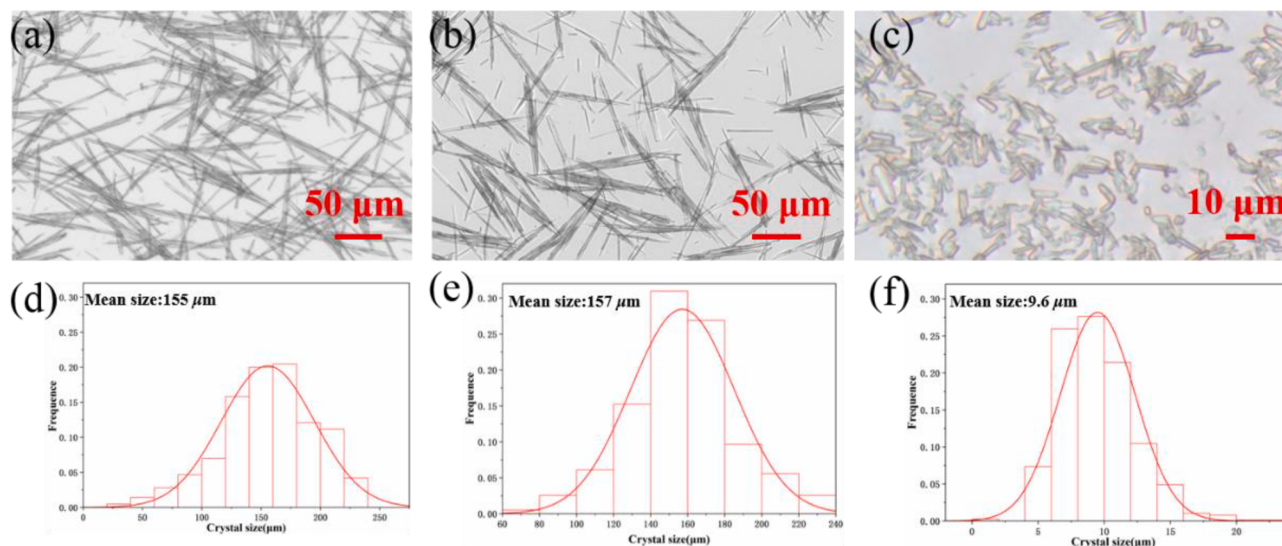


Fig. 6. Microscope images for FBMS crystals formed at 303.15 K. (a) direct cooling/antisolvent crystallization (b) with seeding (c) with ultrasound, and the corresponding particle size distribution (d) direct cooling/antisolvent crystallization (e) with seeding (f) with ultrasound.

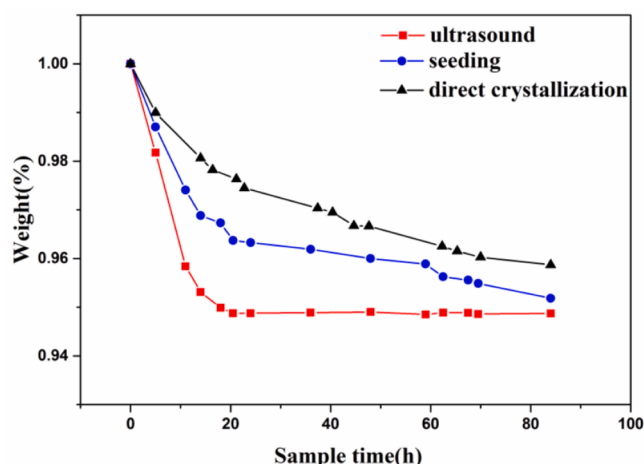


Fig. 7. Drying profile for crystals obtained from three protocols: direct, seeding, and ultrasound cooling/antisolvent crystallization.

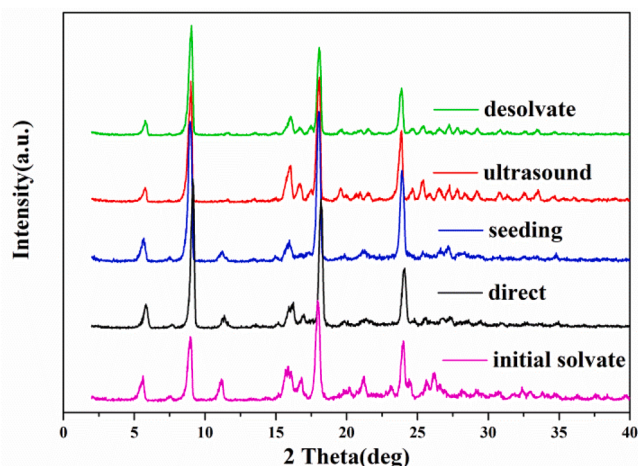


Fig. 8. PXRD spectra of three samples after drying for 84 h, and compared with the initial methanol solvate and the standard spectra of desolvate crystal form.

4. Conclusion

In this paper, ultrasound-assisted crystallization was proposed as a process intensification approach to modify the crystal size and morphology and improve the crystallization unit and downstream processing efficiency. In the direct cooling/antisolvent crystallization process, the induction time was 180 min, and the yield was only 39.86% at the 600 min crystallization process. The addition of seed crystals enhanced the crystallization process, and the yield reached 40.76% at the crystallization time of 330 min, which shortened the crystallization time nearly two times. Further, ultrasonic irradiation was introduced without seeds to optimize the crystallization process. During the ultrasound-assisted crystallization process, the acoustic cavitation and shock waves generated by ultrasound could result in the aggregation of small solute molecules to facilitate the occurrence of nucleation, thereby improving the crystallization process efficiency. The results indicated the induction time was shortened to 30 min, and the yield reached 39.82% at the crystallization time of 90 min. The crystallization time shortened by more than six times compared with that of the direct crystallization method. In addition, the effect of ultrasound to promote nucleation was also reflected in narrowing the MSZW and shortening the induction time, which could improve the process robustness during the crystallization process. For the crystal properties, the ultrasound process could effectively modify the morphology of crystals from needle-like to

rod-like shape during the crystallization process. The modification of the crystal morphology increased the efficiency of filtration and improved the bulk density from 0.2241 g/cm³ to 0.3943 g/cm³. Furthermore, the uniform and small crystal size were preferred in the desolvation process of the solvate, and thus improved the drying efficiency by four times.

Overall, the ultrasound-assisted crystallization process of FBMS showed a significant improvement in the aspects of process efficiency (crystallization, filtration, and drying processes) and product properties (crystal morphology, crystal size, and size distribution). The enhancement of nucleation could improve the process robustness and minimize the product difference between different batches. And the ultrasound-assistant crystallization technique showed great potential in process enhancement and crystalline product optimization. Further, the fine-tuning of ultrasound-based process enhancement and process scaling up with ultrasonic irradiation should be investigated both in academic and industrial applications.

CRediT authorship contribution statement

Lan Fang: Writing - original draft. **Zhenguo Gao:** . **Songgu Wu:** . **Shengzhe Jia:** . **Jingkang Wang:** . **Sohrab Rohani:** . **Junbo Gong:** .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- [1] A. Mersmann, *Crystallization Technology Handbook*, 2nd ed., *Etats-Unis d'Amérique*, Marcel Dekker, New York, 2001.
- [2] H.H. Tung, E.L. Paul, M. Midler, J.A. McCauley, *Crystallization of Organic Compounds: An Industrial Perspective*, Wiley & Sons Inc, Hoboken, New Jersey, 2009.
- [3] M. Giuliatti, M.M. Seckler, S. Derenzo, M.I. Ré, E. Cekinski, Industrial crystallization and precipitation from solutions: state of the technique[J], *Braz. J. Chem. Eng.* 18 (4) (2001) 423–440, <https://doi.org/10.1590/S0104-66322001000400007>.
- [4] M.A. Lovette, A.R. Browning, D.W. Griffin, J.P. Sizemore, R.C. Snyder, M. F. Doherty, Crystal shape engineering, *Ind. Eng. Chem. Res.* 47 (24) (2008) 9812–9833, <https://doi.org/10.1021/ie800900f>.
- [5] N. Variankaval, A.S. Cote, M.F. Doherty, From form to function: crystallization of active pharmaceutical ingredients, *Aiche J.* 54 (7) (2008) 1682–1688, [https://doi.org/10.1002/\(ISSN\)1547-590510.1002/aic.v54:710.1002/aic.11555](https://doi.org/10.1002/(ISSN)1547-590510.1002/aic.v54:710.1002/aic.11555).
- [6] H.U. Rodriguez Vera, F. Baillon, F. Espitalier, P. Accart, O. Louisnard, Crystallization of alpha-glycine by anti-solvent assisted by ultrasound, *Ultrason. Sonochem.* 58 (2019) 104671–104679, <https://doi.org/10.1016/j.ultsonch.2019.104671>.
- [7] Z. Berkovitch-Yellin, J. Van Mil, L. Addadi, M. Idelson, M. Lahav, L. Leiserowitz, Crystal morphology engineering by “tailor-made” inhibitors a new probe to fine intermolecular interactions, *J. Am. Chem. Soc.* 107 (11) (1985) 3111–3122, <https://doi.org/10.1021/ja00297a017>.
- [8] Y. He, Z. Gao, T. Zhang, J. Sun, Y. Ma, N. Tian, J. Gong, Seeding techniques and optimization of solution crystallization processes, *Org. Process Res. Dev.* 24 (10) (2020) 1839–1849, <https://doi.org/10.1021/acs.oprd.0c00151>.
- [9] O. Narducci, A.G. Jones, Seeding in situ the cooling crystallization of adipic acid using ultrasound, *Cryst. Growth Des.* 12 (4) (2012) 1727–1735, <https://doi.org/10.1021/cg200677p>.
- [10] W. Beckmann, Seeding the desired polymorph: background, possibilities, limitations, and case studies, *Org. Process Res. Dev.* 4 (2000) 372–383, <https://doi.org/10.1021/op0000778>.
- [11] Z. Gao, F. Altimimi, J. Gong, Y. Bao, J. Wang, S. Rohani, Ultrasonic irradiation and seeding to prevent metastable liquid–liquid phase separation and intensify crystallization, *Cryst. Growth Des.* 18 (4) (2018) 2628–2635, <https://doi.org/10.1021/acs.cgd.8b0028410.1021/acs.cgd.8b00284.s001>.
- [12] D.K. Sandilya, A. Kannan, Intensification of the dissolution of a sparingly soluble solid from a spinning disk in the presence of power ultrasound, *Ind. Eng. Chem. Res.* 50 (23) (2011) 13083–13091, <https://doi.org/10.1021/ie101702u>.

- [13] R. Prasad, S.V. Dalvi, Sonocrystallization: monitoring and controlling crystallization using ultrasound, *Chem. Eng. Sci.* 226 (2020) 115911–115940, <https://doi.org/10.1016/j.ces.2020.115911>.
- [14] N.I. Wakayama, Effects of a strong magnetic field on protein crystal growth, *Cryst. Growth Des.* 3 (1) (2003) 17–24, <https://doi.org/10.1021/cg025565g>.
- [15] S. Martínez-Caballero, M. Cuéllar-Cruz, N. Demitri, M. Polentarutti, A. Rodríguez-Romero, A. Moreno, Glucose isomerase polymorphs obtained using an Ad Hoc protein crystallization temperature device and a growth cell applying an electric field, *Cryst. Growth Des.* 16 (3) (2016) 1679–1686, <https://doi.org/10.1021/acs.cgd.5b01755>.
- [16] N. Radacsi, J.H. ter Horst, G.D. Stefanidis, Microwave-assisted evaporative crystallization of niflumic acid for particle size reduction, *Cryst. Growth Des.* 13 (10) (2013) 4186–4189, <https://doi.org/10.1021/cg4010906>.
- [17] U.N. Hatkar, P.R. Gogate, Process intensification of anti-solvent crystallization of salicylic acid using ultrasonic irradiations, *Chem. Eng. Process* 57–58 (2012) 16–24, <https://doi.org/10.1016/j.cep.2012.04.005>.
- [18] C. Fang, W. Tang, S. Wu, J. Wang, Z. Gao, J. Gong, Ultrasound-assisted intensified crystallization of L-glutamic acid: crystal nucleation and polymorph transformation, *Ultrason. Sonochem.* 68 (2020) 105227, <https://doi.org/10.1016/j.ultsonch.2020.105227>.
- [19] C.N. Gajendragadkar, P.R. Gogate, Intensified recovery of valuable products from whey by use of ultrasound in processing steps - a review, *Ultrason. Sonochem.* 32 (2016) 102–118, <https://doi.org/10.1016/j.ultsonch.2016.02.023>.
- [20] S. Bhoi, D. Sarkar, Constructing regions of attainable sizes and achieving target size distribution in a batch cooling sonocrystallization process, *Ultrason. Sonochem.* 42 (2018) 162–170, <https://doi.org/10.1016/j.ultsonch.2017.11.017>.
- [21] J. Lee, M. Ashokkumar, S.E. Kentish, Influence of mixing and ultrasound frequency on antisolvent crystallization of sodium chloride, *Ultrason. Sonochem.* 21 (1) (2014) 60–68, <https://doi.org/10.1016/j.ultsonch.2013.07.005>.
- [22] A.H. Batghare, K. Roy, V.S. Moholkar, Investigations in physical mechanism of ultrasound-assisted antisolvent batch crystallization of lactose monohydrate from aqueous solutions, *Ultrason. Sonochem.* 67 (2020) 105127–105138, <https://doi.org/10.1016/j.ultsonch.2020.105127>.
- [23] E.W. Conder, A.S. Cosbie, J. Gaertner, W. Hicks, S. Huggins, C.S. MacLeod, B. Remy, B.-S. Yang, J.D. Engstrom, D.J. Lamberto, C.D. Papageorgiou, The pharmaceutical drying unit operation: an industry perspective on advancing the science and development approach for scale-up and technology transfer, *Org. Process Res. Dev.* 21 (3) (2017) 420–429, <https://doi.org/10.1021/acs.oprd.6b00406>.
- [24] M. Murru, G. Giorgio, S. Montomoli, F. Ricard, F. Stepanek, Model-based scale-up of vacuum contact drying of pharmaceutical compounds, *Chem. Eng. Sci.* 66 (21) (2011) 5045–5054, <https://doi.org/10.1016/j.ces.2011.06.059>.
- [25] P. Suvarnakuta, S. Devahastin, S. Soponronnarit, A.S. Mujumdar, Drying kinetics and inversion temperature in a low-pressure superheated steam-drying system, *Ind. Eng. Chem. Res.* 44 (6) (2005) 1934–1941, <https://doi.org/10.1021/ie049675r>.
- [26] D.S. Hsieh, Q.I. Gao, M. Huang, L.M. DiMemmo, M. Lindrud, T. Razler, From drying kinetics, solvate structure, particle morphology, and modeling to optimal drying protocol, *Org. Process Res. Dev.* 21 (10) (2017) 1509–1520, <https://doi.org/10.1021/acs.oprd.7b00162>.
- [27] E.K. Sahni, R.H. Bogner, B. Chaudhuri, Systematic investigation of parameters affecting the performance of an agitated filter-dryer, *J. Pharm. Sci.* 102 (7) (2013) 2198–2213, <https://doi.org/10.1002/jps.23572>.
- [28] E. Tsotsas, E.U. Schlünder, Vacuum contact drying of mechanically agitated beds: the influence of hygroscopic behaviour on the drying rate curve, *Chem. Eng. Process* 21 (4) (1987) 199–208, [https://doi.org/10.1016/0255-2701\(87\)80017-X](https://doi.org/10.1016/0255-2701(87)80017-X).
- [29] M. Kohout, A.P. Collier, F. Stepanek, Vacuum contact drying kinetics: an experimental parametric study, *Dry. Technol.* 23 (9–11) (2005) 1825–1839, <https://doi.org/10.1080/07373930500209954>.
- [30] B. Remy, W. Kightlinger, E.M. Saurer, N. Domagalski, B.J. Glasser, Scale-up of agitated drying: effect of shear stress and hydrostatic pressure on active pharmaceutical ingredient powder properties, *AIChE Journal*. 61 (2) (2015) 407–418, <https://doi.org/10.1002/aic.14669>.
- [31] D.J. Lamberto, A. Diaz-Santana, G. Zhou, Form conversion and solvent entrapment during API drying, *Org. Process Res. Dev.* 21 (11) (2017) 1828–1834, <https://doi.org/10.1021/acs.oprd.7b00270>.
- [32] M. Birch, I. Marziano, Understanding and avoidance of agglomeration during drying processes: a case study, *Org. Process Res. Dev.* 17 (10) (2013) 1359–1366, <https://doi.org/10.1021/op4000972>.
- [33] S. Zhang, D.J. Lamberto, Development of new laboratory tools for assessment of granulation behavior during bulk active pharmaceutical ingredient drying, *J. Pharm. Sci.* 103 (1) (2014) 152–160, <https://doi.org/10.1002/jps.23762>.
- [34] N.K. Nere, K.C. Allen, J.C. Marek, S.V. Bordawekar, Drying process optimization for an API solvate using heat transfer model of an agitated filter dryer, *J. Pharm.* 101 (10) (2012) 3886–3895, <https://doi.org/10.1002/jps.23237>.
- [35] O. Narducci, A.G. Jones, E. Kougoulos, An assessment of the use of ultrasound in the particle engineering of micrometer-scale adipic acid crystals, *Cryst. Growth Des.* 11 (5) (2011) 1742–1749, <https://doi.org/10.1021/cg1016593>.
- [36] S. Kaur Bhangui, M. Ashokkumar, J. Lee, Ultrasound assisted crystallization of paracetamol: crystal size distribution and polymorph control, *Cryst. Growth Des.* 16 (4) (2016) 1934–1941, <https://doi.org/10.1021/acs.cgd.5b01470>.
- [37] M.-W. Park*, S.-D. Yeo, Antisolvent crystallization of roxithromycin and the effect of ultrasound, *Sep. Sci. Technol.* 45 (10) (2010) 1402–1410, <https://doi.org/10.1080/01496391003689538>.
- [38] K.A. Ramisetty, A.B. Pandit, P.R. Gogate, Ultrasound-assisted antisolvent crystallization of benzoic acid: effect of process variables supported by theoretical simulations, *Ind. Eng. Chem. Res.* 52 (49) (2013) 17573–17582, <https://doi.org/10.1021/ie402203k>.
- [39] S.V. Dalvi, R.N. Dave, Controlling particle size of a poorly water-soluble drug using ultrasound and stabilizers in antisolvent precipitation, *Ind. Eng. Chem. Res.* 48 (16) (2009) 7581–7593, <https://doi.org/10.1021/ie900248f>.
- [40] C.-S. Su, C.-Y. Liao, W.-D. Jheng, Particle size control and crystal habit modification of phenacetin using ultrasonic crystallization, *Chem. Eng. Technol.* 38 (1) (2015) 181–186, <https://doi.org/10.1002/ceat.v38.110.1002/ceat.201300573>.
- [41] H. Hatakka, H. Alatalo, M. Louhi-Kultanen, I. Lassila, E. Hægström, Closed-loop control of reactive crystallization PART II: polymorphism control of L-glutamic acid by sonocrystallization and seeding, *Chem. Eng. Technol.* 33 (2010) 751–756, <https://doi.org/10.1002/ceat.200900577>.
- [42] G. Ruecroft, D. Hipkiss, T. Ly, N. Maxted, P.W. Cains, Sonocrystallization: the use of ultrasound for improved industrial crystallization, *Org. process Res. dev.* 9 (2005) 923–932, <https://doi.org/10.1021/op050109x>.
- [43] Z. Wang, J. Jiang, P. Hu, Q. Zhao, Development and validation of a UPLC-MS/MS method for simultaneous determination of fentanyl and its two major metabolites in human plasma and urine, *Bioanalysis* 9 (4) (2017) 381–393, <https://doi.org/10.4155/bio-2016-0243>.
- [44] Y. Liu, M. Chen, J. Lin, M. Li, K. Li, Z. Gao, Solubility measurement and data correlation of clopidogrel hydrogen sulfate (form I) in four binary solvents systems at temperature from 278.15 to 318.15 K, *J. Chem. Eng. Data* 65 (5) (2020) 2903–2911, <https://doi.org/10.1021/acs.jced.0c00190>.
- [45] G. Morgado, S. Miquel, R.C. Felix, Measurement of ultrasound power using a calorimeter, *Journal of Physics Conference*. 975 (2018) 012010–012016, <https://doi.org/10.1088/1742-6596/975/1/012010>.
- [46] M.N. Hussain, J. Jordens, S. Kuhn, L. Braeken, T.V. Gerven, Ultrasound as a tool for polymorph control and high yield in flow crystallization, *Chem. Eng. J.* 408 (2020) 127272–127285, <https://doi.org/10.1016/j.cej.2020.127272>.
- [47] G.K. Patil, P.B. Patil, S.R. Pardeshi, R.L. Rajput, S.H. Sonawane, A. Mujumdar, J. B. Naik, Effect of process parameters on the recovery of lactose in an antisolvent acetone/acetone-ethanol mixture: A comparative study based on sonication medium, *Ultrason. Sonochem.* 67 (2020) 105128–105136, <https://doi.org/10.1016/j.ultsonch.2020.105128>.
- [48] A.S. Myerson, *Handbook of Industrial Crystallization*, 2nd ed., Butterworth-Heinemann, Woburn, MA, 2002.
- [49] S.S. Kadam, H.J.M. Kramer, J.H. ter Horst, Combination of a single primary nucleation event and secondary nucleation in crystallization processes, *Cryst. Growth Des.* 11 (4) (2011) 1271–1277, <https://doi.org/10.1021/cg101504c>.
- [50] V.S. Nalajala, V.S. Moholkar, Investigations in the physical mechanism of sonocrystallization, *Ultrason. Sonochem.* 18 (1) (2011) 345–355, <https://doi.org/10.1016/j.ultsonch.2010.06.016>.
- [51] H. Kiani, D.-W. Sun, A. Delgado, Z. Zhang, Investigation of the effect of power ultrasound on the nucleation of water during freezing of agar gel samples in tubing vials, *Ultrason. Sonochem.* 19 (3) (2012) 576–581, <https://doi.org/10.1016/j.ultsonch.2011.10.009>.
- [52] B. Jja, B. Bga, A. Cx, A. Mnh, A. Gds, B. Lcjt, B. Lb, A. Tvg, Sonocrystallization: observations, theories and guidelines, *Chem. Eng. Process*. 139 (2019) 130–154, <https://doi.org/10.1016/j.cep.2019.03.017>.
- [53] M. Ashokkumar, The characterization of acoustic cavitation bubbles – An overview, *Ultrason. Sonochem.* 18 (4) (2011) 864–872, <https://doi.org/10.1016/j.ultsonch.2010.11.016>.
- [54] H. Harzali, F. Baillon, O. Louisnard, F. Espitalier, A. Mgaidi, Experimental study of sono-crystallization of ZnSO₄·7H₂O, and interpretation by the segregation theory, *Ultrason. Sonochem.* 18 (2011) 1097–1106, <https://doi.org/10.1016/j.ultsonch.2011.03.007>.
- [55] A.A. Thorat, M.D. Yadav, S.V. Dalvi, Simple criterion for stability of aqueous suspensions of ultrafine particles of a poorly water soluble drug, *Langmuir* 30 (16) (2014) 4576–4592, <https://doi.org/10.1021/la500825j>.
- [56] Z. Guo, A.G. Jones, H. Hao, B. Patel, N. Li, Effect of ultrasound on the heterogeneous nucleation of BaSO₄ during reactive crystallization, *J. Appl. Phys.* 101 (2007) 054907–054915, <https://doi.org/10.1063/1.2472652>.
- [57] S.V. Dalvi, M.D. Yadav, Effect of ultrasound and stabilizers on nucleation kinetics of curcumin during liquid antisolvent precipitation, *Ultrason. Sonochem.* 24 (2015) 114–122, <https://doi.org/10.1016/j.ultsonch.2014.11.016>.
- [58] A. Kuldipkumar, G.S. Kwon, G.G.Z. Zhang, Determining the growth mechanism of tolazamide by induction time measurement, *Cryst. Growth Des.* 7 (2) (2007) 234–242, <https://doi.org/10.1021/cg0602212>.
- [59] S. Doktycz, K. Suslick, Interparticle collisions driven by ultrasound, *Science* 247 (4946) (1990) 1067–1069, <https://doi.org/10.1126/science.2309118>.
- [60] U.N. Hatkar, P.R. Gogate, Ultrasound assisted cooling crystallization of sodium acetate, *Ind. Eng. Chem. Res.* 51 (39) (2012) 12901–12909, <https://doi.org/10.1021/ie202220q>.