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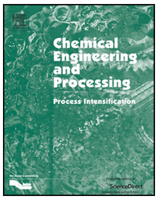

Effect of jet velocity on crystal size distribution from antisolvent and cooling crystallizations in a dual impinging jet mixer

Mo Jiang[a], Yao-En David Li[b], Hsien-Hsin Tung[b], Richard D. Braatz[a,*]

[a] *Massachusetts Institute of Technology, Department of Chemical Engineering, 77 Massachusetts Avenue, Room E19-551, Cambridge, MA 02139, USA*
[b] *AbbVie Inc., 1 N Waukegan Rd., North Chicago, IL 60064, USA*

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ABSTRACT

In the pharmaceutical industry, good control of the crystal size distribution (CSD) can improve process efficiency and formulation of the drug product. An effective method to continuously generate small crystals of narrow size distribution for some drug/solvent systems is by using a dual-impinging jet (DIJ) mixer. This paper demonstrates the first use of a DIJ mixer combining cooling and antisolvent crystallization to generate crystals with a typical pharmaceutical solubility. In a confined Y-shaped DIJ mixer by this approach, product crystals are obtained with smaller sizes and aspect ratios than a conventional batch process. We also quantify the relationships between the particle size, distribution width, and distribution modality on the inlet jet velocity. This combination of cooling and antisolvent crystallization may widen the application of DIJ mixers for the generation of small uniform pharmaceutical crystals.

1. Introduction

The crystal size distribution (CSD) of active pharmaceutical ingredients affects many aspects of pharmaceutical processes and products [1–6]. The CSD of product crystals is largely affected by the CSD of seed crystals in a common industrial crystallization. The production of small crystals with a narrow CSD has been demonstrated in reactive and antisolvent crystallizations from dual-impinging jet (DIJ) mixers, by generating high-intensity micromixing of fluids to achieve an almost homogeneous composition of high supersaturation before the onset of nucleation [2–6]. Compared to other methods to generate small crystals (e.g., high-speed rotor-stator homogenization or wet milling), DIJ mixers have the potential advantage of high-throughput with an inexpensive small-volume setup [7,8], and some commercial pharmaceutical processes have adopted this technology [2,9–13]. A key factor for controlling the CSD obtained from such DIJ crystallizers is the jet Reynolds number—the lower the Reynolds number, the higher the average crystal size and the wider the CSD [4,14,15]. It is commonly argued that the effectiveness of DIJ mixers relies on the need for the micromixing time to be shorter than the mean residence time [14].

We have recently reported a cooling DIJ mixer configuration that combines hot and cold saturated solutions to generate seed crystals with a narrow size distribution for an amino acid, L asparagine monohydrate (LAM) [1,16]. To our knowledge, this was the first experimental demonstration and first theoretical analysis of the feasibility of using a dual-impinging jet mixer for the cooling crystallization of an organic compound. We identified that the main reason for the successful crystallization within a cooling DIJ mixer is the delayed mixing of compositions compared to temperature. This phenomenon enabled the temperature of the hot solution to drop near the average temperature of the two solutions before its solution concentration had significantly changed, resulting in a local supersaturation sufficiently high to nucleate crystals. In particular, it was shown that the lack of perfect compositional mixing of fluids within the cooling DIJ mixer was required for primary nucleation to occur for the particular drug/solvent combination.

A DIJ mixer may be used to continuously manufacture other drug compounds, but this technology will not work for drug/solvent combinations that have insufficient supersaturation to nucleate crystals at a high enough rate within the mixer. This paper extends the application of DIJ crystallizers to more drug compounds by combining cooling with antisolvent crystallization,

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* Corresponding author. Fax: +1 617 258 0546.
E-mail address: braatz@mit.edu (R.D. Braatz).

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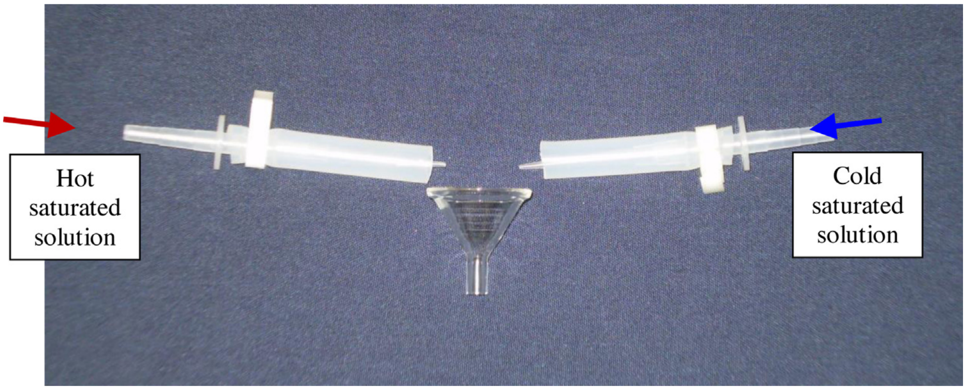

Fig. 1. Open DIJ mixing configuration used in cooling crystallization experiments. This design allowed a quick test of the feasibility of DIJ mixing for a specified compound and solvents. The inlet jet velocity is adjustable with jet tips of different inner diameters.

which enables the generation of higher nucleation rates in the DIJ mixer than can be obtained by cooling or antisolvent crystallization alone. A Compound X was used to demonstrate the feasibility of the combined (cooling and antisolvent) DIJ mixer to generate crystals of uniform size. Compound X is an active pharmaceutical ingredient that has a typical solubility for soluble pharmaceuticals, with only one polymorphic form. The DIJ-manufactured Compound X crystals are sufficiently small to eliminate the milling step after drying. We also studied the effect of jet velocity on CSD from a confined Y-shaped DIJ mixer. To our knowledge, this is the first investigation of the relationship between inlet jet velocity and CSD from a combined DIJ mixer.

2. Experimental methods

Several different DIJ mixer configurations have been investigated in the literature [1–4]. Two configurations were implemented in this study: an open DIJ mixer (Fig. 1) for preliminary experiments, which is easy and flexible to handle with low clogging probability, and a confined Y-shaped DIJ mixer (Fig. 2) for optimized experiments to avoid solvent evaporation and to allow more precise control of flow direction, especially at higher jet velocities. The Y shape was chosen rather than T shape to reduce stagnant volume in the mixer. Preliminary experiments to demonstrate the effect of jet velocity for an open cooling DIJ mixer were carried out using LAM. LAM was used as a surrogate inexpensive and non-toxic small-molecule compound with similar aqueous solubility to some pharmaceutical compounds.

2.1. Preliminary experiments with LAM in an open cooling DIJ mixer

The cooling DIJ mixer (Fig. 1) with two streams containing hot and cold saturated solutions (0.20 g LAM/g water at 70 °C, and 0.03 g LAM/g water at 25 °C, respectively) were run at two different jet velocities. A Masterflex peristaltic pump (console drive R7520-40) with dual pump heads (Masterflex easy load II models 77201-62 and 77200-62) was used, for the flow rate ratio of hot and cold solutions of 1:1. At this ratio, the average concentration of the two streams, 0.115 g LAM/g water, is larger than the LAM aqueous solubility, 0.07 g LAM/g water, at the mixing temperature (47.5 °C, the average of two streams). Norprene® food tubing (Masterflex 6402-15) was used for its working temperature range (−20 to 100 °C) and long pumping life. Connectors and adaptors made of ethylene tetrafluoroethylene (ETFE) were used between the tubing and DIJ mixer, due to the high melting temperature and excellent chemical resistance property of ETFE. The hot and cold temperature baths (BUCHI™ B-481 and water bath with IKA® RET Control-Visc hot plate stirrer, respectively) were used to maintain the constant temperature of the stock solution for the two streams of DIJ. The success of the DIJ experiment relies on maintaining the temperature of the hot stream before DIJ impingement (e.g., through insulation of the part of tubing not in temperature bath) to prevent early nucleation. These experiences are reflected in the design of the combined confined DIJ mixer as discussed in more detail in the next subsection.

2.2. Experimental equipment, materials, and procedures with Compound X in a combined DIJ mixer

The design of combined DIJ mixer for preliminary studies is based on our past design of an open cooling DIJ mixer [1,16]. The hot stream contained a saturated solution of Compound X (see Fig. 3 for source material) in ethanol (0.135 g solute/g ethanol) at 65 °C in translucent silicone tubing (Masterflex 96410-15, for confirmation of no early nucleation in the tubing). The temperature of the hot solution was limited by the boiling point of ethanol. The cold stream contained antisolvent heptane (miscible with ethanol) at 25 °C in Viton® tubing (Masterflex 96412-15, compatible with organic solvent, but with limited pump life). The same peristaltic pump with dual-pump-head was used as in the preliminary experiments in Section 2.1 (e.g., the volumetric flow rate ratio between the two streams was still 1:1).

Jet velocities from 1 to 15 m/s were achieved with various pump rates and Y-shaped mixers (shown in Fig. 2, IDEX® P-512 series, made of chemical-resistant high-temperature-tolerable PEEK™ material) at different inner diameters (0.5 mm, 1 mm, and

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[1] Adjustment of the inlet jet velocity was accomplished by either changing the pumping rate for the same DIJ mixer (the same diameter), or by changing the inner diameter of the DIJ mixer (among available sizes) at the same pumping rate. For example, a 10 m/s jet velocity is achieved with a Y-mixer with 0.5 mm inner diameter at a pump reading of 200 rpm. For the available experimental setup, a pump reading lower than 200 did not provide enough force to push fluid through the system, while a pump reading larger than 300 would cause the tubing to shake violently, which would increase the difficulty of jet alignment for impingement. Thus, for the 0.5 mm Y-mixer, the jet velocity ranges reliably from 10 m/s (at a pump reading of 200) to 15 m/s (at a pump reading of 300). As the inlet flow rate is proportional to the square of the inner diameter of mixer, the range of jet velocities are 2.5–3.75 m/s, and 1.1–1.65 m/s, for 1 mm and 1.5 mm mixers, respectively. Jet velocities of 3.75 m/s and 1.65 m/s were not chosen for analysis because the outlet flow was pulsing at these velocities with the corresponding mixers (from experimental observation).

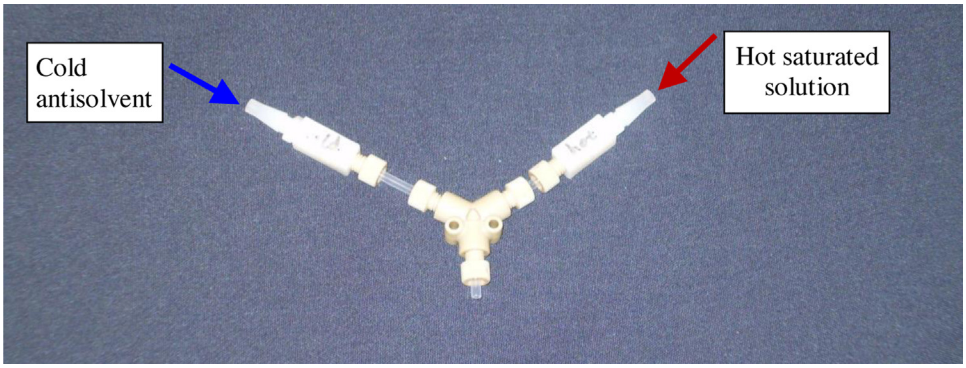

Fig. 2. Confined Y-shaped DIJ mixer configuration used in combined cooling-antisolvent crystallization experiments. This design allows for the convenient adjustment of jet velocity with implementation of Y-shaped mixers of different inner diameters with the same flangeless fitting connection.

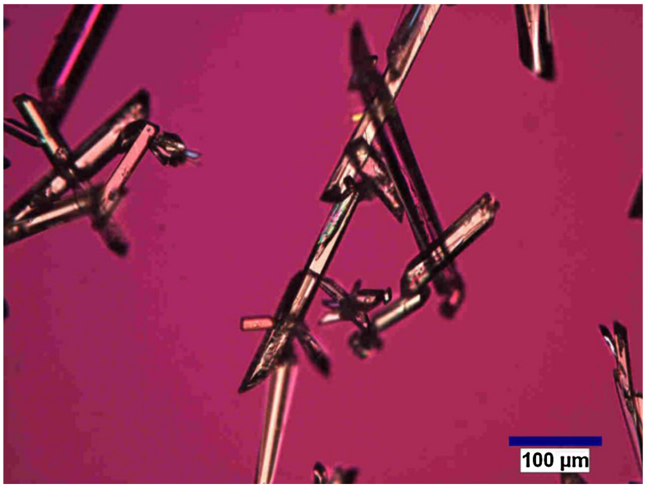

Fig. 3. Microscope images (with polarizers) of Compound X crystals in wet cake produced at the industrial scale by combined cooling-antisolvent crystallization in a mixed tank. These crystals were used as the source material in the DIJ crystallization experiments.

1.5 mm).[1] All experiments were carried out within the peristaltic pump's optimal operation range so as to have continuous flow and minimize shaking of the tubing. The detailed experimental procedure is in Table 1.

3. Results and discussion

3.1. Crystal size and shape from DIJ mixers

The cooling open DIJ mixer was able to produce small LAM crystals (see Fig. 4). The maximum crystal size was about 40 μm, which is much larger than observed in a previous study for LAM in the same solvent but using a different DIJ mixer [1,16]. These results are indicative of a drawback of employing open DIJ mixers instead of confined DIJ mixers, which is that the open designs are very sensitive to small shifts in the angle in which the two jets hit each other at the region of impingement. This observation motivated the switch from an open to a confined configuration for the subsequent combined DIJ crystallization of Compound X crystals.

To achieve high solids density during DIJ crystallization of Compound X, a combination of cooling and antisolvent DIJ mixer was designed, instead of the pure cooling DIJ mixer, to increase the average supersaturation level thus the crystallization yield. Various jet velocities (1.1, 2.5, 10, and 15 m/s) were examined to produce a range of particle size and shape (Fig. 5). For inlet velocities of 2.5–10 m/s, the product crystals were mostly under 100 μm in length, much smaller than the typical crystals obtained from a conventional batch combining cooling and antisolvent crystallization of Compound X (shown in Fig. 3). Three shapes of Compound X crystals (plate, rod, and needle) were obtained at varying proportions depending on the jet velocity. These crystal shapes were also observed in batch experiments during the industrial manufacturing process.

The aspect ratio of the crystals is much larger for the inlet jet velocity of 1.1 m/s (Fig. 5d), compared to higher velocities (Fig. 5a–c). These needle-like crystals are very close in shape to the source crystals produced by batch crystallizations (see Fig. 3). Possible reasons include the low spatial uniformity of supersaturation in both batch crystallizer and DIJ mixer at a low inlet jet velocity. The crystals produced at higher inlet jet velocities have smaller aspect ratios that are much more amenable to downstream operations such as washing, filtering, and milling (see Fig. 5a–c). As most crystals produced by the combined DIJ mixer are smaller than the mean size of crystals obtained from batches (see Fig. 6 and Table 2),

Table 1
Experimental procedure for crystallization of compound X within a combined DIJ mixer.

1. A Y-shaped mixer with a proper inner diameter was connected to the tubing. Make sure there is no leakage at the connection and the distance between outlet of the DIJ mixer and the filtration funnel is constant between different experiments. A chiller was used to keep the temperature of the jacketed fritted funnel at the mixing temperature (45 °C, average of the temperatures of two stock solutions). Stock solvent (ethanol) was heated in a hot water bath to reach the target temperature 65 °C.
2. The solvent and antisolvent at the target temperatures (ethanol at 65 °C and heptane at 20 °C, respectively) were primed through the tubing connected to mixer. The vacuum connected to the jacketed fritted funnel below the filter paper was turned on when both stock solvents (solvent and antisolvent) were pumped through the mixer to wet the filter paper.
3. Streams of Compound X saturated solution and antisolvent were pumped at a proper pump flow rate to ensure that these two streams reach the Y mixer at the same time. Solids were collected on filter paper (Whatman®, grade 542, particle retention size 2.7 μm) after filtration with vacuum.
4. Immediately after the collection is completed, temporarily stop the vacuum and pipette some solution mixture from the vacuum bottle (under the filter, which was all liquid) for a composition check using high-performance liquid chromatography (HPLC). Then resume vacuum to continue drying the filter paper.
5. The crystals were rinsed with heptane and analyzed using a Malvern Mastersizer 2000, with Hydro 2000s wet cell for particle size distribution (PSD) analysis.

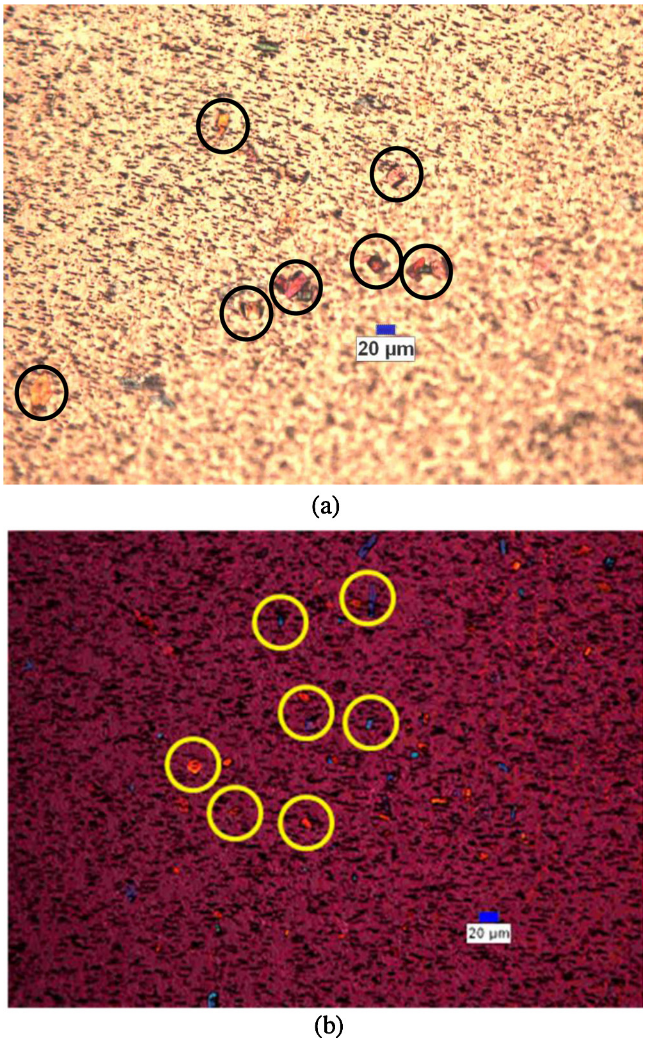

Fig. 4. LAM crystals (some circled) produced from an open cooling DIJ mixer (Fig. 1) at jet velocity of (a) 10 m/s and (b) 20 m/s. The black dots in the background are the pores of membrane filters (the same as used in Fig. 6a of [1]) on which the crystals were filtered.

the crystals would require less milling during the manufacture of the final drug product.

3.2. Effect of jet velocity and Reynolds number on crystal size distribution and median size from DIJ mixer

The measured PSDs for different jet velocities are unimodal at higher inlet jet velocities (10 and 15 m/s) and bimodal at lower inlet velocities (1.1 and 2.5 m/s) (see Fig. 6). The velocity range agrees with the reported minimum value of jet linear velocity (5 m/s) for good mono-dispersed crystals reported by Midler et al. [2]. The bimodal distribution at lower inlet jet velocities could come from spatially varying supersaturation within the DIJ mixer caused by non-ideal mixing (similar to the non-ideal situation in batch crystallizers). The Reynolds number for the jet velocities and length scales shown in Table 1 is on the order of 2000–10,000, indicating turbulence. It is well-known, however, that the presence of turbulence does not necessarily ensure uniform mixing.

The larger median particle size (D50 in Table 2) and wider PSD width at a reduced inlet jet velocity (see Fig. 6) is consistent with published experimental and simulation data for antisolvent or reaction crystallization of other compounds in DIJ mixers [14,15,17,18], and cooling crystallization of LAM (Fig. 4a,b). This

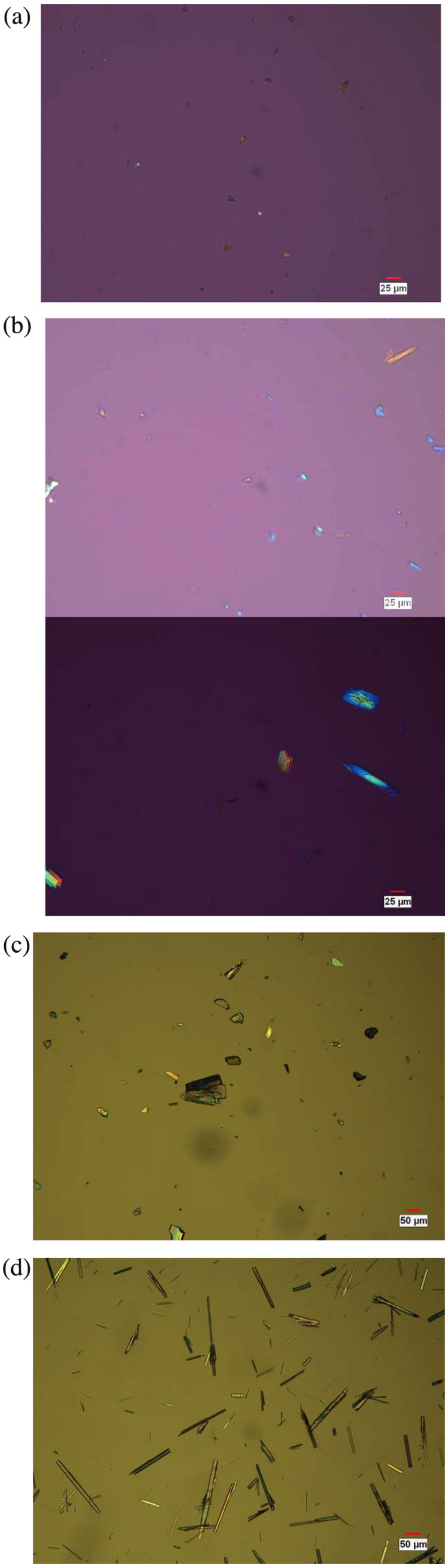

Fig. 5. Microscope images (with polarizers) of compound X crystals in heptane obtained from the combined confined Y-shaped DIJ mixer, after Malvern particle size analysis (so some crystals may have been broken), at a jet velocity of (a) 15 m/s, (b) 10 m/s (two photos from same sample), (c) 2.5 m/s, (d) 1.1 m/s. The corresponding PSDs are the green, red, blue, and purple curves in Fig. 6. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

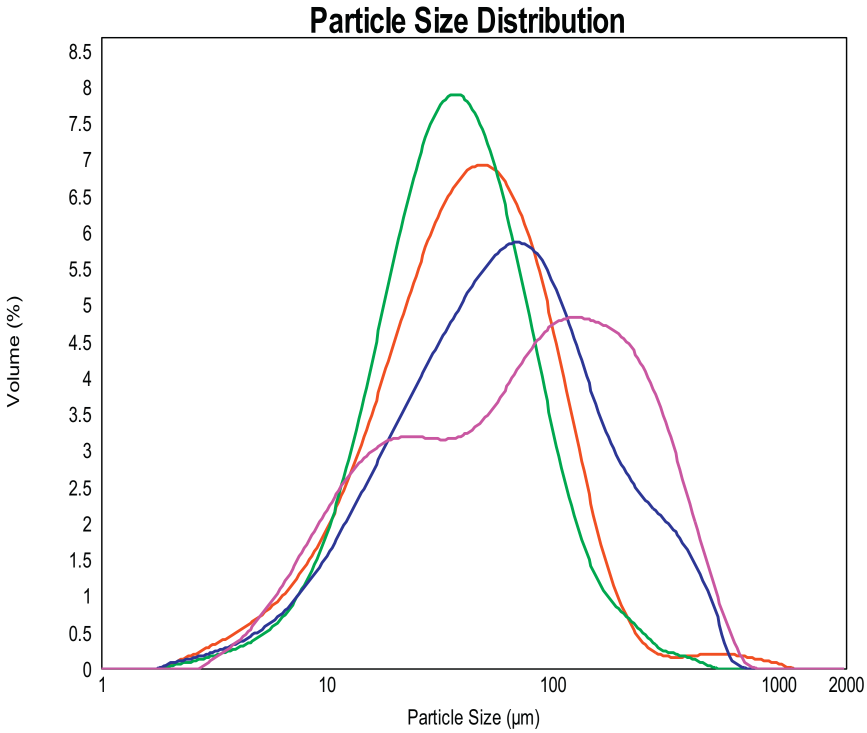

Fig. 6. Size distributions (measured by Malvern Particle-Size Analyzer) of Compound X crystals from the combined confined Y-shaped DIJ at inlet jet velocities of 15 m/s (green), 10 m/s (red), 2.5 m/s (blue), and 1.1 m/s (pink). Note that the Malvern analysis will undercount small crystals with high aspect ratio, especially for the inlet velocity of 1.1 m/s, due to their needle-like shape (as seen in Fig. 5d). For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

Table 2
Particle sizes (measured by Malvern Particle-Size Analyzer) of Compound X crystallized from ethanol solution at different inlet jet velocities.[a]

Jet velocity (m/s)	Mixer inner diameter (mm)	D10 (μm)	D50 (μm)	D90 (μm)	Mixer channel branch length (in.)	Mean residence time (ms)
15	0.5	13	37	99	0.33	0.56
10	0.5	12	42	117	0.33	0.84
2.5	1.0	14	60	233	0.29	3.0
1.1	1.5	12	77	297	0.29	7.4

[a] D10, D50, and D90 are the particle diameters below which 10%, 50%, and 90% of the sample volume exists, respectively.

trend can be attributed to a longer mean residence time (for nucleation and growth) at a lower inlet jet velocity. In addition, the higher energy input (associated with a higher inlet jet velocity) increases the nucleation rate when the nucleation process is limited by mixing. From solute mass balance, a higher nucleation rate with a larger number of nuclei results in smaller median particle size [17,19–21].

The median crystal size can be related to the inlet jet velocity through a power-law expression (see Fig. 7), which could be used for design purposes.

3.3. Yield comparison between cooling, antisolvent, and combined DIJ crystallizers

At a volumetric flow rate ratio between two streams of 1:1, the theoretical yield for a cooling DIJ mixer is (0.135 – 0.066)/0.135 × 100% = 51%, where 0.033 g solute/g ethanol is the solubility of Compound X in ethanol at 25 °C and 0.135 g solute/g ethanol its concentration in hot stream. For an antisolvent DIJ mixer (using 45 °C as an example), the theoretical yield is (0.083 – 0.02)/0.083 × 100% = 76%. For the combined DIJ mixer, the yield is about

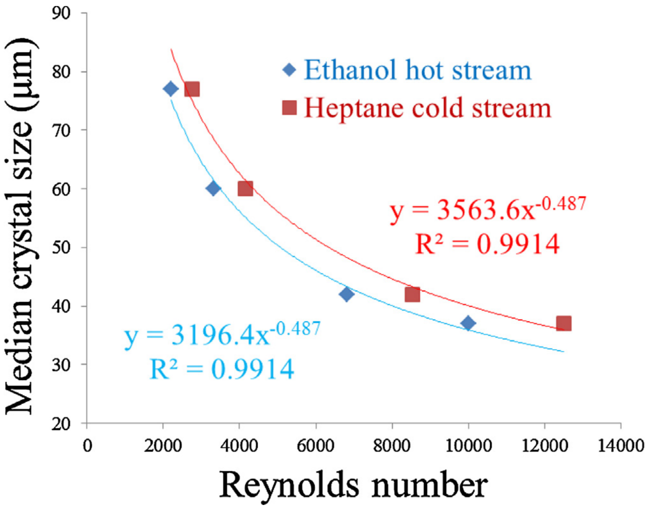

Fig. 7. Power-law fitting of median crystal size vs. Reynolds number for the combined confined Y-shaped DIJ mixer (from data in Table 2).

$(0.135 - 0.02)/0.135 \times 100\% = 85\%$. The combined operation, which combines the crystallization driving force from both cooling and antisolvent, has higher yield than these two operations alone.

4. Conclusions

This paper describes the continuous generation of small crystals of an active pharmaceutical ingredient by combined cooling and anti-solvent crystallization within a confined Y-shaped DIJ mixer. As the inlet jet velocity of the DIJ mixer increased, the mean crystal size decreased, the CSD narrowed, and the CSD transitioned from a bimodal to unimodal distribution. The median crystal size were fit to a power law function of the jet Reynolds number, which can be used to reduce the number of experiments needed to determine the inlet jet velocity for the production of crystals of a desired size. Combined cooling and anti-solvent crystallization within a DIJ mixer is a promising approach for the manufacture of pharmaceutical crystals whose solubilities depend on both temperature and composition of an antisolvent, and expands the practical application of DIJ mixers to more pharmaceutical compounds.

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