

# Particle Engineering in a Continuous Crystallizer Cascade

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**ABSTRACT:** Crystallization is central to the purification and manufacturing of nearly all small-molecule pharmaceuticals. However, continuous crystallization remains sparsely adopted, in part due to the lack of standardized off-the-shelf platforms ( $\leq 100$  mL) for reproducible development. This study reports the benchmarking of a continuous tower crystallizer (TWC) that constitutes a cascade of 10 mixed-suspension, mixed-product removal (MSMPR) crystallizers to approach plug-flow-like residence time distribution (RTD) in a compact and robust setup ( $\leq 80$  mL). Using ketoconazole, an agglomeration-prone active pharmaceutical ingredient (API), as a case study, the TWC's particle engineering capability is compared to a conventional single-tank MSMPR (with similar total volume) utilized as baseline. The advanced supersaturation control achieved in the cascade enables shifting the broad bimodal crystal size distribution (CSD,  $D_{90} = 225$   $\mu\text{m}$ , span = 4.5) to a unimodal CSD ( $D_{90} = 57$   $\mu\text{m}$ , span = 3.2) while significantly increasing process yield from 66% (MSMPR) to 90% (TWC). This tunability was further demonstrated through a proof-of-concept for distributed antisolvent addition in the TWC ( $D_{90} = 44$   $\mu\text{m}$ , span = 2.7).

## 1. INTRODUCTION

Crystallization is a cost-effective unit operation for the isolation and purification of products across various industries, including, e.g., chemical, food, and pharmaceutical.<sup>1–3</sup> Besides achieving the materials' purity, this process defines the crystal size, morphology, and solid form, which dictates, e.g., how easily a product can be filtered (downstream processability) and how well the material performs defined by critical quality attributes.<sup>4</sup> To offer advanced quality control and efficiency compared to batch processing, continuous manufacturing is increasingly adopted and incentivized in the pharmaceutical sector.<sup>5</sup> Despite its reported advantages, continuous crystallization remains a significant bottleneck due to the difficulty in handling solid–liquid mixtures (slurries) at small scales ( $\leq 100$  mL) and the lack of off-the-shelf equipment at such scales.<sup>5,6</sup> Consequently, customized setups are reported, some offering specialized transport mechanisms aimed at resolving these typical barriers.<sup>4,7–9</sup>

Existing continuous platforms generally fall into two categories: tubular and mixed-suspension, mixed-product removal (MSMPR) crystallizers.<sup>10</sup> Tubular designs are known

to provide a narrow residence time distribution (RTD) but often clog at the low flow rates needed for longer residence times (low Reynolds numbers), and their high surface-area-to-volume ratios exacerbate fouling.<sup>5</sup> In contrast, MSMPRs handle dense slurries effectively through mechanical mixing but exhibit broader RTDs, leading to inconsistent supersaturation histories, wide crystal size distributions (CSD), low yield, and poor morphological control, to name a few.<sup>6,11–13</sup> Broad RTDs are particularly problematic for systems prone to agglomeration, as crystals that stay relatively longer in the crystallizer undergo repeated collisions and runaway cluster growth.<sup>14,15</sup>

Cascaded MSMPRs (multiple MSMPRs in series) can narrow the RTD while utilizing the benefits of a well-mixed stirred crystallizer.<sup>16,17</sup> While multistage MSMPR cascades have been

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adopted across modern industrial manufacturing campaigns ( $\leq 23$  L),<sup>18–23</sup> they are difficult to implement at small scales.<sup>4,5,24,25</sup> At small-scale ( $\leq 100$  mL), cascades typically require external hardware larger than the crystallizer itself (e.g., pumps<sup>26</sup> or pressure/vacuum systems<sup>8</sup>). In addition, the transfer lines often act as heat sinks, which increases the tendency of clogging and disrupting the flow of solids.<sup>5,19</sup> Such challenges lead to frequent cleaning requirements, bimodal CSDs, process shut-downs, and nonidealities.<sup>27,28</sup> To overcome these drawbacks, a seven-tank tower crystallizer (TWC) has been reported, demonstrating near-ideal RTD (liquid and solid phase) and thus, isokinetic withdrawal.<sup>6</sup> While this prior study using a TWC prototype provided proof-of-concept of robust crystallization process operation using glycine as a model compound, the present work focuses on the benchmarking of the TWC are compared to a conventional single-tank MSMPR<sup>29,30</sup> with a similar total working volume of  $\leq 100$  mL.<sup>6</sup>

Specifically, this study utilizes a second-generation TWC (Figure S1), which integrates 11 stages with a pump-free upward slurry-handling mechanism. For the benchmarking against a conventional MSMPR, ketoconazole, an active pharmaceutical ingredient (API) used to treat mucocutaneous infections, was selected as a challenging stress-test model compound. Ketoconazole possesses a high-nucleation rate, slow growth kinetics, and pronounced propensity for agglomeration, especially in the methanol–water system,<sup>31</sup> which is difficult to manage in a single-tank MSMPR<sup>32</sup> from a particle engineering perspective.

This study reports the improved control over nucleation, growth, and agglomeration of ketoconazole in the TWC. A single-tank MSMPR was used as a baseline to compare CSD characteristics (modality, uniformity, span) and process yield. Additionally, the RTD (liquid, solid) and micromixing behavior of the TWC were characterized and compared with a single-tank MSMPR. By assessing the mixing characteristics (macro, micro)<sup>33</sup> and shear environments, we demonstrate how the TWC achieves plug-flow-like control, enabling it to produce a narrower unimodal CSD at a higher yield. Ultimately, the insights and characterization methods reported in this study provide a versatile framework for crystallizing a broad range of molecules that require precise crystallization process control for particle engineering (size, CSD).

## 2. MATERIALS AND METHODS

### 2.1. Materials

Ketoconazole (>99% purity) was purchased from Ria International. HPLC-grade acetonitrile, formic acid, glycine, methanol, and water were sourced from Sigma-Aldrich, besides microcrystalline cellulose (MCC) particles with an average size of 20  $\mu$ m. Deionized water (18.20 M $\Omega$ /cm, pH = 7.03, mV = –42.0) for crystallization experiments was obtained using a Barnstead MicroPure water purification system (Thermo Fisher Scientific Inc., USA). All materials were used “as received” without purification.

### 2.2. Experimental Setups and Procedures

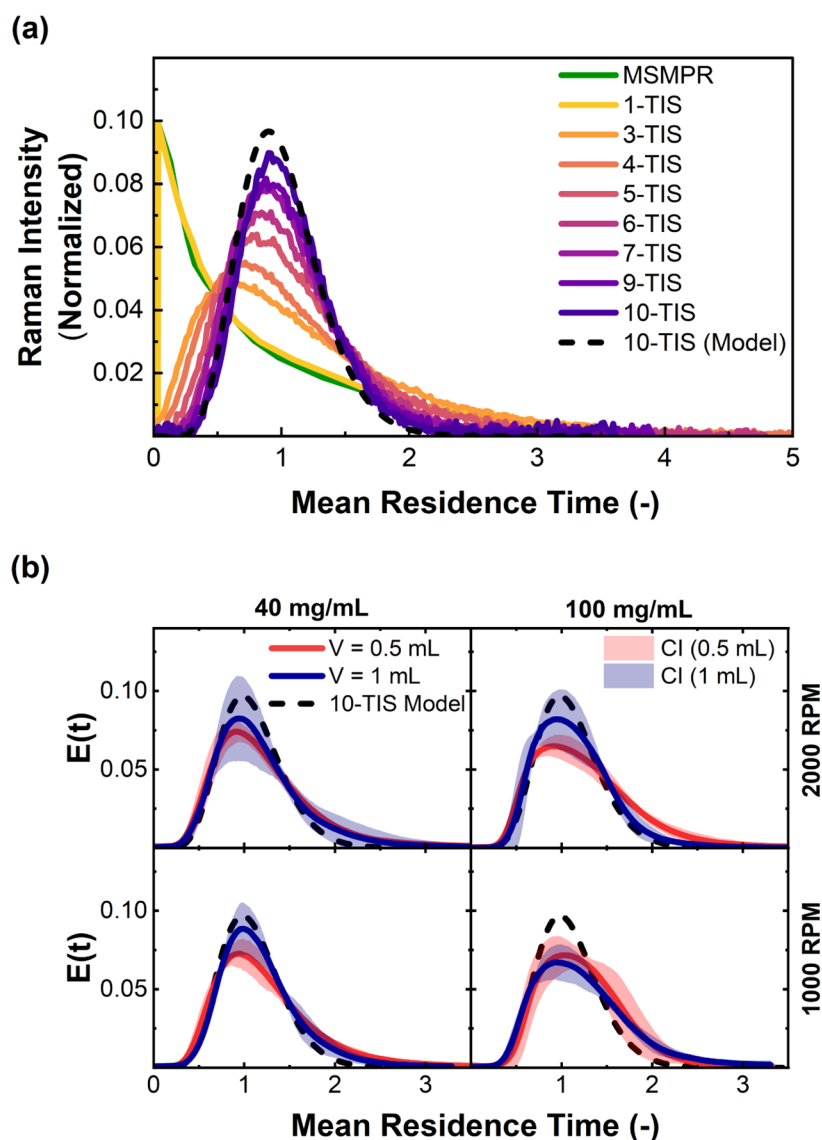
**2.2.1. Mixed Suspension Mixed Product Removal Crystallizer (MSMPR) Experiments.** Setup. Continuous crystallization in the MSMPR was conducted in an EasyMax 102 (Mettler Toledo, 100 mL working volume) equipped with a standard downward-pumping pitched 4-blade impeller (38 mm diameter, 45° pitch) and overhead stirrer operated at 300 rpm (tip speed = 0.6 m/s) and temperature-controlled at 25 °C. The MSMPR (glass tank) had a 52 mm internal diameter, yielding an impeller-to-tank diameter ratio of 0.73. The

impeller was positioned with a preset bottom clearance of  $\sim 5$  mm (from bottom of the blade). Three peristaltic pumps were employed for the feed and antisolvent addition as well as intermittent slurry withdrawal: two programmable Masterflex L/S pumps (Cole-Parmer, USA) fitted with Masterflex ChemDurance Bio tubing (gauge 13, ID = 0.8 mm) for the continuous introduction of the feed solution and the antisolvent above the surface, respectively, and one Masterflex P/S pump (Cole-Parmer, USA) fitted with gauge 16 (ID = 3.1 mm) ChemDurance Bio tubing for the intermittent slurry withdrawal via a dip tube.<sup>17,26</sup> The slurry transfer out of the MSMPR was performed at the maximum pump flow rate ( $\sim 80$  mL/min) every 5% of the mean residence time ( $\sim 60$  min), thus, every 3 min for 10 s. In addition, the crystallizer was equipped with a BlazePlatform Micro probe (Blaze Metrics, USA), further detailed below. Schematic of the standalone MSMPR is depicted in Figure 2a. A photo of the setup is provided in Figure S9.

**Procedure.** For the continuous antisolvent crystallization experiments, a method reported in the literature was adapted.<sup>27</sup> Briefly, a feed solution of saturated ketoconazole in methanol (80 mg/mL at 25 °C) was used with water as the antisolvent, yielding a 70:30 vol % methanol–water system. During the startup phase, the MSMPR was operated as a semibatch crystallizer by first adding 70 mL of the feed (room temperature). Subsequently, 30 mL of the antisolvent (room temperature) was continuously added at 0.498 mL/min. Once the 70:30 volumetric ratio of feed and antisolvent was reached, inducing nucleation of ketoconazole inside the crystallizer, the continuous feed at 1.162 mL/min and the intermittent withdrawal (detailed above) were started to initiate the continuous operation with a mean residence time of  $\sim 60$  min. Crystal evolution was monitored *in situ* by tracking the image-derived total chord length using the Blaze probe (detailed below). In addition, slurry samples were collected every residence time to measure the mother liquor concentration. The samples were immediately filtered in disposable filter funnels (Nalgene, pore size 0.2  $\mu$ m), and the filtrate was diluted as detailed in the HPLC method below. The recovered crystals were dried (unwashed) at 50 °C at ambient pressure in a Yamato ADP31 oven (Yamato Scientific) for at least 24 h before being analyzed by powder X-ray diffraction and differential scanning calorimetry (described in Section S1).

**2.2.2. Tower Crystallizer (TWC) Experiments. Setup.** Since this study builds on a prior work that demonstrated the TWC (spherical tanks) with full details on the equipment and operating principle<sup>6</sup> only a brief description is provided here for completeness. In this work, a second-generation TWC (Figure 2b, tanks with cylindrical portions closed by hemispheres at the top and bottom) was used, consisting of 11 vertically cascaded tanks, each with a working volume of 8 mL, for a total operating volume of 88 mL. Each tank is equipped with dual downward-pumping pitched 3-blade impellers with a pitch of 30° from the horizontal and a diameter of 10.2 mm. The clearance from the top and bottom of the tank is 5.5 mm. The slurry transport upward in the TWC occurs through a push mechanism in the first tank (bottom tank). A single mechanical piston served as the pulsation actuator, providing control over the delivered push volume (0.2–1 mL). Since each tank is filled with no headspace and free surface, and considering the incompressibility of liquids, with each push, an equal volume is moved from one tank into the next one, resulting in reproducible stage-to-stage slurry transfer.<sup>6</sup> Backflow between stages is prevented by nonreturn valves located at the interstage connections (Figure S1a), which open during the upward push step and close during piston retraction.<sup>6</sup> Additional information on the TWC architecture and slurry transfer mechanism, including a schematic depiction of their action, is provided in Section S2. High-purity perfluoroalkoxy tubing (1.58 mm OD; 0.762 mm ID) equipped with Super Flangeless polyetheretherketone connectors (IDEX/Upchurch Scientific, USA) were used for the feed and antisolvent lines connected to the TWC ports, respectively. Both the feed and antisolvent solutions were injected using M50 positive displacement pumps (VICI, USA).

**Procedure.** Similar to the MSMPR experiments, a saturated ketoconazole solution (detailed above) was used for continuous crystallization experiments in the TWC. For this study, the first TWC tank (bottom) was used as a mere buffer for the feed prior to the



**Figure 1.** Residence Time Distribution (RTD) characterization. (a) Liquid-RTD measured by *in situ* Raman spectroscopy for mixed-suspension, mixed-product removal (MSMPR) and tower crystallizer (TWC) operated with different numbers of effective tanks, compared with the tanks-in-series (TIS) model (broken line). Raman data are normalized with the area under the curve. (b) Solid-RTD measured using a microcrystalline cellulose (MCC) slurry as tracer for different push volumes ( $V = 0.5, 1$  mL), slurry loadings (40, 100 mg/mL), and stirring speeds (1000, 2000 rpm) for the TWC, compared with the 10-TIS model. Shaded areas represent the 95% confidence interval (CI).

antisolvent addition in the second tank, providing ten effective crystallization stages (TWC-10). The second-generation prototype lacked a sealed piston compartment, resulting in direct contact between crystals and the piston, which occasionally caused clogging. This limitation motivated the upstream placement of the antisolvent feed. Thus, mimicking a 10-tanks-in-series cascade (TWC-10), the feed solution was introduced in tank 1 at 0.9328 mL/min, while the antisolvent (water) was added in tank 2 at 0.3998 mL/min, yielding a mean residence time of  $\sim 60$  min across tanks 2 to 11. The continuous crystallization reached a steady state within  $\sim 4$  residence times, and the total operational run spanned 10 residence times (10 h). The push function was operated at the solution feed flow rate (added to the first stage, 0.9328 mL/min), rather than at the total inlet flow rate (antisolvent is added in the second tank), to prevent transient void formation or back-leakage during piston expansion. The RTD experiments confirmed that this operating strategy closely followed the tanks-in-series (TIS) behavior, further discussed below (Figure 1). As in the MSMPR experiments, the crystal evolution was monitored *in situ* using the Blaze probe inserted into the 11th stage. Slurry samples were also taken each residence time to determine the mother liquor

concentration as detailed above. For the startup, all tanks were filled with feed solution using the feed pump at the maximum flow rate. Once the solution visually exited the TWC, the continuous operation was initiated by activating the antisolvent pump and piston.

To mimic a single-tank configuration (TWC-1), the TWC was operated with only one tank (8 mL working volume). To achieve a mean residence time of 60 min, the feed solution and antisolvent flow rates were set to 0.09 mL/min and 0.04 mL/min, respectively. While the feed solution was continuously introduced in the bottom tank, similar to TWC-10 experiments, the antisolvent was fed into tank 11 for TWC-1, thereby replicating a single-tank MSMPR operation. The piston was again operated at the feed solution flow rate.

**2.2.3. Residence Time Distribution (RTD) Experiments. Liquid-RTD.** The tracer concentration via pulse injection method<sup>33</sup> was monitored by tracking the glycine-characteristic Raman band at  $898\text{ cm}^{-1}$ , following a calibration-free approach previously reported by the authors.<sup>6</sup> Briefly, the Raman probe (detailed below) was inserted in the collection tank to monitor the cumulative collection of solution flowing out from the setup. Details of the supporting experiments are provided in Section S5.

**Solid-RTD.** Solid-RTD was only determined for the TWC. A previously reported method was adapted<sup>6</sup> using MCC as an inert tracer<sup>33</sup> suspended in the liquid carrier (water). The particle counts during the solid-RTD experiments were monitored *in situ* in the 11th tank of the TWC using the Blaze probe (detailed below). Details of the supporting experiments are provided in Section S5.

### 2.3. Characterization

**2.3.1. HPLC Method.** Chromatographic analyses were performed using a Poroshell 120 EC-C18 column ( $2.1 \times 100$  mm,  $2.7 \mu\text{m}$ ) (Agilent, USA). The mobile phase consisted of solvent A (water–acetonitrile, 95:5 v/v, containing 0.1% formic acid) and solvent B (acetonitrile containing 0.1% formic acid). The gradient program was as follows: 95% A and 5% B at 0 min, linearly ramped to 0% A and 100% B over 10 min, held at 100% B until 12 min, and returned to 95% A and 5% B at 12.1 min. Mobile phase B was prepared by adding 1 mL of formic acid to 1 L of acetonitrile. Mobile phase A was prepared by diluting 50 mL of mobile phase B with HPLC-grade water to a final volume of 1 L, yielding the required 95:5 water–acetonitrile composition with 0.1% formic acid.

**2.3.2. Raman Spectroscopy.** Raman spectra were acquired in the collection tank using a Hyperflux Pro Plus 785 nm Raman spectrometer (Tornado Spectral Systems, Canada) controlled by SpectraSoft software (version 3.5.0.0), with dark correction and cosmic-ray filtering enabled.<sup>6</sup> Spectra were collected with an exposure time of 1 s; each spectrum was averaged over 15 acquisitions and recorded at 1 s intervals. For subsequent data analysis, the raw spectra were baseline-corrected in the Panorama environment using the AirPLS algorithm, with a  $\lambda$  value of 10 and five iterations.<sup>34</sup>

**2.3.3. Particle Size Distribution.** The particle size distribution and particle counts were monitored *in situ* by tracking the image-derived total chord length counts per second using the BlazePlatform Micro probe (Blaze Metrics, USA) and its user interface (Blaze UI, version 148.04.03).<sup>6</sup> A representative photo of the mounted probe is shown in Figure S7. Measurements were acquired over 10 s intervals, with up to 58 images/s analyzed, such that each image-derived chord length distribution (ID-CLD) was based on  $\sim 580$  images. The image plane was set to  $40 \mu\text{m}$  using the Blaze user interface, which was identified during preliminary experiments as providing optimal image quality (data not shown). For all reported data, a length-weighted chord length distribution (CLD) was utilized to interpret particle size evolution. Length-weighting was selected over square- or cube-weighted distributions to distinguish aggregates from nonaggregates.<sup>35</sup>

## 3. RESULTS AND DISCUSSION

### 3.1. Solubility

The system, ketoconazole, methanol, and water, is a known system for crystallization studies.<sup>31</sup> For this study, supporting solubility experiments have been conducted. Additionally, preliminary experiments revealed no visual evidence of liquid–liquid phase separation (LLPS) for the operating conditions explored. Monitoring for LLPS is critical in such ternary systems, as the presence of a metastable liquid-rich phase can significantly alter the nucleation kinetics and crystal morphology, often leading to oil-induced agglomeration.<sup>36</sup> While these results suggest operation within a phase-stable regime, the possibility of transient liquid–liquid phase separation under the crystallization conditions cannot be completely ruled out. Such transient states are often short-lived and difficult to capture via static solubility tests; therefore, a thorough investigation of this behavior warrants a dedicated manuscript.<sup>37</sup> Additional details regarding the supporting solubility experiments, data, and phase behavior are provided in Sections S3 and S4.

### 3.2. Residence Time Distribution (RTD)

The RTD dictates the time history of supersaturation experienced by crystals, impacting nucleation, growth, and agglomeration that control the resulting particle properties (e.g., CSD).<sup>1</sup> Therefore, the RTD behavior of the 10-tank configuration (TWC-10) was quantified and compared to the MSMMPR prior to benchmarking. The RTD measurements were used to probe the macromixing characteristics while possibly revealing hydrodynamic nonidealities such as dead zones, short-circuiting, or bypassing.<sup>33</sup> The resulting RTD curves are compared to the theoretical *n*-TIS model<sup>33</sup> corresponding to the number of stages (*n*) in the crystallizer. Agreement with the *n*-TIS model indicates ideal tank performance and uniform tank-to-tank transport. In this study, both the liquid- and solid-phase RTD were measured. The solid-RTD was only measured in the TWC. Detailed experimental procedures and data analysis are provided in Section S5.<sup>33</sup>

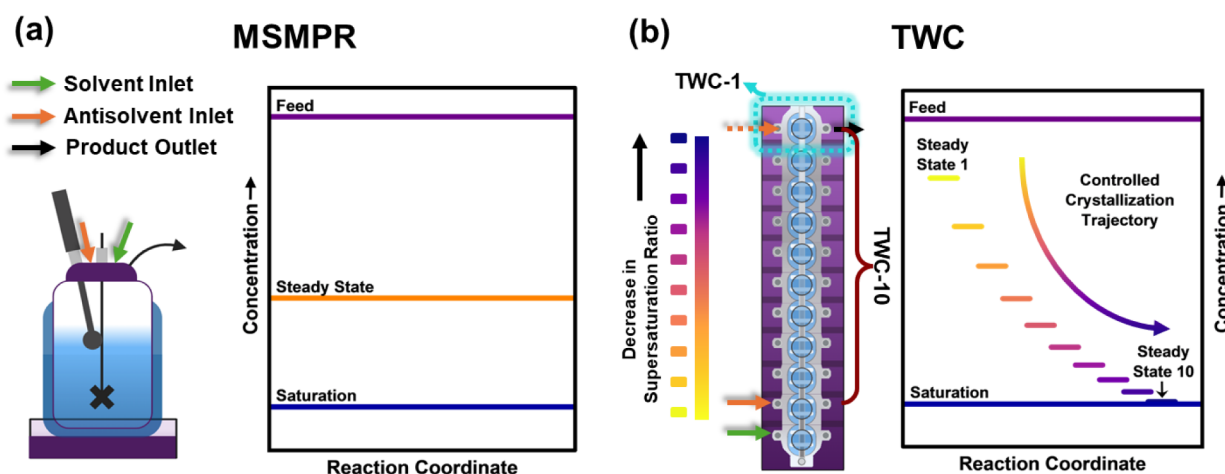
The MSMMPR exhibited a broad liquid-RTD (Figure 1a), similar to that of one tank of the TWC (TWC-1), confirming that the TWC under single-tank operation provided equivalent RTD behavior. Increasing the number of active tanks in the TWC progressively narrowed the liquid-RTD. The TWC-10 yielded the sharpest distribution aligning well with the 10-TIS model, quantified by relatively low root-mean-square error (RMSE = 0.005), which indicates plug-flow-like behavior.<sup>33</sup> It also confirms that each tank functioned as an effective continuous stirred tank reactor in series, which is analogous to an MSMMPR cascade.<sup>16,17</sup>

Our previous work<sup>6</sup> demonstrated that the solid-RTD depends on particle size and solid loading in the TWC. In this study, the impact of the push-volume of the piston in the first tank and the stirring speed was evaluated, along with solid loading, without claiming to be exhaustive (Figure 1b). Similar to the previous work,<sup>6</sup> the solid-RTD is increasingly deviating from the TIS model with increasing solids loading. Based on the calculated confidence intervals of the experiments (shaded areas), the effect of the push-volume (0.5 vs 1 mL per push) was negligible, with no clear evolving tendency. Moreover, Figure 1b confirms the trends reported in an *in-silico* study for the TWC using spherically shaped tanks, that the stirring speed alters the uniformity of the suspension.<sup>38</sup> Specifically, at 2000 rpm, the solid-RTD for the 40 and 100 mg/mL loadings closely matches within the 95% confidence interval (shaded areas) the TIS model, while at 1000 rpm, only 40 mg/mL is comparable. More detailed discussions of the TWC's mixing characteristics are beyond the scope of this study and the interested reader is referred to the literature<sup>38</sup> and future dedicated investigations.

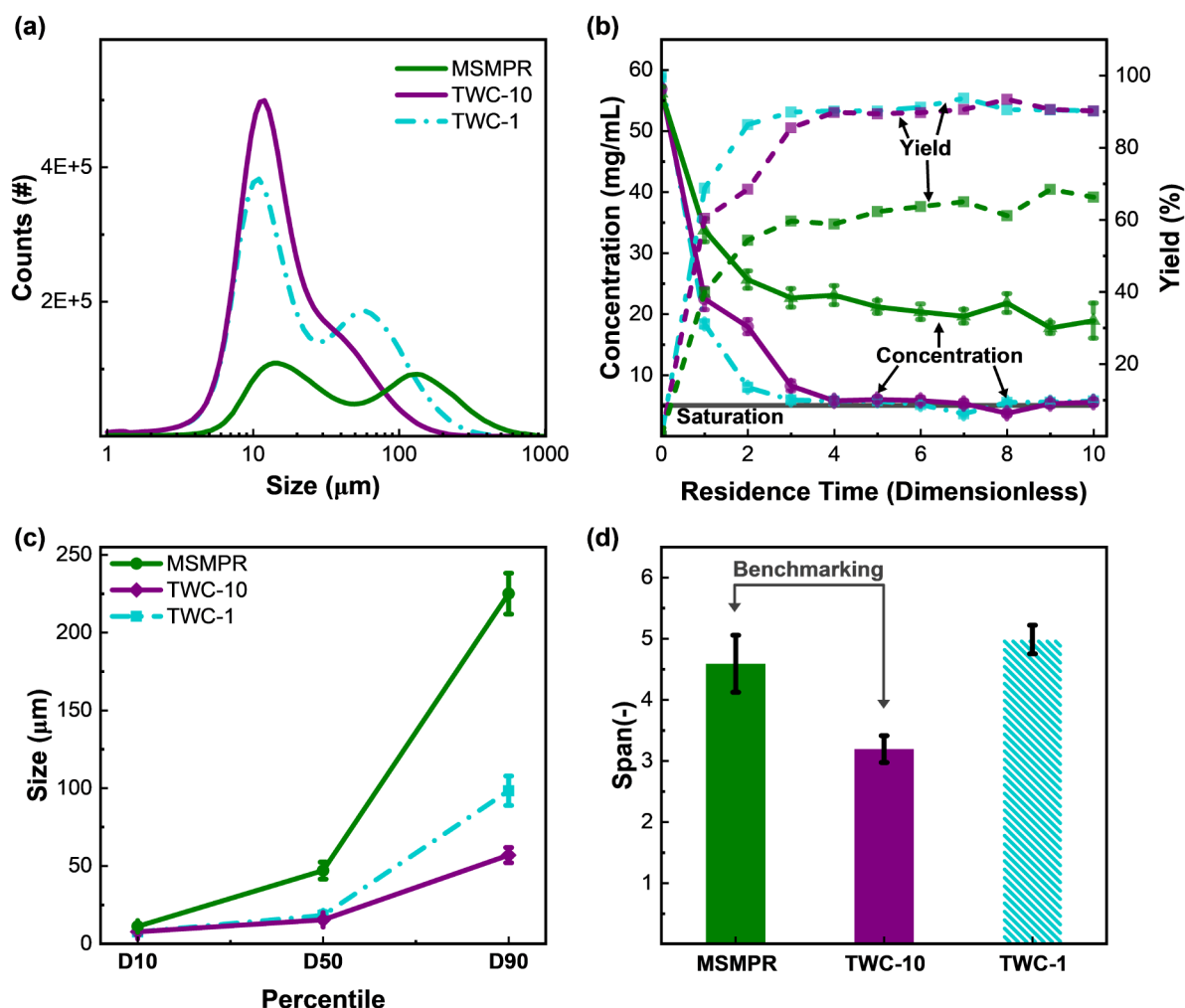
For the benchmarking experiments in this study, the stirring speed (2000 rpm), push volume (1 mL), and solids loading ( $\sim 80$  mg/mL, ketoconazole solubility) were chosen, without claiming to be optimized. While optimizing these variables was beyond the scope of this benchmarking study, the chosen settings ensure reliable solids handling within the TWC. Generally, such comprehensive mixing optimization studies depend on various factors that influence the operational window of the crystallizer, e.g., API and solvent/antisolvent system properties (e.g., densities, crystal morphologies), and crystallization conditions.<sup>38–40</sup>

### 3.3. Crystallizer Cascade

Controlling supersaturation is essential for controlling crystallization processes as it governs nucleation, growth, agglomeration, CSD, and yield.<sup>1</sup> One way to generate and control



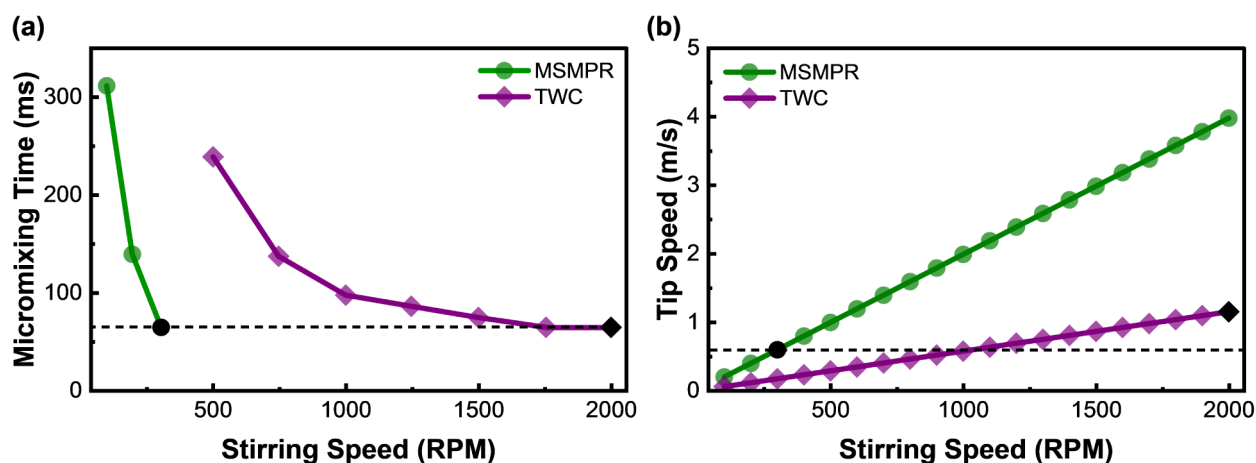
**Figure 2.** Schematic of (a) mixed-suspension, mixed-product removal (MSMPR) and solute concentration at steady state, (b) tower crystallizer (TWC-10) with multiple tanks and corresponding supersaturation ratio throughout the cascade. A single-tank TWC operation (TWC-1) is displayed by a cyan dotted frame in the top tank.



**Figure 3.** Benchmarking results of continuous crystallization in mixed-suspension, mixed-product-removal (MSMPR) vs tower crystallizer (TWC-10 and TWC-1). (a) Image-derived chord length distribution (ID-CLD) results for the three configurations. (b) Steady-state solute concentrations and calculated yields. (c) Percentiles ( $D_{10}$ ,  $D_{50}$ ,  $D_{90}$ ) and (d) span values, defined as  $(D_{90} - D_{10})/D_{50}$ . If error bars are not visible, they are covered by the data points.

supersaturation is through antisolvent addition.<sup>1–3</sup> In a single-tank MSMPR, an antisolvent can be added along with the feed,

resulting in a constant supersaturation ratio at steady state, as schematically illustrated in Figure 2a.



**Figure 4.** Comparison of (a) micromixing time and (b) tip speed in the mixed-suspension, mixed-product-removal (MSMPR) and single-tank tower crystallizer (TWC-1). Black symbols represent the MSMPR and TWC conditions in the benchmarking experiments, respectively. Broken line is used for visualization purposes displaying the MSMPR conditions.

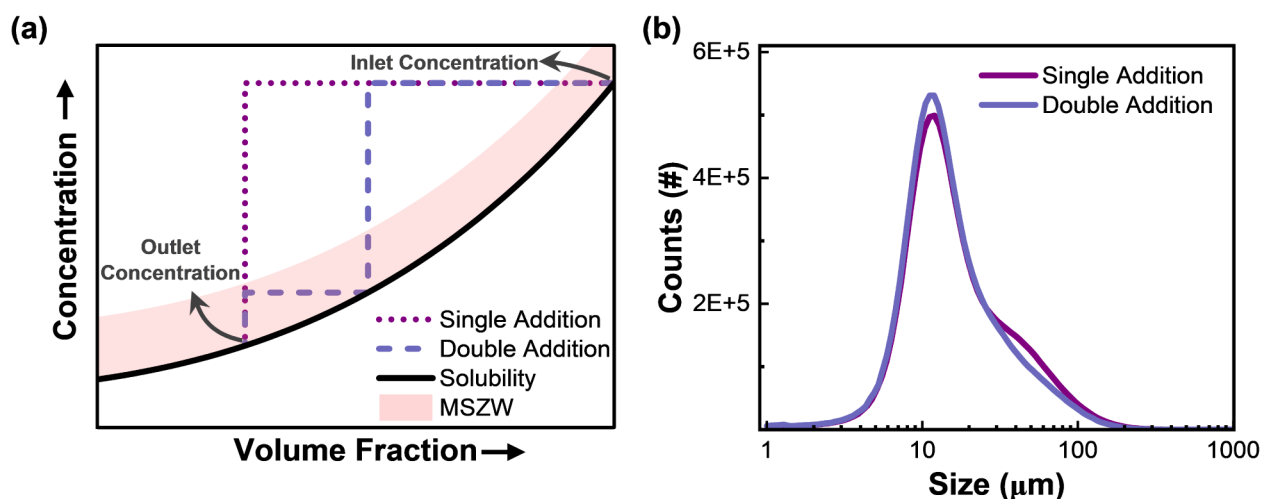
Regardless of the feed rate or seed load, the single-tank crystallization system is constrained to a single steady state (global) supersaturation, which limits the tunability of the CSD.<sup>1,3,17</sup> Additionally, nucleation, growth, and agglomeration are simultaneously competing, as a result, within a single-tank MSMPR the nucleation cannot spatially or temporally be separated from growth or growth from agglomeration. TWC, on the other hand, provides supersaturation control and separation through multiple tanks, enabling CSD tunability (Figure 2b).<sup>1,3,17,41</sup> The first tank with antisolvent addition in the TWC-10 operates at similar high supersaturation to the MSMPR to promote nucleation and rapid initial desupersaturation. The subsequent tanks run at moderate supersaturation that will balance crystal growth and secondary nucleation.<sup>42</sup> The later tanks in the TWC-10 operate at lower supersaturation conditions, at their respective steady states, enabling crystal growth and maximizing yield. Thus, the separation achieved in the TWC effectively transforms the crystallization pathway into a sequence of controlled MSMPRs with different steady state environments rather than a single mixed state endured in a single-tank MSMPR.<sup>1,3,17</sup> Such an approach should yield superior CSD control, further discussed below.

**3.3.1. Benchmarking TWC against Conventional MSMPR.** Continuous crystallization was conducted at an initial high supersaturation ratio ( $\sigma = 9.4$ ) as illustrated in Figure 3. This condition intentionally promotes a nucleation-dominated regime while maintaining particle sizes below 100  $\mu\text{m}$ .<sup>31</sup> The *in situ* Blaze data reveal extensive agglomeration of ketoconazole in the MSMPR (Figure S10), characterized by a broad bimodal CSD (Figure 3a). This agglomeration likely stems from the MSMPR's broad RTD (Figure 1a), which subjects individual crystals to extended residence times yielding frequent crystal collisions, known to drive the formation of large, irregular aggregates.<sup>15</sup> Conversely, the TWC-10 with its narrower RTD (Figure 1a) produces a narrower unimodal CSD with a little visible shoulder toward larger particles (Figure 3a).

In addition, the TWC-10 spatially divides the supersaturation and thereby crystallization kinetics over multiple tanks (Figure 2b). While the early tanks operate at high supersaturations similar to the MSMPR to drive nucleation, the downstream tanks provide progressively milder supersaturation levels that favor controlled surface growth over uncontrolled agglomeration. Moreover, the TWC-10 achieved a 90% process yield

significantly outperforming the 66% yield of the single-tank MSMPR (Figure 3c). In this study, yield is defined as  $\text{yield} = \frac{C_{\text{Feed}} - C_{\text{MotherLiquor}}}{C_{\text{Feed}}}$  where  $C$  is the concentration measured by HPLC, and  $C_{\text{Feed}}$  represents the ketoconazole concentration in the mixed feed after accounting for antisolvent dilution. This superior performance is a direct result of the TWC-10's ability to drive desupersaturation much further, reaching a final solute concentration close to equilibrium  $\sim 5$  mg/mL compared to  $\sim 19$  mg/mL in the MSMPR. Beyond these productivity gains, this enhanced control over the concentration trajectory also reshapes the product's physical properties. The averaged percentiles ( $D_{10}$ ,  $D_{50}$ , and  $D_{90}$ ) in the MSMPR reached 11, 47, and 225  $\mu\text{m}$ , respectively, while the TWC-10 reduced these values to 8, 15, and 57  $\mu\text{m}$ , narrowing the distribution across all size classes (Figure 3c). Specifically, the span ( $[D_{90} - D_{10}]/D_{50}$ ) reduced from 4.5 in the MSMPR to 3.2 for the TWC-10 (Figure 3d), representing a 29% reduction in the span of the CSD compared to the MSMPR. Despite these significant improvements summarized in Figure 3, the agglomeration of ketoconazole cannot be avoided in the TWC-10. This observation hints at the intrinsic characteristic of the system ketoconazole, methanol, water, which shall be investigated in future efforts.

To further test the impact of spatial separation of the supersaturation and kinetics on the particle characteristics achieved in the TWC-10, it was hypothesized that a TWC operated at a single-tank (TWC-1) would yield similar bimodal CSD as achieved in the MSMPR. Because the TWC-1 ( $\sim 8$  mL) shares a nearly identical RTD with the MSMPR ( $\sim 100$  mL), as illustrated in Figure 1a, and will similarly maintain a relatively high supersaturation at steady state. Figure 3a confirms this hypothesis, revealing that both single-tank setups yield bimodal CSDs with a similar broad span (Figure 3b). Notably, the bimodal CSD in the TWC-1 is shifted to smaller crystal sizes than the MSMPR. The smaller scale of the TWC-1 may explain this shift compared to the MSMPR, which is an order of magnitude larger. It is known that scaling down crystallizers enhances process performance by improving uniformity in, e.g., temperature, suspension density, concentration/supersaturation, and energy dissipation.<sup>43,44</sup> The latter impacts the hydrodynamic stress on the particles,<sup>1</sup> which is further discussed in Section 3.3.3 below. Higher stresses may disrupt loosely



**Figure 5.** (a) Schematic illustration of supersaturation control via multiple antisolvent addition points (1 and 2). (b) Image-derived chord-length distribution (ID-CLD) for tower crystallizer (TWC-10) with single (2nd tank) and double additions (2nd and 5th tank). For tank numbers, see Figure S11. Detailed data leading to the averaged ID-CLD displayed here are provided in Figure S13.

bound clusters of ketoconazole crystals before they can grow into the larger, irregular aggregates observed in the MSMPR experiment. In addition, the higher energy dissipation in the TWC-1 compared to the MSMPR with similar broad RTD enhances contact nucleation. By increasing the number of primary particles and the total available crystal surface area, mass transfer and supersaturation consumption are accelerated, resulting in higher process yield (Figure 3b).

Consequently, these benchmarking results indicate that while the RTD defines the span of the CSD and modality to some extent, the final achievable crystal size is scale-dependent and governed by the specific conditions within the crystallizer, e.g., local mixing efficiency and shear stress. Both aspects are further discussed below.

**3.3.2. Micromixing.** The CSD performance discrepancy between the MSMPR and TWC-1 (Figure 3), despite similar liquid-RTDs (Figure 2a), suggests that additional hydrodynamic factors govern the outcome. The micromixing time is a critical parameter in antisolvent crystallization, as rapid homogenization prevents localized high supersaturation and segregated nucleation.<sup>1</sup> Insufficient micromixing can amplify fines formation, promote uncontrolled agglomeration, and broaden the CSD.<sup>45,46</sup> To investigate this aspect, the mixing times for both MSMPR and TWC-1 were evaluated using the Villermaux-Dushman protocol.<sup>47–49</sup> More details are present in Section S6.

Figure 4a illustrates that both MSMPR and TWC-1 exhibited decreasing micromixing times with increasing stirring speed. Notably, the MSMPR at 300 rpm achieved a mixing time of 64.6 ms, equivalent to that of the TWC-1 operated at 2000 rpm. Although faster mixing time could be measured in the MSMPR by increasing the stirring speed (>300 rpm), probing those in crystallization experiments led to visible air intake (bubbles). Such air bubbles should be avoided when mixing liquids and suspensions (e.g., crystallizers).<sup>50</sup> Because the MSMPR and TWC-1 achieve equivalent fast times at their respective operating conditions, the observed CSD differences cannot be attributed to discrepancies in micromixing efficiency. Consequently, other hydrodynamic features must underlie the divergent crystallization behaviors, e.g., shear stress.

**3.3.3. Tip Speed.** Hydrodynamic conditions, such as fluid shear and particle collisions, strongly influence crystallization

and can significantly alter crystal size and morphology.<sup>51</sup> While a full characterization of the shear fields was beyond the scope of this work, it is reported that the maximum shear rate in a mixed system (e.g., crystallizer) is directly proportional to the tip speed of the impeller.<sup>1,52</sup> Tip speed is a product of impeller diameter and the rotation speed ( $Tip\ Speed = \pi D\omega$ , where  $D$  and  $\omega$  are diameter and rotation speed). As shown in Figure 4b, the TWC operated at 2000 rpm ( $D_{TWC} = 11\ mm$ ) exhibits a tip speed of 1.2 m/s; double the 0.6 m/s generated by the MSMPR at 300 rpm ( $D_{MSMPR} = 38\ mm$ ). This higher tip speed in the smaller TWC-1 tank volume translates to a significantly higher power input per unit volume, intensifying the hydrodynamic stresses that enhance nucleation and growth while reducing agglomeration.<sup>53</sup> These shear-driven mechanisms may explain the observed CSD differences.

Specifically, the bimodal CSDs generated in the MSMPR and TWC-1 (Figure 3a) at similar broad RTDs (Figure 1) are mainly driven by the competition between nucleation, crystal growth, and agglomeration.<sup>1,53</sup> Secondary nucleation is particularly sensitive to the local hydrodynamic environment, often correlating directly with stirring speed and leading to the production of fine particles.<sup>53,54</sup> In particular, crystal–crystallizer (e.g., impeller, walls) collisions are more dominant in small crystallizers, resulting in more nuclei formation, yielding a higher mass transfer and, thus, process yield (Figure 3b).

Further discussion of the hydrodynamic differences, coupled with the complex multiphase nature of crystallization processes, is beyond the scope of this study and merits future work. For instance, coupling computational fluid dynamics with the population balance equation into process models would permit connecting crystallization kinetics and crystal size with the underlying hydrodynamics (transport phenomena).<sup>1,38,55</sup>

**3.3.4. Distributed Antisolvent Addition.** Beyond providing a narrower RTD compared to a single-tank MSMPR, the segmented architecture of the TWC-10 also enables a “staircase” supersaturation profile (Figure 2b). This profile can be further controlled by distributing antisolvent additions across multiple addition points and tanks. Such an approach cannot be accomplished in a conventional single-tank MSMPR. To demonstrate this aspect for the TWC-10, without claiming to be comprehensive, initial experiments have been conducted with

double-addition (not optimized) and compared with single-addition (Figure 3a). The schematic of the two pathways of distributed antisolvent addition studied in this work is illustrated in Figure 5a.

In a single addition of the total antisolvent volume needed, the solute concentration jumps into the unstable region far beyond the metastable zone width (MSZW). This initially high supersaturation drives excessive primary nucleation and promotes the formation of irregular aggregates.<sup>52</sup> As the crystallization progresses through the cascade, the supersaturation is consumed and never replenished (see also Figure 2), limiting the potential for impacting crystal growth in later stages.

Conversely, increasing the number of addition points creates a “staircase” concentration profile that tracks the solubility curve more closely (Figure 5a). By partitioning the total antisolvent volume, the system could maintain lower supersaturation levels within or near the MSZW throughout the TWC. It has been reported that distributed antisolvent addition spatially separates the supersaturation and therefore manipulates the crystallization kinetics (experimentally<sup>56</sup> and theoretically,<sup>27</sup>).<sup>57,58</sup> Such spatial separation by antisolvent addition builds on the spatial separation capabilities of a cascade alone, already discussed above. Briefly, the first antisolvent addition generates moderate supersaturation required to initiate nucleation without generating excessive fines. In contrast, subsequent antisolvent additions replenish supersaturation at low to moderate levels, favoring growth and reducing agglomeration tendency (Figure 5b).<sup>59</sup>

Figure 5b compares the CSDs achieved for the antisolvent additions in the TWC-10 when 100% of the volume is added in a single (2nd) tank (also shown in Figure 3a) with two additions (60% added in the second tank and 40% in the fifth tank, not optimized), at a mean residence time of ~60 min. Figure S11 illustrates the location of the tanks in the TWC. Splitting the antisolvent visually suppressed the agglomeration, as evidenced by the visual disappearance of the small shoulder observed in the CSD with single addition (Figure 5b), as well as the reduced  $D_{90}$  (22%) and span (17%). Detailed comparison of percentile and span results between single and double addition experiments are summarized in Figure S12. The reduction of the shoulder further demonstrates that the particle population responds directly to the modified supersaturation trajectory induced by distributed antisolvent addition, thereby providing a tunable design space for particle engineering (size, CSD). The complexities of optimizing the number of addition-points and flow-split ratios were beyond the scope of this proof-of-concept but warrant a dedicated investigation, which is the focus of future work.

#### 4. CONCLUSION

In this work, a 10-stage tower crystallizer (TWC-10,  $\leq 80$  mL) was used for continuous antisolvent crystallization. It was benchmarked against a conventional single-tank mixed-suspension, mixed-product removal (MSMPR) crystallizer with a similar total working volume ( $\leq 100$  mL). Residence time distribution (RTD), mixing time, and shear analyses demonstrate that the TWC configuration (each tank functions as an MSMPR) delivers a narrower RTD that approaches plug-flow characteristics, reliable isokinetic slurry transport, and spatial separation of crystallization kinetics compared to the single-tank MSMPR. These hydrodynamic features improve control over nucleation, growth, and agglomeration.

Using ketoconazole, a challenging API prone to fast nucleation and agglomeration, as a case study, the TWC-10

improved the crystal-size distributions (CSDs) uniformity and mitigated agglomeration more effectively than either a conventional single-tank MSMPR (used as baseline) or a single-tank TWC (TWC-1). Although the MSMPR ( $\leq 100$  mL) and TWC-1 (8 mL) exhibit similar RTDs, yielding bimodal CSDs, their distinct crystallization outcomes reveal how different crystallizer scales and shear environments shape particle-size evolution. The TWC-10 enhances this effect by spatially separating crystallization mechanisms: early stages drive nucleation under high supersaturation, while downstream stages provide milder environments that favor growth and suppress agglomeration. Additionally, antisolvent addition distributed across multiple tanks provided further control over the supersaturation trajectory, leading to unimodal CSDs (without shoulders).

This study demonstrates that a continuous crystallizer cascade provides a more tunable process history, laying the foundation for sophisticated control of the critical quality attributes of crystals (e.g., CSD, modality, span). Additionally, TWC provides a compact, robust platform for leveraging the benefits of a cascaded crystallization process.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.cgd.6c00525>.

Details of the analysis, equipment, solubility of ketoconazole, phase behavior, residence time measurements, Villermaux–Dushman measurements, Tables S1–S2, and Figures S1–S12 (PDF)

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## Notes

The authors declare no competing financial interest.

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