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# Establishment of a Continuous Sonocrystallization Process for Lactose in an Oscillatory Baffled Crystallizer

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**S** Supporting Information

**ABSTRACT:** Crystallization at production scale (>10 kg) is typically a poorly understood unit operation with limited application of first-principles understanding of crystallization to routine design, optimization, and control. In this study, a systematic approach has been established to transfer an existing batch process enabling the implementation of a continuous process in an oscillatory baffled crystallizer (OBC) using ultrasound. Process analytical technology (PAT) was used to understand and monitor the process. Kinetic and thermodynamic parameters have been investigated for lactose sonocrystallization using focused beam reflectance measurement (FBRM) (Mettler Toledo) and mid-infrared spectroscopy (mid-IR) (ABB) in a multiorifice batch oscillatory baffled crystallizer (Batch-OBC). This platform provides an ideal mimic of the mixing, hydrodynamics and operating conditions of the continuous oscillatory flow crystallizer (COBC) while requiring only limited material. Full characterization of the hydrodynamics of the COBC was carried out to identify conditions that deliver plug-flow behavior with residence times of 1–5 h. The results show that continuous crystallization offers significant advantages in terms of process outcomes and operability, including particle size distribution (mean particle size <1500  $\mu\text{m}$ ) of alpha lactose monohydrate (LMH), as well as reduced cycle time (4 h compared to the 13–20 h in a batch process). Continuous sonocrystallization was performed for the first time at a throughput of 356  $\text{g}\cdot\text{h}^{-1}$  for 12–16 h. During the run at near plug flow, with supersaturation and controlled nucleation using sonication, no issues with fouling or agglomeration were observed. This approach has demonstrated the capability to provide close control of particle attributes at an industrially relevant scale.

## 1. INTRODUCTION

A recent review of the literature has revealed an increasing number of patents and published applications demonstrating the increased intensity of activities in process engineering for continuous manufacturing of chemicals.<sup>1</sup> The benefits, often declared in continuous processing, include better product yields and quality; use of lower amount of solvent and other materials; less extreme operating conditions; more efficient consistent mixing; better control over process parameters; improved safety, improved purity profiles, and ease of scale-up.

In a manufacturing process, downstream processing stages can be a bottleneck to making a quality product in an economic, safe, and profitable way, as the components and processes involved are often time-consuming, inefficient, and poorly understood.

Crystallization is one of the most important downstream processes in determining the purity, form, shape, size, and size distribution of the final particles and is governed by complex interacting variables—a simultaneous heat and mass transfer process with a strong dependence on fluid and particle mechanics. A number of continuous reactor designs have been described and have the potential to deliver crystallization. These includes mixed suspension mixed product removal (MSMPR), continuous stirred tank reactor (CSTR) cascade systems, plug-flow reactors (PFRs), and oscillatory baffled crystallizers (OBC).<sup>2–4</sup>

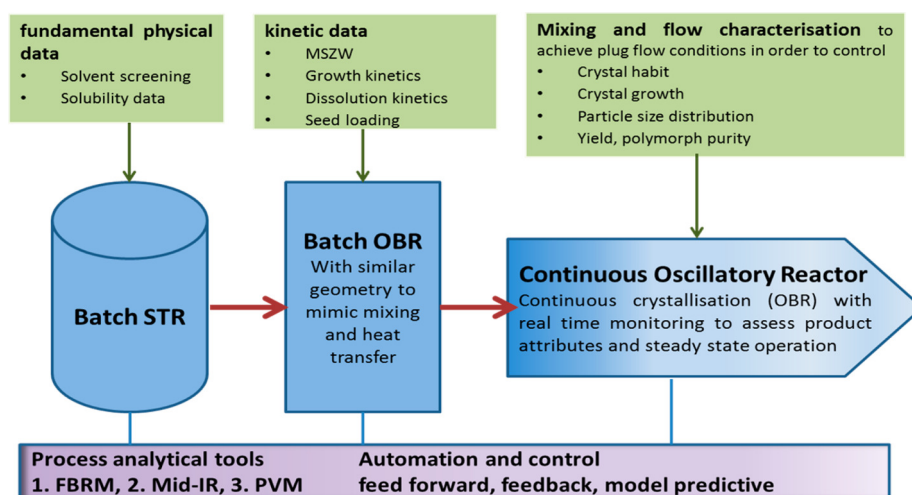
A batch OBC has been investigated for a number of reactions,<sup>2–7</sup> but its use for crystallization has not received immediate attention.<sup>2–7</sup> The basic design and operating

principle of OBC has been described elsewhere.<sup>4,5</sup> The basic design comprises a tubular network containing periodically spaced orifice baffles superimposed with oscillatory motion of a fluid. Oscillatory flow mixing has been developed and investigated as a process intensification technology to achieve efficient and controlled mixing in tubular crystallizers. Unlike conventional tubular crystallizers in which the mixing is caused by the turbulent net flow, the mixing achieved in an OBC is mainly obtained by fluid oscillations and thereby the residence time distribution within the device can be adjusted by the oscillatory conditions and net flow rate allowing longer residence times in short reactors and hence is more suitable for slower processes like crystallization.<sup>7–12</sup> Previous studies have shown that processing in an OBC resulted a greater regularity of crystal shape with fewer defects and better control over the crystallization process. A recent review provides a detailed description of OBCs for crystallization as well as summarizing the relevant literature.<sup>63</sup> These are attributed to the uniform mixing when compared to a batch stirred tank system.<sup>3</sup> Batch to continuous translation of crystallization processes can be achieved by maintaining same geometric ratios in continuous as in batch and ensuring similar values for oscillatory and net flow Reynolds number.<sup>4</sup>

In addition to the recent advances in developing continuous crystallization systems, use of process analytical technologies

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**Figure 1.** Sequence of steps to transfer from batch to continuous crystallization process.

(PAT) for real time monitoring of crystallization process is also progressing well.<sup>13–15</sup> For a crystallization process, it is important to know in real-time the stories of particle size distribution, crystal form, and the solution-phase concentration of active ingredient. With recent advances in technology, more online analytical tools have become available for these measurements.<sup>13</sup> Among these FBRM, particle vision measurement (PVM), Raman, ultraviolet (UV), and mid-IR spectroscopy are most commonly used analytical tools. These PAT help in relating OBC process conditions to the crystallization process and then to product attributes.

Lactose is a disaccharide of glucose and galactose with two isomeric forms,  $\alpha$  and  $\beta$ , that interconvert by mutarotation and exist at equilibrium in solution.<sup>16</sup> When a lactose solution in water is supersaturated at moderate temperatures (below 95 °C),  $\alpha$  lactose monohydrate (ALM) crystals will be obtained since the  $\alpha$  form is less soluble and crystallization will continue so long as  $\alpha$ -lactose in solution can be replenished fast enough by mutarotation.<sup>16</sup> Lactose cooling crystallization in batch under constant stirring from aqueous lactose solutions of different concentration results in varied crystal size, shape, and surface texture.<sup>17–21</sup> Induction times as long as 3–10 h with crystallization growth times ranging from 8–20 h are required to reach D90 of 85–100  $\mu\text{m}$ . The yield varied from 45 to 60% with the lactose concentration from 44% to 53% (w/w). Further, these particles exhibited a wide particle size distribution (PSD) (particle span 3–4), resulting in a relatively small fraction of crystals in the desired size range.<sup>17–21</sup> In recent years sonocrystallization of lactose has been investigated to optimize crystallization time and particle size distribution.<sup>22–29</sup> Additionally, the implementation of sonocrystallization to OBC has already been achieved.<sup>62</sup>

A notable challenge in lactose crystallization is the long induction times. To overcome this problem seeding methodologies are adopted. Lactose sonocrystallization has shown rapid nuclei induction and crystal growth.<sup>22,23</sup> When ultrasound propagates through a liquid medium, its power is not only a driving force for mass transfer but also initiates an important phenomenon known as cavitation. When a cavitation bubble implodes, a localized hot spot is formed with a high temperature and pressure releasing a powerful shock wave. This cavitation generates high local supersaturation leading to spontaneous nucleation in otherwise unsaturated liquid. The

acoustic streaming, microstreaming, and highly localized temperature and pressure within the fluid causes spontaneous induction of primary nucleation, reduction of crystal size, inhibition of agglomeration, and manipulation of crystal size distribution.<sup>30–34</sup> Sonication can promote fines in batch processes, so sonication should only be used for nucleation, and then production of larger crystals can be achieved by growth of those seed crystals.

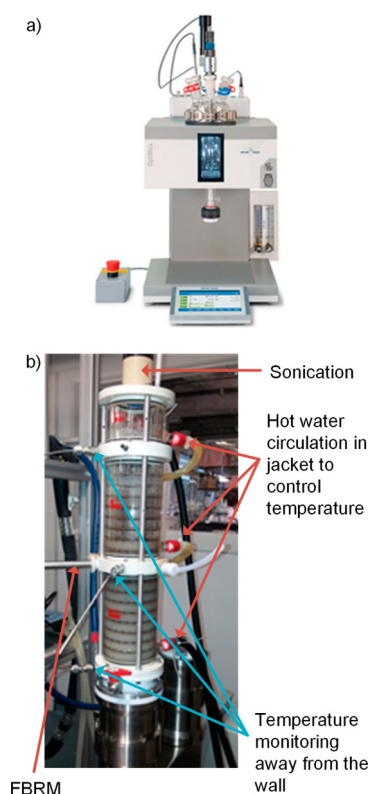
This work sets out to develop a rational approach (Figure 1) (direct control) based on crystallization fundamentals to offer a continuous sonocrystallization process for ALM in a COBC (Rattlesnake from Cambridge Reactor Design). A sequence of steps is followed to acquire the relevant process parameters to enable the transfer from a batch to continuous process (Figure 1). The initial focus is on control of particle size with no fouling or blockage with direct control method and demonstration of the feasibility of continuous crystallization process for ALM and use of sonication for seed generation to control particle size distribution while maintaining a good yield.

## 2. MATERIALS AND METHODS

**2.1. Materials.** ALM and sodium benzoate (tracer material) were purchased from Sigma-Aldrich, UK.

**2.2. Methods.** **2.2.1. Crystallization Setup.** **2.2.1.1. Batch crystallizer (Solubility Study, Thermodynamics).** Mettler Toledo “Optimax-1001” was used to determine the solubility profile and metastable zone width of ALM. The Optimax-1001 platform is a stirred tank crystallizer (STC) with a working volume of 1 L and a 45° pitched four-blade impeller. Ports are available in the STC to introduce process analytical tools such as FBRM, mid-IR, PVM, and thermocouples. Mid IR was used in the STC to measure the solubility of lactose at different temperatures.

**2.2.1.2. Batch Oscillatory Baffle Crystallizer (Optimization of Cooling Profile, MSZW).** The batch OBC used here consists of a glass jacketed cylindrical reactor, having a length of 500 mm and an internal diameter of 69 mm (Figure 2). The module contains 23 baffles, constructed from stainless steel with a FEP (fluorinated ethylene propylene) nonstick coating. The baffles are positioned 18 mm from one another with the openings in adjacent baffles aligned. Each baffle comprises 33 circular openings of 6 mm in diameter. Temperature control within the reactor is provided through a water filled jacket



**Figure 2.** (a) Optimax (STC) and (b) batch OBR with FBRM and sonication equipment.

159 connected to a heater/chiller. The temperature is monitored at  
 160 three different points: the top, middle, and bottom. Oscillatory  
 161 mixing is provided by pistons operated using a hydraulic  
 162 actuator. Lactose solution was introduced into the batch OBC  
 163 from the top of the reactor. Cooling crystallization was  
 164 performed using defined cooling profile. At the end of each  
 165 crystallization, crystals were filtered using a vacuum filter and  
 166 washed with pure ethanol. The crystals were allowed to dry at  
 167 40 °C in an oven for 24 h. After drying, a small amount of  
 168 sample was taken from the batch for characterization.

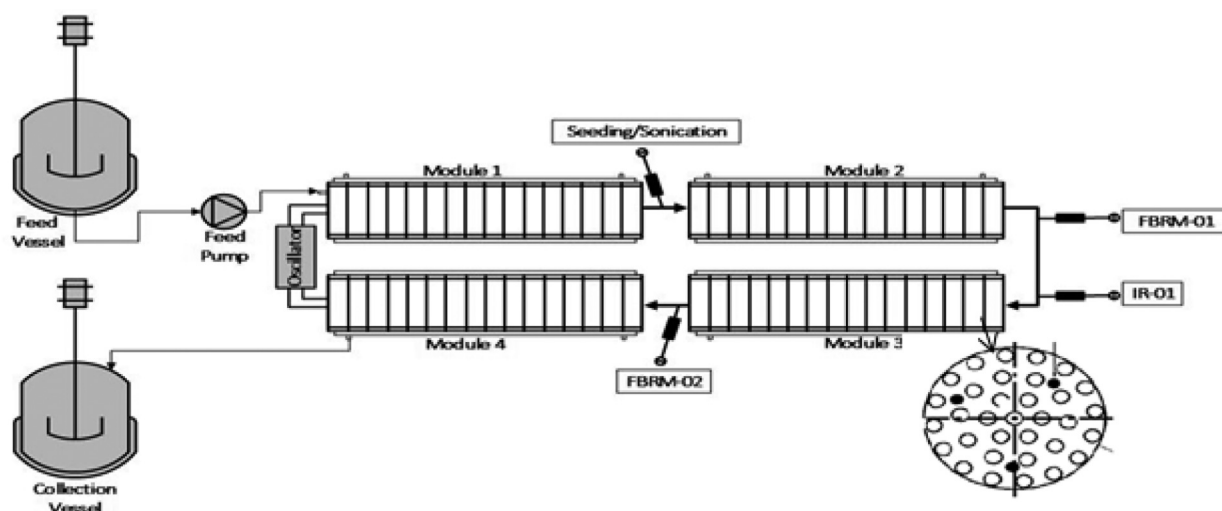
2.2.1.3. *Continuous Oscillatory Baffle Crystallizer (Rattle-  
 snake from Cambridge Reactor Design)*. The COBC consists  
 of four jacketed modules and has been described elsewhere.<sup>35</sup>  
 The crystallizer is illustrated diagrammatically in Figure 3. Each  
 module is cylindrical, constructed from polished stainless steel,  
 having a length of 740 mm and an internal diameter of 69 mm.  
 Each module has an internal baffle/obstruction design as  
 described in Section 2.2.1.2. Temperature control within a  
 module is provided through a double water filled jacket: a  
 primary jacket arranged with liquid flow in a cocurrent  
 configuration, within which a secondary coil is positioned  
 with liquid flow in a counter-current configuration.<sup>35</sup> This shell  
 and tube jacketed design provide a smooth temperature  
 control, which is the most important parameter in cooling  
 crystallization.

Temperature monitoring is possible at the junctions at the  
 end of the modules allowing six monitoring points. Based on  
 the temperature readouts, the operation of the water filled  
 jacket on each module can be adapted to mimic a desired  
 cooling profile. Oscillatory mixing is provided using the same  
 mechanism as the batch platform. Both the frequency and the  
 stroke of the piston can be varied on demand to achieve  
 optimum mixing conditions and solid suspension.

The crystallization setup also includes means for initiating  
 crystallization (Sonicator 4000, Misonix). The ultrasonic device  
 can be located at any position at the ends of the module and  
 can be operated in pulsed or continuous mode. The solution  
 weight and the position of the probe inside the solution were  
 kept constant for all experiments. The device works at a  
 constant frequency of 20 kHz and allows the amplitude to  
 change from 0 to 100%, delivering a power range between 10  
 and 70 W. Ultrasonic energy ( $Q$ ) dissipated to the solution was  
 calculated using a calorimetric method according to eq 1:

$$Q = (m_{\text{water}} C_{p,\text{water}} + m_{\text{lactose}} C_{p,\text{lactose}})(T_f - T_i) \quad (1)$$

where  $m$  is the weight of solution,  $C_p$  is the heat capacity, and  $T_f$   
 and  $T_i$  are the final and initial solution temperatures.<sup>52</sup> Heat  
 capacities of lactose and water are 0.45 and 4.181 kJ·kg<sup>-1</sup>·K<sup>-1</sup>  
 respectively. Power and energy density were expressed as W·  
 g<sup>-1</sup>.



**Figure 3.** Schematic of continuous oscillatory baffle reactor (module details are taken from ref 35). The inset illustrates the baffle multiforce design in plan view.



208 **2.2.2. Residence Time Distribution Characterization.** To  
 209 investigate the effect of oscillatory flow conditions on the  
 210 mixing behavior in continuous crystallization, the residence  
 211 time distribution was determined under different oscillatory  
 212 conditions. The nature of oscillatory flow has been charac-  
 213 terized quantitatively and qualitatively in previous stud-  
 214 ies.<sup>7–12,42–48</sup> Oscillatory flows are characterized by three  
 215 dimensionless numbers, the oscillatory Reynolds number (eq  
 216 2), the velocity ratio (eq 3), and the Strouhal number (eq 4),  
 217 defined as,

$$\text{Re}_o = \frac{2\pi f \chi_o \rho d}{\mu} \quad (2)$$

$$\psi = \frac{\text{Re}_o}{\text{Re}_n} \quad (3)$$

$$\text{St} = \frac{d}{4\pi \chi_o} \quad (4)$$

221 where  $\text{Re}_o$  is the oscillatory Reynold number,  $f$  is the frequency  
 222 of oscillation (Hz),  $\chi_o$  is the amplitude of oscillation (m),  $\rho$  is  
 223 the density of material ( $\text{kg}\cdot\text{m}^{-3}$ ),  $d$  is the column diameter (m),  
 224 and  $\mu$  is fluid viscosity ( $\text{kg}\cdot\text{m}^{-1}\cdot\text{s}^{-1}$ ).

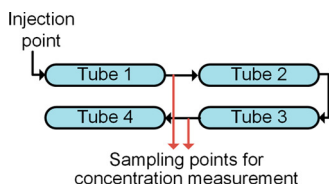
225 The axial dispersion coefficient  $D$  [eq 5;  $D = E/uL$ , where  $E$   
 226 is the axial dispersion number,  $u$  is the mean axial velocity ( $\text{m}\cdot$   
 227  $\text{s}^{-1}$ ), and  $L$  is the length of reactor (m)] is used to describe the  
 228 characteristics of mixing in continuous reactors.<sup>36</sup> It is a  
 229 measure of the degree of deviation in flow from the true plug  
 230 flow scenario: in theory it should be zero for truly plug flow  
 231 behavior. The equation governing  $D$  in a continuous system is

$$\frac{dc}{dt} = D \frac{d^2c}{dx^2} - U \frac{dc}{dx} \quad (5)$$

233 where  $c$  is dimensionless concentration,  $t$  is dimensionless time,  
 234 and  $x$  is dimensionless length. The dispersion model (eq 5),  
 235 where the reactor is seen as a continuous path, is used to study  
 236 RTD in oscillatory baffled flow systems. This model is applied  
 237 on a continuous reactor when Bodenstein number is the range  
 238 of 1–100.<sup>2,36–41</sup>

239 Most of the previous RTD studies<sup>41</sup> were performed by  
 240 standard imperfect pulse injection techniques in which the  
 241 concentration time profile at the two points of the system was  
 242 measured and an axial dispersion model was applied following  
 243 statistical analysis of data.<sup>10</sup>

244 Twelve milliliters of  $20 \text{ g}\cdot\text{L}^{-1}$  sodium benzoate tracer was  
 245 injected “instantaneously” above the feed position (Figure 4). A



**Figure 4.** Injection and sampling points in rattlesnakes for RTD study.

246 UV transmittance probe positioned in situ at the end of the first  
 247 and third straight of COBC is used to record absorbance  
 248 against time as the tracer elutes. The  $\lambda_{\text{max}}$  for sodium benzoate  
 249 in water was determined at 226 nm. Different concentrations of  
 250 sodium benzoate were tested to establish the calibration for the  
 251 absorbance to concentration conversion. The limit of detection

for sodium benzoate was determined as  $2.501 \times 10^{-6} \text{ g}\cdot\text{L}^{-1}$  252  
 (signal: noise, 3:1). Finally, experimental concentration–time 253  
 data was used to determine deviation from plug flow ( $D/uL$ ). 254  
 Operating conditions are summarized in Table 1. 255

256 **2.2.3. Particle Size Analysis.** Particle size was measured by a  
 257 laser diffractometer, Mastersizer 3000 Ver.2.00 (Malvern  
 258 Instruments, Malvern, UK). Analysis was done in triplicate, 258  
 and mean results are presented as D10, D50, and D90. Ethanol 259  
 was used as a dispersant, and obscuration was not less than 10% 260  
 for each measurement. Data analysis was carried out using 261  
 Malvern Software Version 5.2. 262

263 **2.2.4. Chord Length Distribution from FBRM.** The  
 264 operating principle of FBRM has been described elsewhere.<sup>15</sup> 264  
 All FBRM measurements were carried out using the Mettler 265  
 Toledo G400-FBRM system. 266

267 **2.2.5. Infrared Spectroscopy (IR).** The mid-IR is an in-line 267  
 based analytical technique in which information can be 268  
 obtained via a probe about solution concentration, even in 269  
 the presence of particles. The analysis is based on the mid-IR 270  
 region ( $650\text{--}2000 \text{ cm}^{-1}$ ). In general the main condition is that 271  
 a distinctive peak for the solute is present and can be separated 272  
 from the chosen solvent. An ABB mid-IR MBX3000 system 273  
 with the 12 mm diameter probe was used for this study. 274

275 **2.2.6. Differential Scanning Calorimetry (DSC).** DSC 275  
 studies were carried out using NETZSCH DSC STA 449C 276  
 instrument equipped with an intracooler (CC 200). Indium and 277  
 zinc standards were used to calibrate the DSC temperature and 278  
 enthalpy scale. The samples were pierced in aluminum crucibles 279  
 and heated at a constant rate of  $10 \text{ }^\circ\text{C}\cdot\text{min}^{-1}$  over a 280  
 temperature range of  $25\text{--}250 \text{ }^\circ\text{C}$ . An inert atmosphere was 281  
 maintained by purging helium gas at flow rate of  $70 \text{ mL}\cdot\text{min}^{-1}$ . 282

283 **2.2.7. X-ray Powder Diffraction Analysis (XRPD).** The 283  
 XRPD patterns were recorded on X-ray diffractometer. For 284  
 sample fingerprinting, 10–50 mg of sample was placed on a 285  
 well plate supported on a polyimide (Kapton,  $7.5 \text{ }\mu\text{m}$  286  
 thickness) film. Data were collected on a Bruker AXS D8- 287  
 Advance transmission diffractometer equipped with  $\theta/\theta$  288  
 geometry, primary monochromatic radiation ( $\text{Cu K}\alpha_1$ ,  $\lambda =$  289  
 $1.54056 \text{ \AA}$ ), a Vantec 1-D position sensitive detector (PSD), 290  
 and an automated multiposition  $x$ – $y$  sample stage. Data were 291  
 collected in the range  $4\text{--}35^\circ 2\theta$  with a  $0.015^\circ 2\theta$  step size and 292  
 $1 \text{ s step}^{-1}$  count time. Samples were oscillated  $\pm 0.5 \text{ mm}$  in the 293  
 $x$ – $y$  plane at a speed of  $0.3 \text{ mm}\cdot\text{s}^{-1}$  throughout data collection 294  
 to maximize particle sampling and minimize preferred 295  
 orientation effects. 296

297 **2.2.8. Power Density Calculations in Crystallizers.** The 297  
 power density was calculated for MSZW comparison in an STR 298  
 and batch OBR. 299

The equation used for power density calculation in Optimax 300  
 (STC) is given below: 301

$$\epsilon_{\text{STC}} = \frac{P_o \rho N_s^3 D_s^5}{V_L} \quad (6)$$

302 where  $P_o$  is the power number of impeller,  $\rho$  is the density of 303  
 fluid ( $\text{kg}\cdot\text{m}^{-3}$ ),  $N$  is the rotational speed of impeller ( $\text{s}^{-1}$ ),  $D_s$  is 304  
 the diameter of impeller (m), and  $V_L$  is the volume of liquid 305  
 ( $\text{m}^3$ ). The power density for the batch OBC was calculated by 306  
 using eq 7. 307

$$\epsilon_{\text{OBC}} = \frac{2\rho N_b}{3\pi C_D^2} \left( \frac{1 - S^2}{S^2} \right) \chi_o^3 (2\pi f)^3 \quad (7)$$

Table 1. Summary of the Oscillatory and Net Flow Conditions

flow rate (mL·min <sup>-1</sup> )	frequency (Hz)	amplitude (mm)	module length (mm)	T (min)	mean velocity (mm·s <sup>-1</sup> )	Re <sub>n</sub>	Re <sub>o</sub>	Ψ velocity ratio	St
130	8	1	740	23	19.2	223.2	585.1	2.6	1.0
130	8	2	740	23	19.2	223.2	1170.3	5.2	0.5
130	4	1	740	23	19.2	223.2	292.6	1.3	1.0
130	4	2	740	23	19.2	223.2	585.1	2.6	0.5
50	8	1	740	60	7.4	85.9	585.1	6.8	1.0
50	8	2	740	60	7.4	85.9	1170.3	13.6	0.5
50	4	1	740	60	7.4	85.9	292.6	3.4	1.0
50	4	2	740	60	7.4	85.9	585.1	6.8	0.5
130	8	1	2500	69	19.2	223.2	585.1	2.6	1.0
130	8	2	2500	69	19.2	223.2	1170.3	5.2	0.5
130	4	1	2500	69	19.2	223.2	292.6	1.3	1.0
130	4	2	2500	69	19.2	223.2	585.1	2.6	0.5
50	8	1	2500	180	7.4	85.9	585.1	6.8	1.0
50	8	2	2500	180	7.4	85.9	1170.3	13.6	0.5
50	4	1	2500	180	7.4	85.9	292.6	3.4	1.0
50	4	2	2500	180	7.4	85.9	585.1	6.8	0.5
130	2	1	740	23	19.2	223.2	146.3	0.7	1.0
130	2	1	2500	69	19.2	223.2	146.3	0.7	1.0

where  $f$  is frequency of oscillation (Hz),  $X_o$  is the center to peak amplitude of oscillation (m),  $S$  is the ratio of effective baffle area to tube area,  $C_D$  is discharge coefficient, and  $N_b$  is the number of baffles per unit length.

In calculating the values of  $Re_n$ ,  $Re_o$ , and  $St$ , each term was redefined to account for the multi orifice geometry: the characteristic dimension  $d$  (formerly the crystallizer diameter) was replaced by  $d_e$  (equivalent diameter of a notional tube surrounding each orifice), which was the diameter equivalent to the total baffle area divided by the number of orifices.<sup>12,41</sup>  $T$  is the residence time calculated based on volume and volumetric flow rate of each module

### 3. RESULTS AND DISCUSSION

#### 3.1. Solubility and Metastable Zone Width (MSZW)

**Investigation.** Initial dissolution of ALM occurs rapidly upon addition of solid to water. Subsequently, as mutarotation occurs and conversion from alpha lactose to beta lactose proceeds, then more alpha lactose dissolves until the equilibrium ratio of isomers is reached.<sup>49</sup> The rate-determining step of dissolution is the mutarotation of isomers.<sup>50</sup> Hence the final solubility of lactose can be determined by adding excess alpha lactose monohydrate to water and agitating it, at constant temperature for long enough to establish the mutarotation and solubility equilibria. To investigate the solubility of alpha lactose monohydrate an in situ Mid IR probe (reactIR, Mettler Toledo) was used. A 1 L feed solution was prepared by adding 60 wt % of lactose and stirred at 200 rpm. A program was established to obtain the solubility curve based on the equilibrium dissolution point of ALM solid in contact with aqueous solution. The solution was heated from 0 to 10 °C at a rate of 0.1 °C·min<sup>-1</sup> and then held at this temperature for 8 h until a constant peak area from the IR probe indicated and the mutarotation and solubility equilibrium had been reached. This procedure was performed continuously at 10 °C intervals between 10 and 80 °C (Figure 5). After the preprocessing of spectral data (second order derivative), the equilibrium concentration points were plotted to obtain the temperature-dependent solubility curve (Figure 5). Concentration calibra-

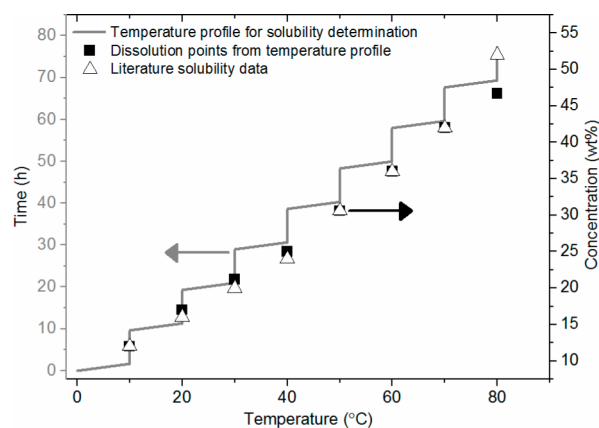
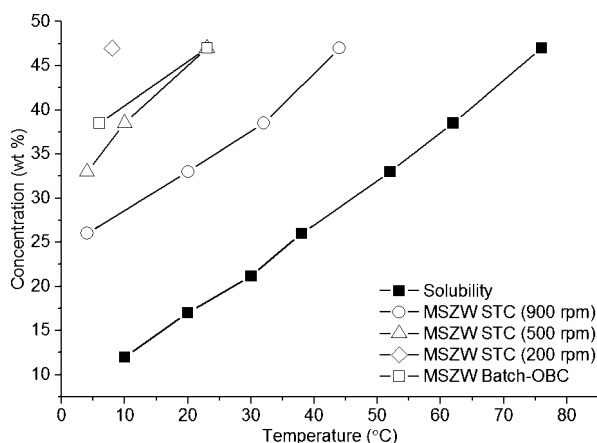


Figure 5. Comparison of solubility curve from the literature with experimentally derived solubility curve in the STC and programmed temperature profile for determination of the temperature-dependent equilibrium solubility points.

tion on data from Mid-IR was performed using PharmaMV software (Perceptive Engineering).<sup>54</sup>

The MSZW was investigated using IR and FBRM to detect concentration and nucleation, respectively. In the STC, a 1 L solution of 47% (w/w) lactose was introduced. The pitched blade agitator speed was set at 900 rpm, and the solution was cooled at a rate of 0.18 °C·min<sup>-1</sup>. This experiment was also performed at 500 and 200 rpm. Nucleation was detected by the particle count on the FBRM and concentration drop. A similar procedure was adopted to get the MSZW in the batch OBC. 1.8 L of feed solution was introduced into the batch OBC and cooled at 0.18 °C·min<sup>-1</sup> using 4 Hz and 1 mm oscillatory conditions. The MSZW is narrower in the STC compared to the batch OBC operated at 900 rpm as shown in Figure 6. It has been reported that the volume averaged shear rate in OBCs is generally of order 10–20 s<sup>-1</sup>, which is significantly lower than that in stirred tank crystallizers (STC), which are typically 100 s<sup>-1</sup> or greater.<sup>51</sup> Power density<sup>51</sup> calculations were carried out for both reactors showing the power density to be 50 times lower in the batch OBC as compared to STC for the same MSZW (Table 2). Abbott et al.<sup>55</sup> has made a comparison of



**Figure 6.** MSZW in STC at 900 rpm, 500 rpm, 200 rpm, and batch OBC operated at 4 Hz frequency and 1 mm amplitude. Table 2 summarizes the power density values under each condition.

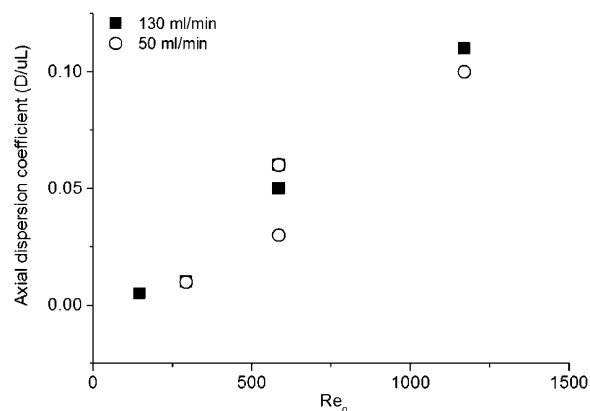
**Table 2. Mixing Conditions and Power Density for Optimax (STC) and Batch OBC**

system	mixing (rpm/Re <sub>o</sub> )	power density (W·m <sup>-2</sup> )
STC	200	54
STC	500	841.3
STC	900	3447
batch OBC	300	10

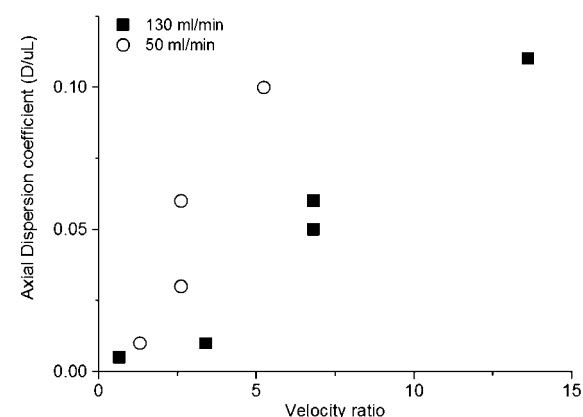
power consumption in an OBR vs STR for enzymatic saccharification of alpha cellulose. According to their study, 2.36 W·m<sup>-3</sup> power input was sufficient to produce maximum conversion in the OBR which was 12% higher after 24 h and 25% higher after 6 h than the STR (250 W·m<sup>-3</sup> required for equivalent conversion). They concluded that efficient mixing performance in an OBR at very low power density is responsible for higher conversion. Unlike STRs that rely on stirring mechanisms for mixing, the OBR uses oscillations to produce vortices. These form periodically along the entire length of the reactor, effectively causing each interbaffle zone to act as a CSTR; the entire reactor therefore consists of a large finite number of CSTRs connected in series.<sup>59</sup>

**3.2. Mixing and Flow Characterization of COBC.** The aim of this study was to produce a design space of operating parameters to ensure plug flow conditions are achieved in the COBC during operation. The axial dispersion coefficient was analyzed for different oscillatory and net flow conditions (amplitude, frequency, and flow rate). These flow conditions were established based on accepted ranges of Re<sub>o</sub>, St, Re<sub>n</sub>, and Ψ for traditional continuous oscillatory baffled crystallizers.<sup>7–12</sup> In a continuous crystallizer, the mean residence time can be used as a basis to determine Re<sub>n</sub>. When Re<sub>n</sub> is known, the frequency and amplitude should be chosen such that Re<sub>o</sub> satisfies the velocity ratio, in the range 2–10 (range selected based on previous RTD studies in oscillatory flow crystallizers<sup>8,10</sup>). Another important factor is terminal velocity calculations for particle suspension at the above-mentioned flow conditions. Solid loading was reduced for lactose crystallization to 33 wt % to maintain particle suspension in the COBC under these design conditions.

Experimental RTD response is presented in Figures 7 and 8. For each value of flow rate investigated, the RTD response can be seen to be dependent on both frequency and amplitude of oscillation. There is an optimum range of frequency and



**Figure 7.** Relationship between axial dispersion coefficient and oscillatory Reynolds number at experimental net flow conditions.



**Figure 8.** Relationship between axial dispersion coefficient and velocity ratio at experimental net flow conditions.

amplitude at which the system displays a minimum axial dispersion coefficient which is the desired state for near plug flow operation.

Based on the results above, there is an effective minimum value of axial dispersion in the range of  $100 \leq Re_o \leq 400$ , which is an acceptable limit (axial dispersion below 0.02) for plug flow in a reactor. These results are consistent with the experimental literature observations for sharp edge baffled systems.<sup>9,12</sup> At these Re<sub>o</sub> values the vortices formed as a result of oscillations are powerful enough to give effective radial mixing. These results also indicate that the axial dispersion coefficient decreases with increasing Re<sub>n</sub>, which indicates that as expected net flow rate improves the overall RTD performance. It is clear from Figure 8 that, with velocity ratio 1–5, a reasonable plug flow response is achievable.

### 3.3. Optimisation of Cooling Profile and Sonication.

The effect of sonication energy density and residence time on particle size and yield was investigated for 33 wt % lactose feed solution. To achieve minimum axial dispersion the oscillatory conditions were fixed at a frequency of 4 Hz and 1 mm amplitude. A cooling profile for crystallization process was established by applying direct control (model predictive control)<sup>55</sup> on supersaturation using the PharmMV control system from Perceptive Engineering.<sup>54</sup> The methodology for sonocrystallization in batch-OBC and COBC is presented in Figure 9. Sonication was introduced at a fixed supersaturation of 1.2. Results of sonocrystallization studies from batch

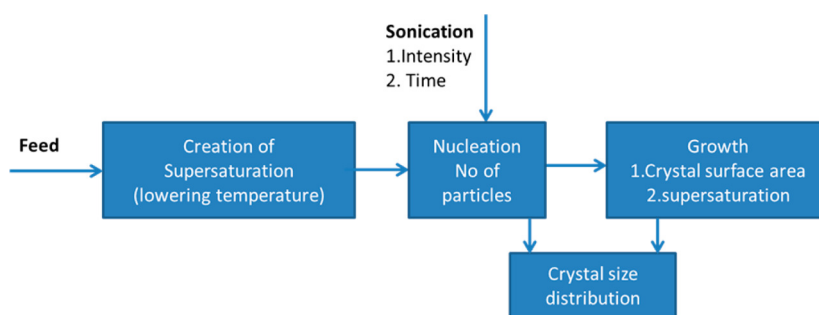


Figure 9. A simple information flow diagram for sonocrystallization of lactose in batch OBC and COBC.

Table 3. Batch Lactose Crystallization with Varying Sonication Power and Residence Time with Kinetic Parameters Estimated by the Previously Described Population Balance Model

residence time (h)	sonication power ( $\text{W}\cdot\text{g}^{-1}$ )	yield %	mean particle size ( $\mu\text{m}$ )	$\ln(k_b)$	$b$	$-\ln(k_g)$	$g$
2.5	0.10	$17.4 \pm 0.7$	$1010 \pm 10$	17.627	2.137	5.425	3.765
2.5	0.15	$25.1 \pm 0.5$	$970 \pm 7$	23.219	5.112	7.641	2.195
4.0	0.10	$19.7 \pm 0.8$	$1530 \pm 9$	22.205	5.960	5.728	3.476
4.0	0.15	$28.3 \pm 0.7$	$1150 \pm 6$	28.049	8.679	6.597	2.922

experiments are presented in Table 3. Nalajala et al.<sup>48</sup> investigated the physical mechanism of sonocrystallization for a KCl–methanol–water system and reported that the shock waves created by ultrasound affected nucleation, while micro turbulence (microconvection) governed the growth rate.

One major benefit of sononucleation is the reproducibility of the size and number of nuclei; the use of ultrasound to generate nuclei in a controlled and reproducible way provides therefore a well-defined starting point for the crystallization process through consistent surface area available for growth.<sup>53</sup> This enables control of the crystal growth via supersaturation and residence time in the crystallizer. It has been reported in the literature that crystal size distribution can be tailored by optimizing sonication intensity.<sup>53</sup> From batch work it has been shown that a short burst of ultrasound generates small number of nuclei allow their growth to a larger crystal size. However, continuous (or perhaps a single long burst) sonication can produce a large number of small crystals. In this study a short burst of sonication was introduced in lactose solution at a supersaturation of 1.2, and then cooling crystallization was performed to grow the generated nuclei from sonication as explained in Figure 9. Table 3 summarizes the sonication power delivered in batch system and kinetic parameters estimated using population balance model.

When only a one-dimensional characteristic size is considered, the  $j$ th moment can be defined as

$$\mu_j = \int_0^{\infty} L^j f_n(L, t) dL \quad (8)$$

where  $f_n(L, t)$  is the crystal size distribution,  $t$  is the time, and  $L$  is the characteristic crystal size. Therefore, a complete model of the crystallization process can be described by considering the first five moment equations and the mass balance equation<sup>56</sup> as

$$\begin{bmatrix} d\mu_0/dt \\ d\mu_1/dt \\ d\mu_2/dt \\ d\mu_3/dt \\ d\mu_4/dt \\ dC/dt \end{bmatrix} = \begin{bmatrix} B \\ G\mu_0 + BL_0 \\ 2G\mu_1 + BL_0^2 \\ 3G\mu_2 + BL_0^3 \\ 4G\mu_3 + BL_0^4 \\ -\rho_c k_v (3G\mu_2 + BL_0^3) \end{bmatrix}$$

where  $C$  is the solution concentration (g/mL water),  $L_0$  is the crystal size at nucleation,  $\rho_c$  the crystal density (1.545 g/mL for lactose),<sup>57</sup>  $k_v$  the volume shape factor (0.524),<sup>57</sup> and  $B$  and  $G$  are the primary nucleation and size independent growth rates, respectively, which are described by the power law expressions: 464

$$B = k_b \Delta C^b \quad (9)$$

$$G = k_g \Delta C^g \quad (10)$$

The calculations of the fourth and third moments allow for the determination of the volume mean size ( $L_{43}$ ) of the crystal size distribution: 469

$$L_{43} = \frac{\mu_4}{\mu_3} \quad (11)$$

In addition the solubility of lactose (g/mL water) as a function of temperature,  $T$  (in °C), is defined by 472

$$C = 0.1098e^{0.0276T} \quad (12)$$

For unseeded systems, the initial conditions for the moments and mass balance are defined as  $\mu_i(0) = 0$  ( $i = 0, 1, 2, 3, 4, 5$ ) and  $C(0) = C_i = C(@50^\circ\text{C})$ . Furthermore, the size of the nuclei is considered negligible ( $L_0 = 0$ ).<sup>58</sup>

Solutions of the system of differentials were obtained by utilizing a Runge–Kutta numerical integration from the time at which ultrasound was activated to the end of the cooling profile. The kinetic parameters ( $k_b$ ,  $b$ ,  $k_g$ , and  $g$ ) were estimated by performing a nonlinear optimization via a multiobjective genetic algorithm to minimize the root-mean-square deviation (RMSD) between the experimental measurements and model 484



485 predictions. The values of  $L_{43}$  and  $C$  at the end of the cooling  
486 profile were chosen as the two objectives for the estimation:

$$487 \quad \text{obj}_1 = \sqrt{(L_{43}^{\text{exp}} - L_{43}^{\text{pred}})^2}_{@t,\text{end}} \quad (13)$$

$$488 \quad \text{obj}_2 = \sqrt{(C^{\text{exp}} - C^{\text{pred}})^2}_{@t,\text{end}} \quad (14)$$

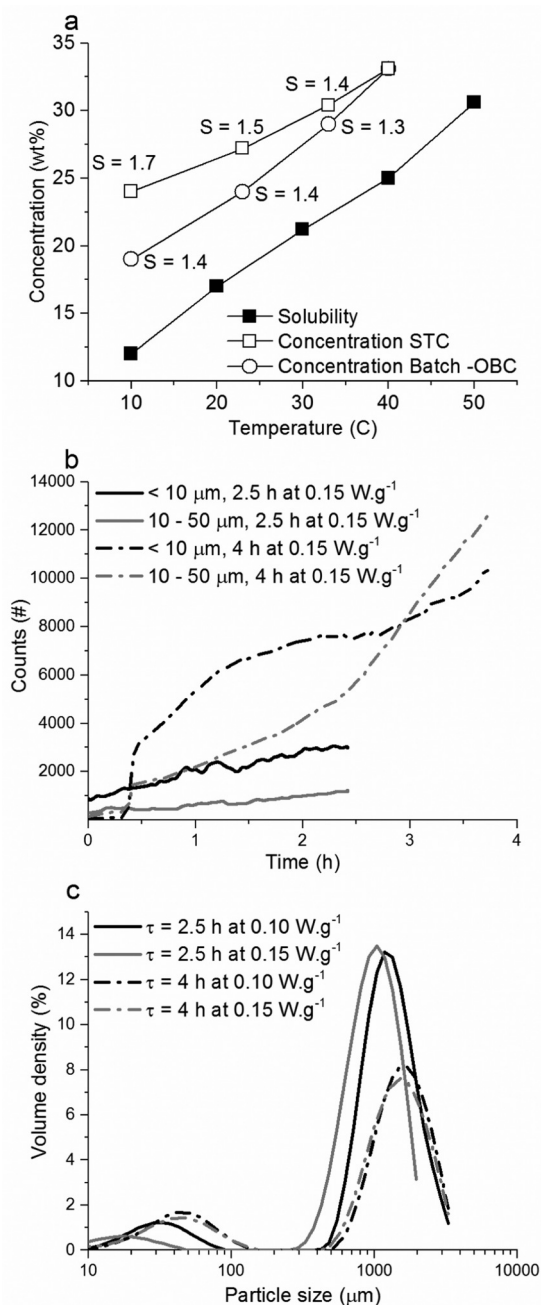
489 Overall yield was low in all sonocrystallization experiments  
490 due to low sonication energy density applied. By varying  
491 residence time, a change in particle size distribution was  
492 observed in batch experiments (Table 3). It can be seen from  
493 Table 3 that, with an increase in sonication power, product  
494 yield was increased, and particle size was decreased as more  
495 nuclei were formed.

496 In all experiments, a bimodal particle size distribution was  
497 observed. Lactose has a very slow growth rate, and a large  
498 surface area is required to achieve good yield in the process  
499 over the residence times studied. Insufficient nuclei were  
500 generated by sonication to produce high yield, as sonication  
501 power was limited by the specific probe used. Therefore, the  
502 degree of supersaturation increased during the crystallization  
503 from the target of 1.2–1.4 as shown in Figure 10a. This higher  
504 supersaturation may be responsible for observed secondary  
505 nucleation and consequent fines in the product (Figure 10c).  
506 Attrition could be another reason for the appearance of smaller  
507 particles in the product. The particle size distribution and yield  
508 can be optimized by providing high power sonication energy  
509 with the help of multiple probes along the length of the reactor.  
510 The benefit of using multiple probes is to avoid extra heat  
511 generation which could be a problem with one high power  
512 ultrasound source and better control on sonication intensity.  
513 Another possible way to reduce fines is to control super-  
514 saturation with the help of a slow quadratic cooling profile and  
515 hence providing a longer residence time.

516 **3.4. Continuous Lactose Crystallization in COBC.** To  
517 maximize the yield, based on the batch work, a 4 h mean  
518 residence time was selected for continuous crystallization, using  
519 a feed flow rate of  $50 \text{ mL}\cdot\text{min}^{-1}$ , frequency of oscillation 4 Hz,  
520 and amplitude of oscillation 1 mm. The scale up operation in  
521 the COBC was carried out by implementing the same  
522 conditions as identified from the batch OBC experiments  
523 described in section 3.2. Oscillatory conditions were selected  
524 based on residence time distribution study to achieve near plug  
525 flow in COBC (section 3.3). Sonication was introduced at the  
526 start of the second straight at a supersaturation of 1.2 to  
527 generate seeds ( $0.15 \text{ W}\cdot\text{g}^{-1}$ ). FBRM and reactIR probes were  
528 placed at the end of second straight to monitor the state of the  
529 process.

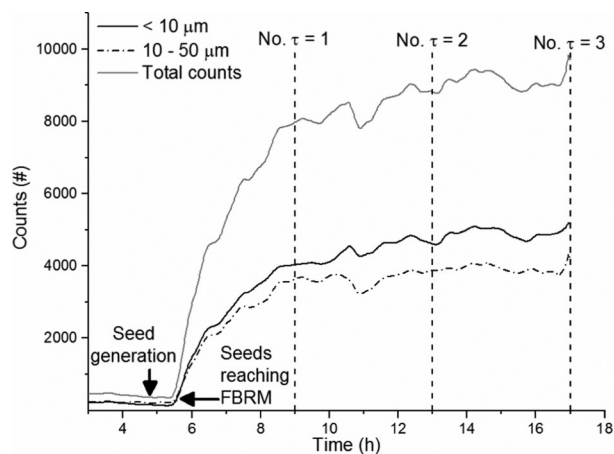
530 At the start of the process, the COBC was filled with water,  
531 and the required temperature profile was achieved by  
532 controlling the cold and hot water flow in the jacket side of  
533 the crystallizer. Once the required temperature profile was  
534 achieved, the saturated feed solution was introduced in the  
535 crystallizer. The system was run for three residence times, and  
536 the product collected was analyzed using DSC and laser  
537 diffraction for particle size. The system attained steady state  
538 after one and a half residence times as shown in Figures 11 and  
539 12. No signs of fouling or blockage were observed during the  
540 continuous trial. Images of the crystals produced in the COBC  
541 showed that the crystals were of the well-known tomahawk  
542 shape (Figure 13).

543 The product form was confirmed as ALM by DSC, TGA, and  
544 XRPD. Full data can be found in Supporting Information.

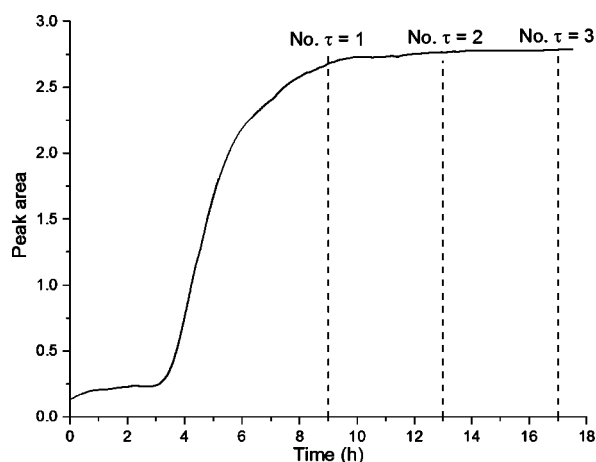


**Figure 10.** (a) Concentration profile for seeded lactose sonocrystallization in the STC and Batch-OBC (4 h,  $0.15 \text{ W}\cdot\text{g}^{-1}$ ) showing the different desupersaturation levels achieved. (b) FBRM data for lactose crystallization in batch OBC indicating secondary nucleation during the process due to elevated supersaturation after 2 h. (c) Particle size distribution for batch sonocrystallization in batch-OBC (Each set of conditions was repeated three times, and the coefficient of variation was less than 5%).

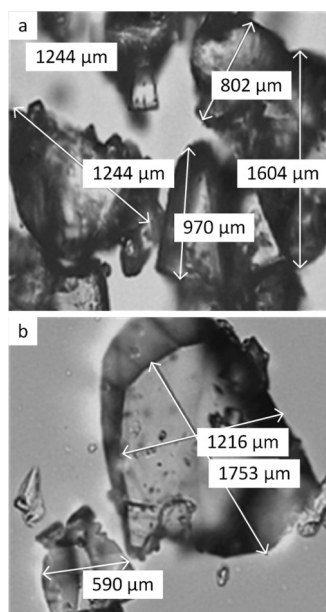
The crystals obtained from the COBC had similar bimodal  
particle size distribution (PSD) and morphology (Figure 14) as  
obtained from the batch OBC experiments with a mean particle  
size of  $1530 \mu\text{m}$ . However, a wider particle span and slow  
particle growth was observed in the STC as compared to batch  
OBC and COBC. It has been reported previously that mass  
transfer coefficient is approximately 75% higher in the OBC as  
compared to the STC.<sup>60</sup> The yield was higher (38%) in the  
continuous trial compared to batch OBC (28.3%) which could



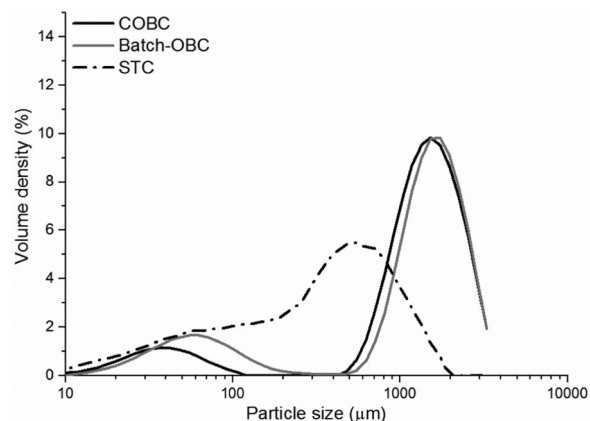
**Figure 11.** FBRM data showing steady state after one and half residence time during a 4 h cooling profile.



**Figure 12.** ReactIR data showing approximate steady state after two residence times in 4 h cooling profile.



**Figure 13.** Images of crystals from continuous crystallization process (a) second residence time and (b) third residence time.



**Figure 14.** Particle size analysis of final product in three crystallizers.

be associated with more even distribution of shear rate, which 554 on average leads to thinner liquid film (reduced boundary layer 555 thickness).<sup>61</sup> The intensity of mixing is known to affect the 556 mass transfer process in which solute leaves the solution and 557 becomes part of the crystal. The high intensity of mixing 558 enhances the mass transfer process, increasing the amount of 559 solute incorporated into the solid phase. In case of continuous 560 operation, net flow rate is an important factor increasing the 561 overall mixing intensity consequently increasing the mass 562 transfer. However, overall product attributes confirmed that the 563 methodology established to move from batch to continuous 564 COBC operation achieved the same product form with a higher 565 yield. Further work is in progress to optimize the crystallization 566 process to deliver improved control on product attributes, size, 567 impurity rejection, and yield and will be reported in subsequent 568 papers in this series. 569

#### 4. CONCLUSION

A new systematic approach has been proven to develop a 570 continuous sonocrystallization process using inline PAT and 571 direct control approach. Thermodynamic and kinetic param- 572 eters were established for lactose crystallization using FBRM and 573 mid-IR. Sonication was used to initiate nucleation, and the 574 cycle time has been successfully reduced from 13 to 20 h in 575 batch to 4 h in this COBC. The yield was relatively low 576 compared with previous studies on batch lactose sonocrystal- 577 lization due to the limitations of the maximum power gen- 578 eration from the sonicator used here generating insufficient 579 seeds. As a result of not being able to generate enough nuclei 580 secondary nucleation and fines, generation was observed at the 581 end of the process which can be minimized by further 582 improvements in providing multiple sonication generation units 583 within the crystallizer and control of supersaturation through 584 optimization of process. Narrower particle size distribution of 585 crystals as compared to batch process with ability to vary D50 is 586 achievable in continuous sonocrystallization process established 587 in current work. With the ability to run COBC system for 1–5 588 h under near plug flow conditions, continuous sonocrystalliza- 589 tion was successfully performed for the first time in COBC at a 590 throughput of 356 g·h<sup>-1</sup> with a consistent product quality and 591 product attributes for 12 h. Further studies are under progress 592 for optimization of lactose crystallization using process 593 analytical tools and control models. 594

## 595 ■ ASSOCIATED CONTENT

## 596 ■ Supporting Information

597 The Supporting Information is available free of charge on the  
598 ACS Publications website at DOI: 10.1021/acs.oprd.5b00127.

599 DSC and XRPD analysis of lactose feed stock and  
600 product (PDF)

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## 618 ■ ABBREVIATIONS

619 ALM	Alpha lactose monohydrate
620 Batch-OBC	Batch oscillatory baffled crystallizer
621 COBC	Continuous oscillatory flow crystallizer
622 CSTR	Continuous stirred tank reactor
623 DSC	Differential scanning calorimetry
624 FBRM	Focused beam reflectance measurement
625 FEP	Fluorinated ethylene propylene
626 MSMPR	Mixed suspension mixed product removal reactor
627 MSZW	Metastable zone width
628 Mid-IR	Mid infrared
629 PAT	Process analytical technologies
630 PFR	Plug flow reactor
631 PSD	Particle size distribution
632 PVM	Particle vision measurement
633 RTD	Residence time distribution
634 STC	Stirred tank crystallizer
636 XRPD	X-ray powder diffraction

## 637 Nomenclature

638 $Re_o$	Oscillatory Reynolds number
639 $Re_n$	Net flow Reynolds number
640 $St$	Strouhal number
641 $\chi_o$	Centre to peak amplitude (mm)
642 $d$	Tube diameter (mm)
643 $\mu$	Fluid viscosity ( $\text{kg}\cdot\text{m}^{-1}\cdot\text{s}^{-1}$ )
644 $f$	Frequency
645 $\psi$	Velocity ratio
646 $t$	Dimensionless time
647 $E$	Exit age distribution
648 $D$	Axial dispersion coefficient
649 $u$	Mean axial velocity
650 $c$	Dimensionless concentration
651 $x$	Dimensionless length
652 $l$	Length of reactor
653 $\epsilon$	Power density

$P_o$	Power number for impeller	654
$V_L$	Volume of liquid	655
$N_s$	Rotational speed of impeller	656
$D_s$	Diameter of impeller	657
$N_b$	Number of baffles per unit length	658
$C_d$	Discharge coefficient	659
$S$	Ratio of orifice area to baffle area	660
$C_p$	Heat capacity	661
$T_f$	Final solution temperature	662
$T_i$	Initial solution temperature	663
$m$	Weight of solution	664
$f_n(L,t)$	Crystal size distribution	665
$L$	Characteristic crystal size	666
$C$	Solution concentration ( $\text{g}\cdot\text{ml}^{-1}$ water)	667
$r_o$	Crystal size at nucleation	668
$\rho_c$	Crystal density	669
$k_v$	Volume shape factor	670
$B$	Primary nucleation	671
$G$	Size independent growth rates	672
		673

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