Fluidic Oscillator as a Continuous Crystallizer: Feasibility Evaluation
Ajinkya Vikram Pandit, and Vivek V. Ranade

Ind. Eng. Chem. Res., Just Accepted Manuscript • DOI: 10.1021/acs.iecr.9b04637 • Publication Date (Web): 14 Jan 2020
Downloaded from pubs.acs.org on January 15, 2020

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.
Fluidic Oscillator as a Continuous Crystallizer: Feasibility Evaluation

Ajinkya V Pandit and Vivek V Ranade

1School of Chemistry and Chemical Engineering
Queen’s University Belfast, Belfast, BT7 1NN, UK
2Bernal Institute, University of Limerick,
Limerick, V94 T9PX, Ireland

*Email: V.Ranade@qub.ac.uk; Vivek.Ranade@ul.ie
Abstract

Crystallisation is an important separation unit operation accounting for nearly 90% of organic molecules in the pharmaceutical and fine chemical industries. Recently, continuous crystallisation was demonstrated to have several advantages over the conventional batch crystallisation in terms of improved product consistency, reduced labor costs/economic footprint and better process control. Continuous stirred tank crystallisers, however, are limited in mixing/heat transfer capabilities and have issues like cyclical oscillations in product quality. Tubular crystallisers can mitigate these issues, however, suffer from issues related to particle settling and blockages. Fluidic oscillators with one or more feedback channels are gaining popularity in recent years due to the advent of microfluidics. Jet oscillations in fluidic oscillators were shown to consistently provide vigorous mixing and heat transfer above a critical Reynold’s number. In the present study, the feasibility of the fluidic oscillator as a continuous crystalliser was evaluated to mitigate challenges faced by previous continuous crystallisation technology. A novel ‘loop setup’ was proposed for continuous
crystallisation and was investigated using the seeded anti-solvent crystallisation of paracetamol in a methanol-water system. The effect of key operating conditions of residence time, supersaturation ratio, operational mode, fluidic device, device orientation and seed size were investigated. Throughout the study it was observed that the loop setup gave product particle size distributions consistent with enhanced mixing behavior. Further, it was demonstrated that the proposed continuous crystalliser was better in terms of scale up in comparison with batch crystallisers. The presented results and approach will be useful to develop fluidic oscillators as a useful platform for continuous crystallization.

**Keywords:** Continuous Crystallization, Fluidic Oscillators, Anti-solvent Crystallisation, Mixing
1. Introduction

Crystallization is an important unit operation in the pharmaceutical and fine chemical industries for the separation of high value solid products. Nearly 90% organic molecules in the pharmaceutical and fine chemical sectors are produced via crystallization. The quality of a crystalline product quality may be assessed by looking for variations in crystal habits, crystal polymorphs and particle size distribution (PSD). These product characteristics have a considerable impact on downstream manufacturing processes (filtration, drying, formulation) as well as on the product efficacy (bioavailability, dissolution, stability). The above-mentioned characteristics of crystalline products are primarily dependent on:

- Spatio-temporal variation of super-saturation: Can be controlled by mixing, heat transfer, circulation time or residence time distributions and different ways of realizing super-saturation (cooling, anti-solvent, evaporation and combinations thereof)
- Nucleation (primary and secondary) and growth kinetics
- Physico-chemical properties: Solubility, heat of crystallization, viscosity, density, surface charges, agglomeration and breakage characteristics.

It is therefore essential, wherever possible, to control these parameters so that desired characteristics of crystalline products may be obtained, with minimal variation in product quality.
Typically, crystallization is carried out in batch mode in mechanically agitated stirred tanks\(^2\). However, batch crystallisation techniques can suffer from problems such as poor utilization of equipment, high maintenance costs and batch to batch variation in product quality\(^1,2,4\). Moreover, batch processing generally offers poor control on the PSD requiring an additional energy intensive milling operation to achieve target product size distributions. The expiration on patents of an increasing number of chemicals is pushing industries to explore new avenues to make the manufacturing processes more efficient and competitive\(^1\). Industries have therefore been driven towards researching continuous crystallisation processes. Commonly used continuous crystallizers include stirred tanks (singe or cascade) and tubular crystallisers with different types of agitation (for example oscillatory baffle crystallizer)\(^1\).

Despite progress in recent years, the existing methods for continuous crystallisation suffer from several limitations. For instance, continuous stirred crystallizers suffer from broad residence time distribution implying spatial inhomogeneities in concentration resulting in broad PSDs\(^6\) as well as limited heat transfer and mixing capabilities\(^3\). Large variations in shear stress and turbulent intensity within large stirred tanks can often lead to severe issues on scale-up\(^7\). Further, there are known issues of cyclical oscillations of the PSD in mixed suspension mixed product removal (MSMPR) crystallisers\(^2,8\).
Tubular crystallizers can potentially mitigate these challenges and offer the possibility of multiple anti-solvent addition points and lengthwise variation in temperature for improved control of product quality. Tubular devices however, suffer from undesired blockages which often occur because of sedimentation of particles. Possible workarounds to address this problem involve complicated moving machinery, for example, the oscillating baffle crystallizer, addition of a second immiscible phase which wets tube walls and encases the crystallising phase or increasing flow rates (thereby reducing process yields). Thus, there is still a sufficient need for the development of continuous crystallization technology which addresses one or more of the challenges presented.

Fluidic oscillators were developed almost 50 years ago. Previously, such oscillators were used for flow measurement, as passive mixers for the mixing of miscible liquids and even for radioactive spent fuel treatment. Fluidic oscillators exploit the Coanda effect which is the tendency of a fluid jet to attach itself to an adjacent flat or curved surface. A schematic of the working principle of a planar fluidic oscillator considered in the present study is shown in Figure 1. A jet of fluid entering a chamber through the inlet will attach itself to a wall adjacent to the inlet increasing the flow through the feedback channel on the side of the attached wall. The increased flow in the feedback channel is reintroduced at the inlet such that it pushes the main inlet jet away from the first wall, to the other wall of the chamber which in turn activates the flow through the other feedback
channel. The symmetrical position of the inlet thus leads to sustained oscillations of the jet due to the alternate activation of the feedback channels resulting in intense mixing inside the mixing chamber$^{12,13,14}$.

In recent years, with the advent of microfluidics, there has been a renewed interest in fluidic oscillators as described above or some geometrical variations thereof. Khalde et al. (2019) presented results of a computational study of different configurations of fluidic oscillators for effectiveness in terms of mixing intensity and heat transfer$^{13}$. It was reported that the investigated feedback oscillators showed a consistent good mixing and heat transfer behavior over a critical value of Reynold's number. Xu et al. (2015) investigated an oscillating feedback micro mixer for its application for the in situ passive mixing of two miscible fluids$^{12}$. Wang et al. (2014) investigated a novel multi-stage extractor without moving parts comprising of multiple units of a feedback fluidic oscillator with two feedback channels and was seen to provide a good extraction efficiency for liquid-liquid extraction$^{14}$. 
Figure 1: Schematic representation of jet switching and mixing mechanisms in a fluidic device based on the Coanda effect

The present work borrows from the work done previously on the feedback fluidic oscillators. It is usually hypothesized that the mechanism of secondary nucleation is due to crystal-impeller, crystal-crystal or crystal-wall collisions\textsuperscript{15,16}. Hence, it was hypothesized that a crystalliser without moving parts would go a long way towards suppressing secondary nucleation thereby allowing more control on the product PSD. Continuous oscillations in fluidic oscillators would serve to enhance mixing and heat transfer in the solution as well as avoid settling of particles possibly mitigating problems associated with encrustation. Further, it was hypothesized that smaller particles would preferentially be recycled through the feedback channels due to drag forces spending more time growing in the crystallizer leading to narrower size distributions. Potential
benefits of fluidic oscillators as continuous crystallisers seem promising and could translate to improved control of product quality (crystal shape, PSD) and enhanced crystalliser operation (mixing/heat-transfer, blockage-free operation).

In this work, we have assessed the fluidic oscillator design studied by Khalde et al. (2019) for its application as a continuous crystallizer. The investigation focused on the seeded anti-solvent crystallisation of paracetamol using methanol-water solution as the solvent and water as the anti-solvent. A novel ‘loop setup’ was proposed which allowed to harness the enhanced characteristics of fluidic oscillators at high Reynold’s number at lab-scale throughputs. The impact of several operating variables such as residence time, supersaturation ratio, fluidic device and seed size on the product PSD were investigated experimentally. A comparison with the conventional batch stirred tank crystallisers was also performed and common issues related to scale-up of batch crystallisers were addressed. The results will be useful to identify potential of fluidic oscillators as continuous crystallisers and provide a basis for further work in this area.

2. Experimental Section

2.1 Crystallisation System

In the present study, seeded anti-solvent crystallisation of paracetamol in a methanol-water system was considered. Continuous unseeded anti-solvent crystallisation experiments were first carried out with high (>2) super saturation ratios (SSRs). It was
found in these experiments that transfer lines and the crystalliser got clogged after around 20 minutes of continuous operation. The clogging was attributed to the sedimentation of particles and successive encrustation and is a typical nuisance in continuous crystallisation processes. When the SSR was reduced to 1.6, it was found that onset of crystallisation was visually not observed to occur in the time scale of the experiment (60 - 90 minutes) in the crystalliser. A suitable mitigation strategy needed to be devised to ensure a stable and meaningful operation of the continuous crystalliser.

Previous studies proposed different strategies to mitigate the clogging/blockage in transfer lines of MSMPRs and in plug flow crystallisers (PFCs). Mujumdar et. al. (2015), proposed a mitigation strategy for the recovery of valuable API by addition of the pure solvent after operation\(^\text{17}\). Brown et. al. (2015) observed that increasing the oscillation amplitude in the COBC or increasing the anti-solvent flow rate - thus reducing mean residence time were seen to enable extended blockage free operation\(^\text{18}\). Powell (2017) addressed the problem of blockages in transfer lines of MSMPR crystallisers by periodically pulsing the solution through the transfer lines at high flow rates\(^\text{19}\). Onyemelukwe (2019) argued that excessive primary and secondary nucleation gave rise to the blockages in the crystalliser and mitigated the problem of blockage using seeded crystallisation at lower supersaturation ratios (to suppress excessive nucleation)\(^\text{20}\). Based on analysis of the published attempts, a strategy of reducing the SSR and introducing seeding was applied in this work and a sustained operation of the
crystalliser was verified for over 90 minutes for the base case (RTD1 as described later).

Table 1: Composition of Base Solution S and Mixture for different values of Supersaturation Ratio (SSR) studied

<table>
<thead>
<tr>
<th></th>
<th>RTD1</th>
<th></th>
<th>SS1</th>
<th></th>
<th>SS2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solution S</td>
<td>Mixture S</td>
<td>Solution S</td>
<td>Mixture S</td>
<td>Solution S</td>
<td>Mixture S</td>
</tr>
<tr>
<td>Water (g)</td>
<td>1200</td>
<td>3300</td>
<td>1300</td>
<td>3400</td>
<td>1000</td>
<td>3000</td>
</tr>
<tr>
<td>Methanol (g)</td>
<td>711</td>
<td>711</td>
<td>632</td>
<td>632</td>
<td>790</td>
<td>790</td>
</tr>
<tr>
<td>Paracetamol (g)</td>
<td>210</td>
<td>210</td>
<td>169</td>
<td>169</td>
<td>275</td>
<td>275</td>
</tr>
<tr>
<td>Saturation Paracetamol (g)</td>
<td>191.14</td>
<td>117.36</td>
<td>149.57</td>
<td>103.67</td>
<td>255.32</td>
<td>136.42</td>
</tr>
<tr>
<td>Excess Paracetamol (g)</td>
<td>18.86 (seed)</td>
<td>73.78 (+seed)</td>
<td>19.42 (+seed)</td>
<td>45.91 (+seed)</td>
<td>19.68 (+seed)</td>
<td>118.89 (+seed)</td>
</tr>
<tr>
<td>SSR</td>
<td></td>
<td>1.63</td>
<td></td>
<td>1.44</td>
<td></td>
<td>1.87</td>
</tr>
</tbody>
</table>

A solution containing paracetamol (4-Acetamidophenol, 98%, Acros Organics), methanol (99.8%, Fisher Chemicals) and distilled water was prepared to be used as the base solution. Distilled water was used as an anti-solvent and was added in an equal volumetric flow rate as the base solution. The total amount of paracetamol to be added (inclusive of seeds) was calculated based on the SSR required and to ensure seeding equivalent to ~ 0.5% of the total mixture weight. All calculations related to solubility were
done considering the solubility profile reported by Ó’Ciardhá et. al. (2011)\textsuperscript{21} at 25°C. Experiments were performed by keeping the temperatures of the base solution, antisolvent and the mixture between 26 to 27°C. The compositions of the base solution for different SSRs considered in the present study are shown in Table 1.

2.2 Crystallization Setup

Typical laboratory scale continuous crystallizers are operated at a low flow rate which usually results in poor mixing. To get around this, the COBC superimposed an oscillating motion using a piston on top of a low inlet flow rate\textsuperscript{11}. Due to oscillations, locally the fluid velocity was high enough to avoid particle settling, but overall the residence time was high enough to accommodate crystallisation processes. In the fluidic oscillator considered in this work, significantly high flow rates are needed to realize desired mixing. An inlet velocity of 0.75m/s (~1L/min flow rate) was expected to give good mixing characteristics for the fluidic oscillator\textsuperscript{13}. Higher flow rates also help in avoiding encrustation and particle settling\textsuperscript{18,19}. In the present study, a novel ‘loop setup’ was used to reconcile between the high flow rate requirement of fluidic oscillators and the high residence time requirement for crystallisation processes at lab-scale throughputs. The schematic of the loop setup is shown in the Figure 2.

The exact dimensions of the fluidic device used in the present study are given in Section S1 of the Supporting Information. In the loop setup, there is a loop wherein the
fluid was circulated at sufficiently high flow rates (~1L/min) using a VWR FASTLoad series auto-controlled peristaltic pump. The direction of the flow in the loop was such that a ‘short-circuit’ of flow between the inlet and outlet of the loop setup was avoided. There were two glass T-junctions in the loop to connect it to the inlet and the outlet lines of the setup. The inlet feed was an equal volume mixture of the base solution and the anti-solvent and was fed to the loop setup using a single VWR FASTLoad series auto-controlled peristaltic pump with two pump heads. Fluids drawn from the base solution and the anti-solvent were mixed using a glass T-junction and then fed into the inlet T-junction of the loop setup.

The outlet flow rate was self-controlled in the loop setup due to the fixed volume of the loop setup and the incompressible nature of the fluid. The outlet stream was collected in a 5L baffled glass beaker. An overhead stirrer with a pitched blade downflow impeller was used at an impeller speed of 500RPM to maintain the stirring conditions throughout the experiment. The outlet flow rate was quantitatively verified for the first 10-15 minutes for most experiments using a Fisherbrand Precision series mass balance (capacity of 2100g, sensitivity of 0.01g, response time of 3s) to ensure a steady outlet flow and to obtain accurate values for residence time.
Figure 2: Schematic diagram of the anti-solvent continuous crystallization ‘loop’ setup

Though using a recycle is a known strategy to improve yield in continuous crystallization processes, to the author’s knowledge, the proposed loop setup has not been used before for crystallization. Fundamentally, the loop setup considered in the present study is equivalent to a PFC with recycle albeit with very high (~ 50) recycle ratio (defined here as the flow rate ratio between the recycle stream and the inlet stream). Previous studies dealing with recycle streams did not consider such high recycle ratios. Wong et al. (2012) found that a recycle system (recycle ratios of 1.49 – 1.87 for cooling crystallisation, 14.31 for anti-solvent crystallisation) used with a single stage MSMPR setup obtained higher yields, higher purity and more control on the PSD as compared to multistage MSMPRs. Using a recycle however leads to increased impurities. Ferguson
et al. (2014) used a continuous crystallization process with a recycle stream fitted with an inline nanofiltration unit which simultaneously improved yield and reduced impurities\textsuperscript{23}. Cogoni et. al. (2015) found through a simulation study that the recycle ratio (values less than 1) and the extraction position were effective parameters in controlling the product PSD and improving process yields\textsuperscript{24}.

Li et. al. (2016) found that using a solids recycle stream (solids’ recycle ratio of 0.45 – 0.9) increased the overall surface area in the crystalliser and hence improved the yield\textsuperscript{25}. Another advantage of the present fluidic device is that apart from the recycle in the loop setup, some part of the fluid (~ 5 - 10\%) was continuously recycled in the device itself due to the feedback channels (Figure 1)\textsuperscript{13}. Thus, it was expected that the smaller sized solids which could be carried by fluid flow into the feedback channels would accumulate in the device increasing the overall surface area and improving process yield as found out by Li et. al (2016)\textsuperscript{25}. The solids feedback in the device was also expected to increase the residence time of the smaller particles leading to preferential growth of smaller particles and hence a narrower PSD.

To ensure a stable operation, the liquid phase refractive index was measured at the outlet of the loop setup using an offline Mettler Toledo RM40 refractometer at a 35°C cell temperature using an air-water system as a baseline. For a given solution solvent-anti-solvent composition (in this case methanol-water), the refractive index is linearly
proportional to the solute concentration. A constant value of the refractive index at the outlet thus ensured the base solution and the anti-solvent were dosed properly and there were no blockages/complications due to progressive encrustation. No attempt was made to correlate the solute concentration to the refractive index measurements. Liquid samples were drawn from the outlet stream using a 2mL syringe and filtered into a sample vial using 0.22\(\mu m\) 28mm Sirius syringe filters.

After approximately 3 liters of the mixture was collected, the experiment was stopped. The time for the collection of 3 liters of the solution varied depending upon different residence times considered. The solution was then allowed to equilibrate in the 5L baffled glass beaker under constant stirring conditions for 60 minutes after the completion of the experiment. The liquid phase refractive index was measured after 60 minutes to ensure steady state. The solution was then filtered using a Büchner funnel assembly connected to a vacuum line and the filtered cake was dried for 48 hours at 50°C to obtain the final product in a powder form. The procedure to measure the PSD of the final product is explained in the next section.

As the crystals were circulated using a peristaltic pump in the loop setup and collected in the collection tank, it may be inferred that the two steps would affect the PSD. Crystal breakage might occur in the peristaltic pump or during equilibration in the collection tank. In order to clear this ambiguity, an additional experiment (RTD6 as described later) was performed. In this experiment, after the first equilibration step, the mixture
was kept under stirring conditions for another hour while simultaneously setting up a simple loop using a peristaltic pump. The simple loop was a tube which took the mixture from the collection tank and put it back into the collection tank while passing through the peristaltic pump. The pump was operated at 220RPM as for the rest of the experiments. The PSD was then measured and compared with other experiments.

2.3. Measuring the PSD

The product PSD was the key product quality parameter considered in the present work. The effect of key operating conditions on the product PSD was investigated. To obtain the product PSD, particles from the dried product were taken on a glass slide and viewed under a trinocular Brunel SP-400 microscope using 5X and 10X objectives. A Canon EOS2000D digital SLR camera with a microscope to camera adaptor having an effective magnification of 10X was mounted on the microscope which provided an effective magnification of 50X and 100X respectively. At least 300 individual particles were approximated using an oval shape as shown in the Figure 3A and 3B. The particle projected area was approximated to be equal to the area enclosed by the oval used to encompass it. The individual particle size was estimated as the diameter of a circle having the same area as the approximate projected area of the particle.

A Matlab function - HISTOGRAM (MATLAB R2018b), was used to distribute the measured particle diameters into bins of a uniform width of 5\( \mu m \) ranging from 0 to
310μm to obtain the number distribution function histogram as shown in Figure 3C. It was observed that the PSD obtained from all the crystallisation experiments performed resembled the shape described by the lognormal distribution function. A normalized lognormal distribution function (denoted by \( f(x) \) where \( f(x)dx \) is the probability distribution between the sizes \( x \) and \( x+dx \)) as described by Equation 1 was used for the regression of the normalized experimental product PSD\(^{26}\). The normalized lognormal distribution functions enabled a convenient comparison across different experimental PSDs. The mean (\( m \)) and the variance (\( \nu^2 \)) of the PSD in the conventional sense were obtained using the parameters \( \mu \) and \( \sigma \) as given by Equations 2 and 3\(^{26-28}\).

\[
 f(x) = \frac{1}{x\sigma\sqrt{2\pi}}e^{-\frac{(\ln x - \mu)^2}{2\sigma^2}}
\]

(1)

\[
 m = \exp\left(\mu + \frac{\sigma^2}{2}\right)
\]

(2)

\[
 \nu^2 = m^2[\exp(\sigma^2) - 1]
\]

(3)

\[
 \int_{0}^{\infty} f(x)dx = 1
\]

(4)

The parameters \( \mu \) and \( \sigma \) used to represent an experimental PSD using Equation (1) were worked out by maximizing the \( R^2 \) value of fit between the experimental PSD (normalized by the total number of particles) and the discretized PSD represented using Equation 1 (normalized by the total sum of the individual values in each bin) as shown
in Figure 3C. A $R^2$ value closest to one represented the best fit between experimental and fitted data. It was ensured that the final distribution used for comparison followed Equation (4) to ensure that it accurately represented a continuous number distribution function. For the optimization problem of maximizing the $R^2$ value (or minimizing $1 - R^2$) by varying the parameters $\mu$ and $\sigma$, the solver add-in in Microsoft Excel for Office 365 was used. The solver add-in used the GRG Nonlinear method for the solution of the optimization problem.

To demonstrate the repeatability of PSD measurement, the PSD was measured for two samples of the RTD6 experiment (Table 3). A comparison between the mean, variance and the $R^2$ is shown in Table 2 and comparison between the respective PSDs in Figure 3C. The mean and variance were close, and the PSDs were in good agreement. Hence, it was thus concluded that repeatable measurements were obtained using the present method. RTD6A was considered as the base sample of the RTD6 experiment for further analysis.
Figure 3: (A) Typical microscopic image of dried paracetamol crystal sample for RTD1 experiment with inspection area (B) Crystals in the magnified inspection area approximated using oval shape (outlines marked in red) for estimating individual particle projected area (C) Comparison between normalized PSD obtained using image analysis and through regression for RTD6A and RTD6B.

Table 2: Comparison between the mean, variance and $R^2$ values measured for RTD6A and RTD6B samples

<table>
<thead>
<tr>
<th>Name</th>
<th>Mean</th>
<th>Variance</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTD6A</td>
<td>62.90</td>
<td>46.43</td>
<td>0.95</td>
</tr>
<tr>
<td>RTD6B</td>
<td>65.38</td>
<td>45.47</td>
<td>0.93</td>
</tr>
</tbody>
</table>
3. Results and discussion

When two streams containing a paracetamol solution and anti-solvent are mixed with each other, the local concentration gradients within the mixture will reduce via mass transfer (convection, shearing – folding and molecular diffusion). In such systems, the rate of generation of supersaturation is controlled by the extent of mixing - a superior mixing behavior leading to a higher rate generation of supersaturation. In general, a higher initial level of supersaturation implies a higher initial nucleation rate leading to the supersaturated solute getting deposited onto a larger number of particle surfaces. As the same quantity of supersaturated solute is deposited onto a larger number of particles, the effective mean size for crystallisation under high supersaturation conditions is lower. Additionally, as mixing is faster, all the supersaturated solute is consumed within a brief time period after the onset of crystallisation. Thus, prolonged nucleation is suppressed thereby avoiding broad PSDs.

There is a lot of ambiguity in reporting the shapes for paracetamol crystals with numerous shape types being reported previously:

- Plate like, prism shaped
- Mono clinic, orthorhombic
- Polygonal prismatic, rod-shaped, ellipsoidal, spherical, triangular$^{31}$
- Prismatic polyhedral$^{32}$

Other studies dealing with shape modification of paracetamol crystals have stayed away from explicitly describing the shape and instead characterized the shape in terms of measurable quantities such as distance from the phase plane or roundness, aspect ratio$^{33}$. The accurate characterization of crystal shape was beyond the scope of the present work. However, crystals obtained in all the experiments were similar in shape to crystals shown in Figure 3A. Although there was variation in the shape of the crystals, the crystals may be described as 'nearly orthorhombic' or more accurately as prismatic polyhedral.

In the present study, the PSD of the sample filtered from the collection vessel after equilibration was the measured product parameter. The PSD at the outlet of the loop setup was not directly measured. Hence, meaningful interpretations regarding the effect of operating conditions on the PSD must factor in the additional step of equilibration in the collection vessel. The values for the mean, variance, $R^2$ value and the operating conditions for all the experiments are listed in Table 3. The influence of operating conditions on the performance of the loop setup in terms of the product PSD are discussed in the following sections. Comparisons between the fitted PSD and raw PSD...
obtained from image analysis for all experiments are provided in the Supporting Information.

**Table 3: List of experimental conditions investigated in the present manuscript and the corresponding mean and variance of the PSD**

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode</th>
<th>Unit</th>
<th>RTD (s)</th>
<th>SS</th>
<th>m (μm)</th>
<th>v (μm)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTD1</td>
<td>Continuous</td>
<td>Loop +</td>
<td>150 to 1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTD2</td>
<td>Continuous</td>
<td>Loop +</td>
<td>150 to 1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTD3</td>
<td>Continuous</td>
<td>Loop +</td>
<td>198.7</td>
<td>3</td>
<td>44.11</td>
<td>25.48</td>
<td>0.975</td>
</tr>
<tr>
<td>RTD4</td>
<td>Continuous</td>
<td>Loop +</td>
<td>204.4</td>
<td>3</td>
<td>52.65</td>
<td>32.29</td>
<td>0.97</td>
</tr>
<tr>
<td>RTD5</td>
<td>Continuous</td>
<td>Loop +</td>
<td>121.5</td>
<td>3</td>
<td>96.02</td>
<td>66.21</td>
<td>0.95</td>
</tr>
<tr>
<td>RTD6</td>
<td>Continuous</td>
<td>Loop +</td>
<td>158</td>
<td>3</td>
<td>62.91</td>
<td>46.43</td>
<td>0.95</td>
</tr>
<tr>
<td>SS1</td>
<td>Continuous</td>
<td>Loop +</td>
<td>156.4</td>
<td>4</td>
<td>108.26</td>
<td>85.36</td>
<td>0.89</td>
</tr>
<tr>
<td>SS2</td>
<td>Continuous</td>
<td>Loop +</td>
<td>153.3</td>
<td>7</td>
<td>147.43</td>
<td>1</td>
<td>0.896</td>
</tr>
<tr>
<td>BATCH1</td>
<td>Batch</td>
<td>Beaker</td>
<td>200mL</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BATCH2</td>
<td>Batch</td>
<td>1L Beaker</td>
<td>-</td>
<td>3</td>
<td>75.29</td>
<td>27.97</td>
<td>0.965</td>
</tr>
</tbody>
</table>

Page 24 of 48
<table>
<thead>
<tr>
<th></th>
<th>Continuous Loop + CFI</th>
<th>Loop + Vertical</th>
<th>1.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFI</td>
<td></td>
<td>192.2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>93.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>VERTICAL</td>
<td>Continuous Coanda</td>
<td>~ 150</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>105.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.927</td>
</tr>
<tr>
<td>SEED1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>SEED2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>146.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>88.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>PROD2</td>
<td>Continuous Coanda</td>
<td>156.4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>53.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.96</td>
</tr>
</tbody>
</table>

### 3.1. Effect of Residence Time

The effect of residence time in the loop setup on the product PSD was investigated by varying the combined inlet solution and anti-solvent flow rates (maintaining a 1:1 ratio).

Experiments were performed for loop residence times of 120 to 200s. It was seen that the experiments having similar residence times (three experiments having RT = 150 to 160; two experiments with RT = 198.7s and 204.4s) had similar PSDs (Figure 4). Based on the results, it was said that the experiments were repeatable with a reasonable error bar. Further, the RTD6 experiment was performed to clear the ambiguity of whether
crystal breakage was occurring during stirring or in the peristaltic pump. It was observed that the PSDs for the two experiments having similar operating conditions as RTD6 (RTD1, RTD2), matched the PSD for the RTD6 experiment (Figure 4A). As the PSD was not affected, it was inferred that there was no effect of crystal breakage due to the peristaltic pump or due to stirring.
Figure 4: Comparison between the (A) normalized PSDs for RTD1, RTD2 and RTD6 (B) normalized PSDs for RTD1, RTD3, RTD4 and RTD5 and (C) mean, variance and $R^2$ of
fit for the normalized particle size distribution profiles for effect of residence time experiments

It was seen that for increasing residence times, the mean particle size decreased. Further, the PSD was seen to be narrower (reduced variance). Supersaturation is the key driving force governing product quality parameters like particle size and shape. In the present study, the outlet of the loop setup was collected in a 5L batch crystalliser - used as a collection vessel after passage through the loop setup. It was argued that for higher residence times, the mixture spent more time in an enhanced mixing environment of the loop setup. Hence, for higher residence times, the mixing between the solution and the anti-solvent had progressed further leading to a higher overall initial supersaturation at the outlet of the loop setup. A higher initial supersaturation lead to higher initial nucleation rates and hence a smaller mean particle size. Additionally, an earlier onset of well mixed conditions would lead to a shortened nucleation and growth period leading to narrower particle size distributions. Hence, improving the mixing quality particularly for anti-solvent crystallization, would lead to smaller mean sizes and narrower size distributions. Thus, from the experimental observations dealing with residence time, it was inferred that the loop setup provided a superior (and tuneable) mixing performance than a batch crystalliser. Further, it was observed that the $R^2$ value for the regression was good (>0.95) throughout all the data sets and was higher for
increasing residence times. Thus, it was inferred that the product PSD was increasingly better described by the lognormal distribution for enhanced mixing conditions.

3.2. Effect of Supersaturation

Experiments were performed at supersaturation ratios of 1.44, 1.63 and 1.87 with the solution and mixture compositions as described in Table 1. Flow rates corresponding to a residence time of around 150s were considered for all the supersaturation experiments (exact values are specified in Table 3). A comparison between the mean, variance, $R^2$ value and the PSD for different experiments is shown in Figure 5. It was observed that the mean particle size was seen to be lowest for the intermediate supersaturation ratio of 1.63. The variance was also seen to be the lowest for the intermediate supersaturation ratio. It was also observed that the $R^2$ value of fit for the lognormal distribution was close to one at this value of supersaturation ratio. The observations of low mean size, narrow PSD and high value for $R^2$ are consistent with each other indicating better mixing/crystallizer performance. Thus, it was observed that there was a definite non-linear dependence of the mean PSD on the SSR. Results indicated an optimal SSR for the anti-solvent crystallisation experiments although further elaborate experimentation would be required to establish such a claim.

According to conventional rate laws for the quantitative prediction of secondary nucleation (Mullin et. al., 2001), a higher supersaturation implied a higher nucleation
rate. Consequently, as the solute distributes onto a larger number of particles, the resulting mean particle size is lesser. Hence, for increasing SSRs, it was expected that the mean particle size would reduce. However, in the present work, instead of a monotonically decreasing trend in the mean particle size, a non-linear dependence on the SSR was observed. One possible explanation to explain this counter-intuitive trend would be to include the effect of mixing between solvent and anti-solvent. Even though the theoretical supersaturation ratio was higher (1.87, Experiment SS2, Table 3), realizing that SSR may be limited briefly during the initial nucleation period by mixing, resulting into a higher mean particle size. However, further experimentation would be necessary to investigate this claim of an optimal SSR.

3.3. Effect of Operational Mode and Scale-Up

Experiments were carried out at 200mL and 1L scales in a batch mode of operation for comparison with the continuous mode of operation using the loop setup. For the 200mL case, a simple 250mL beaker with a magnetic stirrer assembly was used (stirring speed of 400 RPM). For the 1L case, a baffled 2.5L beaker with a corresponding magnetic stirrer assembly (stirring speed of 400 RPM) was used. Adequate time was given to ensure the mixture had equilibrated and the crystallization was completed. A comparison between the mean, variance, $R^2$ value and the PSD for the different experiments is shown in Figure 6.
It was observed that the 200mL batch scale resulted in a low mean particle size and the
lowest variance. This was expected as the mixing performance in low volume batch
processes is very good. However, as expected, the mixing performance worsened for
increasing batch scale, with the 1L scale batch process showing the worst mean and
variance of the PSD. In the comparison, the continuous mode of operation using the
loop setup could process 3L of total mixture volume with the mean particle size
comparable to the 200mL batch process while the variance was marginally higher.
Further, it was observed that for conditions consistent with good mixing performance
(lower mean particle size, narrower PSD), a high $R^2$ value of fit was obtained (>0.95).

From the PSDs, it was inferred that during scale up, the mixing performance for stirred
tanks deteriorated due to increasing batch size and as a result the product quality also
suffered. In comparison, the loop setup with a single unit of the device provided three
times the product quantity as the 1L batch case in roughly the same amount of time and
with a product quality comparable to the 200mL batch case. Further, the continuous
loop setup can be scaled up by simply adding additional units of the device in series
and increasing the inlet flow rates to maintain the same residence time. Hence, it was
concluded that the loop setup showed great potential for scaled up continuous
operation.
Figure 5: Comparison between the (A) normalized PSDs and (B) mean, variance and R² of fit for the normalized particle size distribution profiles for effect of supersaturation experiments.
Figure 6: Comparison between the (A) normalized PSDs and (B) mean, variance and $R^2$ of fit for the normalized particle size distribution profiles for batch scale experiments and a continuous experiment.
3.4. Effect of Fluidic Device and Device Orientation

Experiments were performed by replacing the fluidic device in the loop setup using a coiled flow inverter (CFI) and by positioning the present fluidic device in a vertical orientation. An image of the CFI used in the present study and the corresponding dimensions are listed in Section S5 of the Supporting Information. In a vertical orientation of the present device, one arm would be above the inlet and the second, below the inlet. The vertical orientation was tested as it was expected to have a different solid residence time distribution than the horizontal orientation (both arms and inlet in the same horizontal plane) due to gravitational forces on individual particles. The residence times considered for the experiments were around 150s for the vertical orientation of the fluidic device and 192.2s for the CFI. A comparison between the mean, variance, $R^2$ value and the PSD for the different experiments is shown in Figure 7.
Figure 7: Comparison between the (A) normalized PSDs and (B) mean, variance and $R^2$ of fit for the normalized particle size distribution profiles for effect of supersaturation experiments.
It was observed that the horizontal orientation (RTD1) of the present fluidic device gave the lowest mean particle size and the narrowest PSD amongst the three scenarios considered. Further the present device was seen to perform better than the CFI even for a lower residence time indicating that the present device is more efficient in terms of mixing than the CFI. Also, it was observed that for conditions consistent with improved mixing (lower mean size, narrower PSD), the $R^2$ value of fit was higher while maintaining a high $R^2$ value throughout all experiments.

### 3.5. Effect of Seed Size

Experiments were carried out using two different seed PSDs in the loop setup while maintaining the other operating conditions. A comparison between the mean, variance, $R^2$ value and the PSD for the different experiments is shown in Figure 8. It was observed that for a higher mean seed size, a smaller mean particle size and a narrower PSD was obtained. The $R^2$ values for both the experimental conditions was observed to be high (>0.95).

As mentioned previously, the seeding strategy was used to hasten the onset of nucleation typically at supersaturation ratios where homogeneous nucleation was insignificant. Also, lower levels of supersaturation ratios were used to avoid problems related to encrustation/blockages. Secondary nucleation was deemed as the primary
source of new particles and occurred either due to impact and particles chipping off from existing crystal surfaces\textsuperscript{15,16} or due to crystal breeding\textsuperscript{16}. In either case, particles formed due to secondary nucleation grow and later themselves contribute as seeds. Due to this, the onset of nucleation is followed by an exponential growth in the number of particles - or a period of ‘significant secondary nucleation’ in which period most (on a weight basis) of the supersaturated solute is consumed.

A consequence of having seed particles with a higher mean particle size but the same seed loading (0.5\% of total weight of the mixture) was that the total number of seed particles was lesser. Thus, it was possible that having a lesser number of particles to start with would a delay in the period of ‘significant secondary nucleation’. In this delay time, it was possible that the mixing progressed to a higher extent before significant nucleation initiated and as inferred before, a higher extent of initial supersaturation lead to lower particle sizes and narrower PSDs. Thus, even though the observation of lower mean particle size and narrower PSD for a larger mean seed size with a broader PSD seemed counter-intuitive, it can be rationally explained through the interplay of mixing and secondary nucleation.
3.6. Mixing, Secondary Nucleation and $R^2$

To enable a convenient comparison across different experimental data sets, the experimental PSD obtained through image analysis was fitted using a log normal distribution. The $R^2$ value of fit between the normalized experimental PSD and the corresponding lognormal distribution was maximized (closest to 1) through optimization of two lognormal distribution parameters (Equation 1). Throughout the present study, it was observed that the $R^2$ value was consistently high (>0.9) for conditions of enhanced mixing (inferred from the mean and variance of the PSD) and low (~0.7 - 0.8) for conditions of relatively poor mixing.

It should be noted that the $R^2$ value by itself cannot give an insight into the mean and the variance of the PSD but the goodness of fit to a lognormal distribution can give an insight into mechanisms prevailing at good mixing. It was clear from the present study that mixing was one of the most important factors affecting the product quality especially for anti-solvent crystallisation. As discussed in the effect of seed size section, understanding of crystallisation processes is often complicated due to an inter-play of mixing (possibly micro-mixing) and secondary nucleation. Both phenomena are not well-understood and need to be decoupled for any meaningful interpretation. This is to say
that for any meaningful interpretation of secondary nucleation, one must first ensure that mixing is sufficiently rapid in comparison.

Theories for secondary nucleation suggest either an impact mechanism\textsuperscript{15,16}, or more recently, a crystal breeding mechanism\textsuperscript{16}. In the crystal breeding mechanism, it was proposed that the new ‘daughter crystals’ form on the surfaces of the bigger ‘parent crystals’ through the mechanisms of heterogeneous nucleation and growth. These ‘daughter crystals’ after sufficient growth detach from the ‘parent crystals’ due to fluid shear. The freshly detached ‘daughter crystals’ would themselves form the ‘parent crystals’ and eventually be breeding grounds for new ‘daughter crystals’. In the impact mechanism for secondary nucleation, it was proposed that new nuclei are formed due to crystal breakage resulting from particle-particle or particle-impeller collisions. In the present study, it was observed that even without moving parts, secondary nucleation was still the primary source of nucleation which suggested that the impact theory may not be the likely mechanism.

Adequate description of the PSD with a lognormal distribution was consistent with similar observations in biology or ecology to describe growth of organisms or the population of species, for growth of users and websites on the Internet in computer science and in various other disciplines\textsuperscript{26}. In all these systems, a recurring theme was a ‘parent-daughter’ dynamic as described in biological systems, where in the parent entity
(crystals, organisms, internet users, websites etc.) gave ‘birth’ to new daughter entities which grow and themselves became parent entities. Thus, it can be argued that the findings of the present study seek to promote crystal breeding type of a mechanism for secondary nucleation. However, the present study does not definitively address the mechanism for secondary nucleation and further experimentation and analysis would be necessary to bolster such a claim.

The work on detailed crystallization model integrated with the multiphase CFD model (using the work of Khalde et al., 201913 as a starting point) was initiated and will be presented separately. Such a study would be helpful to quantitatively capture the impact of mixing on crystallisation. The results presented in this work provide adequate data to evaluate and validate such computational models. The approach and the methodology will be useful to further develop fluidic oscillators as a robust platform for continuous crystallization without any moving parts.

4. Conclusions

The present work dealt with the feasibility evaluation of a fluidic oscillator as a continuous crystalliser. A novel loop setup was proposed which enabled the ‘flow activated’ operation of high throughput fluidic devices at lab scale throughputs. The seeded anti-solvent crystallisation of paracetamol using water as the anti-solvent and a water-methanol mixture as the solvent was considered. The effects of residence time,
supersaturation ratio, operational mode, scale-up, fluidic device, device orientation and seed size on the product PSD were investigated.

It was found that the extent of mixing played a big role in determining product quality – enhanced mixing leading to narrower PSDs and smaller mean particle sizes. Increasing the residence time spent by the fluid in the loop setup was seen to reduce the mean sizes and lead to narrower PSDs. It was observed that there was a definite non-linear dependence of the mean PSD on the SSR. Results indicated a possible optimum SSR in terms of obtaining smaller mean sizes and narrower PSDs, although elaborate experimentation would be necessary to prove such a claim.

Increasing batch scale resulted in an increased mean size and broader PSDs. In contrast, continuous processing allowed for 3 times the volume processed by the 1L batch scale in roughly the same time while maintaining the mean particle size obtained in the 200mL batch scale. Thus, the advantages of continuous processing in terms of reduction in process times, enhanced mixing performance and improved scalability were successfully realized.

A higher mean seed size with a broader PSD was found to result in a product with a smaller mean size and a narrower PSD. This appeared to be due to the interplay
between the mixing and the late onset of ‘significant secondary nucleation’ caused due by a lesser overall number of seed particles resulting from an increased seed size.

It was found that the $R^2$ value of fit between the PSD obtained through image analysis and the log-normal distribution obtained through regression of the PSD increased for enhanced mixing behavior. This description of the PSD was consistent with a ‘parent-daughter’ dynamic of cell populations observed in biological systems. Further, in the present study, even though there were no moving parts, secondary nucleation was the main source of nuclei and hence the impact mechanism for the secondary nucleation was not deemed likely. The results indicated that crystal breeding was a more likely mechanism for secondary nucleation although further experimentation would be necessary to establish such a claim.

**Acknowledgements**

The present investigation is supported by a Proof of Concept project (R3021CCE) funded by the InvestNI organization in Northern Ireland, UK. The authors would like to thank InvestNI for providing the funding to enable the present research.

**Supporting Information**

S1. Dimensions of the Fluidic Oscillator, S2. Particle Size Distributions for Effect of Residence Time Experiments, S3. Particle Size Distributions for Supersaturation

References


TOC Graphic

Seeded Saturated Solution

Coanda Fluidic Oscillator Unit(s)

Filtration & Drying

Anti-Solvent

Feasibility Evaluation / Effect of Operating Parameters
- Operating Mode (Continuous/Batch)
- Residence Time
- Fluidic Device
- Super Saturation
- Seed Size

Enhanced Mixing - Narrower PSDs - Smaller Size

Continuous Anti-Solvent Crystallisation Product

Batch Crystallisation Product