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On the effect of added impurity on crystal purity of urea in an oscillatory baffled crystallizer and a stirred tank crystallizer

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Abstract

Previous work has indicated that crystals produced in oscillatory baffled crystallisers (OBC) from a relatively ‘pure’ starting environment gave statistically higher purities than that in stirred tank crystallisers (STC) under comparable conditions. In this work, a known amount of biuret (the impurity) was added to the ‘pure’ urea system and the results show that the OBC still produced higher purity crystals than the STC, although these purity values were statistically lower than from the ‘pure’ environment in both vessels. By evaluating crystallisation rates of both urea and biuret, we noticed that these rates are higher in the STC than in the OBC, which would have led to small crystals in the former vessel. The CSD data however gave the opposite result where the CSD is wider with more, large crystals in the STC than in the OBC, in particular in the presence of added impurity. These larger crystals are likely formed due to agglomeration coupled with incorporation of impurity, which leads to a lower purity.

Keywords: Crystallization; Purity; Impurity; Cooling; Mixing; Oscillatory baffled crystallizers; Stirred tank crystallizers

Introduction

Crystallization is an important purification tool in pharmaceutical and chemical industries [1, 2], as any unwanted impurity can cause defect in product quality or side effects in patients [3, 4], consequently the production of high purity crystals is paramount. Cooling crystallization is one of the more popular forms of crystallization and involves lowering the solution temperature beyond its saturation point to induce nucleation [5]. Generally a decrease in crystal purity is attributed to either mother liquor entrapped between agglomerating single crystals or specific impurity being included in the growing crystals [6].

A stirred tank crystallizer (STC) is often used to carry out crystallizations in the pharmaceutical industry and generally consists of a large jacketed vessel fitted with an impeller to mix the contents. This is a well understood process with Regulatory approval and has advantages of optimized
productivity and flexibility of processing multiple drugs. The STC is however prone to poor mixing and heat transfer [7], depending on the type of impeller used, leading to problematic scale up and inconsistent crystal qualities. Efficient mixing and heat transfer leading to better temperature control are key parameters in cooling crystallisation and can be achieved in the oscillatory baffled crystallizer (OBC) [8-10] which has attracted increasing attention from the pharmaceutical industry. Previous investigations [11] have shown that higher purity crystals were obtained in the OBC under all comparable conditions. This was likely caused by the combination of a higher supersaturation level obtained in the STC with a lower temperature required to induce nucleation. This allowed less time for crystal growth and subsequently smaller single crystals that were more likely to agglomerate when mixing became poorer due to increased solid loading upon further cooling in the STC [12]. The aim of this work is to extend the previous research by investigating the effect of an impure starting environment on the final crystal purity at different cooling rates and mixing intensities.

Experimental Set-Up, Calibration and Procedures

Experimental system

The OBC consists of a glass column 76 mm in diameter and 1 L in volume, with a working volume of 0.5 L. Two stainless steel orifice baffles are connected by metal rods to form a baffle string; these are attached to a linear actuator above the OBC vessel. Different oscillation amplitudes and frequencies can be delivered by the actuator via a control box, therefore providing the oscillatory motion within the column. The outer diameter, orifice diameter and spacing of the baffles are 72 mm, 35 mm and 52 mm respectively, giving the overall surface area of the baffle string as 13320 mm². The temperature within the column was achieved by controlling the jacket temperature using a water bath (Grant Instruments GP 200/R2), thus enabling different linear cooling rates to be operated.

The STC is a jacketed glass vessel, 90 mm in diameter, with a total volume of 1 L and a working volume of 0.6 L. A stainless steel two-blade flat-paddle impeller, 60 mm in diameter, was used to generate mixing and was centrally aligned within the vessel. The impeller was attached to an overhead stirrer to control the rotation speeds. Four stainless steel wall-baffle inserts were added into the system to aid mixing. The total surface area of the impeller and wall baffles in contact with the solution is 3070 mm². Temperature control was identical to that used in the OBC. The schematic illustration of both STC and OBC is given in Figure 1.
To ensure comparable experimental conditions, the power density or dissipation rate was kept approximately equal. The determinations of power density are well documented for both the STC [13] and OBC [9]. The mixing conditions for each crystallizer are outlined in Table 1.

Table 1 – Mixing conditions and corresponding mixing intensities

**Experimental compound**

Urea was the model compound and its chemical structure is shown in Figure 2. This compound was selected as it is relatively safe, highly soluble in water, stable and has only one known polymorph under normal process conditions. Technical grade urea was sourced from VWR with an average initial purity of 95%.

**Figure 2 – Chemical structure of urea**

For the ‘impure’ tests, specific amounts of impurity (biuret with an average purity of 97 % from Acros Organics) were added into both vessels to investigate its effect on crystal purity. Biuret is a main condensation product of two urea molecules [14] and its structure (Figure 3) is similar to that of urea.

**Figure 3 – Chemical structure of biuret**

When urea crystallizes as a pure compound it forms long, needle-like crystals. This habit is distorted when impurity is present within the crystal [14], becoming a more cubic shape as the incorporation of biuret increases towards 5 wt. %. This change in habit can be used to verify whether any impurity is being incorporated into the product crystal.

**Procedure**

For each experimental run, a certain amount of technical grade urea was weighed using an electronic balance and was poured into the vessel using a funnel to minimise loss. To this the required volume of distilled water was added, as indicated by the previously confirmed solubility curve. The base amount of urea was kept the same in the all runs, however in the added impurity (AI) experiments specific amounts of biuret were mixed into the solutions to achieve the impurity level of 5 wt. % (5 % AI). The solution was then heated to 40 °C until all the solid had dissolved and was held at this temperature for one hour under the required mixing. The solution was then cooled at a given linear rate to a final temperature. Once the final temperature had been reached, the
solution temperature was held under mixing for a further 30 minutes to allow the crystals to grow. The solution conditions and components added to each system are shown in Table 2.

Table 2 – Components added to the systems and operating temperatures

From Table 2 it can be seen that the final temperature of crystallization was lowered in the impure system. This is related to the effect that the impurity has on the nucleation and crystal growth of the system [15, 16], as the presence of impurity has been shown to suppress growth by blocking the addition sites on some crystal surfaces [15]. This can lead to an increase in the induction time of the system and a reduction in the noted nucleation temperature. Prior to experiments, trials were undertaken in-house to understand the effect of the final temperature on the system at each impurity level. The effect of lowering the final temperature to 20 °C at the 0 % Al level was an increase in the overall yield with a minimal drop in purity, due to the increased amount of crystallized solids observed within each vessel. The downside of this is poorer mixing over time due to the excessive solids leading to more agglomeration and ultimately the slightly lower purity. In contrast to the case of 0 % Al, nucleation did not universally occur when cooling was stopped at 24 °C for the 5 % Al, e.g. it never occurred in the STC and it only took place at certain conditions in the OBC even then it did not always lead to crystal growth. This is related to the aforementioned effect of impurity on the nucleation and crystal growth of the system [16]. As a consequence of this, the final temperature was lowered to 20 °C for the 5 % Al system to ensure that crystallization had occurred in both vessels to a level which can be analysed.

Following completion of each experimental run, the crystallizer was dismantled with the flow in the jacket left on in order to maintain the final temperature. The slurry was then poured into a pre-warmed beaker and taken immediately to a special ‘temperature controlled box’. This box was built so that the temperature can precisely be controlled and maintained throughout the filtration and washing process, therefore minimising any additional crystallisation which may occur due to potential lower room temperature during these downstream separation processes. Within the box, the slurry was filtered using a Büchner filter attached to a vacuum pump and two washes of isopropanol (2 x 50 ml) were then applied to remove any remaining mother liquor from crystal surfaces. Isopropanol was selected as the wash liquor based on multiple washing trials carried out to establish the best filtration-washing medium and methodology that removes mother liquor without causing any further nucleation by means of anti-solvent crystallisation or possible dissolution of crystals in the wash liquor. In addition, isopropanol is relatively safe and has a low urea solubility [17] compared with other possible wash solvents. The samples were then transferred into a dish and dried in an oven overnight to give consistent drying conditions for all batches. Once dried, the solids were weighed to obtain the yields and then transferred into sample bottles before being analysed further.

*Calibration for purity measurement*
To quantify the purity of the crystals produced, off-line Fourier Transform Infra-Red (FTIR) spectroscopy with the Shimadzu Bench-top ATR-FTIR Prestige-21 was used. Prior to the analysis, a calibration curve was established by dissolving high purity urea (99.5% pure) in distilled water to form a series of solutions with known concentrations. A small amount of the sample was placed on the analysis plate of the SPECAC® module fitted into the FTIR and peak absorbance measurements were taken at the specific wave-number of the ‘urea’ peak, around 1460 cm$^{-1}$, This peak was the clearest indication of urea concentration in various solution and solid samples, and relates to the N-C-N asymmetric bond stretching of the urea molecule [18]. Following these measurements and using the in-built Shimadzu quantification package, the off-line calibration curve shown in Figure 4 (open squares) was produced.

Once the calibration curve has been established, each individual sample can be analysed. The procedure for determining purity for each run is as follows: a specific amount of dry sample was accurately weighed (to 4 decimal places) and recorded before the specific volume of distilled water was added. Following dissolution, 0.5 ml of the solution was placed on top of the diamond embedded in the off-line plate and the peak height registered. The corresponding urea concentration was then determined using the calibration curve. To ensure repeatability, two repeats for each sample were performed; with the plate and the diamond being thoroughly cleaned between each run. A background scan was also taken between runs to ensure that any residue present from previous samples was accounted for and did not affect the calculated concentration of the sample. The purity can then be evaluated by the ratio of the measured concentration from the sample divided by the theoretical concentration of the samples. The latter is calculated from the solid added into the sample, assuming that the initial solid collected from the experiment was 100% pure.

![Figure 4 – Off-line and on-line calibration curve of peak height vs. urea concentration](image)

*Calibration for solution concentration measurement*

An advantage of the off-line FTIR system is that it has a relatively short signal path length, minimizing the loss of IR signals which are consequently strong with little interference [19]. There are disadvantages however, one of these is that the sample plate is not temperature controlled and can only be operated at room temperature. This limits the range of concentrations which can be analysed, as higher concentrations need corresponding high temperatures to ensure that the entire solid added is dissolved and the reading is accurate, particularly when impurity is present within the system. The other main disadvantage of the off-line system is that in order to follow the concentration of the system during crystallization, samples would need to be removed from the vessel constantly and then analysed [2]. This could cause issues with the reliability of the data as the continued removal could affect the system, possibly causing nucleation of the supersaturated solution [20] or invalid results due to the variations of local room temperature as the measurement
is strongly temperature dependent [21, 22]. To overcome these limitations an in-situ ATR-FTIR probe was used.

To minimise potential errors [23], a second calibration curve must be produced under the new instrumental conditions. This has to account for several additional factors including the probe having a much longer path length, the higher concentration range used, any possible solution temperature effects [24] and high temperature signal drift [25]. Due to this longer path length the IR output is likely to be low compared to that of the off-line system, therefore an external MCT (mercury cadmium telluride) detector is used which has a much higher sensitivity level than the DLaTGS (deuterated L-alanine doped triglycine sulfate) detector used in the off-line system [26]. The calibration is carried out in a similar manner to the off-line system, and each sample is analysed using the on-line probe at various set temperatures. The on-line calibration curve shown in Figure 4 (filled squares) was then produced using MATLAB® and the partial least squares (PLS) function. Note that the angle and bend-radius of the FTIR probe can also have an effect on the signal obtained [27] and a standardisation procedure was performed by taking the raw data obtained from the peak trace and plotting it onto a Microsoft Excel® spreadsheet. By analysing the graph produced, any high temperature signal drift noted was removed from the raw data. The resulting curve was then normalised to the peak height corresponding to the actual recorded solution concentration. Once the initial concentration of the solution as the start point had been fixed, any alteration in signal intensity was applied to the remaining points of the peak trace. The calibration correlation was subsequently used to convert the peak traces to concentrations, from which concentration and supersaturation curves can be constructed.

**Experimental Results and Discussions**

The results from the added impurity work are analysed in two different ways: initially purity data with the presence of impurity are compared between the OBC and STC, this is to investigate whether the trends obtained in the 'pure' system are still valid in an impure starting environment. Secondly purity data with and without the addition of impurity are compared in each vessel to gain understanding of how the added impurity has affected the overall purity.

**Comparisons between vessels**

Before the effect of impurity can be examined it is important to present the baseline data without biuret, i.e. the 0 % Al system; this is tabulated in Table 3 for three cooling rates at a fixed mixing intensity and three different mixing intensities at a fixed cooling rate. Statistical analysis was performed for each condition using the non-parametric Kolmogorov-Smirnov Statistical test [28] which calculates a statistical probability value (P), giving an indication of whether the data pairs are similar. For data to be statistically different, the P value should be less than 0.1.
For the ‘pure’ system, the OBC produced crystals with a statistically higher purity than the STC at almost all investigated conditions. It is also noted in Table 3 that the crystal purity decreased in both vessels as the cooling rate increased. This was in line with previous work by Givand et. Al [29], who indicated that this purity drop was related to an increased rate of supersaturation generation causing more crystal inclusions [6]. Furthermore, the purity in Table 3 increased as the mixing intensity was increased, this is probably due to a decrease in the size of agglomerates [30] with the increased probability of crystal attrition at faster mixing.

Table 4 – Supersaturation level upon nucleation for the ‘pure’ system (0 % AI)

Analysis of the level of supersaturation at nucleation (Table 4) and the corresponding nucleation temperature (Table 5) has indicated that the combination of a higher supersaturation level and a lower nucleation temperature in the STC gave the crystals less time to grow. This consequently led to small crystals that were more likely to agglomerate when the increased amount of solids in the vessel resulted in poorer mixing [12]. The inclusion of mother liquor in the said agglomeration is the main mechanism for the purity differences.

Table 5 – Nucleation temperatures for the ‘pure’ system (0 % AI)

The same line of approach was adopted for the added impurity experiments with the purity data given in Table 6, supersaturation level at nucleation in Table 7 and the associated nucleation temperatures at Table 8.

Table 6 – Purity results for the ‘impure’ system (5 % AI)

Table 7 – Supersaturation level upon nucleation for the ‘impure’ system (5 % AI)

Table 8 – Nucleation temperatures for the ‘impure’ system (5 % AI)
The purity values in Table 6 still show higher final crystal purities in the OBC than in the STC at every condition, with similar trends for the supersaturation at nucleation, as well as the nucleation temperature. However, almost all the data pairs between the OBC and STC are statistically similar, indicating that the results evaluated in Tables 7 & 8 cannot explain the differences in purity noted in Table 6.

Comparison between impurity levels

For simplicity only one condition (a cooling rate of 0.75 °C/min and a mixing intensity of 750 W/m^3) is used for the comparison and is representative of all five conditions outlined in the previous section. It has been proposed that a faster urea crystallization rate is related to an increased amount of urea being crystallized with more small single crystals. Similarly an increased crystallization rate for the biuret is linked to more biuret leaving the solution and being incorporated into growing urea crystals. In order to establish the parameters responsible for the observed trends, crystallisation rates of urea and biuret were determined directly from the concentration profiles measured by FTIR. The crystallisation rate (combining both nucleation and growth for simplicity) is taken as the inverse rate of the decreasing solute concentration. Table 9 summarizes all aforementioned parameters with the standard error value and the corresponding statistical probability factor (P). It should be noted that due to trace amounts of biuret in the ‘pure’ urea, a crystallization rate for the biuret is obtained at the 0 % level.

From these results in Table 9, we see that the purity and the supersaturation level upon nucleation are statistically different between the two impurity levels. Furthermore, there are marked differences in the crystallization rates between the two impurity levels with much faster rate for the 5 % AI than for the ‘pure’ system. It is interesting that the crystallisation rates of both urea and biuret are faster in the STC than these in the OBC, suggesting smaller crystal sizes in the former than in the latter. The crystal size distributions (CSD) obtained from the Mastersizer in Figure 5 show that there are longer tails in the size distributions of the STC than the OBC; indicating that there are more larger crystals in this vessel than in the OBC, particularly at 5% Al. The mean sizes listed in Table 10 confirm the finding for both starting impurity levels. The larger sizes of crystals are most likely formed due to a number of possible mechanisms: the change of crystal habit due to the incorporation of biuret that inhibits crystal growth in certain phases while promoting other sides or the increased agglomeration that traps mother liquor containing impurity or the combination of both.

Table 9 – Results for both the ‘pure’ (0 % AI) and ‘impure’ system (5 % AI)

Furthermore, the CSDs in the OBC are narrower than that in the STC, particularly for 5% Al; this would indicate that there is increased crystal attrition due to more uniform mixing in the former
than in the latter, preventing some agglomeration from taking place and minimizing the activities of inclusion of mother liquor containing biuret.

Figure 5 – CSD for both ‘pure’ (0 % AI) and ‘impure’ (5 % AI) systems in OBC and STC

Table 10 – Mean crystal size and shape factors for OBC and STC at both impurity levels

Figure 6 – Microscopy images of crystals with 0 % AI and 5 % AI in both OBC and STC

The microscopic images of crystals obtained at both impurity levels in Figure 6 show that the images of the crystals in the OBC are similar in length between the 0 and 5 % level (Fig. 5 a & b), but much wider for crystals of the latter. This increase in crystal width is likely due to the increasing incorporation of the biuret, which decreases growth along certain faces causing the production of more block-like or cubic crystals [31]. Using the Malvern Morphologi G3, the aspect ratio of a crystal can be determined, quantifying the ratio between the width and the length of the crystals [32], where the value of 1 indicates a fully cubic crystal. The increased aspect ratio at 5% AI (Table 10) is in good agreement with the images presented in Figure 6.

Unlike the ‘block’ like crystals produced in the OBC, the crystal images of the STC at 5 % AI are more cubic in nature (Figure 6 (d)). These broader crystals are an indicator of a change in crystal habit due to more impurity incorporation at this condition. The larger aspect ratio in the STC in Table 10 also supports our discussion.

Conclusion

In our previous publication, we verified confidential industrial trials that crystal purities obtained in the OBC are higher than in the STC at comparable operational conditions in a “pure” starting environment. We demonstrated that the combination of a higher supersaturation level and a lower nucleation temperature in the STC was the possible reason for the measured outcomes, as these led to small crystals that are prone to agglomerate, which traps solvent or impurity in the crystal cluster. In this work, we extend our effort to an “impure” starting environment with the addition of a known amount of biuret. The results show that the purity of the crystals produced in the OBC is still higher than that in the STC, albeit not statistically. By evaluating the crystallisation (nucleation) rates (taking it as the inverse rate of the decreasing solute concentration at nucleation temperature) of both urea and biuret, we notice that these rates are higher in the STC than in the OBC, which would have led to small crystals in the former vessel. The CSD data however gave the opposite result where the CSD is wider with more and larger crystals in the STC than in the OBC, in particular in the presence of biuret. These larger crystals are likely due to either the change of crystal habits upon incorporation of biuret or the enhanced agglomeration that traps mother liquor containing impurity or both,
leading to lower purity of crystals. In addition, higher crystallisation rates are obtained for the impure system than for the pure system, this validates our methodology and experimental procedures.

Acknowledgement

The authors would like to thank EPSRC and the Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallization for their support and funding.

Nomenclature

\[ f = \text{Frequency of Oscillation [Hz]} \]
\[ N_s = \text{Agitator Speed [s}^{-1}\text{]} \]
\[ x_o = \text{Centre-to-Peak Oscillation Amplitude [m]} \]
\[ \omega = \text{Angular Frequency [rad s}^{-1}\text{]} \]
\[ \% \text{AI} = \text{Percentage Added Impurity} \]
\[ \text{SE} = \text{Standard Error} \]
\[ \text{SD} = \text{Standard Deviation} \]

References

Figures and Tables

Figure 1

![Diagram of an apparatus with labeled parts: Overhead Driver, Stirrer Guide, Stirred Tank Vessel, Impeller, Water Bath, Linear Motor, Moving Baffle OBC, and Baffles.]

Figure 2

![Chemical structure of a compound: H₂N=C=NH₂.]

Figure 3

![Chemical structure of a compound: H₂N=C=N=O=NH₂.]
Figure 4

\[
y = 0.3581x + 0.0467 \\
R^2 = 0.986
\]

\[
y = 0.4795x + 0.1115 \\
R^2 = 0.9914
\]

Figure 5

Peak Height (Abs) vs. Concentration (g ml\(^{-1}\))

Off-Line
On-Line

Volume Density (%) vs. Size Classes (μm)

0 % AI OBC
5 % AI OBC
-0 % Al STC
-5 % Al STC
Figure 6

![Images of crystals with labels: a) OBC 0 % Al, b) OBC 5 % Al, c) STC 0 % Al, d) STC 5 % Al.]

Table 1

<table>
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<th>Mixing Intensity (W m⁻³)</th>
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<th>STC</th>
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<td>Angular Frequency [ω] (Hz)</td>
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### Table 2

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<th>System</th>
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<th>Volume Distilled Water Added (ml)</th>
<th>Urea Concentration (g/ml)</th>
<th>Weight Biuret Added (g)</th>
<th>Added Impurity (wt. %)</th>
<th>Initial Temperature (°C)</th>
<th>Final Temperature (°C)</th>
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### Table 3

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### Table 4

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<td>STC</td>
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Table 5

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Table 6

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Table 7

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<td></td>
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</tr>
<tr>
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<td>750</td>
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</tr>
</tbody>
</table>

Table 8

<table>
<thead>
<tr>
<th>Nucleation Temperature + SE (°C)</th>
<th>Mixing Intensity [W m(^{-3})]</th>
<th>0.25</th>
<th>0.50</th>
<th>0.75</th>
</tr>
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<tbody>
<tr>
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<td>20</td>
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<tr>
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<td>170</td>
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<tr>
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<td>750</td>
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</tr>
</tbody>
</table>
Table 9

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Added Impurity Level</th>
<th>Average Purity Result [%]</th>
<th>Supersaturation Upon Nucleation</th>
<th>Average Crystallization Rate of Urea (x10^{-5}) [g ml^{-1}s^{-1}]</th>
<th>Average Biuret Crystallization Rate (x10^{-6}) [g ml^{-1}s^{-1}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBC</td>
<td>0 % Al</td>
<td>97.3 + 0.04</td>
<td>1.037 + 0.004</td>
<td>5.91 + 0.31</td>
<td>5.83 + 0.14</td>
</tr>
<tr>
<td></td>
<td>5 % Al</td>
<td>93.4 + 0.06</td>
<td>1.163 + 0.021</td>
<td>7.97 + 0.45</td>
<td>7.49 + 0.33</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.03</td>
<td>0.03</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>STC</td>
<td>0 % Al</td>
<td>96.5 + 0.04</td>
<td>1.062 + 0.006</td>
<td>6.12 + 0.45</td>
<td>4.80 + 1.30</td>
</tr>
<tr>
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<td>5 % Al</td>
<td>93.2 + 0.05</td>
<td>1.300 + 0.026</td>
<td>9.33 + 1.08</td>
<td>8.03 + 0.34</td>
</tr>
<tr>
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<td>P</td>
<td>0.03</td>
<td>0.03</td>
<td>0.06</td>
<td>0.32</td>
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</tbody>
</table>

Table 10

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Impurity Level</th>
<th>Mean Crystal Size [µm] + SE</th>
<th>Aspect Ratio + SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBC</td>
<td>0 % Al</td>
<td>151.29 + 1.05</td>
<td>0.59 + 0.16</td>
</tr>
<tr>
<td></td>
<td>5 % Al</td>
<td>332.25 + 6.77</td>
<td>0.61 + 0.15</td>
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<tr>
<td></td>
<td>P</td>
<td>0.06</td>
<td>-</td>
</tr>
<tr>
<td>STC</td>
<td>0 % Al</td>
<td>186.18 + 2.44</td>
<td>0.56 + 0.15</td>
</tr>
<tr>
<td></td>
<td>5 % Al</td>
<td>390.99 + 7.80</td>
<td>0.65 + 0.17</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.06</td>
<td>-</td>
</tr>
</tbody>
</table>

**Highlights**

- Established robust and reliable protocol for quantifying crystal purity.
- Demonstrated that OBC still higher purity crystals from impure starting environments.
- Crystallization rates (urea and biuret) are higher in the STC, leading to smaller crystals.
- CSD is wider in the STC than in the OBC likely due to aggregation.
- Shown higher crystallisation rates for impure systems, validating our procedures.