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Characterization of a Multistage Continuous MSMPR Crystallization Process assisted by Image Analysis of Elongated Crystals

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SUPPORTING INFORMATION

Effect of the number of measured crystals on the size distribution. The number of measurements conducted for image analysis was determined based on the variations in crystal size induced by a change in the crystallization conditions. Figure S1 shows the average crystal width (number based) plotted against the number of measurements for 5 experiments that exhibited different crystal size distributions. The average crystal width typically stabilizes after 200 measurements, after which the fluctuations in the average value (<5%) are significantly lower than the variation between experiments.
Figure S1. Variations in the number based mean crystal width over the number of measured crystals during image analysis of experiments E1, E3, E5, E7 and E9.

Note that the volumetric distribution is based on the higher end of the number based distribution, which contains a smaller amount of samples and thus it is more scattered. To study the accuracy of the volumetric distributions obtained with 700 crystals, the measurements for experiments E1 and E4 were conducted in duplicate with approximately 700 crystals per repetition, coming from different pictures of the same experiment. The mass-based mean sizes were considered to be the least reproducible value for these measurements, since they are heavily dependent on the higher end of the distribution. Thus, the measurement error was estimated from the reproducibility of these values. The obtained results are reported in Table S1.
**Table S1.** Results from the duplicate measurements of the mass-based mean crystal length and width for runs E1 and E4.

<table>
<thead>
<tr>
<th>Run</th>
<th>Dimension</th>
<th>Mass-based mean size, R1 (μm)</th>
<th>Mass-based mean size, R2 (μm)</th>
<th>Average ± SD (μm)</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>Width</td>
<td>27.6</td>
<td>27.0</td>
<td>27.3 ± 0.3</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Length</td>
<td>168</td>
<td>203</td>
<td>185 ± 18</td>
<td>19</td>
</tr>
<tr>
<td>E4</td>
<td>Width</td>
<td>21.4</td>
<td>24.1</td>
<td>22.8 ± 1.4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Length</td>
<td>162</td>
<td>177</td>
<td>169 ± 7</td>
<td>8.7</td>
</tr>
</tbody>
</table>

In this work, E4 and E5 presented the smallest crystal sizes, with a mass-based mean crystal width of 23 μm for both experiments. The largest mass-based crystal width, obtained at the second stage of E9, was 42 μm. Considering that the estimation error can be as high as 19 %, care should be taken when studying small variations in the crystal size distribution. Furthermore, it is important to induce significant variations in the process conditions during the study, and to compensate the uncertainties on the size distribution by using a large amount of experiments. The obtained variations during the MSMPR experiments were considered high enough to study an overall trend, although they may be limited for very similar experiments. This estimation error explains the observed differences between the observed and model predicted crystallization kinetics, and further supports the need for a reliable automated size measurement that increases the number of measurements by at least an order of magnitude.
**Steady state classification in the MSMPR crystallizers.** The fraction between the API concentration in the crystallization magma and that at the feed vessel was used to investigate the steady state classification. The values for each experiment are presented in Figure S2. From all the experiments in this work, only one of the MSMPR crystallizers presented a higher API concentration in the MSMPR than in the feed vessel. Considering that the observed deviations never exceeded 5%, and that the classification levels seem to be independent of the residence time and suspension density, it is reasonable to assume that the deviations come from the experimental error in sampling suspensions and that MSMPR crystallizer is operating close to ideal mixing.

![Figure S2](image.png)

**Figure S2.** Steady state classification values for each continuous crystallization experiment, expressed as the fraction between the API concentration in the magma and that in the feed. Experiments named as EX.Y correspond to the run EX on stage Y. The error bars correspond to the standard deviation from HPLC analysis accounting for error propagation.

**XRPD patterns for the MSMPR product.** The obtained XRD patterns from experiments E1, E3, E6 and E8 are reported in Figure S3. These experiments were selected to include the effects of supersaturation and temperature in the analysis. As it was expected for a system without previous polymorphism issues, the crystal structure remains unaltered in the MSMPR experiments. Furthermore, based on the background of the XRD patterns, the product shows a similar degree of crystallinity than that found in the batch product.
Figure S3. XRD patterns of the crystals obtained from full scale batch and lab scale MSMPR crystallization.