SUPPORTING INFORMATION

Continuous Crystallization with Gas Entrainment: Evaluating the Effect of a Moving Gas Phase in an MSMPR Crystallizer

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Effect of gas injection on solvent evaporation. Given that this study covers the effect of a flowing gas on MSMPR crystallization kinetics, the effects of solvent evaporation that could trigger a supersaturation increase must be mitigated to get reliable conclusions. This is not a concern when the gas is internally circulated from the freeboard, as the gas phase will be saturated and roughly at the same temperature than the magma. However, using an external gas feed requires quantitative knowledge on its effect on supersaturation.

Figure S1 shows the evolution of the solute concentration over 7 hours of gas dispersion in an undersaturated API-ethanol solution at 10 ˚C.

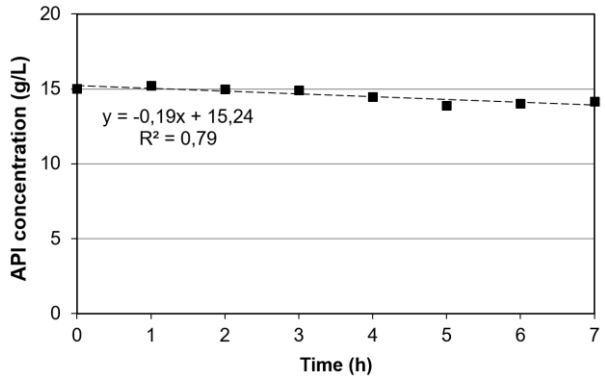

Figure S1. Evolution of the API concentration in the undersaturated solution over 7 hours of gassing. Temperature: 10 ˚C. Impeller speed: 800 rpm. Dispersion from gas entrainment and bottom injection (2.5 L/min, pre-saturated gas).

Over the seven hour long experiment, the API concentration dropped from 15 g/L to 14 g/L, corresponding to a condensation rate of 9 mL/h. Consequently, the ethanol concentration in nitrogen achieved in the gas traps (working at 20 ˚C) falls above the gas saturation point at 10 ˚C. The experiments in this work have a residence time between 45 min and 60 min. Considering the existing variations between experiments and the short residence times, variations in the mother liquor concentration induced by the gas phase are negligible in the MSMPR crystallizer.

Preliminary mixing and product removal studies. To investigate the effects of agitation intensity and foam formation in three-phase mixing, the homogeneous distribution of solids in the MSMPR crystallizer was investigated with an API suspension at equilibrium. A 2 L suspension was prepared with a total concentration of 100 g/L of Melitracen HCl in ethanol. 900 mL of the prepared suspension were poured in the crystallizer and the rest was saved for refilling the vessel between samples. The agitation speed was set to 800 rpm for the measurements. 4 mL HPLC samples were taken from the suspension at three different positions

in the crystallizer, being 5, 63, and 115 mm from the bottom of the vessel. The sampling was conducted in triplicates before the vessel was refilled to 900 mL. Then, gas dispersion was started with the maximum investigated hold-up (12%) and the sampling was repeated in triplicates. To validate the accuracy of the off-line FBRM sampling, the chord length distribution was measured in-line from the top of the crystallizer and from 45 mL off-line samples taken at the three different positions (top, between the two impellers, and bottom). The vessel was refilled to 900 mL before each sample. The obtained results, summarized in Table S1, demonstrate that gas dispersion has no significant impact on the crystal concentration or the size distribution in the crystallizer.

Table S1. API concentrations and square weighted mean chord lengths for the samples taken at different positions in the MSMPR crystallizer. The liquid level had a total approximated height of 120 mm.

Sampling height (mm)	C_{API} (g/L) – No gas	C_{API} (g/L) – 12% hold-up	FBRM Sqr wt mean (μm) – No gas	FBRM Sqr wt mean (μm) – 12% hold-up
5	100.3 ± 1.9	103.8 ± 1.6	44.5 (off-line)	44.3 (off-line)
63	100.6 ± 0.4	99.6 ± 2.5	42.9 (off-line)	44.8 (off-line)
115	102.6 ± 2.3	99.7 ± 2.8	43.2 (off-line) 44.0 (in-line)	43.8 (off-line)

Measured steady state classification in the MSMPR crystallizer. The steady state classification in the MSMPR crystallizer was studied at the end of each experiment by taking three magma samples at different positions in the crystallizer. The classification level was studied from the fraction of API concentration between the MSMPR crystallizer and the dissolver. Results are provided in Figure S2.

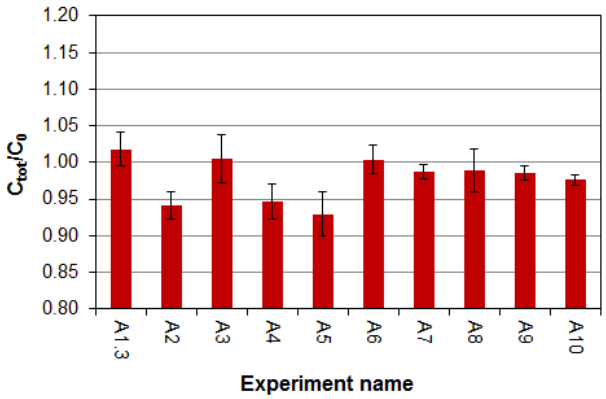

Figure S2. Steady state classification values for each continuous crystallization experiment, expressed as the fraction between the API concentration in the magma and that in the dissolver. The error bars correspond to the standard deviation from HPLC analysis accounting for error propagation.

None of the experiments presented a significant excess in the API concentration at the crystallizer over that at the feed vessel. On the contrary, some of the experiments presented a lower API concentration in the crystallization magma (up to 7%). These results do not show a particular trend, but share similar values with our observations at a smaller scale and are likely related to the accuracy of the sampling method. When a suspension is being sampled, classification of the solid phase can occur during sampling leading to a small reduction in the measured API concentration. As most of the experiments show deviations lower than 2%, it is reasonable to assume that there is no significant classification in the steady state crystallizer.

Unweighted chord length distributions. The unweighted steady state chord length distributions collected during the different experiments are reported in Figure S3, Figure S4 and Figure S5. These correspond to the square weighted measurements reported in the manuscript as Figure 4, Figure 10, and Figure 12, respectively.

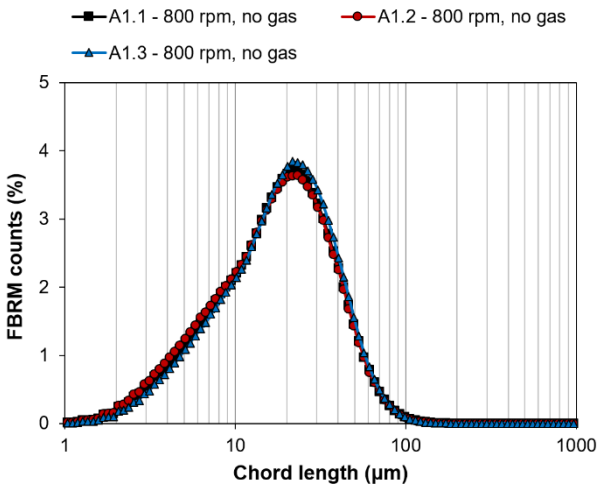

Figure S3. Comparison between the unweighted steady state chord length distributions on three repetitions at the same conditions. These distributions are the average values over four consecutive residence times at steady state.

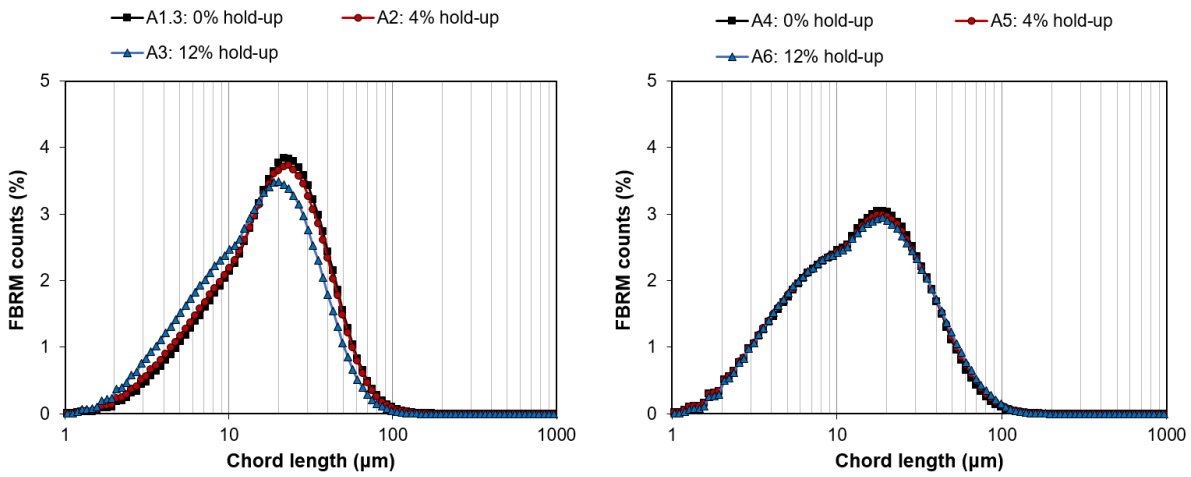

Figure S4. Effect of gas hold-up on the unweighted steady state chord length distribution. Left: Experiments at high suspension densities (A1-3). Right: Experiments at low suspension densities (A4-6).

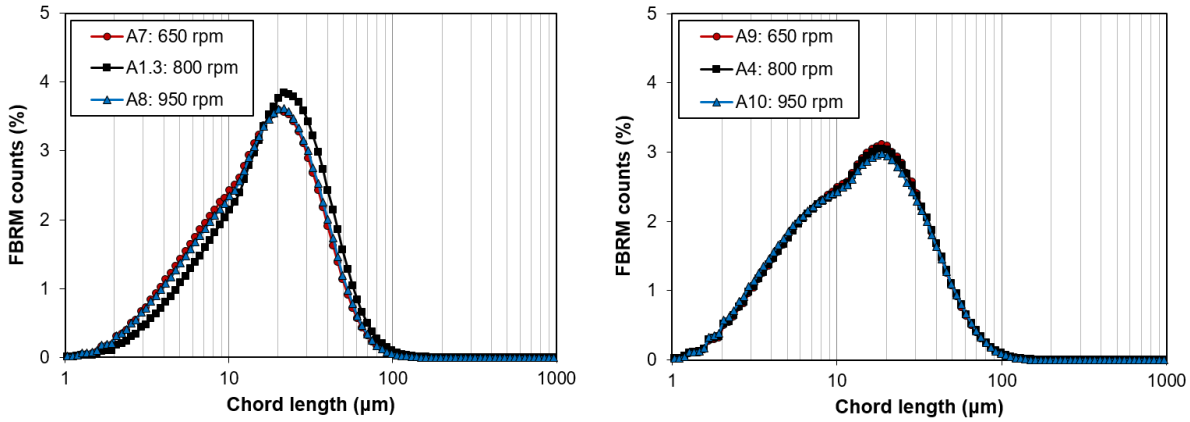

Figure S5. Effect of impeller speed on the unweighted steady state chord length distribution. Left: Experiments at high suspension densities (A1.3, A7, A8). Right: Experiments at low suspension densities (A4, A9, A10).

Detection of crystal breakage in the experiments with variable mixing. To study the reason behind the crystal size distribution variations in experiments A7, A1.3 and A8, optical microscopy pictures showing the 2D projection of the steady state magma were manually analyzed. The analysis was conducted for 700 crystals using the image processing software ImageJ (ver. 1.6.0). The resulting crystal shape distributions, reported in Figure S6, show no significant variation in the crystal shape.

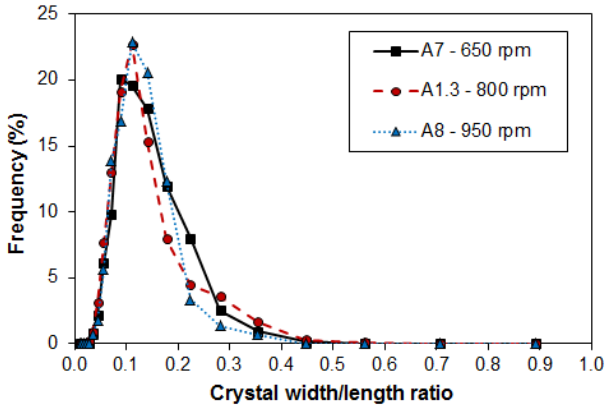

Figure S6. Steady state crystal shape distribution for experiments A7, A1.3 and A8, obtained from the 2D projection of the crystallization magma.