Electronic Supplementary Material (ESI) for CrystEngComm.


## Supplementary information

### A: Error analysis of CSDs

#### I) One image analyzed two times

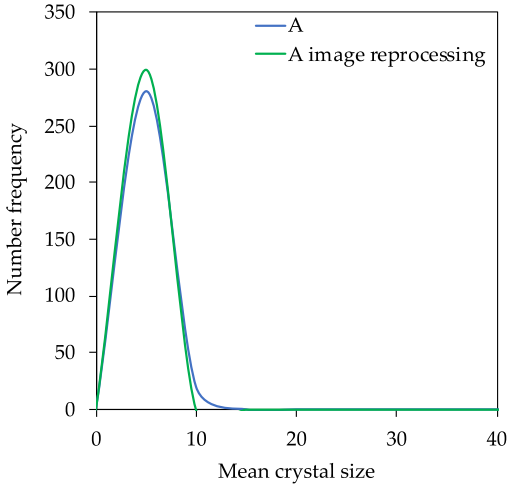



**Figure A.1.** CSD for the product obtained from the unseeded controlled experiment in which 99.95% v/v ethanol was added at 0.01 mL/s using 'top feed' mode and magnetic stirrer. The image from experiment A was reprocessed on Image J® (green curve). The maximum absolute difference in number frequency from the mean is ±10.

#### II) One image in which different number of crystals were analyzed

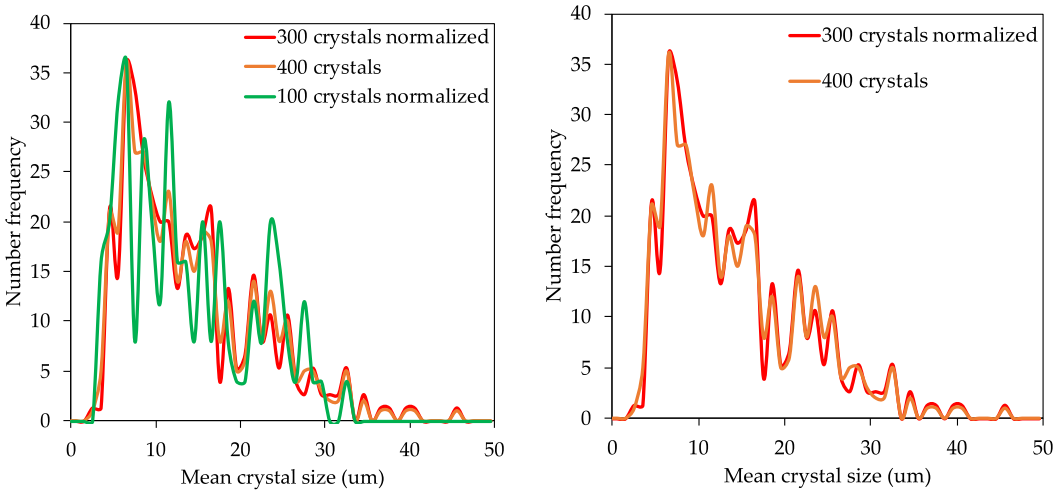



**Figure A.2.** CSDs for the product obtained from the unseeded controlled experiment in which 70% v/v ethanol was added at 0.01 mL/s using 'top feed' mode and magnetic stirrer. Histograms were plotted with different number of crystals and all curves normalized to 400 crystals for comparison. It is noted that a sample of 100 was not quite representative, but the CSDs plotted with 300 and 400 crystals are superimposed on one another. For this reason, it was determined that a sample of 300 crystals is a representative sample size.

In Figure A.2, the maximum absolute difference in number frequency from the

mean of all three datasets for the CSDs with 100, 300 and 400 crystals is ±14.8, ±10.6 and ±4.2, respectively. The maximum absolute difference in number frequency from the mean of two datasets for the CSDs with 300 and 400 crystals is ±3.2 showing improved reproducibility for a larger sample population.

III) **Image analysis of the product from either experimental repeats or analytical repeats.**

In the second graph, the product sample from experimental repeat B was reanalyzed by SEM and the new micrograph was re-processed on Image J®.

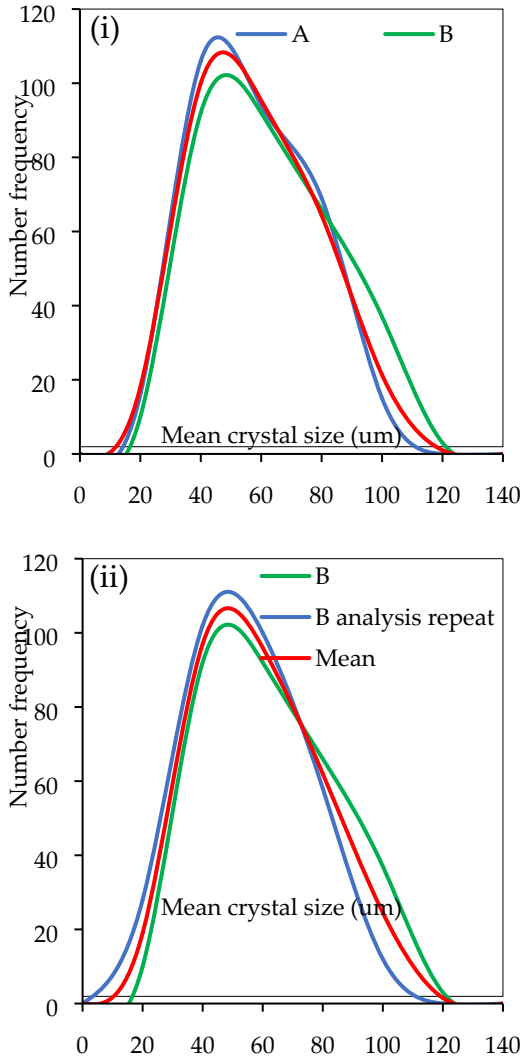



**Figure A.3.** CSDs for the product obtained from the unseeded controlled experiment in which 60% v/v ethanol was fed at 0.01 mL/s using 'top feed' mode and overhead stirrer.

The maximum absolute difference in number frequency from the mean in Figure A.3 (i) is ±11.0 while that in Figure A.3 (ii) is ±12.5.

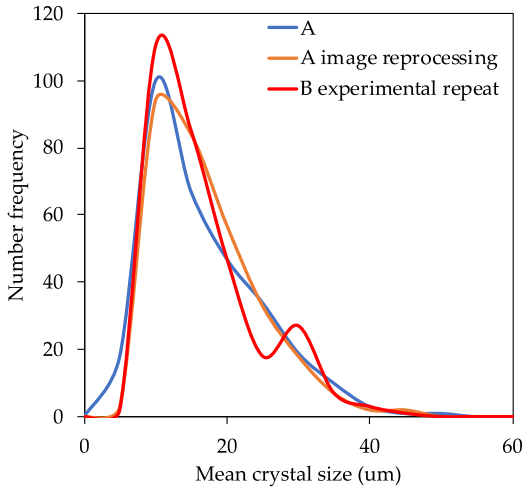



**Figure A.4.** CSDs for the product obtained from the unseeded controlled experiment in which 70% v/v ethanol was fed at 0.01 mL/s using 'top feed' mode and magnetic stirrer. The image from experiment A was reprocessed on Image J® (orange curve) and the red curve is for the product from the experimental repeat.

The maximum absolute difference in number frequency from the mean of all three datasets for the CSDs labelled A, A image reprocessing and B experimental repeat is ±11.7, ±7.3 and ±10.3, respectively.

**B: CSD characteristics**

**Table B.1.** CSD characteristics for all CSDs shown in Figures 1 – 5. Min – minimum, max – maximum, std – standard deviation. Crystal sizes are given in μm.

| | Experiment | Min | Max | D10 | D50 | D90 | Mode | Mean | Std |
|---|---|---|---|---|---|---|---|---|---|
| **Fig 1A** | [1]UC 99.95%E Ft Sm | 0.32 | 1.97 | 0.54 | 0.93 | 1.49 | 0.95 | 0.97 | 0.36 |
| | [9]C0.05 99.95%E Ft Sm | 0.62 | 5.24 | 0.90 | 1.59 | 3.05 | 1.22 | 1.82 | 0.88 |
| | [10]C0.01 99.95%E Ft Sm | 0.43 | 9.41 | 0.89 | 1.59 | 4.49 | 1.05 | 2.18 | 1.54 |
| | [8]C0.005 99.95%E Ft Sm | 0.92 | 6.82 | 1.23 | 2.10 | 3.86 | 2.00 | 2.38 | 1.07 |
| | [7]C0.001 99.95%E Ft Sm | 1.03 | 11.68 | 1.82 | 2.70 | 5.03 | 2.28 | 3.18 | 1.57 |
| | | | | | | | | | |
| **Fig 2A & 2B** | [1]UC 99.95%E Ft Sm | 0.32 | 1.97 | 0.54 | 0.93 | 1.49 | 0.95 | 0.97 | 0.36 |
| | [4]UC 99.95%E Ft So | 0.71 | 4.08 | 0.97 | 1.29 | 1.84 | 0.95 | 1.38 | 0.42 |
| | [10]C0.01 99.95%E Ft Sm | 0.43 | 9.41 | 0.89 | 1.59 | 4.49 | 1.05 | 2.18 | 1.54 |
| | [11]C0.01 70%E Ft Sm | 3.88 | 44.23 | 6.87 | 12.29 | 25.53 | 8.37 | 14.38 | 7.45 |
| | [14]C0.01 60%E Ft Sm | 5.31 | 68.73 | 8.27 | 16.77 | 35.22 | 8.94 | 19.69 | 11.31 |
| | | | | | | | | | |
| **Fig 2C** | [3]UC 60%E Ft Sm | 1.66 | 38.60 | 2.68 | 7.27 | 16.63 | 2.78 | 8.80 | 6.15 |
| | [6]UC 60%E Ft So | 1.61 | 30.72 | 3.07 | 6.94 | 15.76 | 3.58 | 8.41 | 5.41 |
| | [2]UC 70%E Ft Sm | 1.43 | 31.49 | 2.43 | 6.19 | 15.97 | 3.65 | 7.91 | 5.71 |
| | [5]UC 70%E Ft So | 1.03 | 23.40 | 2.19 | 5.64 | 12.88 | 1.72 | 6.62 | 4.29 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Fig 3** | [14]C0.01 60%E Ft Sm | 5.31 | 68.73 | 8.27 | 16.77 | 35.22 | 8.94 | 19.69 | 11.31 |
| | [15]C0.01 60%E Fb Sm | 3.84 | 78.43 | 9.69 | 20.24 | 37.88 | 19.45 | 22.56 | 11.76 |
| | [16]C0.01 60%E Ft So | 11.91 | 98.67 | 24.05 | 45.82 | 76.41 | 27.87 | 48.40 | 19.77 |
| | [17]C0.01 60%E Fb So | 17.88 | 206.50 | 37.66 | 75.85 | 140.00 | 77.15 | 82.82 | 39.70 |
| | | | | | | | | | |
| **Fig 4A** | Seeds | 5.95 | 35.02 | 9.34 | 15.04 | 21.76 | 6.83 | 15.51 | 5.20 |
| | [16]C0.01 60%E Ft So (Control) | 11.91 | 98.67 | 24.05 | 45.82 | 76.41 | 27.87 | 48.40 | 19.77 |
| | [22]C0.01 60%E Ft So 5%S | 11.98 | 87.18 | 21.93 | 42.68 | 67.35 | 49.49 | 44.00 | 16.72 |
| **Fig 4B** | Seeds | 5.95 | 35.02 | 9.34 | 15.04 | 21.76 | 6.83 | 15.51 | 5.20 |
| | [12]C0.01 70%E Ft So (Control) | 11.98 | 95.33 | 20.30 | 36.07 | 57.63 | 20.18 | 37.82 | 14.03 |
| | [21]C0.01 70%E Ft So 5%S | 13.06 | 77.43 | 19.11 | 32.47 | 56.64 | 24.57 | 35.45 | 14.04 |
| | [24]C0.01 70%E Fb So 5%S | 17.51 | 121.41 | 27.04 | 51.79 | 84.07 | 43.15 | 54.28 | 21.85 |
| **Fig 4C** | Seeds | 5.95 | 35.02 | 9.34 | 15.04 | 21.76 | 6.83 | 15.51 | 5.20 |
| | [13]C0.01 70%E Fb So (Control) | 12.17 | 108.80 | 21.76 | 53.60 | 81.70 | 27.67 | 52.68 | 22.26 |
| | [27]C0.01 70%E Fb So 50%S | 10.76 | 72.42 | 18.55 | 30.99 | 45.02 | 29.84 | 31.29 | 10.37 |
| | [26]C0.01 70%E Fb So 20%S | 13.85 | 81.27 | 21.75 | 38.19 | 56.99 | 25.06 | 39.14 | 13.39 |
| | [25]C0.01 70%E Fb So 10%S | 11.95 | 92.53 | 23.51 | 45.51 | 68.67 | 48.68 | 46.23 | 17.16 |
| | [24]C0.01 70%E Fb So 5%S | 17.51 | 121.41 | 27.04 | 51.79 | 84.07 | 43.15 | 54.28 | 21.85 |
| | | | | | | | | | |
| **Fig 5A** | [28]C0.01 60%E1 Fb So | 0.63 | 8.93 | 1.11 | 2.04 | 4.43 | 1.55 | 2.50 | 1.48 |
| | [29]C0.01 60%E2 Fb So | 1.91 | 78.34 | 3.27 | 4.94 | 15.46 | 3.70 | 7.66 | 9.23 |
| | [30]C0.01 60%E4 Fb So | 20.97 | 202.63 | 35.65 | 63.43 | 115.40 | 48.06 | 70.26 | 31.68 |
| | [17]C0.01 60%E Fb So | 17.88 | 206.50 | 37.66 | 75.85 | 140.00 | 77.15 | 82.82 | 39.70 |

## C: CSDs for the product obtained as the ethanol concentration was reduced at 5% seed loading

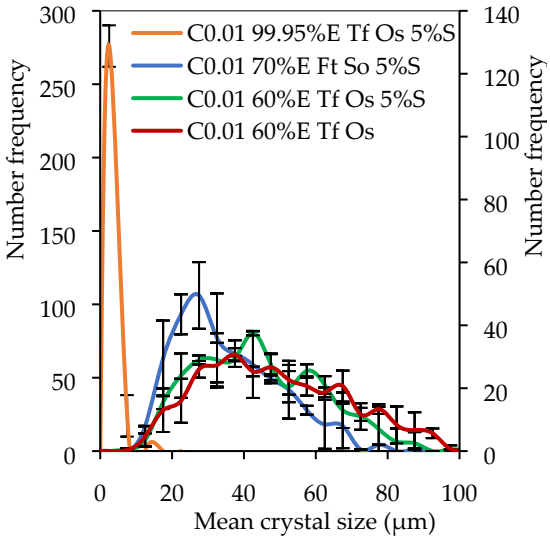



**Figure C.1.** CSDs for the product obtained from the seeded controlled experiments in which 99.95%, 70% and 60% v/v ethanol was fed at 0.01 mL/s using 'top feed' mode and overhead stirrer. The blue, green and maroon curves are read on the secondary axis.

**D: Comparison between CSDs of the product obtained from controlled experiments.**

The black profile is for the product obtained from two-stage antisolvent feeding regime experiments where the intermediate ethanol concentration was 1 mol/L and 'bottom feed' mode was used. The red profile is for the product obtained from the controlled experiment using 99.95% v/v ethanol and 'top feed' mode.

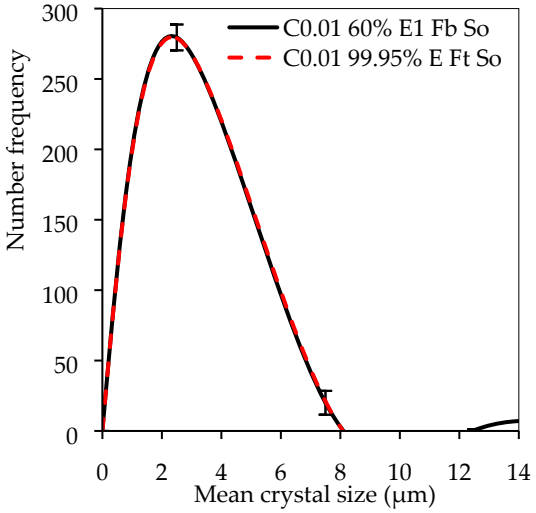
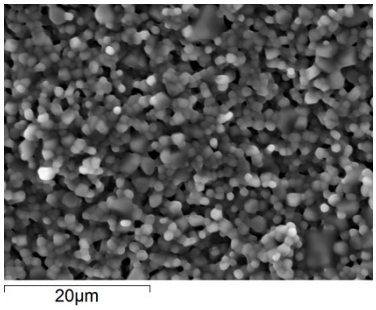


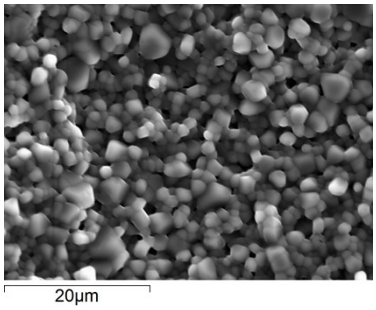

**Figure D.1.** CSDs for the product obtained from some unseeded controlled experiments using 1-stage and 2-stage feeding regimes, different feeding modes, different ethanol concentration and stirring mechanisms.

**E: Reproducibility of crystal morphology for identical experimental repeats.**

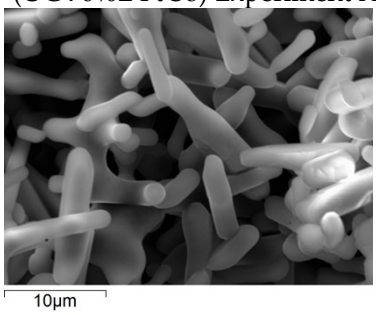
[4](UC 99.95%E Ft So) Experiment A [4](UC 99.95%E Ft So) Experiment B



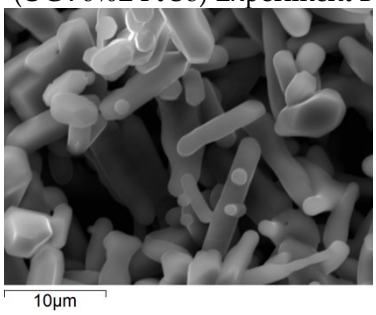

[5](UC 70%E Ft So) Experiment A



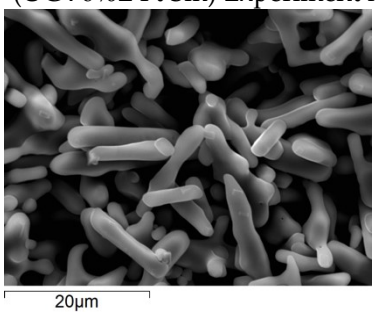

[5](UC 70%E Ft So) Experiment B



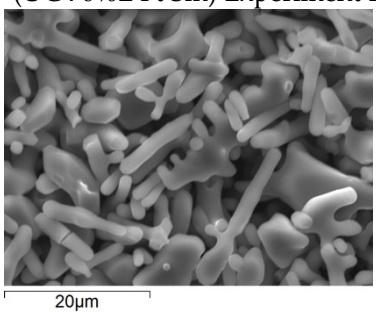

[2](UC 70%E Ft Sm) Experiment A



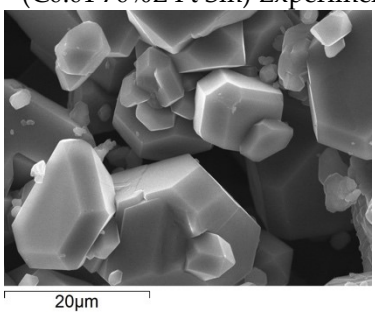

[2](UC 70%E Ft Sm) Experiment B



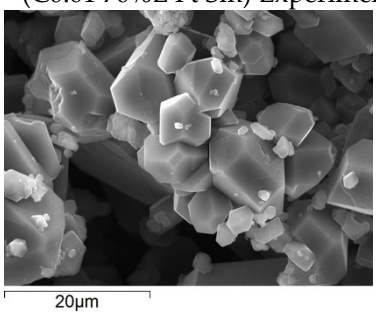

[11](C0.01 70%E Ft Sm) Experiment A



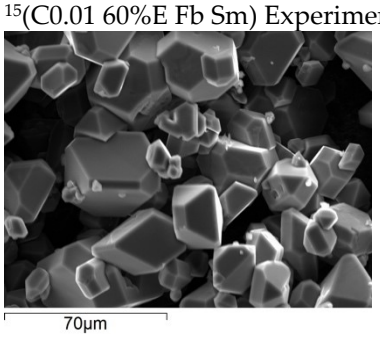

[11](C0.01 70%E Ft Sm) Experiment B



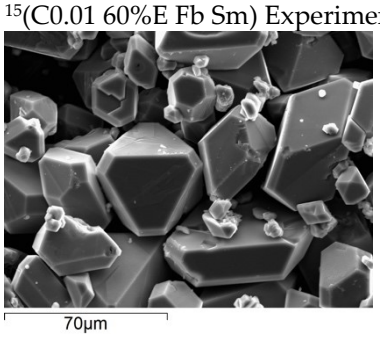

[15](C0.01 60%E Fb Sm) Experiment A



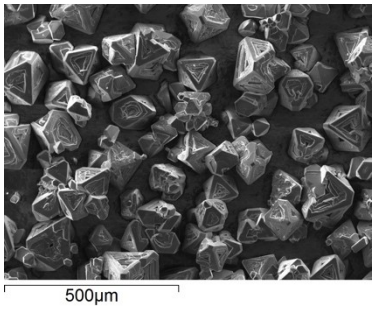

[15](C0.01 60%E Fb Sm) Experiment B



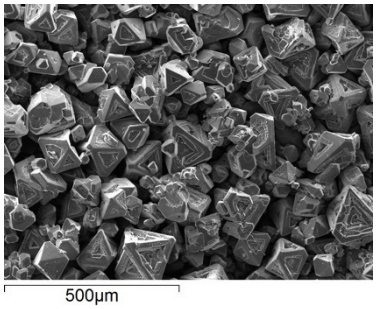

[17](C0.01 60%E Fb So) Experiment A



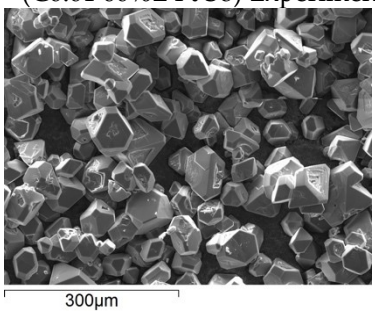

[17](C0.01 60%E Fb So) Experiment B



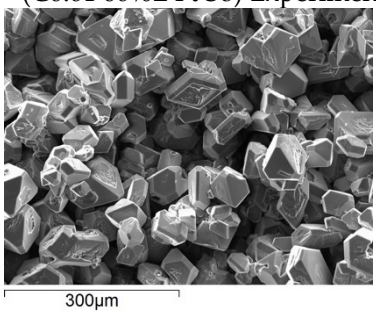

[16](C0.01 60%E Ft So) Experiment A



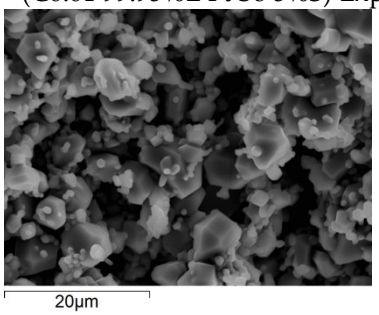

[16](C0.01 60%E Ft So) Experiment B




[20](C0.01 99.95%E Ft So 5%S) Experiment A




[20](C0.01 99.95%E Ft So 5%S) Experiment B



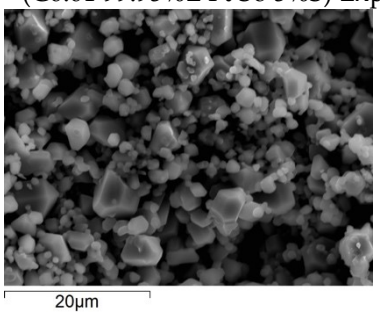
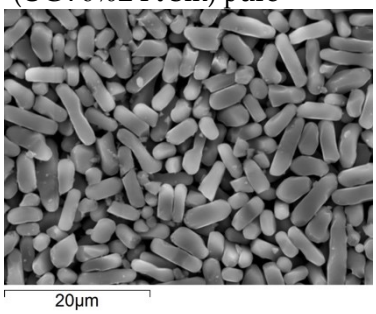




**Figure E.1.** Morphology of crystals obtained from identical experimental repeats. Note the differences in scale bars. The superscript numbers denote the type of experiment as designated in Table 3.

**F: Crystal morphology for the product obtained from the purer Sc containing $NH_4F$ solution ([$NH_4F$] = 3 mol/L) in uncontrolled experiments using 60 or 70% v/v ethanol.**

[2](UC 70%E Ft Sm) pure




C [3](UC 60%E Ft Sm) Pure

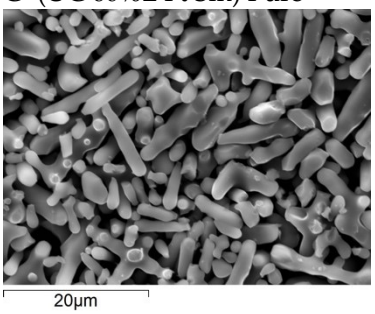



**Figure F.1.** Morphology of crystals obtained from purer solutions with lower levels of inorganic impurities. The superscript numbers denote the type of experiment as designated in Table 3.

**G: Crystal morphology for the product obtained from seeded experiments represented by Figure 4.**

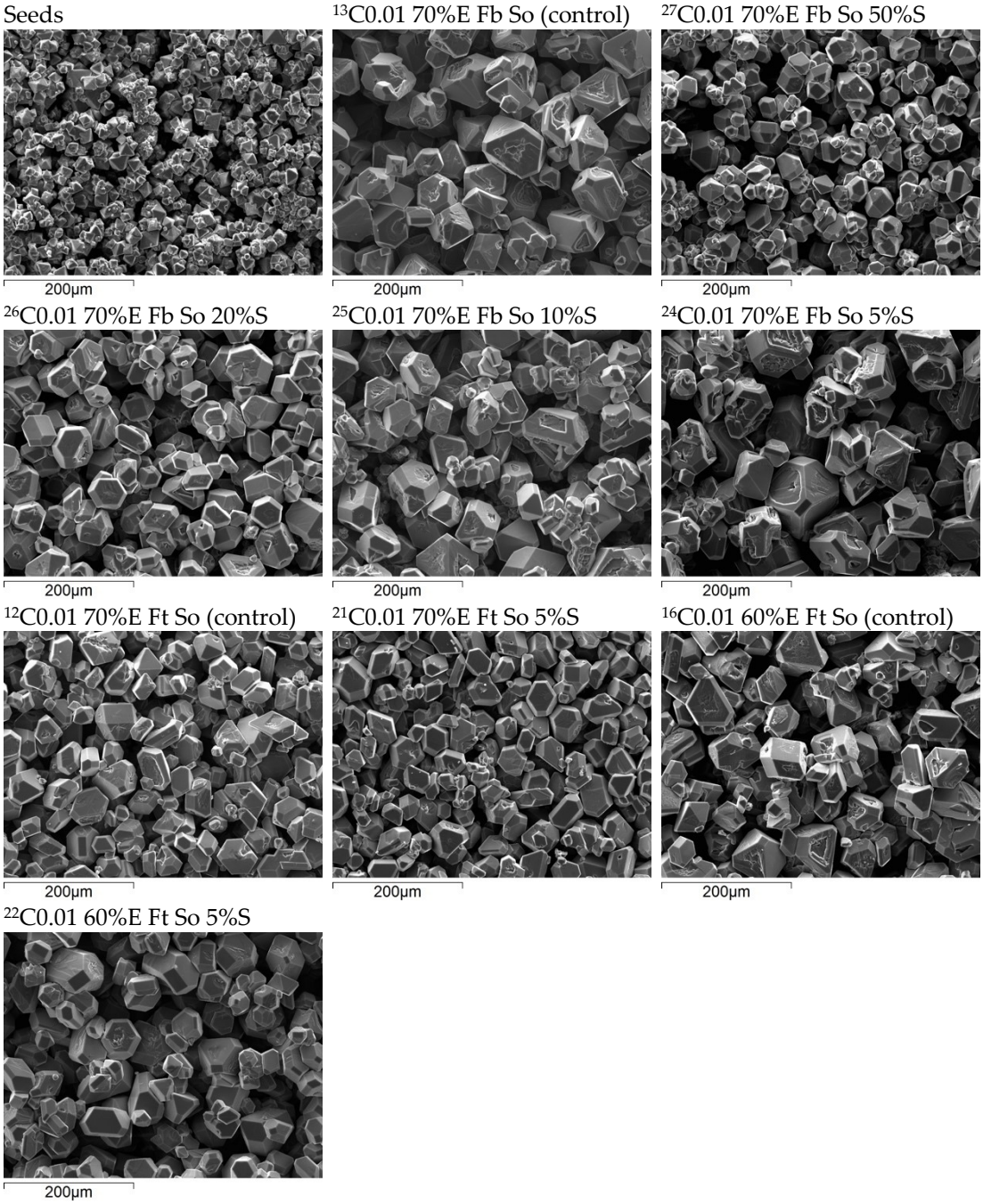



**Figure G.1.** Morphology of crystals obtained from seeded experiments. The superscript numbers denote the type of experiment as designated in Table 3.

## H. Equations used for comparison of agitators

Power input ($P$): $P = N_p \rho_s S^3 d^5$

where, $N_p$ is the power number, $\rho_s$ is the density of the suspension, $S$ is the agitation rate and $d$ is the impeller diameter.

Reynold's number ($Re$): $Re = \frac{S d^2 \rho_s}{\eta_s}$ where, $\eta_s$ is the dynamic viscosity of the suspension.

Density of suspension: $\rho_s = f\rho_c + (1-f)\rho_l$
where, f is the fraction of particles in the suspension taken as 40% wt. as an arbitrary value, $\rho_c$ is the density of particles and $\rho_l$ is the density of the liquid.

Density of crystals was determined experimentally to be 1.5626 g $cm^{-3}$.

Viscosity of suspension: $\eta_s = \eta_0(1-f)^{-2.5}$
where, $\eta_0$ is the viscosity of the aqueous phase and $f$ is the fraction of particles in the suspension.

Power number is estimated using the correlation of Nagata et al. for unbaffled conditions.

$$N_p = \frac{C_1}{Re} + \left[C_2\left(\frac{10^3 + 1.2Re^{0.66}}{10^3 + 3.2Re^{0.66}}\right)^{C_3} \times \left(\frac{h}{D}\right)^{\left(0.35 + \frac{b}{D}\right)} \times (\sin\theta)^{1.2}\right]$$

where, h is the height of the liquid level, D is the diameter of the vessel, b is the width of the impeller blade, θ is the angle between the agitator blade surface and the horizontal surface, $C_1$, $C_2$ and $C_3$ are parameters related to system geometry.

$$C_1 = 14 + \left(\frac{b}{D}\right)\left[670\left(\frac{d}{D} - 0.6\right)^2 + 185\right]$$

$$C_2 = 10^{\left[1.3 - 4\left(b/D - 0.5\right)^2 - 1.14\left(d/D\right)\right]}$$

$$C_3 = 1.1 + 4\left(\frac{b}{D}\right) - 2.5\left(\frac{d}{D} - 0.5\right)^2 - 7\left(\frac{b}{D}\right)^4$$

## I. Ethanol concentration in g/g solution at 8mol/L solution

**Table I.1.** Relative quantities of strip liquor and ethanol mixed.

| Antisolvent concentration (% v/v) | SL (mL) | SL (g) | AS (mL) | EtOH (mL) | EtOH (g) | g EtOH / g solution | mol EtOH / L solution |
|---|---|---|---|---|---|---|---|
| 60 | 19.20 | 20.00 | 67.90 | 40.74 | 32.05 | 0.40 | 8.00 |
| 70 | 19.20 | 20.00 | 38.67 | 27.07 | 21.30 | 0.40 | 8.00 |
| 99.95 | 19.20 | 20.00 | 16.88 | 16.88 | 13.28 | 0.40 | 8.00 |

## J. Illustration of experimental set-up for controlled experiments

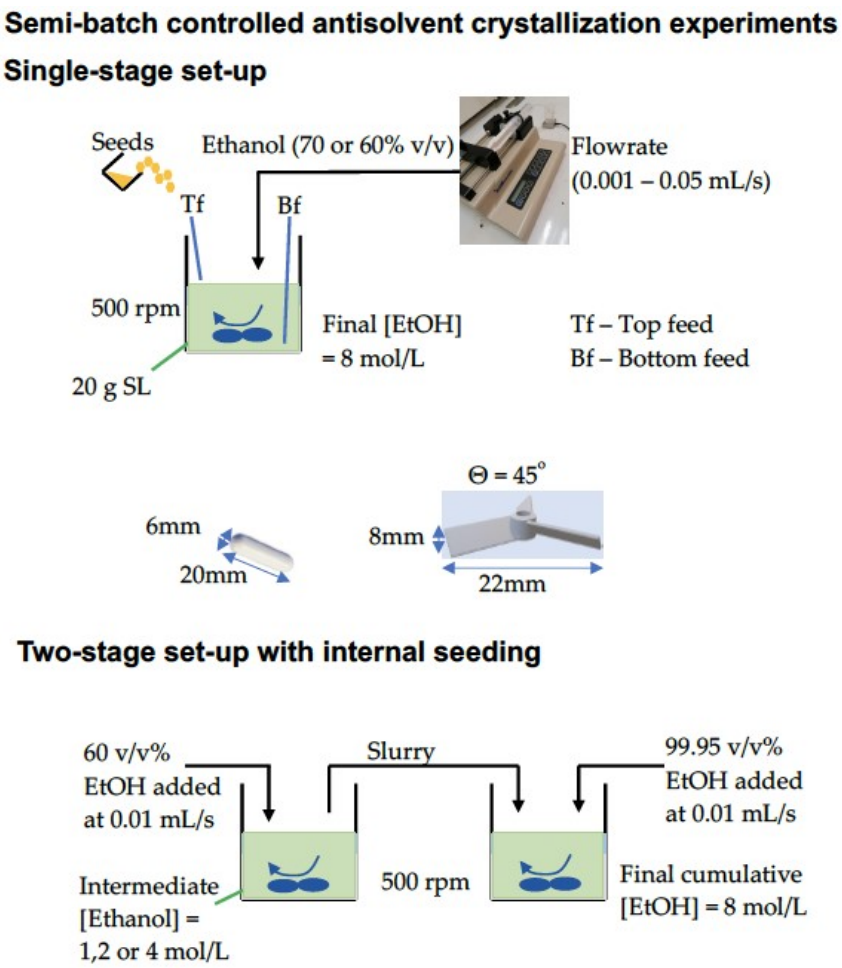



**Figure J.1.** Illustration of experimental set-up for controlled experiments.