Stereoscopic Imaging of Crystal Systems Exhibiting Polymorph Dictated Habit Variance

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Background

Tri-segmented flow (Fig 1) can be used to reduce blockages and enable rapid screening of crystallisation conditions in flow:

- creating a reproducible environment that prevents solution contact with a solid interface during crystallisation
- Improving sustainability through waste minimisation and reagent recovery

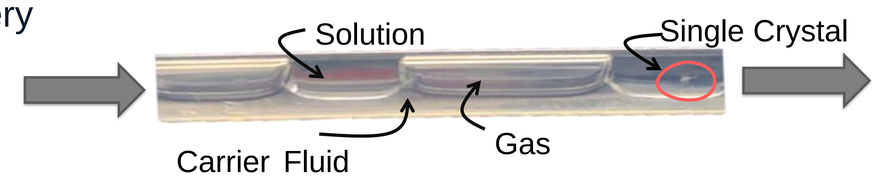

Figure 1. Diagram of a crystal present within a tri segmented flow regime. Diagram shows supersaturated solution slugs separated by air bubbles and coated in a carrier fluid to prevent contact with the internal walls of the FEP tubing.

Inline stereoscopic imaging[1] from orthogonally arranged cameras can accurately assess influence of process variables on attributes of Active Pharmaceutical Ingredients (APIs).

Method

Cooling, seeded crystallisation of Carbamazepine (CBZ), an anticonvulsant. Forms II (metastable) and III (stable) exhibit distinct habits (Fig 2) identifiable through stereoscopic imaging[2].

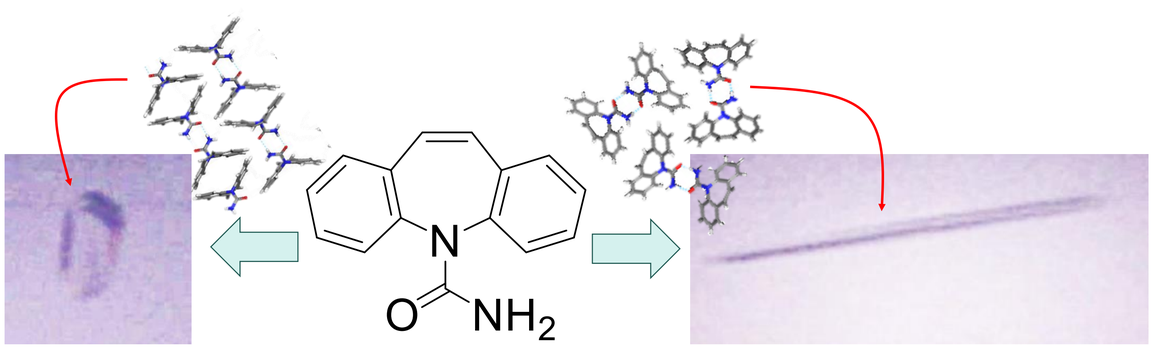

Figure 2. Habit of CBZ Form II (right) and Form III (left) represented in flow

Form II Unseeded Cooling Crystallisation: Varying nucleation promotor temp and solution concentration, imaged at analysis point A (Fig 3).

Form III Post Nucleation Seeded Crystallisation: Seeds added to CBZ II stream at analysis point A. Wt% of seeds and solution concentration varied to study interaction between polymorphs at analysis point B (Fig 3)

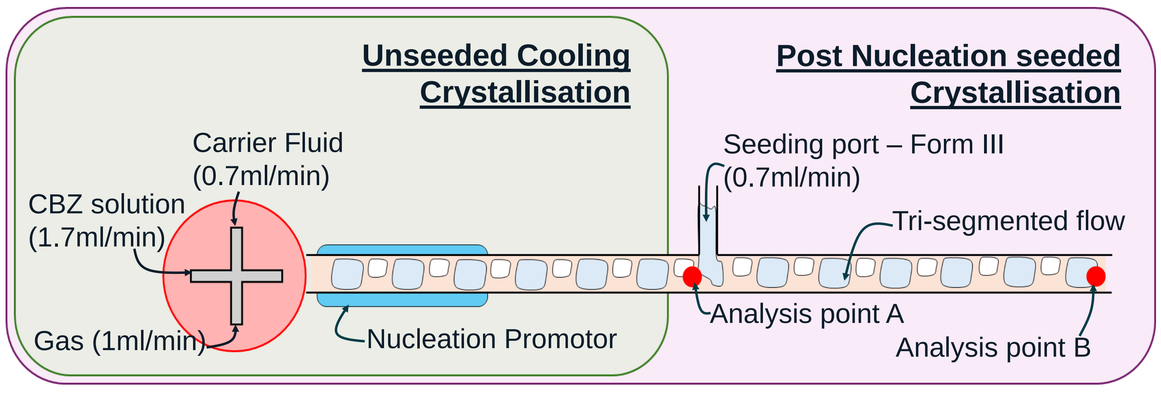

Figure 3. Process schematic showing the flow setup and conditions required for both the unseeded cooling crystallisation runs and the post nucleation seeded crystallisation runs

Results

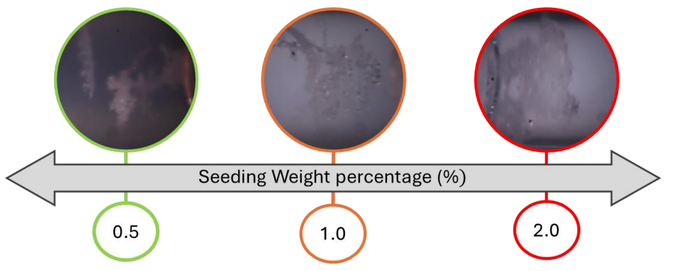

Figure 4. General trends observed during post nucleation seeded crystallisation (solution concentration 54g/l)

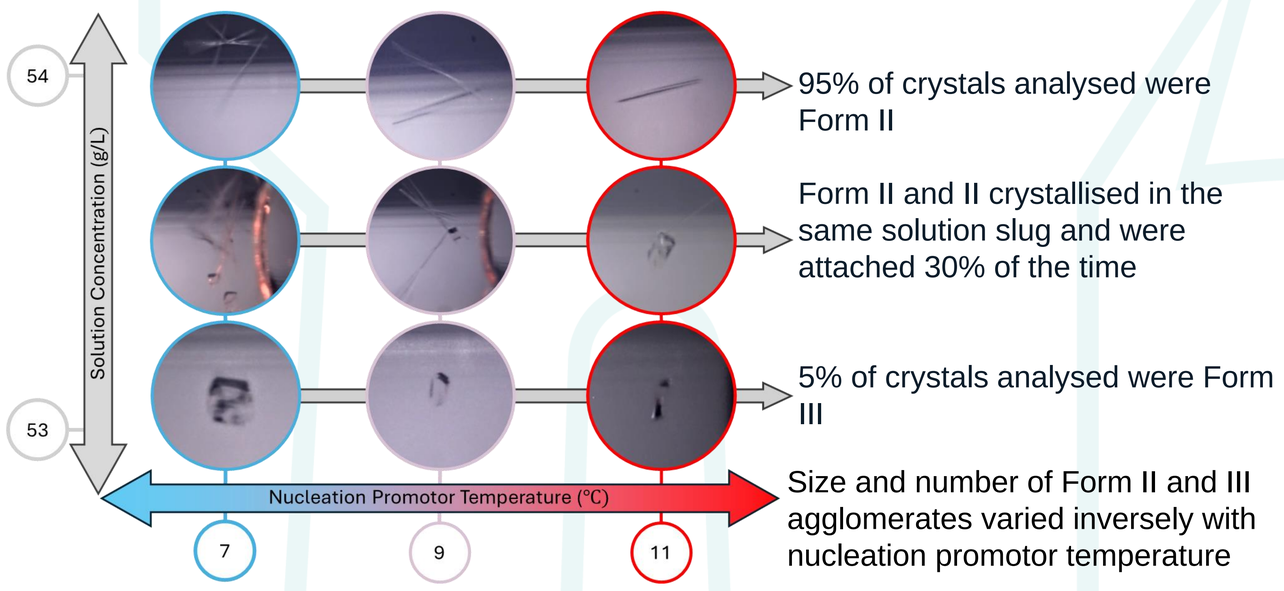

Figure 5. General trends observed during Unseeded Cooling Crystallisation (solution concentration 53,54g/l)

Conclusion

- Stable Form III polymorph forms under rapid cooling; simultaneous crystallisation of both Forms occurs due to Taylor flow variability[3] (Fig 5).
- Bending of Form II needles after Form III introduction needs further study to understand control and impact on CBZ properties (Fig 4).
- Video imaging success rate for extracting usable particle shape and size distribution (PSSD) data was below 5% due to stochastic nature of crystallisation and system limitations.

Future Work

Future work will prioritise developing a dual-camera system capable of consistently capturing clear crystal frames for a prolonged period, enabling accurate data requisition on PSSD (Fig 6).

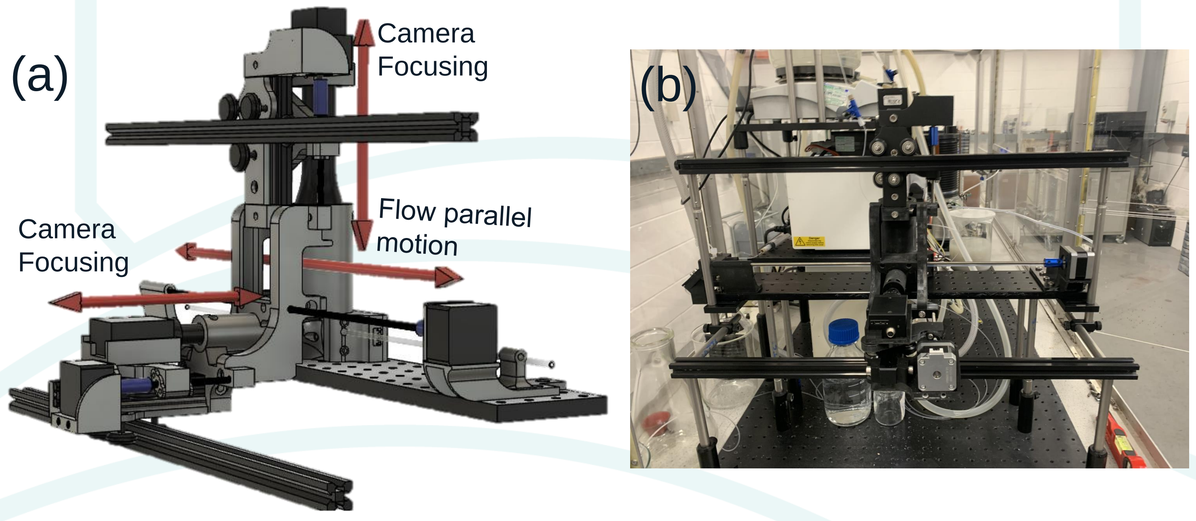

Figure 6. (**a**) Mobile stereoscopic imaging system design model. **(b)** Complete 3D printed design with electronically actuated lightbox, motion stage and focus fully integrated and situated.

With the addition of machine learning and a crystal system exhibiting polymorph dictated habit, reliable predictions of polymorphic ratios from tailored experimental conditions should be possible.

References

1.S. Schorsch, T. Vetter and M. Mazzotti, Chemical Engineering Science, 2012, 77, 130-142.
2.J. McMahon.
3.S. Park and W.-S. Kim, Crystal Growth & Design, 2018, 18, 710-722.

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