Enabling Sustainable Continuous Crystallisation through Inline Analytics and Feedback Control

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Background

- Crystal properties (CSSD and polymorph) govern API performance and manufacturability
- Control of such attributes requires precise process control
- Lab-scale crystallisation often suffers from fouling and blockage[1]
- Tri-segmented flow enables a reproducible, fouling-free environment (Fig 1)

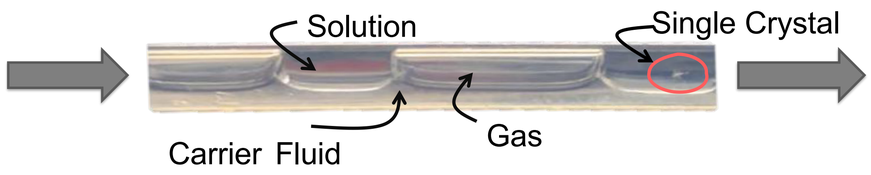

Figure 1. Supersaturated solution slugs separated by air bubbles and coated in a carrier fluid to prevent contact with the internal walls of the FEP tubing.

- Combining tri-segmentation with the Kinetically Regulated Automated Input Crystalliser (KRAIC) platform enables precise control of localised crystallisation conditions[2]

Aim of Study: *Investigate the impact of variable cooling profile on antisolvent, cooling crystallisation of DLM*

Method

DL-methionine (DLM) is the racemic form of the naturally occurring amino acid L-methionine, used in animal and human nutrition. Forms α (stable) and β (metastable) exhibit distinct habits identifiable through offline microscopy and inline stereoscopic imaging[3] (Fig 2).

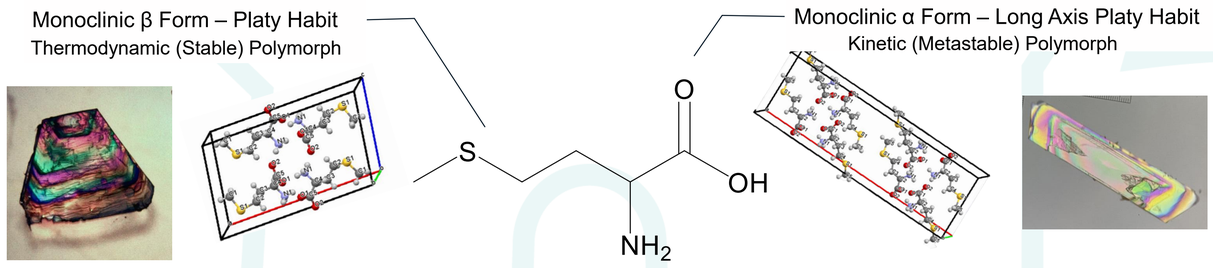

Figure 2. Unit cell and Habit of DLM Form α (right) and Form β (left)

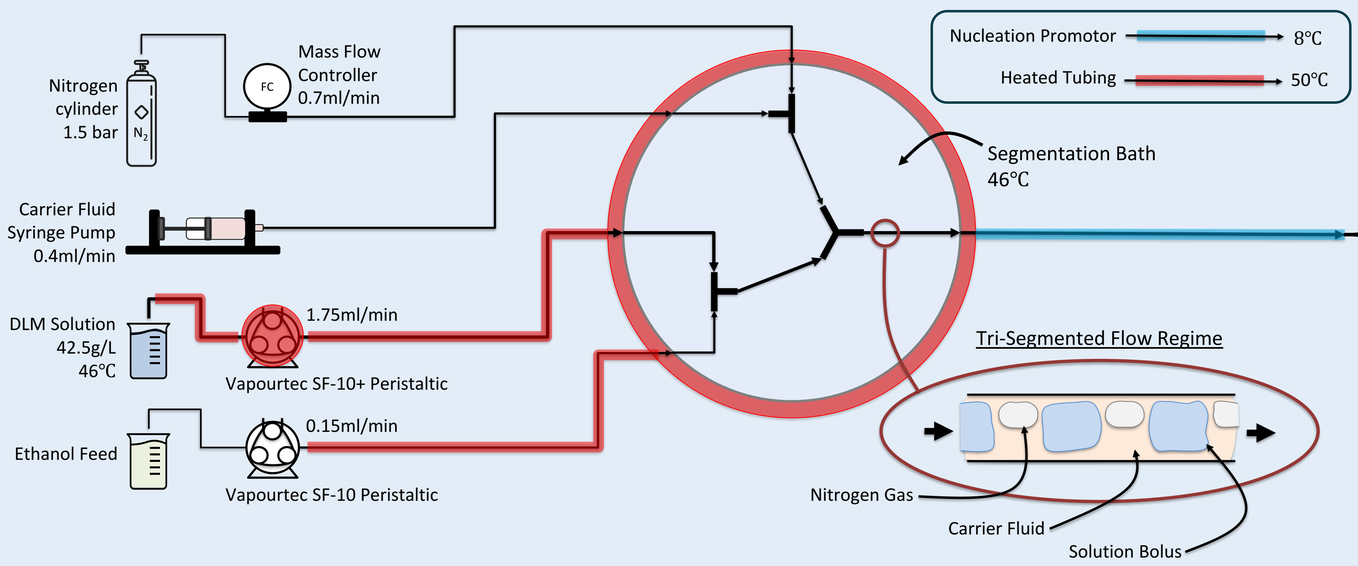

Figure 3. Laboratory setup for the combined antisolvent and cooling crystallisation of DLM. Flow paths are identical until the nucleation promoter, after which solution enters either the **KRAIC-S** or **KRAIC-G**. Inline stereoscopic imaging is performed at the analysis point.

System Design

- Flow paths are identical up to the nucleation promoter
- Following nucleation promotor, two different flow paths were studied
- Inline stereoscopic imaging implemented at the analysis point
- Additional microscopy performed post-collection for validation

Path 1: KRAIC-G

- Solution enters at the heated base and experiences a controlled temperature gradient
- Cooling profile is defined by crystalliser height and operating conditions
- Enables precise thermal control of crystallisation[4]

Path 2: KRAIC-S

- Solution enters and undergoes gradual return to ambient conditions
- Designed for air cooling and inline analysis
- Supports stereoscopic imaging and single crystal XRD at multiple positions[5]

Results

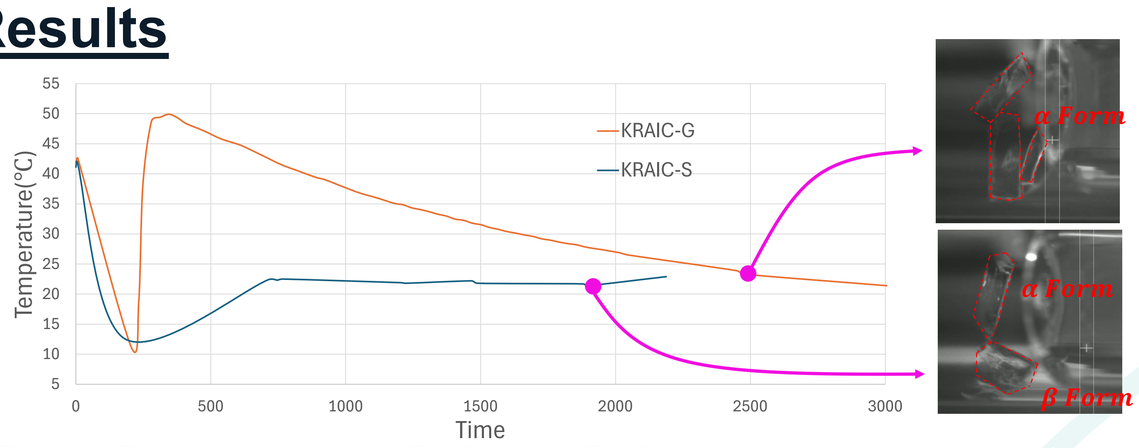

Figure 4. Temperature profile of KRAIC-G and KRAIC-S flow path alongside the associated crystalline product

- Crystallisation in the KRAIC-S produces a concomitant mix of polymorphs
- Crystallisation in the KRIAC-G independently crystallises the α polymorph
- Polymorphic outcome is governed by both the cooling profile and antisolvent volume fraction

Future Work

- Improve stereoscopic imaging → increase usable data (>2%)
- Develop automated feedback control through integration of machine learning for polymorph prediction

References

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