Process Optimisation of L-Glutamic Acid in a Continuous Oscillatory Baffled Crystalliser

EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation

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1. Introduction

Pharmaceutical manufacturing relies heavily on tradition batch stirred tank crystallisers (STC's) for the production of crystalline active pharmaceutical ingredients (APIs). Despite the successful implementation of batch manufacturing of APIs, achieving robust process control of STC's can be limited and there is considerable interest in exploiting the opportunities for enhanced control that continuous processing technologies offer. One such technology, the continuous oscillatory baffled crystalliser (COBC), provides potential benefits over STC's that include:

- Increased surface to volume ratio improving heat transfer
- Enhanced radial mixing provided by oscillation
- Reducing cost , space and production time

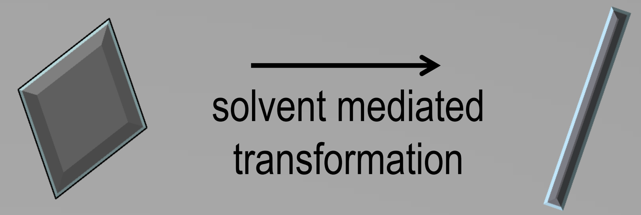
(Provides the ability to linearly scale up)

The focus of this work is to:

- Improve understanding of nucleation and growth in a COBC
- Illustrate control of physically pure solids with desired particle size
- Develop a methodology for reliable continuous crystallisation

2. L-Glutamic Acid

Two known polymorphs of L-Glutamic acid (LGA):



Monotropic system where solvent mediated transformation rates are significantly increased at elevated temperatures.

Different forms can be readily identified using techniques such as X-ray diffraction and Raman spectroscopy.

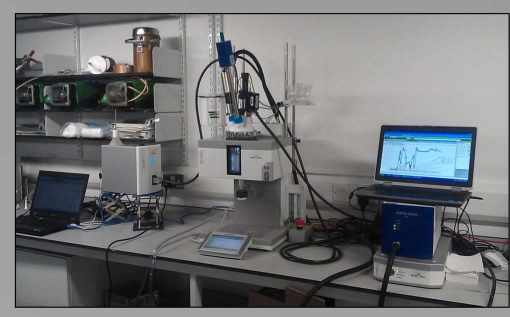


Fig 1 Mettler Toledo Optimax system set up for solubility measurement

β Solubility measured using the "calibration-free" method with an FBRM and mid-IR probe in-situ.

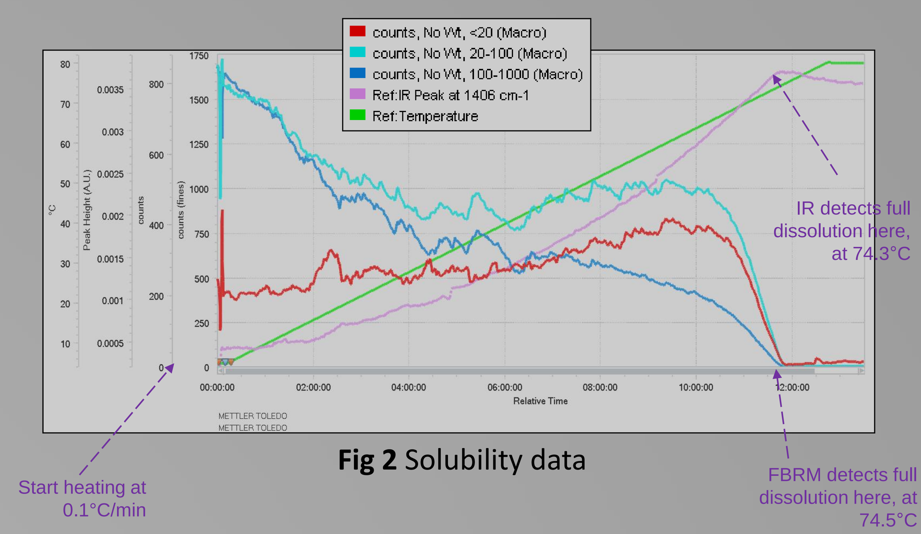


Fig 2 Solubility data

3. Continuous Crystallisations – Polymorphism and particle size distribution

Figure 3 shows the set-up used for continuous crystallisations. A bellow oscillates (Re_o 560-3100) the crystallising fluid while and a peristaltic pump provides a net flow (Re_n 70-280) from the feeding vessel.

Fig 3 COBC DN15 - working volume of 3.2L

Process conditions applied in batch crystallisation allowing for polymorph selectivity where implemented in the COBC. Successful unseeded continuous crystallisation of pure α achieved.

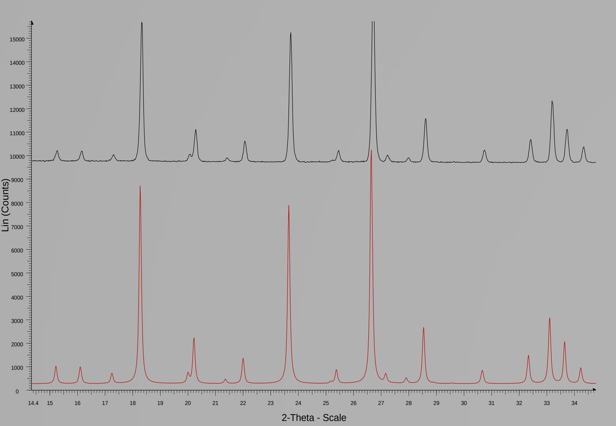


Fig 4 x-ray powder diffraction pattern of α generated from; single crystal data (red) and experimental crystallisation (black)

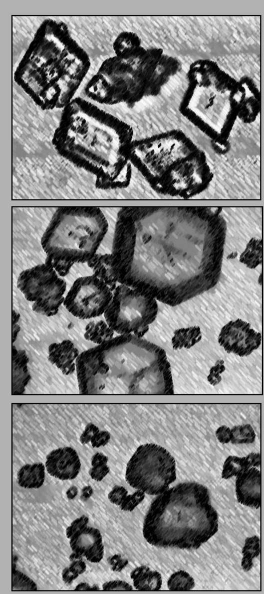


Fig 5 α from COBC

Interestingly when implementing batch crystallisation conditions for the production of β, the stable form could not be isolated in pure phase.

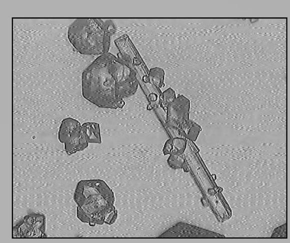


Fig 6 β co-existing with α

Fig 7 β co-existing with α

Fig 8 Pure phase β

Physically pure β LGA can be produced via a seeded continuous crystallisation process under conditions which, without seeding, result in a mixed phase product. Unaided production of pure β remains a challenge.

Evidence of fines in particle size distributions suggests secondary nucleation/attrition is occurring during crystallisation. Evidence of crystal breakage is observed with larger crystals (>800μm).

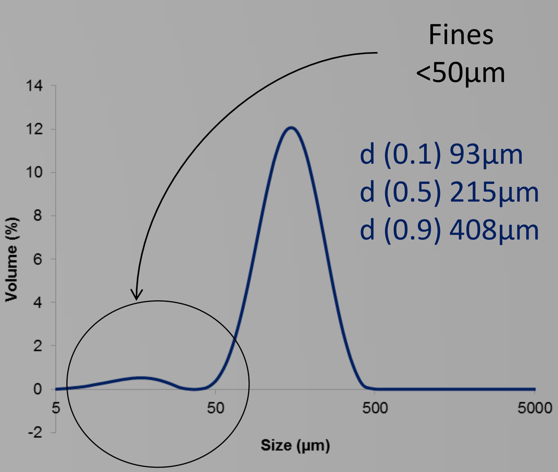


Fig 9 Malvern Mastersizer PSD data

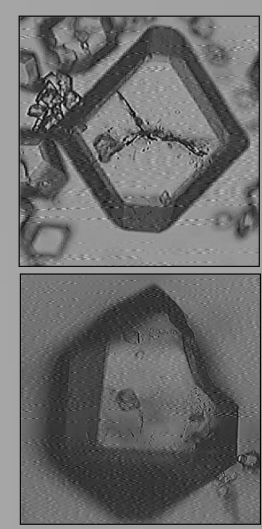


Fig 10 Observed crystal breakage

4. Process Optimisation – Steps to improve control over product attributes

1) Implementation of Process Analytical Technology (PAT) in COBC: Recent modification of COBC glass bends allow for in-situ monitoring of the crystallisation process in real time. The design allows probes to be removed and inserted at different positions along the COBC length providing quantitative information about solution concentration, nucleation and crystal size.

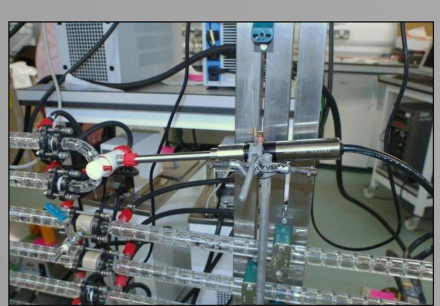


Fig 11 FBRM probe

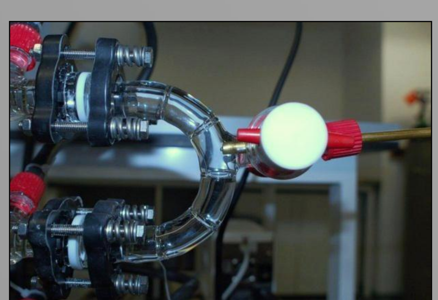


Fig 12 Mid-IR ATR probe

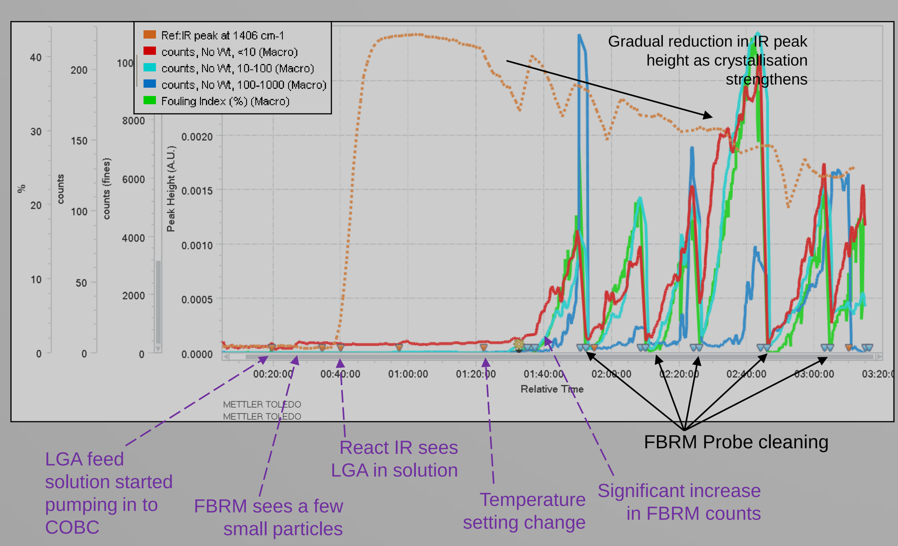


Fig 13 On-line monitoring during a continuous crystallisation

2) Investigate Residence Time Distribution (RTD) in DN15: Long residence times (slow flow rates) can be sought after to allow for sufficient induction times, phase transformations and slow cooling profiles . To evaluate and optimise flow and oscillation conditions RTD experiments were carried out using a 5g/L sodium benzoate solution and an in-situ UV probe to record absorbance as tracer elutes the COBC.

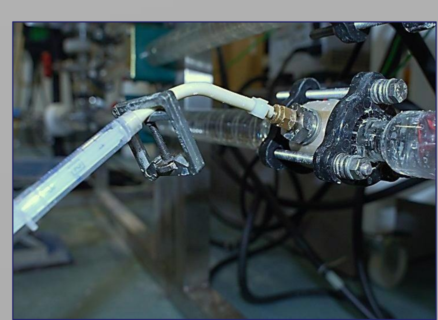


Fig 14: Injection Port

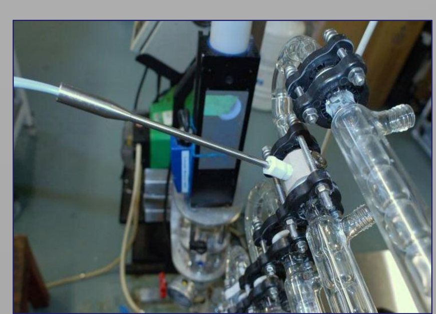


Fig 15: UV Probe In-line

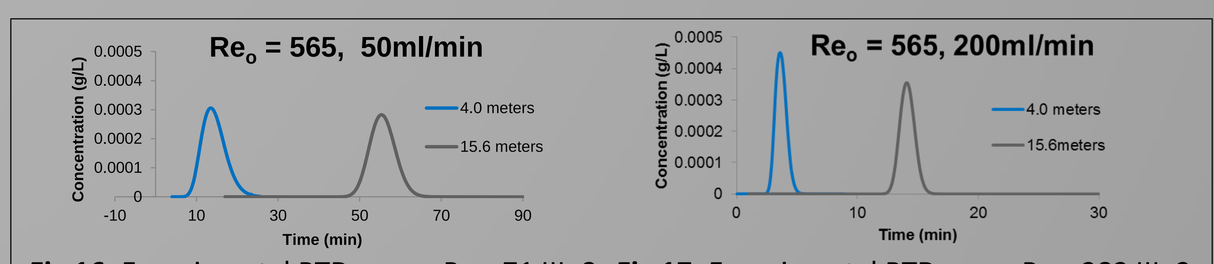


Fig 16: Experimental RTD curve: Re_n=71 Ψ=8 **Fig 17:** Experimental RTD curve Re_n=283 Ψ=2

As expected at longer lengths and increased flow rates deviation from plug flow reduces.

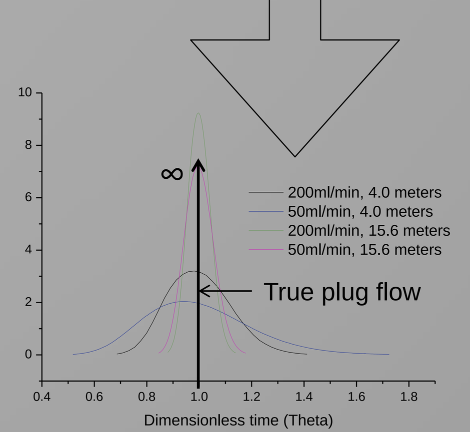


Fig 18: Normalised RTD curves

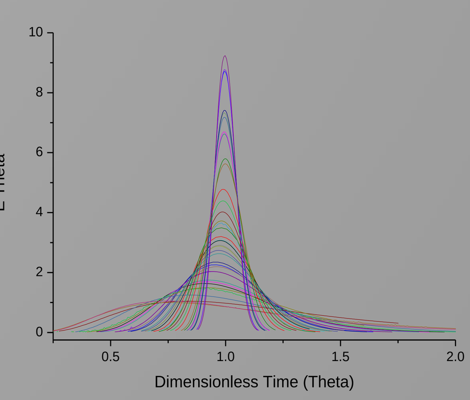


Fig 19: Normalised RTD curves for all experiments

5. Further Work

Each of the following stages are required for development of reliable unseeded crystallisation processes of α and β LGA.

1)Better control over primary nucleation without excessive supersaturation

Pre-nucelated feed and utilisation of COBC as a growth unit. Use of ultra sonics of nucleation induction.

2)Use of PAT

Provides the opportunity for dynamic process control

3)Alternative solvent systems

Screening of water:solvent systems to investigate reduction of encrustation

4)Design space of COBC operating parameters

Completion of RTD experiments with solid loadings to ensure correct flow conditions are achieved during COBC operation

5)Batch-Continuous Crystallisations

Assess crystallisation performance with oscillating fluid (encrustation not observed with moving baffles)

6. Summary

- α LGA is readily obtained through unseeded crystallisation in the COBC
- Continuous crystallisation of pure β remains a challenge but can be achieved via seeding
- Preliminary experiments indicate seeding significantly reduces the tendency for encrustation (a main focus of this research is understanding/controlling nucleation therefore seeding is not investigated further)
- Successful design and implementation of probe ports for on-line monitoring provides a means for dynamic process control
- Preliminary RTD experiments indicate reasonable plug flow has be achieved in continuous experiments to date (neglecting impact of solids content)
- Encrustation remains a major barrier to process optimisation

Fig 20 Encrustation on COBC walls

7. Acknowledgements

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