Crystallisation of L-Glutamic acid polymorphs at constant temperature under various flow conditions

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EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation

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Background

The focus of this project is on the selective formation of L-Glutamic acid polymorphs at constant temperature under different flow conditions, in order to

- Better understand what flow conditions favour certain polymorphs
- Assess the influence of temperature effects
- Identify processing conditions which lead to desired polymorphs

Reactive or antisolvent crystallisation at constant temperature

- Initial pre-mixing step is required to induce supersaturation
- Effect of post-mixing flow treatment for reactive crystallisation of L-Glutamic acid was previously investigated by C.F. Roelands et al. (2007)

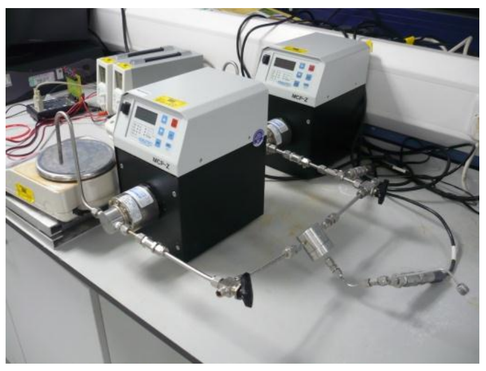
Initial pre-mixing

- Generates a homogeneous initial solution, if the characteristic time of mixing is less than the characteristic time of initial particle formation
- However, nucleation and/or precursor phase(s) formation can have characteristic times less than that of pre-mixing
- Initial particle/precursor formation events and subsequent processes are sensitive to post-mixing fluid flow conditions

Previous work

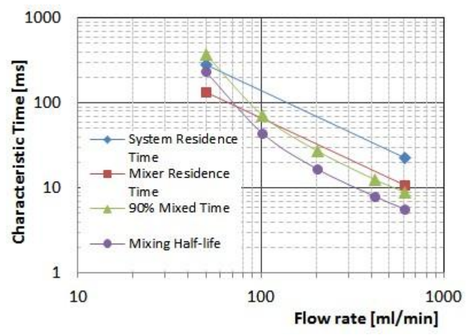
Pre-Mixing set up using static mixer

- Parallel competitive reaction scheme Bourne IV reaction used to characterise mixing performance
- Complete (molecular scale) mixing is achieved, within mixer residence time, for flow rates greater 50 ml/min. (Andrew Brown, PhD Thesis 2012)



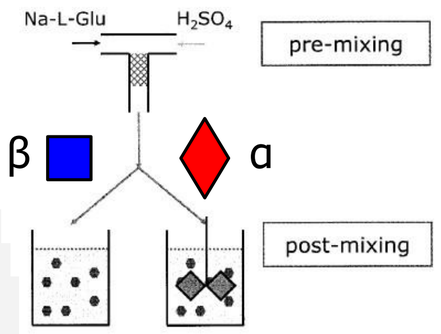
Mixing time measurements

- Flow rate ratio: 1:1 (v/v)
- Viscosity ratio: 1:1
- Static mixer: T-mixer
- Mixer residence time: < 1 sec.
- Supersaturation (SS): 2-4



Reactive crystallisation of L-Glutamic acid from Na-L-Glutamate and sulphuric acid aqueous solution, C.F. Roelands (2007)

- Post-mixing flow treatment showed effect on final polymorphic composition
- Quiescent: Stable Beta polymorph (sheet or needle) predominant
- Magnetically stirred: Metastable Alpha poly-morph (prismatic) predominant

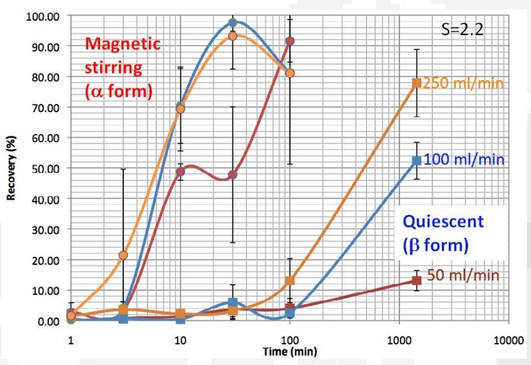


Temperature effects

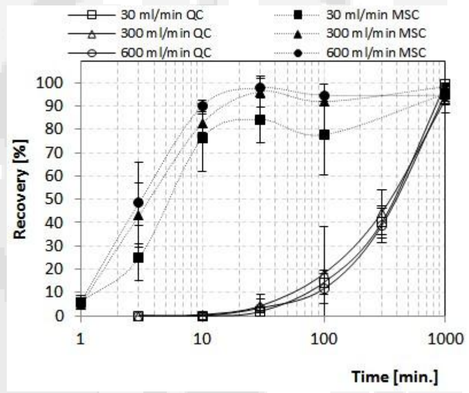
- Literature reports quick solution mediated transformation from Alpha to Beta at temperatures above 45°C and very slow transformation below 25°C

Results

Antisolvent crystallisation
SS = 2.2



Reactive crystallisation
SS = 4.0



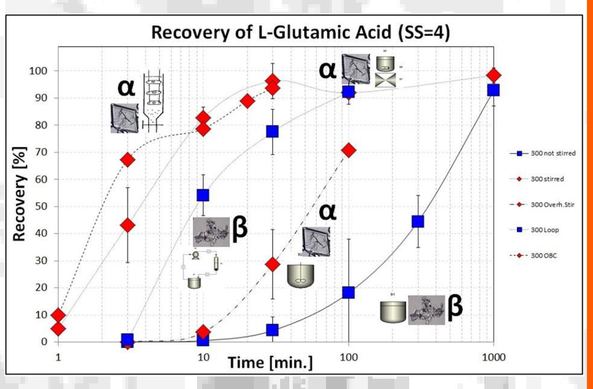
Effect of pre-mixing flow rate

- Mixing ratio: 1:1 (v/v)
- Static mixer: T-mixer
- QC or MSC flow treatment after initial mixing step

Effect of post-mixing flow conditions in reactive crystallisation

- Quiescent: Beta
- Peristaltic Pump Loop: Beta
- Magnetically stirred: Alpha
- Stirred tank: Alpha
- OBC: Alpha

No nucleation observed under these flow conditions at SS = 2 for up to three hours



Effect of temperature

- Sample premixed at shown temperature (SS = 4) in all cases
- Polymorph assessed after 60 min of mixing at constant temperature

Flow Unit	T = 5°C	T = 20°C	T = 45°C
MSC	Alpha	Alpha	Alpha -> Beta (Needle)
STC	Alpha	Alpha	Beta (Needle)
PPL	Mostly Alpha	Beta (Platelet)	-

Conclusions

- In antisolvent crystallisation higher pre-mixing flow rates speed up crystallisation, which is not observed in reactive crystallisation
- Quiescent post-mixing flow conditions and soft grinding, which leads to secondary nucleation of the more brittle Beta but not the Alpha prisms, lead to secondary nucleation of Beta
- Harsh impact or grinding leads to a rapid secondary nucleation of the Alpha form, due to much quicker growth kinetics of Alpha
- Different operating temperatures effect the nucleation & growth kinetics and can favour solution mediated transformation

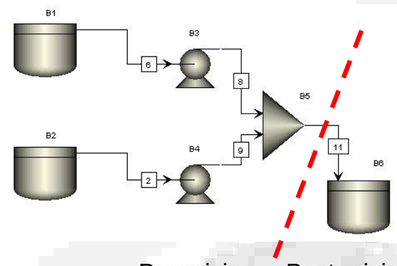
Experiments

Investigation of initial pre-mixing step at constant temperature

- Effects of variable static mixer flow rates on particle formation kinetics were tested for reactive and antisolvent crystallisation.

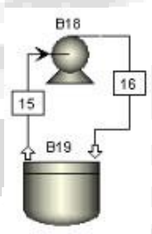
- Reactive crystallisation
  Na-L-Glutamate (c = 78.3 mg/$g_{(Solution)}$)
  H_2SO_4 (c = 21.5 mg/$g_{(Solution)}$)
  Flow rates [g/min.]: 30, 300 & 600

- Antisolvent crystallisation
  L-Glutamic acid (c = 7.3 mg/$g_{(Solution)}$)
  Iso-Propanol (Antisolvent)
  Flow rates [ml/min.]: 50, 100 & 250

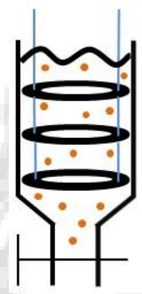


Investigation of different post-mixing flow treatment units

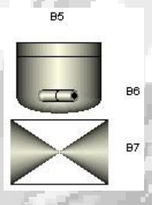
- Quiescent conditions (QC)
- Magnetically stirred crystalliser (MSC)
- Stirred tank crystalliser (STC)
- Peristaltic pump loop (PPL)
- Oscillatory Baffled Crystalliser (OBC)



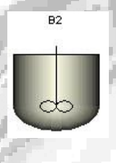
PPL unit



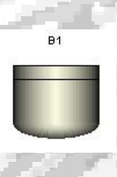
OBC



MSC



STC



QC

Temperature effects

- Temperature effects on isothermal flow units were investigated with the focus on whether the promoted polymorph changes when the temperature changes