



EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation



Developing Continuous Crystallisation in the Continuous Oscillatory Baffled Crystalliser (COBC)

Naomi Briggs
CMAC Open Day 12th September 2013

EPSRC

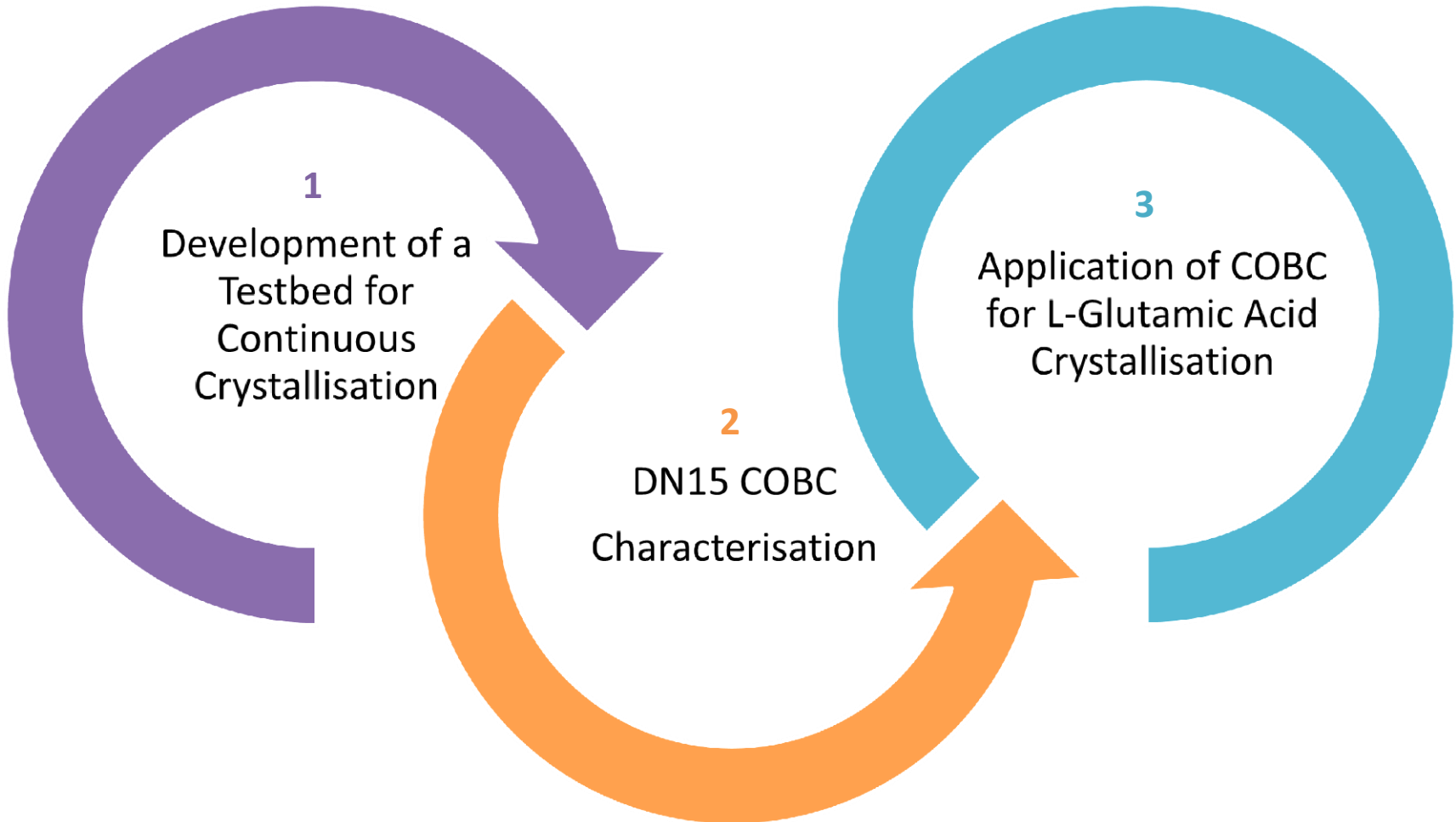
Engineering and Physical Sciences
Research Council



EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

Overview





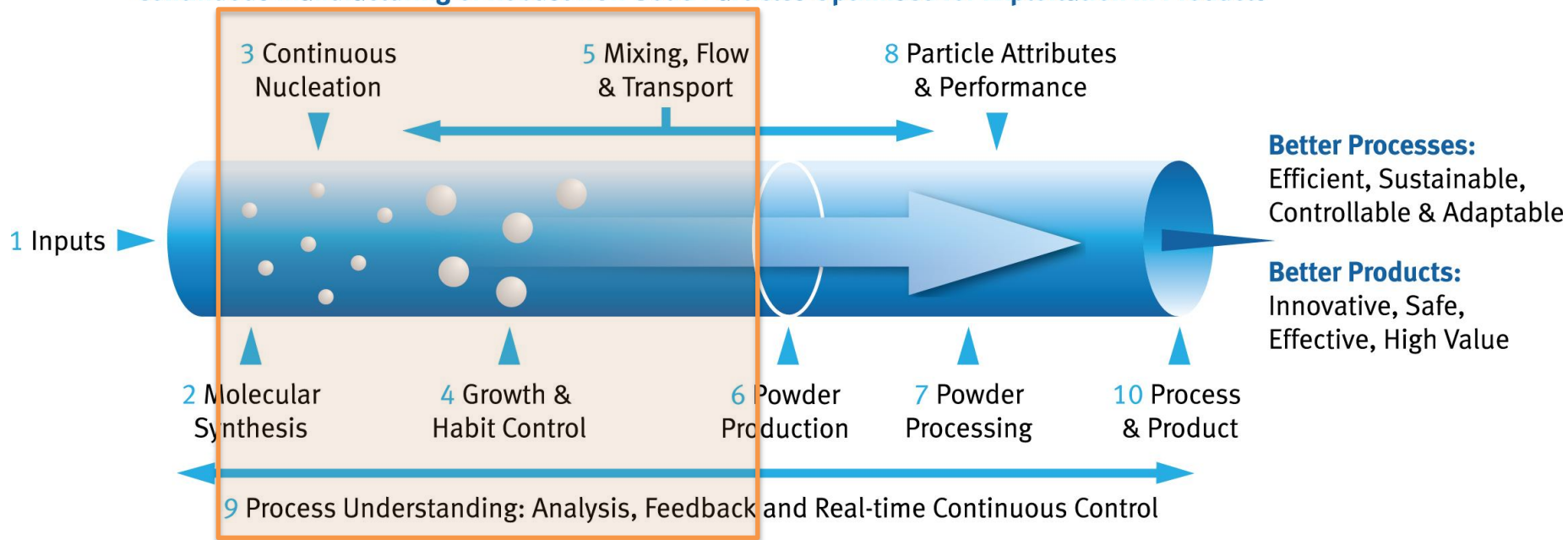
EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

My CMAC Focus Area



Continuous Manufacturing of Robust New Solid Particles Optimised for Exploitation in Products



Control and Understand

Physical Processes:

Polymorphism, Supersaturation, Nucleation, Particle Size Distribution (Growth), Attrition, Agglomeration, Yield, Temperature Profiles, Seeding, Fouling (Encrustation), Material/Solvent properties, Crystallisability, Morphology, Impurities.

Reactor Characteristics:

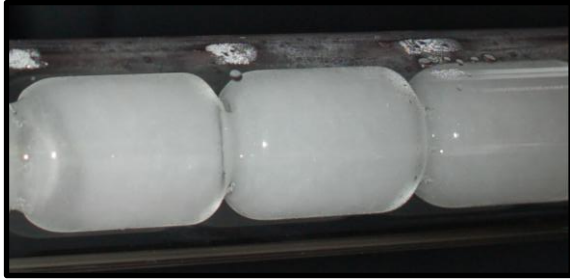
COBC operation, Flow (Residence Time Distribution), Impact of Shear, Heat/Mass Transfer.



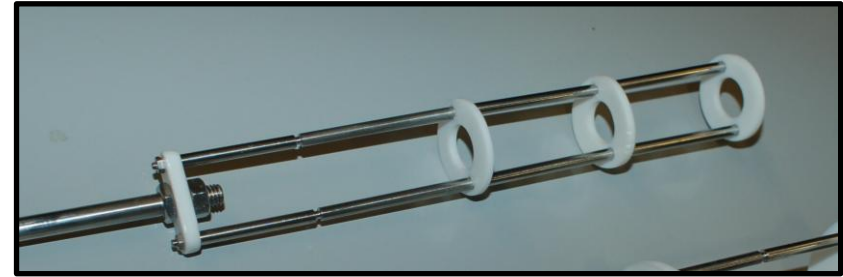
EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

Oscillatory Baffled Crystallisers (OBC's)

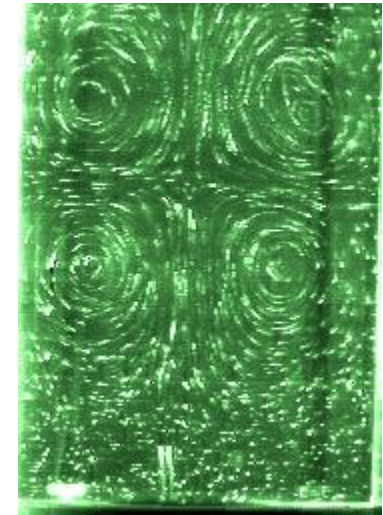
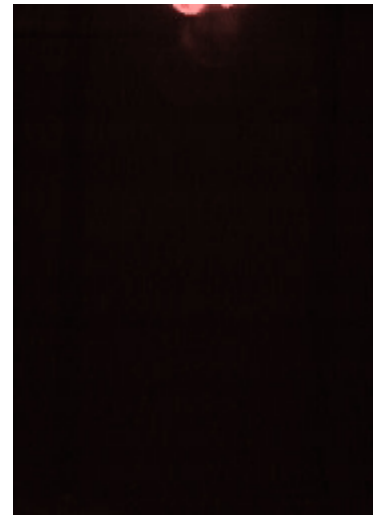


Stationary Baffles



Baffle string

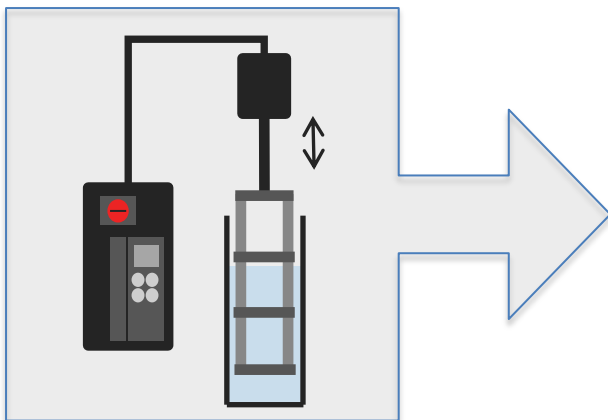
- Uniform & efficient mixing
- Rapid heat transfer
- Scalable
- Reduced shear
- Decouples mixing from net flow
- Plug flow reactor



Oscillatory Baffled Mixing

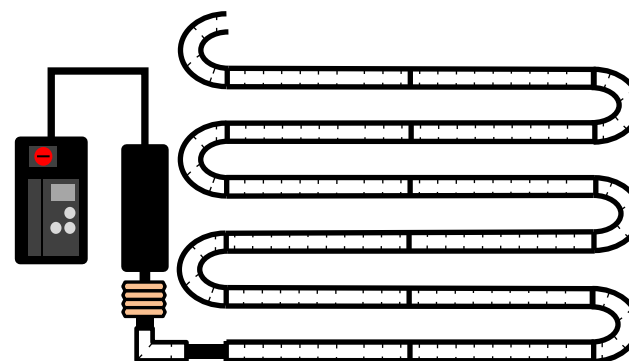
Traditional OBC Approach from Batch to Continuous

Batch



Define crystallisation
conditions

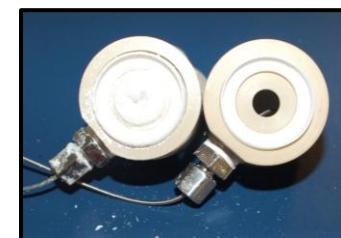
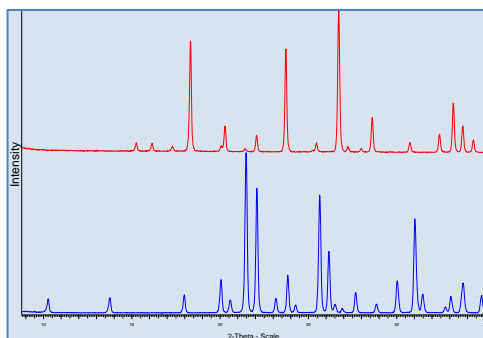
Continuous



Continuous production of API

Model Compound : L-Glutamic Acid

Polymorph
control
successful



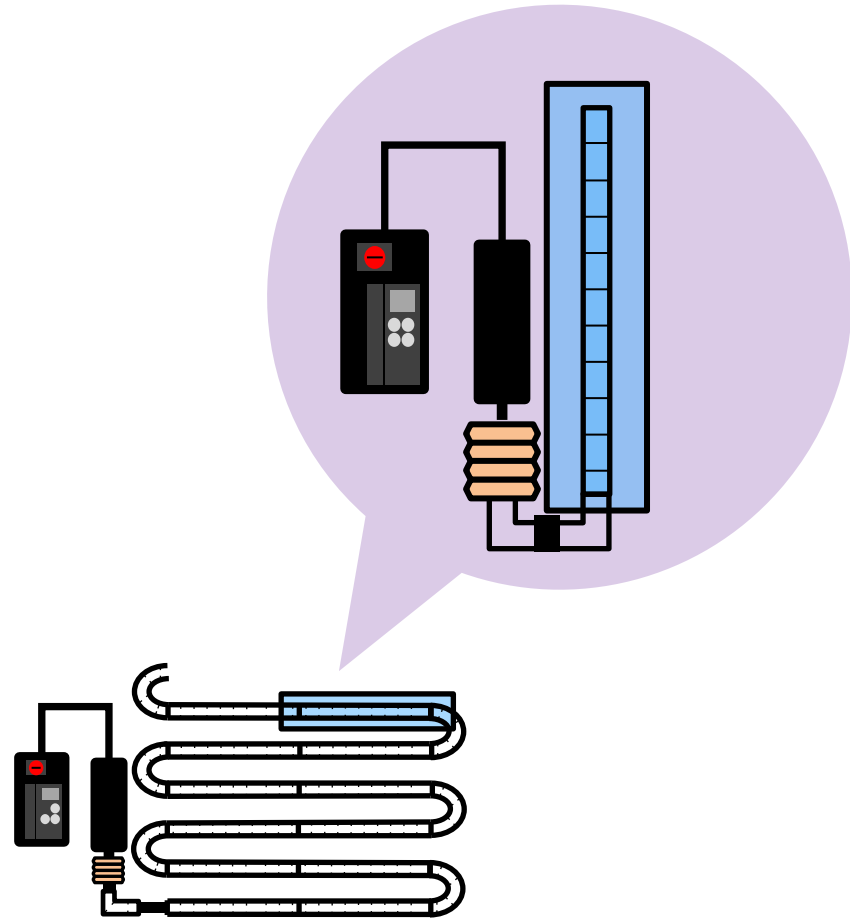
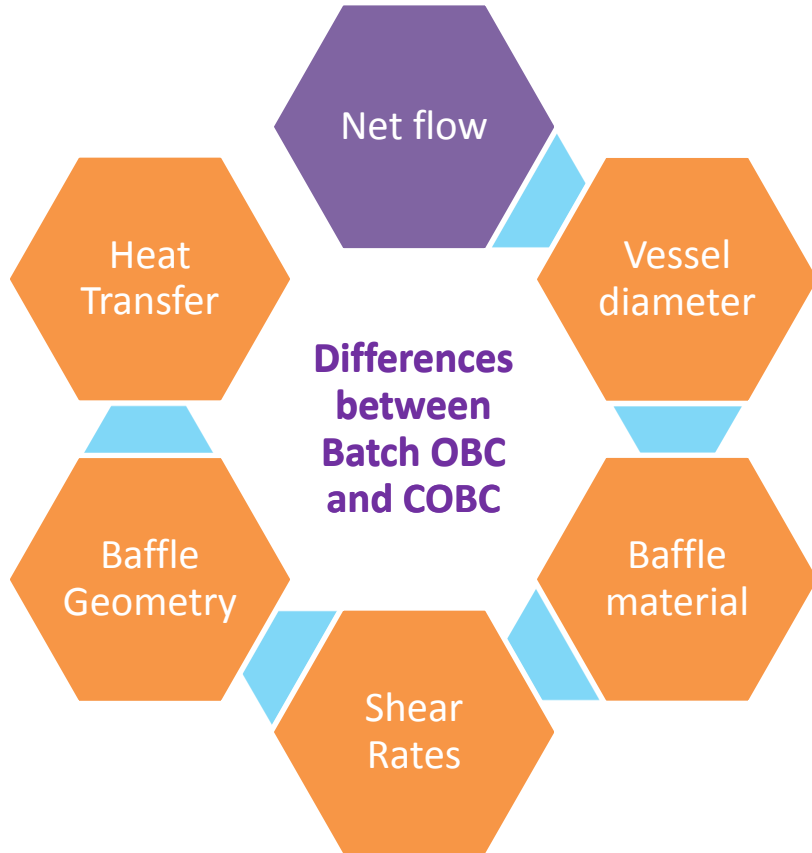
Encrustation, Blockages.
Exclusively metastable polymorph
isolated



EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

Batch vs Continuous



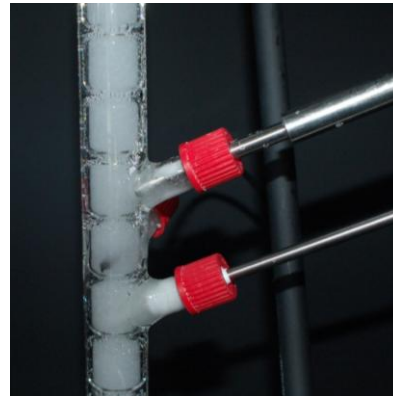
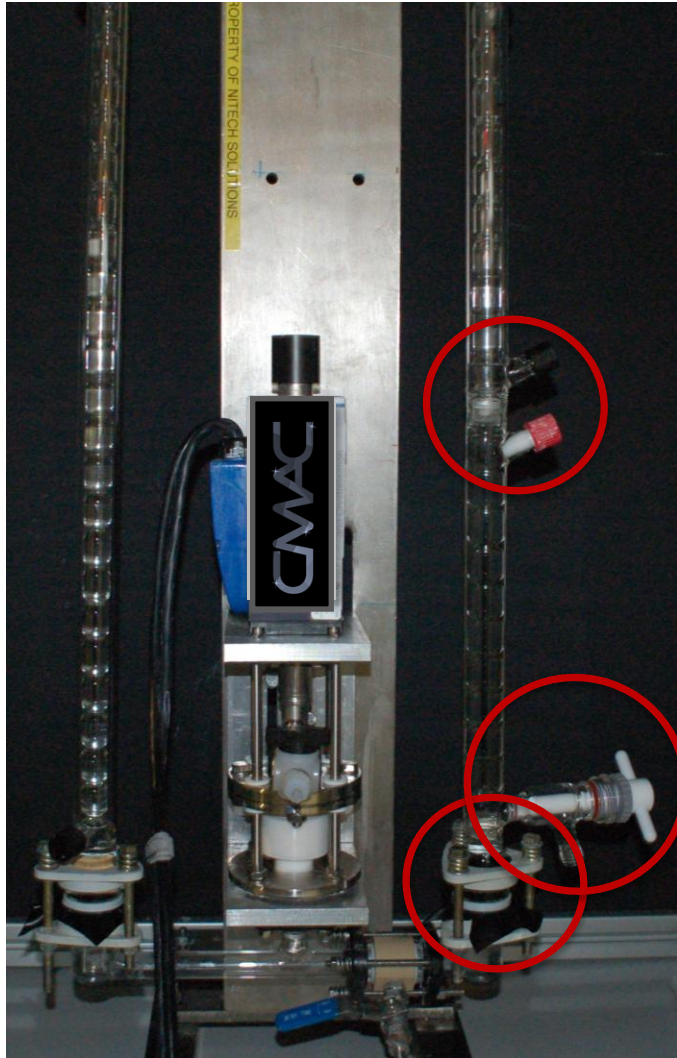
Q. How to maximise similarity between Batch and Continuous?



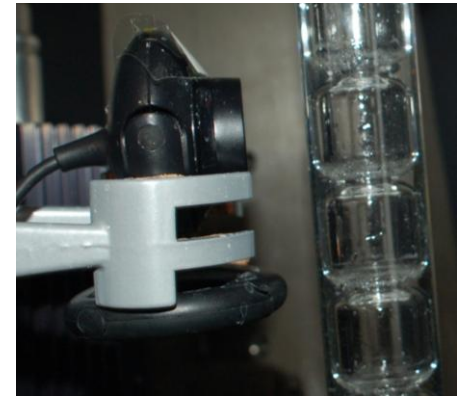
EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

Moving Fluid OBC



Nucleation: Inline
FBRM and UV



Encrustation: webcam
focused on interbaffle
zone

Implement real time PAT feed back for
supersaturation control over crystallisations





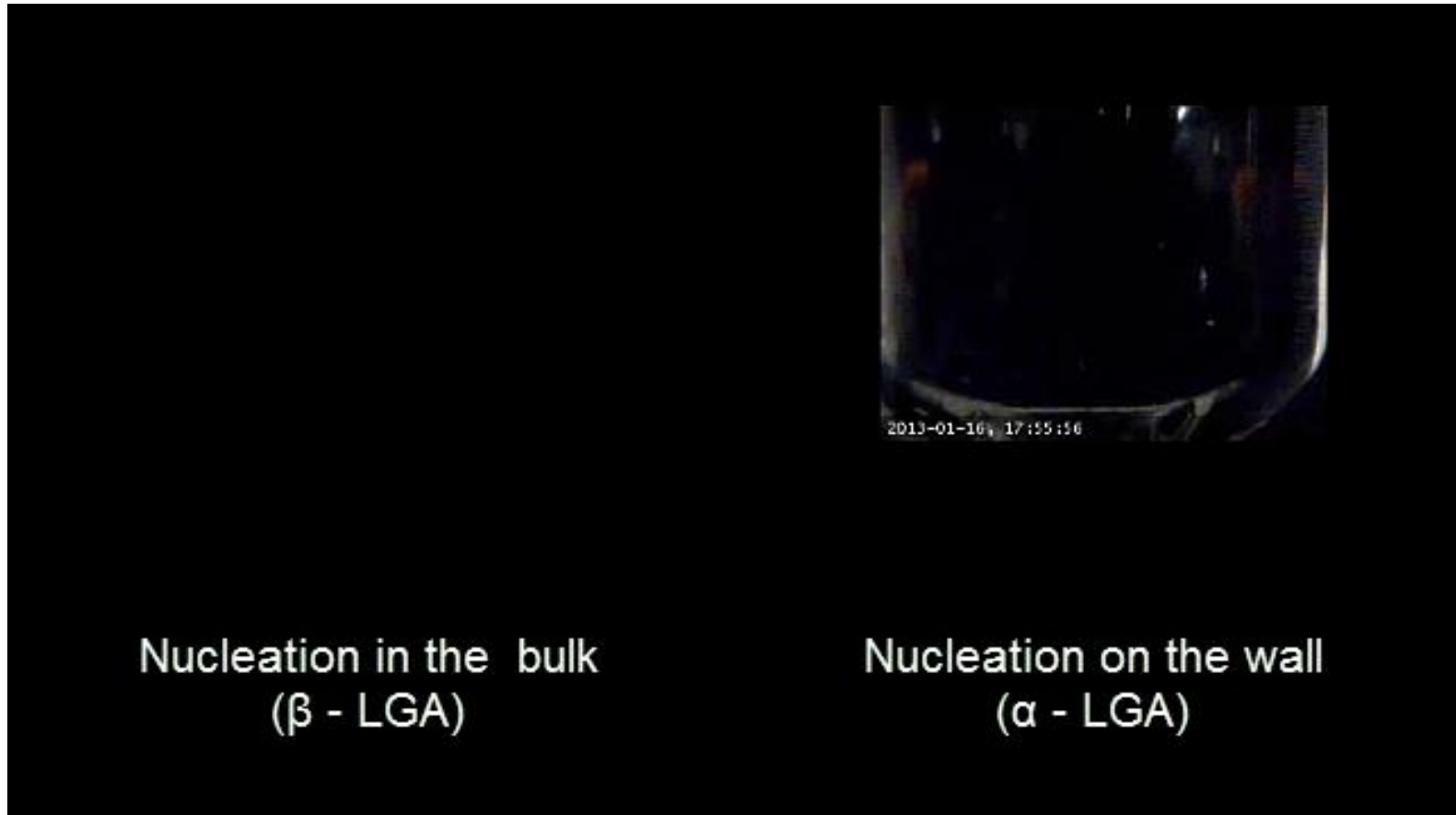
EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

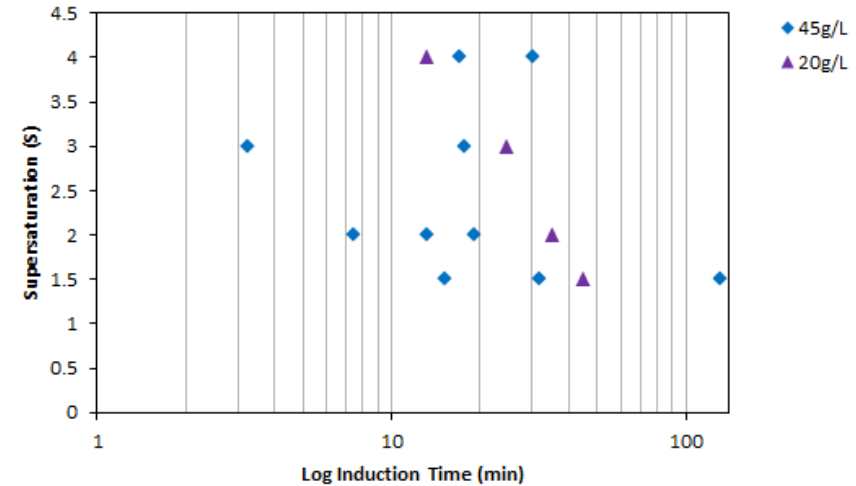
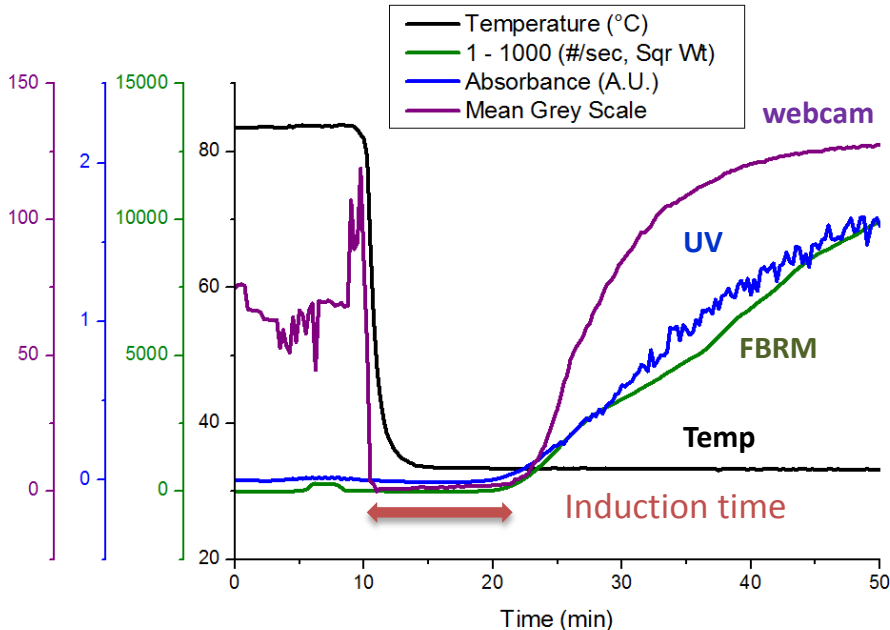
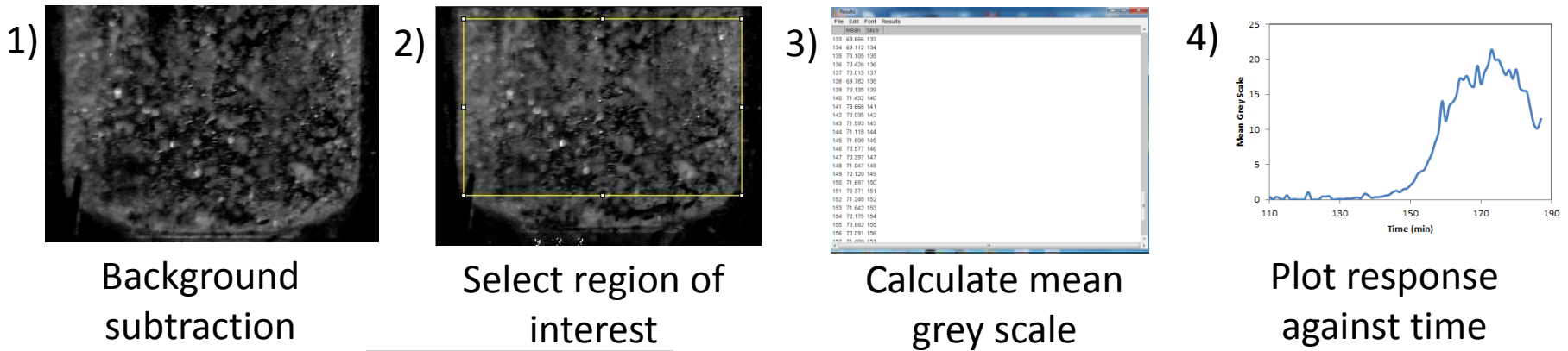
Imaging



Quantify the extent of fouling under a range of process conditions to identify how to encrustation may be monitored/reduced/eliminated.



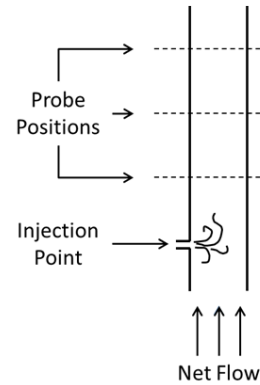
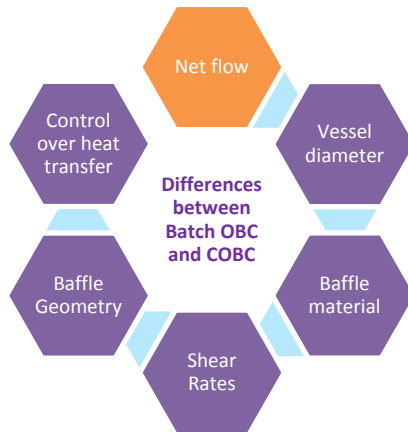
Images converted to 8bit grey scale and Image j software used for analysis.



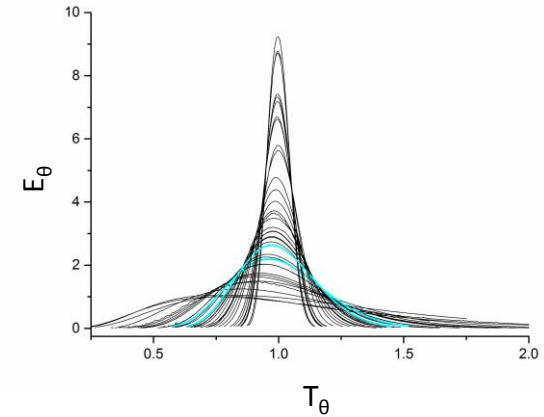
Induction time at various supersaturations

Key Factors:

Heat/Mass Transfer, **Flow**, Mixing, Shear



Schematic of imperfect pulse technique



Dimensionless RTD curves calculated from a range of conditions.

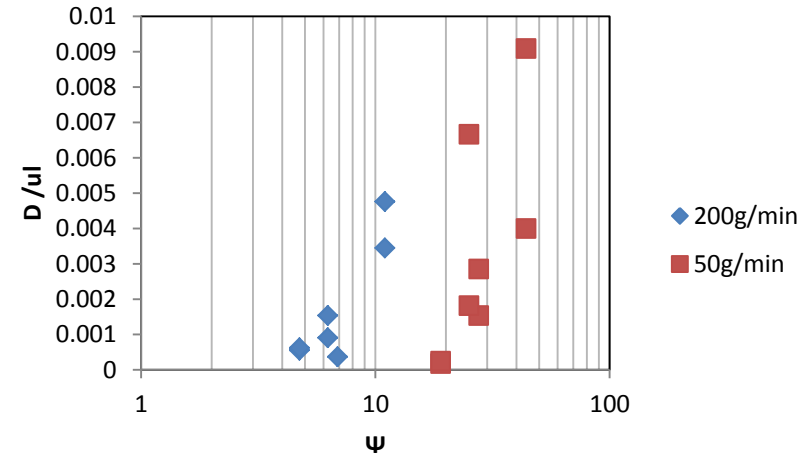
Residence time distribution (RTD) experiment's completed to assess flow.



Injection Port



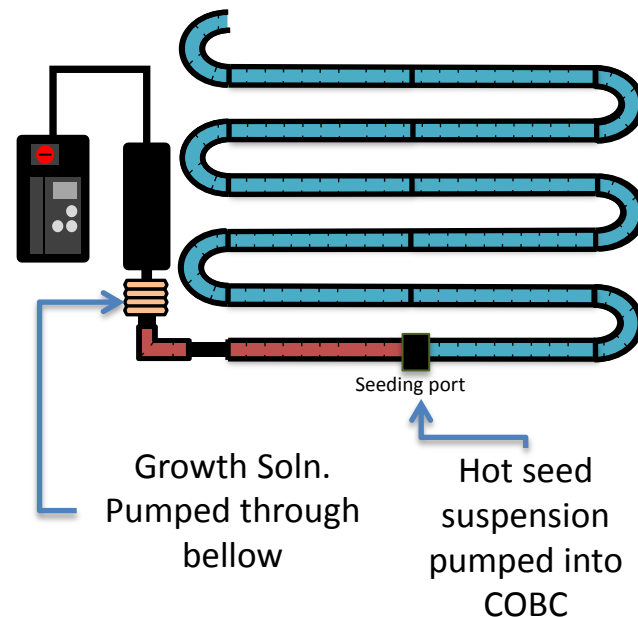
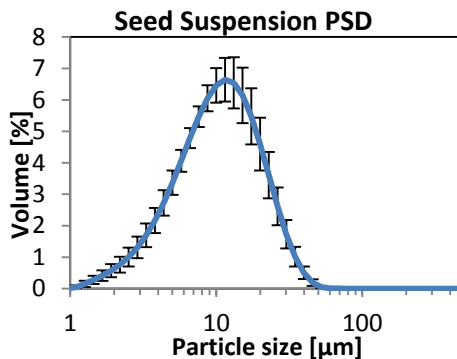
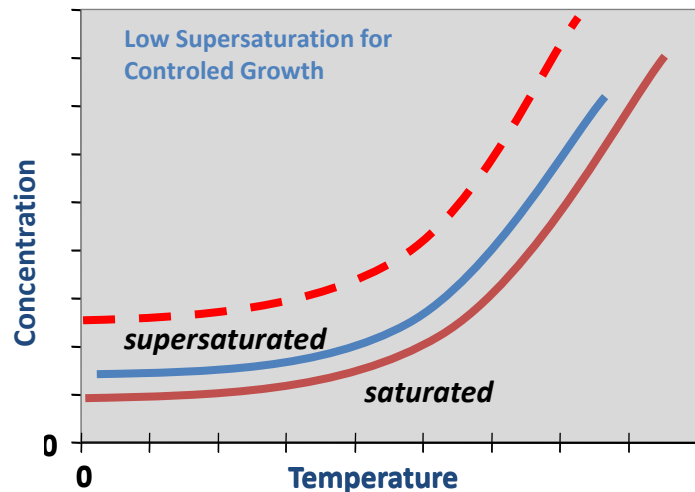
UV Probe In-situ





Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

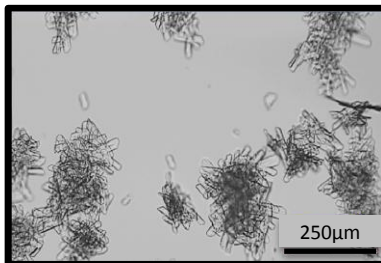
Continuous Seeded Crystallisation of β L-Glutamic Acid



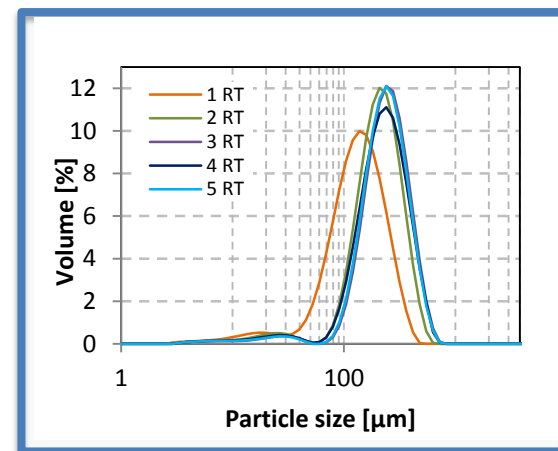
Seed loading.	Growth Soln.	
	High (40mg/g)	Low (18mg/g)
High (0.37mg/g)	No Encrust. Pure β LGA 7hr run (5 RT) Size: 240 μ m	No Encrust. Pure β 8hr run (6 RT) Size: 90 μ m
Low (0.1mg/g)	Encrust., Blockage, 4hr run (3 RT) α and β LGA Size: 240 μ m	No Encrust. Minor fouling Pure β LGA 8hr run (6 RT) Size: 70 μ m



SEM of β LGA product



Microscopy of β LGA product





EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

Summary



- Traditional moving baffle batch OBC doesn't appear to provide the correct information for scaling to continuous OBC
- The development of a improved batch system should accelerate the transition to successful continuous development
- A simple web cam imaging technique can be used to successfully monitor the encrustation process as well as nucleation
- Under all flow conditions used to date the COBC operates with moderate deviation from plug flow
- Through continuous seeding encrustation can be eliminated leading to successful crystallisations for investigations into growth mechanisms of the COBC



EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

Further Work



- What impact does the RTD have on crystallisation process?
(Series of seeded experiments under various flow rates for the same residence time, investigate the impact on the PSD)
- Can alpha LGA be produced successfully in the COBC?
(Series of seeded alpha LGA experiments following same methodology as beta)
- Direct MF OBC and COBC comparison experiments via induction time
- How does oscillatory flow impact the transformation of alpha LGA?
(Monitor the transformation process using Raman in the MFOBC)
- Apply knowledge of OBC operation and understanding to a new compound of interest
(Carbamazepine crystallisation work underway in MF OBC and COBC work planned)

Funding

Scottish Funding Council Strategic Priority Investments in Research and Innovation Translation (SPIRIT) Award



Research

Alastair Florence

Jan Sefcik

Xiong-Wei Ni

Vishal Raval

Ulrich Schacht

Lihua Zhao

John Dempster

Craig Callahan

