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Dr Thomas McGlone

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Optimisation of Industrial Crystallisation Processes: Case Studies from the CMAC Future Manufacturing Research Hub

Synopsis

- Brief overview of the CMAC Future Manufacturing Research Hub
- Case study 1: Using Seeding to Manage a Continuous Crystallisation Process
- Case study 2: Investigation of Crystallisation of a Fine Chemical Product in an Oscillatory Baffled Crystalliser

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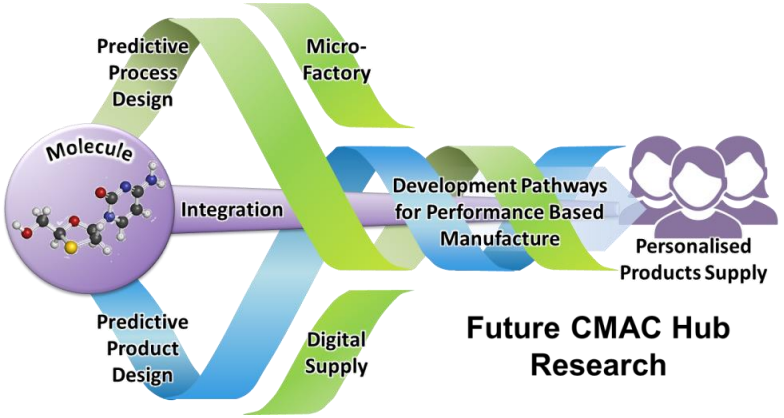
Continuous Manufacturing & Advanced Crystallisation

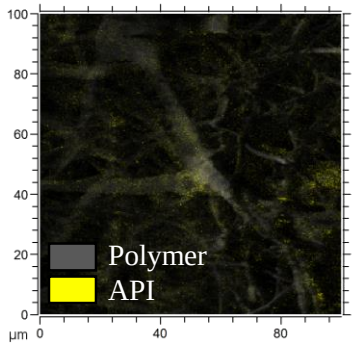
Co-created with industry to address key manufacturing challenges and skills needs

- World leading manufacturing research platform
- A partnership approach for world-class:
  - Research
  - Training & Skills
  - Translation to industry & Impact
  - Facilities & Infrastructure

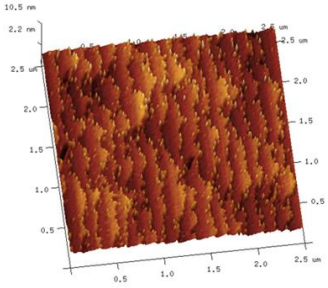


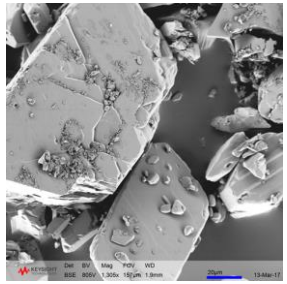
University of Strathclyde Glasgow
UNIVERSITY OF CAMBRIDGE
UNIVERSITY OF LEEDS
UNIVERSITY OF BATH
The University Of Sheffield.
Imperial College London
Loughborough University
gsk
AstraZeneca
NOVARTIS
BAYER
Lilly
Takeda
Roche
EPSRC
Engineering and Physical Sciences Research Council

World Class Facility for Continuous Manufacturing and Advanced Crystallisation Research



- Dedicated technical support within World Class Manufacturing Research Facility
- Unique expertise in advanced crystallisation, process development, formulation and product analysis
- Continuous process skids for process development, state-of-the-art analysis and characterisation capabilities and a comprehensive suite of PAT tools





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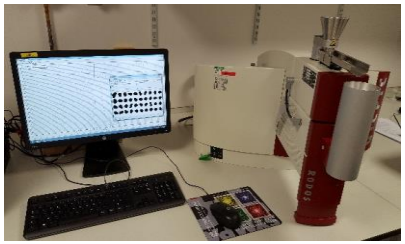
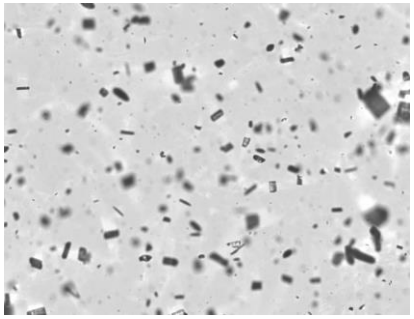
Highlights

- Twin Screw Extrusion Investigation & Process Optimisation



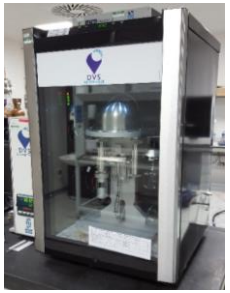
- Direct & Model-predictive Control using In-line PAT for Control of Particle Size in a Continuous Crystallisation

- Particle Sizing – Technique Selection & Method Development
- Improvement of Batch Crystallisation Process Understanding



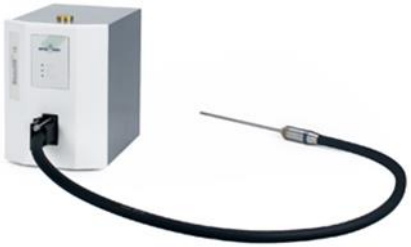
- Optimisation of Particle Morphology in Defined Solvent System
- Final Product Contaminant Investigation via GC-MS Studies Including Method Development
- Spray Drying Viability Study

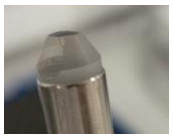
- PAT implementation
- Impact of Microstructure on Moisture Uptake via DVS, Nano CT & XRPD

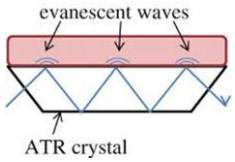


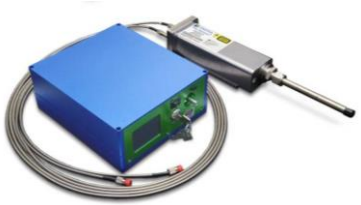
Process Analytical Technology (PAT)

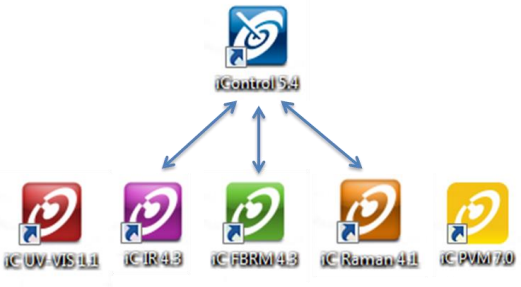
- Implementation (technique selection)
- Process monitoring
- Process control (direct)
- Calibration (quantitative measurements)

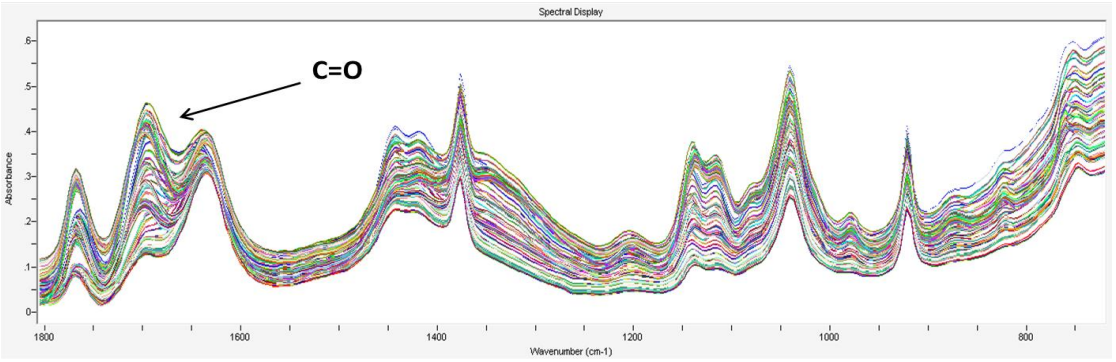


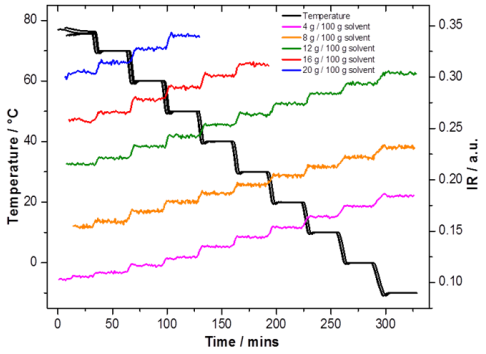












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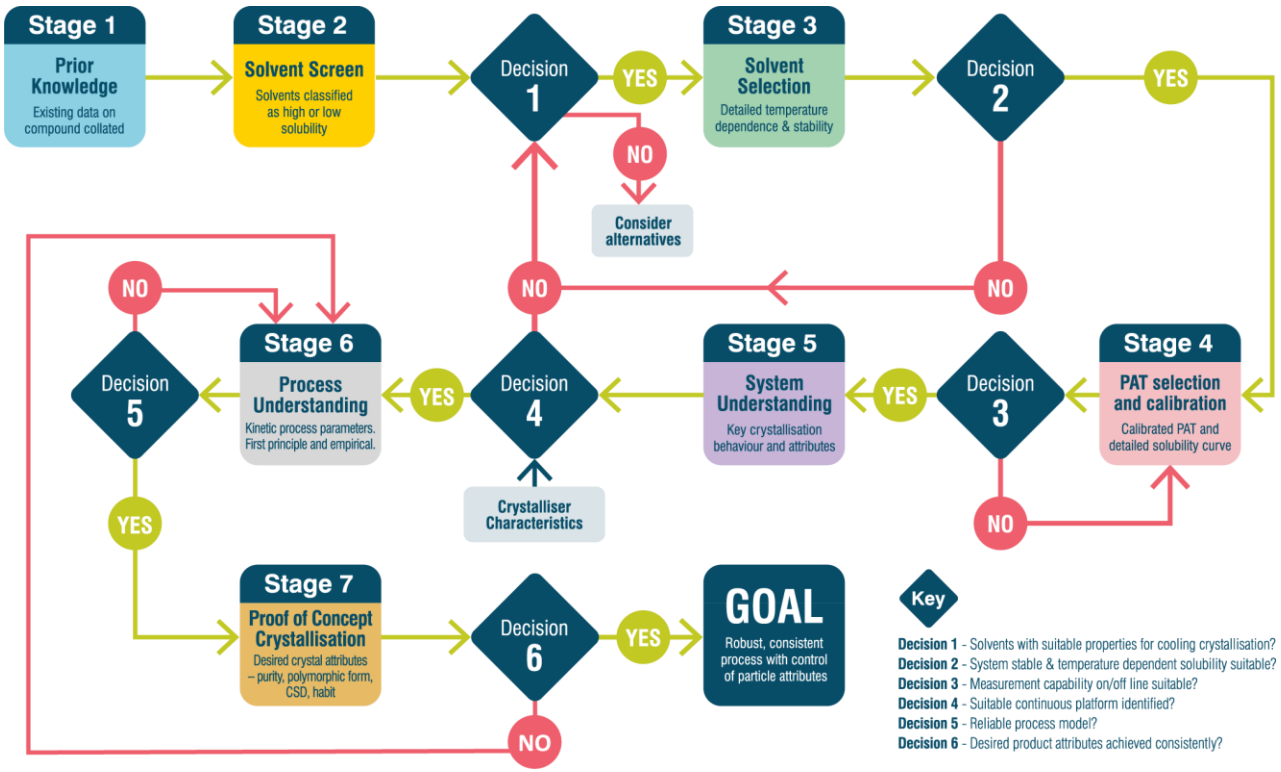
Crystallisation Workflow



- Specific tasks with transparent and systematic, data driven decisions.
- Appropriate use of lab automation and automated data processing.
- Minimise material usage and resource with whilst maximising process understanding via design of experiment (DoE) approaches.
- Realistic estimations of campaign timescales.
- Pre-empt commonly encountered issues and embed their solutions to development tasks and decisions.

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Case Study 1: Using Seeding to Manage a Continuous Crystallisation Process

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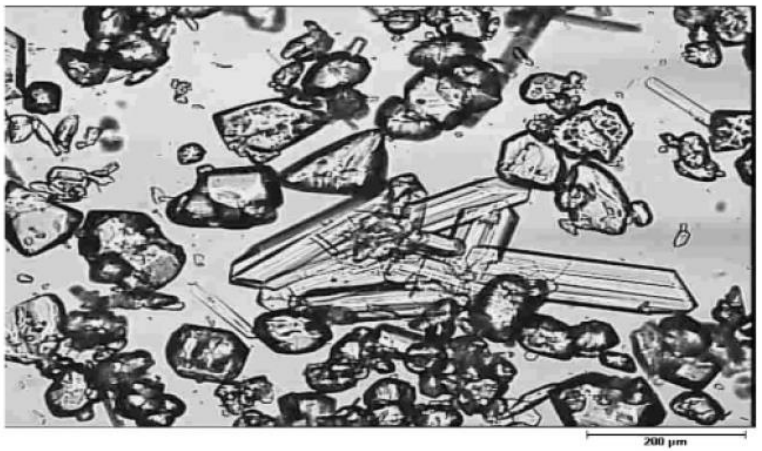
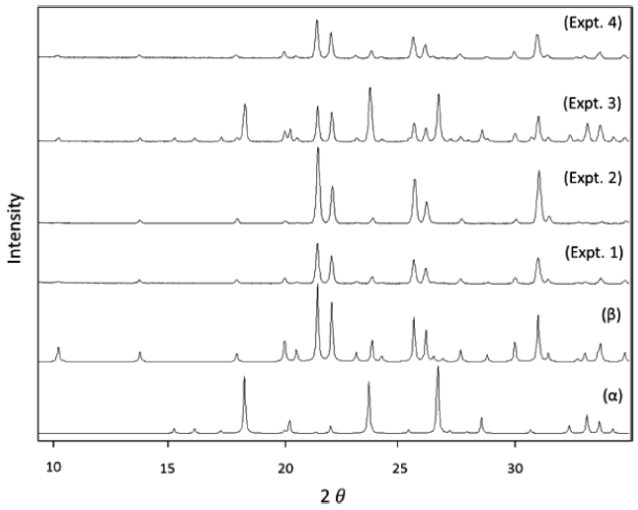
Case Study 1: Background

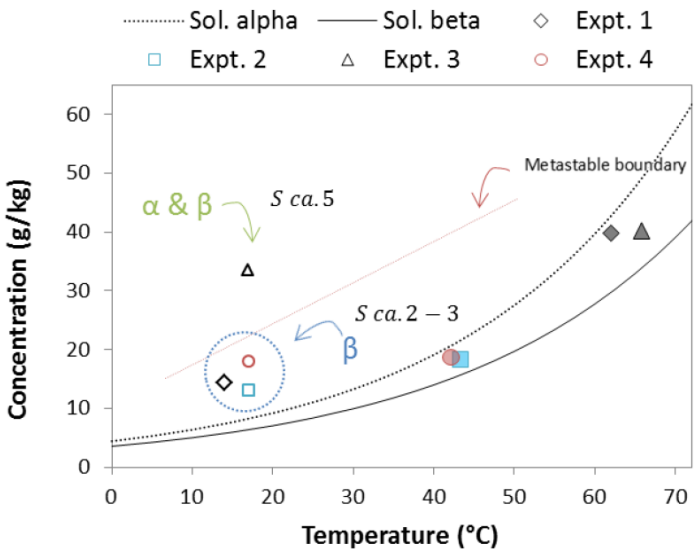
- *L*-glutamic acid – well studied system for crystallisation
- Well characterised polymorphic forms with distinct crystal habits
- Cost effective – good for research purposes
- Poses a low hazard risk (water as solvent)



Ni, Roberts *et al.*, *Crystal Growth & Design*, *4*, **2004**, 1129



XRPD patterns



Phase Diagram

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Ocillatory Flow Reactors

Organic Process Research & Development

Review

pubs.acs.org/OPRD

Oscillatory Flow Reactors (OFRs) for Continuous Manufacturing and Crystallization

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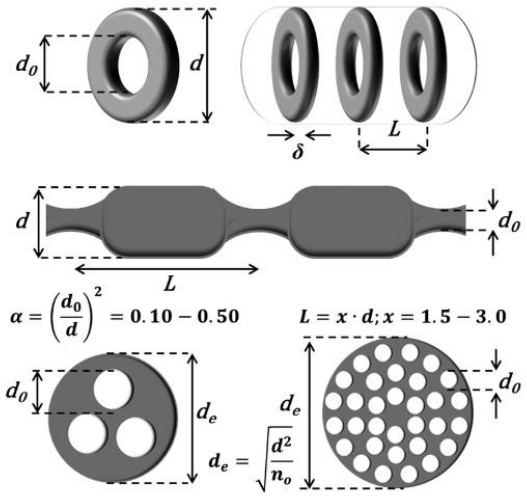
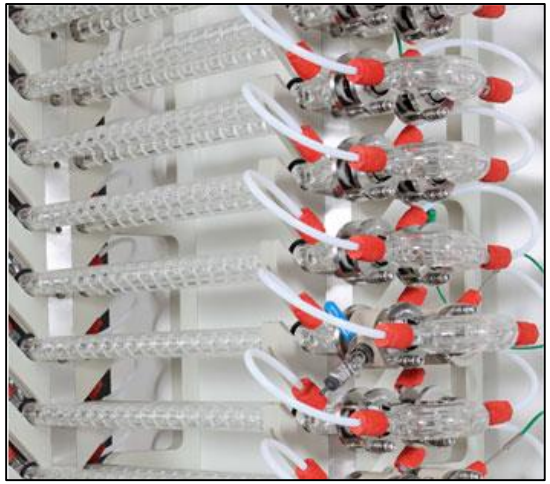
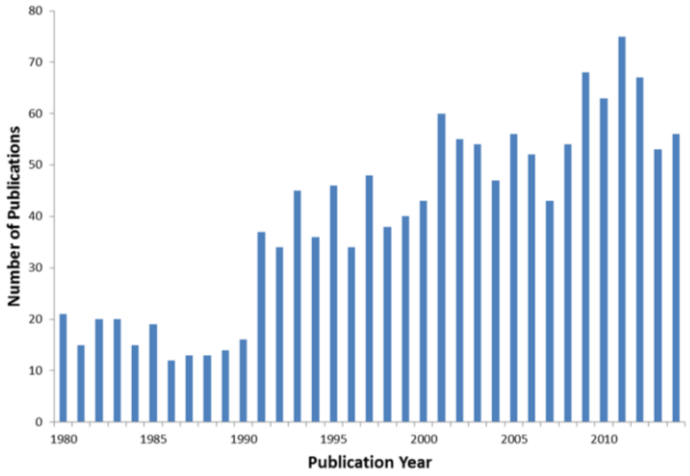
ABSTRACT: Continuous crystallization is an attractive approach for the delivery of consistent particles with specified critical quality attributes (CQAs), which are attracting increased interest for the manufacture of high value materials, including fine chemicals and pharmaceuticals. Oscillatory flow reactors (OFRs) offer a suitable platform to deliver consistent operating conditions under plug-flow operation while maintaining a controlled steady state. This review provides a brief overview of OFR technology before outlining the operating principles and summarizing applications, emphasizing the use for controlled

- OFRs allow turbulent mixing with laminar flow rates
- Optimal operation allows near plug flow conditions
- Enhanced heat/mass transfer
- Chem/bio reactions, polymerisation, catalysis, gas-liquid
- Crystallisation…







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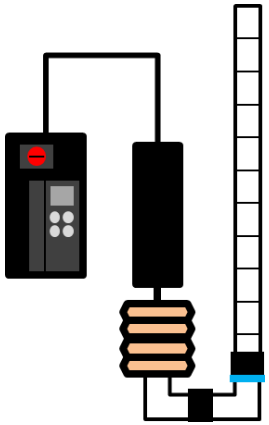
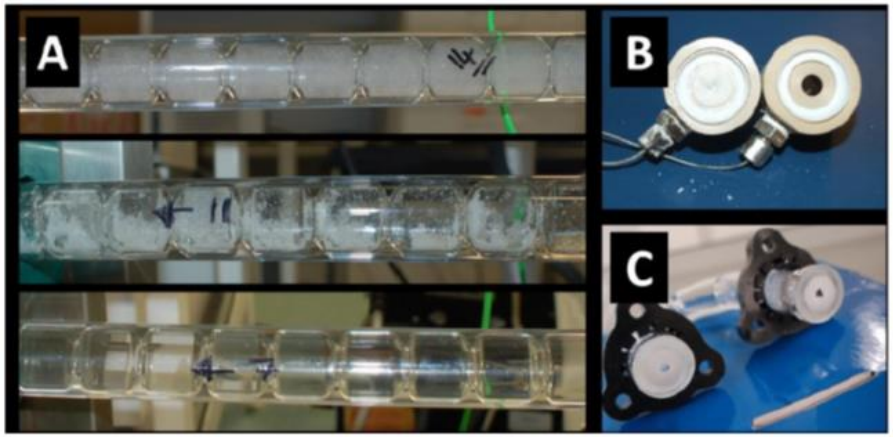
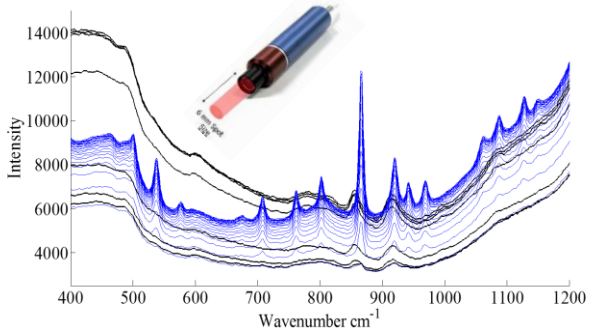
Case Study 1: Process Optimisation

- Batch evaluation platforms
- Process analytics
- Cooling conditions



'Moving-fluid' Imaging In-line





- black=liquid phase
- blue=solid phase

Non-invasive Raman

- Encrustation/blockage a significant challenge
- Metastable alpha-form

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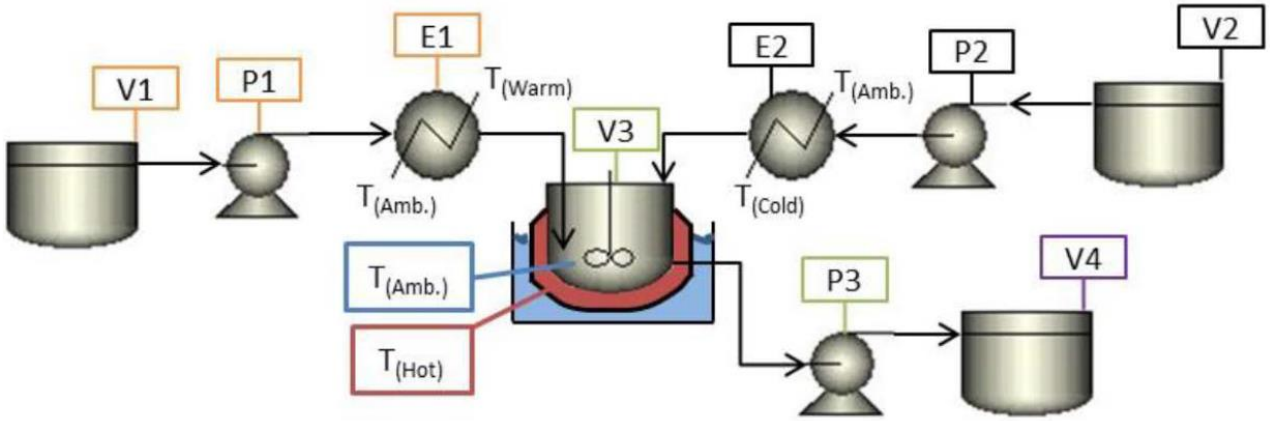
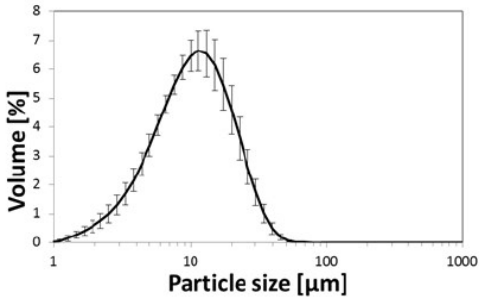
Case Study 1: Seeding Approach

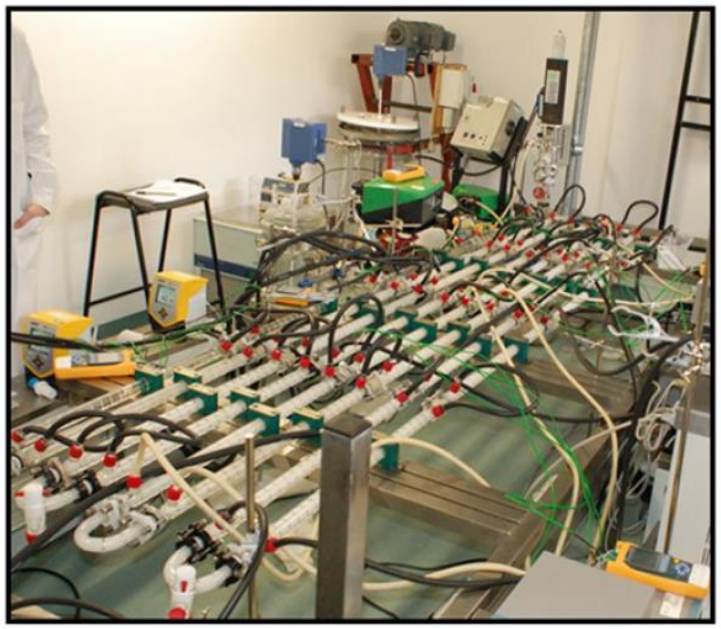
- Unseeded continuous operation not feasible for this system (primary nucleation should be avoided
- Seeding studies using batch evaluation platform successful



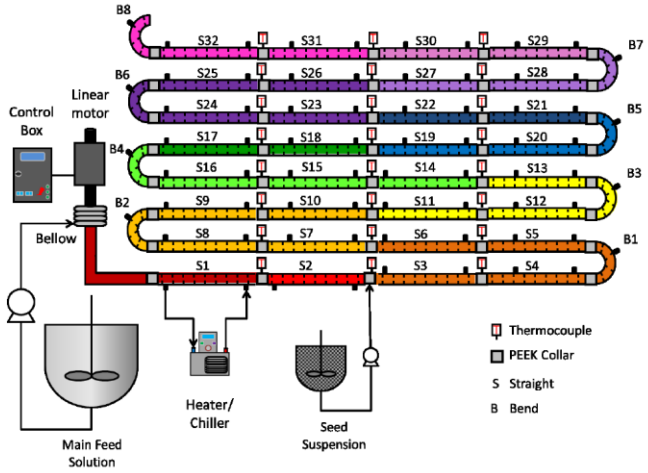


- Bulk seed production via continuous anti-solvent (isopropylalcohol) addition at high supersaturation
- Solution:anti-solvent ratio of 6
- Total run time of 2.5 h (300 residence times)
- Produced seeds pure stable beta-form with fairly narrow CSD

Case Study 1: Continuous Operation



- 25 m glass, horizontally mounted COBC with 15 mm ID
- Hold volume *ca.* 5 l
- 80 min residence time
- Two feeds: growth solution and seed suspension

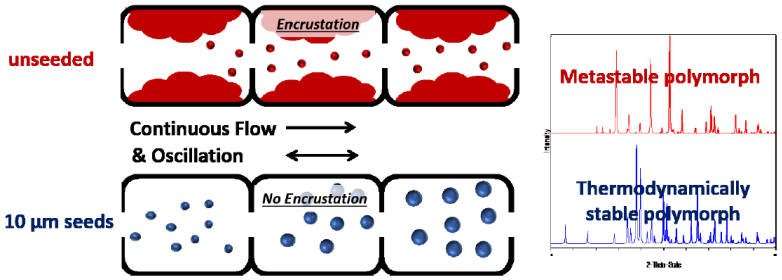


seed mass loading	feed solution concentration ($g/kg_{(solution)}$) high 40 g/kg	low 18 g/kg
high 0.4 (g/kg)	expt. 1	expt. 2
low 0.1 (g/kg)	expt. 3	expt. 4

- Combination of high feed concentration and low seed loading led to primary nucleation of alpha-LGA and encrustation
- Other conditions allowed for successful continuous operation

Case Study 1: Summary

- L-glutamic acid system selected as a well-studied system for crystallisation
- Cooling crystallisation process optimised using batch evaluation setups
- Encrustation highlighted as a processing issue for unseeded experiments
- Continuous, anti-solvent process developed for seed production
- Well managed continuous crystallisation process using seeding demonstrated
- Combination of high feed concentration and low seed loading led to primary nucleation of alpha-LGA and encrustation



Briggs, Schacht, Raval, McGlone *et al.*, *Org. Process Res. & Des.*, **2015**, *19*, 1903

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Case Study 2: Investigation of Crystallisation of a Fine Chemical Product in an Oscillatory Baffled Crystalliser

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WORK WITH US

- Research and Development Project Collaboration
- Improve your understanding of your current API manufacture (batch or continuous processes)
- We work with both large and small companies to deliver research within advanced crystallisation and analytical services

Acknowledgments:

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Case Study 2:
Dr. Lihua Zhao, Vishal Raval

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