



EPSRC

Centre for Innovative Manufacturing

in Continuous Manufacturing and Crystallisation



Workflows and Technologies for Continuous Crystallisation

Alastair J. Florence,
CMAC, University of Strathclyde
Advanced Process Modelling Forum, London, April 20th 2016



Engineering and Physical Sciences
Research Council

CMAC Manufacturing Research Centre

- ***Co-created with industry to address long-term manufacturing challenges and skills needs***

- EPSRC Centre for Innovative Manufacturing— ***Key National Research Platform***
- Partnership approach to industry-academic collaboration to deliver critical mass of:
 - ***Research***
 - ***Training & Skills***
 - ***Knowledge Exchange / Industry***
 - ***Facilities***



- Tier 1s GSK, AZ, Novartis and Bayer + technology providers inc PSE, PEL, Mettler Toledo
- 7 academic partners - leadership and influence in UK research and innovation systems
- Create critical mass of aligned expertise and specialist facilities

Demand Led Research Scope

Accelerate the adoption of continuous processing in pharmaceutical manufacturing



- Improve particulate based product supply via continuous processes
- Develop understanding of complex interactions between process, materials and quality
- Develop flexible continuous process technologies and understanding to deliver:

Robustness

Consistency

Manufacturability

Performance

Crystallisation - Multiple Objectives

Require crystallisation process to deliver:

- Purity (E)
- Form (R)
- Particle size (R)
- Shape (D)
- Yield (D)
- Volume productivity (D)
- Short cycle time (D)

(*E = essential, R = required, D = Desirable*)

- These are not independent - compromises often required
- Key transformations poorly understood
- Need to gather understanding quickly and efficiently
- **Combine structure, product and process understanding to deliver the right particles by first intent**

Perspective

From Form to Function: Crystallization of Active Pharmaceutical Ingredients

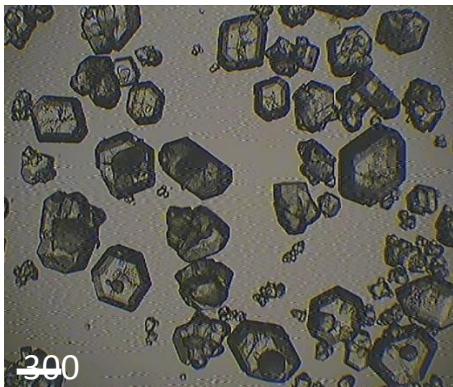
Narayan Variankaval and Aaron S. Cote
Merck & Co., Inc., P.O. Box 2000, Rahway, NJ 07065

Michael F. Doherty
Dept. of Chemical Engineering, University of California Santa Barbara, Santa Barbara, CA 93106

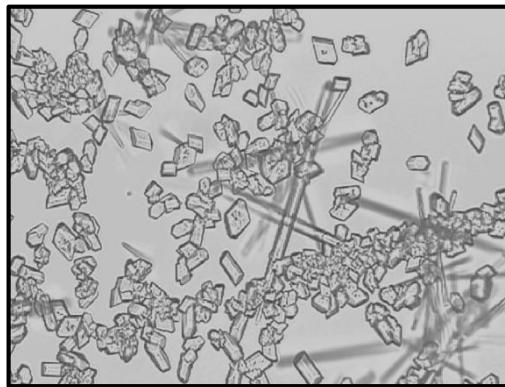
DOI 10.1002/aic.11555
Published online June 3, 2008 in Wiley InterScience (www.interscience.wiley.com).

Keywords: crystallization, pharmaceutical, polymorph, API process development, crystal shape, crystal size, milling

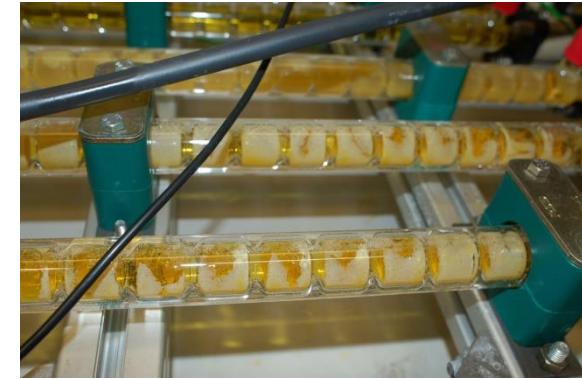
Poor Crystallisation Control



Fines in crystallisation of α form of L-glutamic acid –
e.g. **variable filtration times**



Mixture of carbamazepine forms II and III due to in situ transformation – **variable dissolution rates**



Uncontrolled growth on reactor walls (encrustation/ fouling) – **compromise heat transfer**

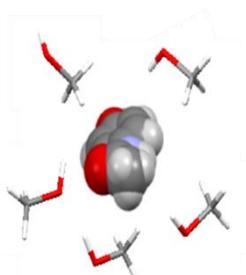
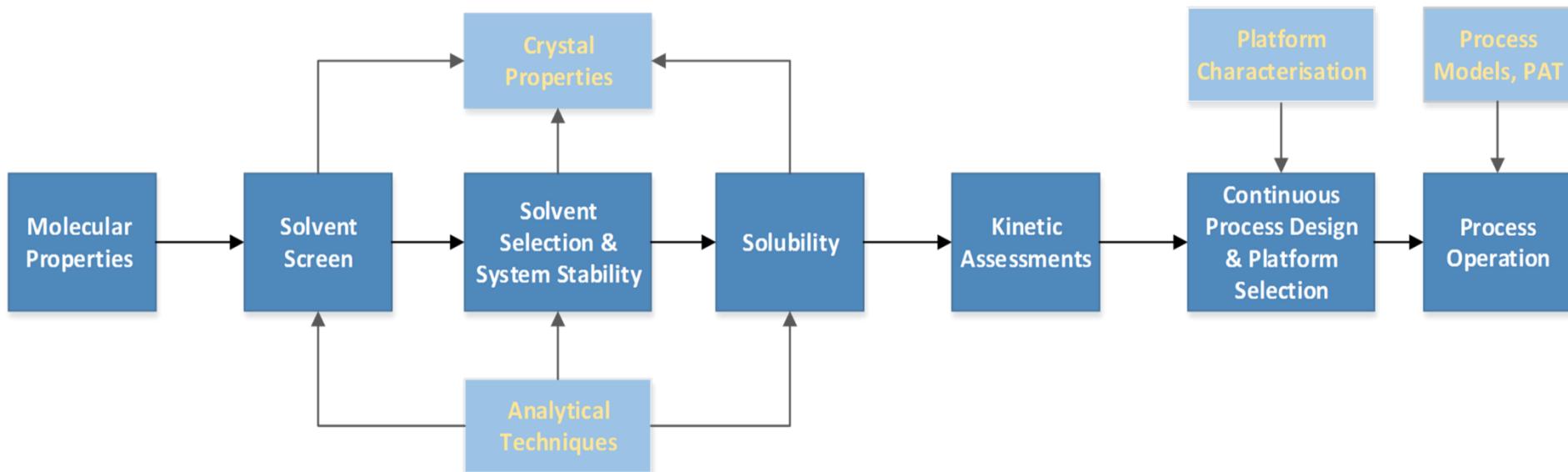


Encrustation on UV probe – **compromise measurement**

Supersaturation, secondary nucleation, attrition, agglomeration, encrustation and transformations can impact on measurement, uniformity and quality

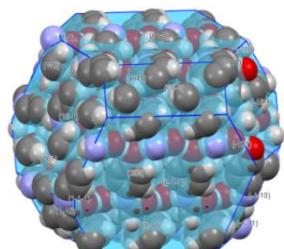
Workflows and Tools for Continuous Crystallisation Development

Implement a consistent, systematic approach across programme



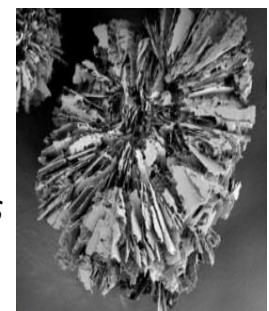
Process parameters
Physical transformations

Molecular attributes

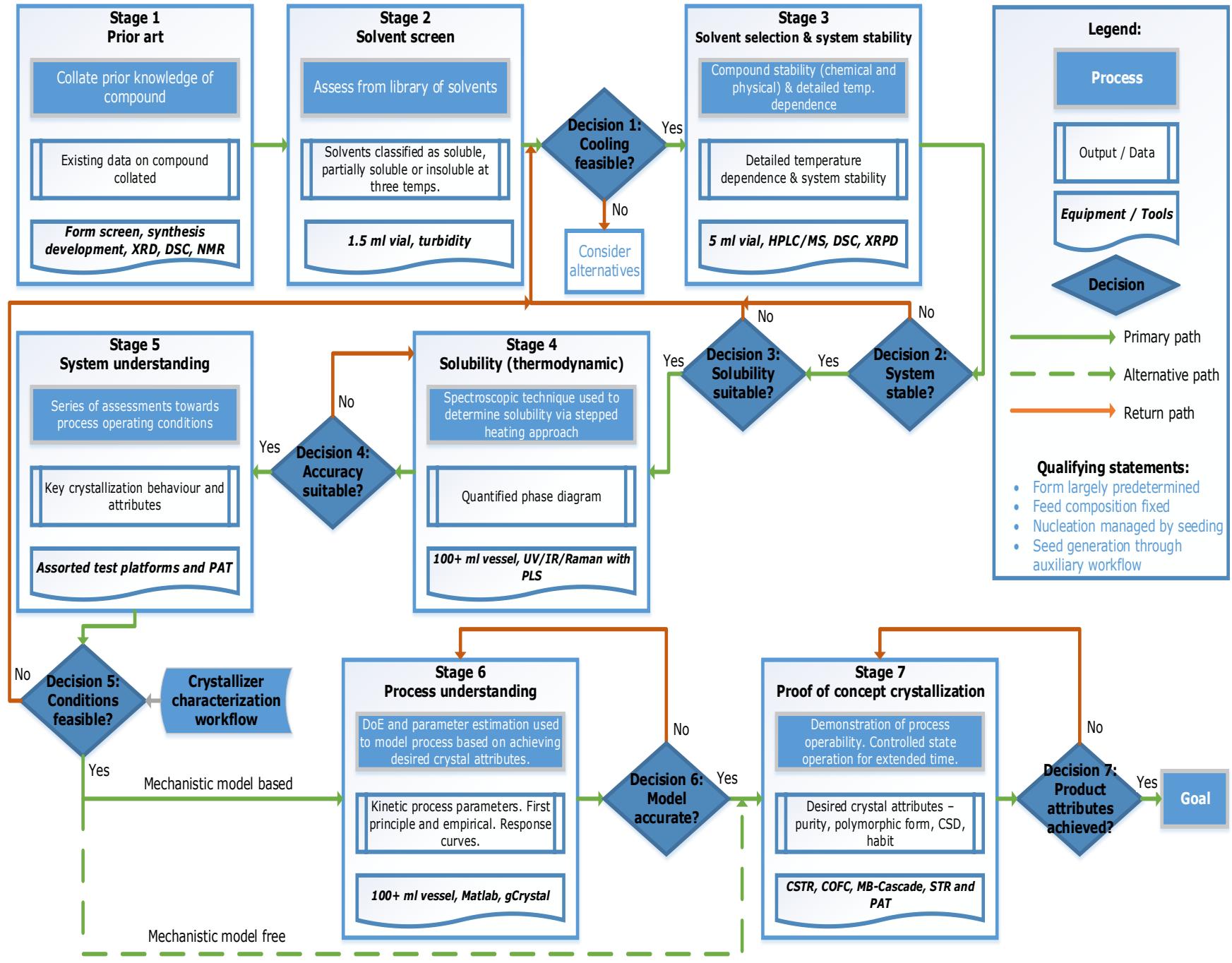


Process parameters
Physical transformations

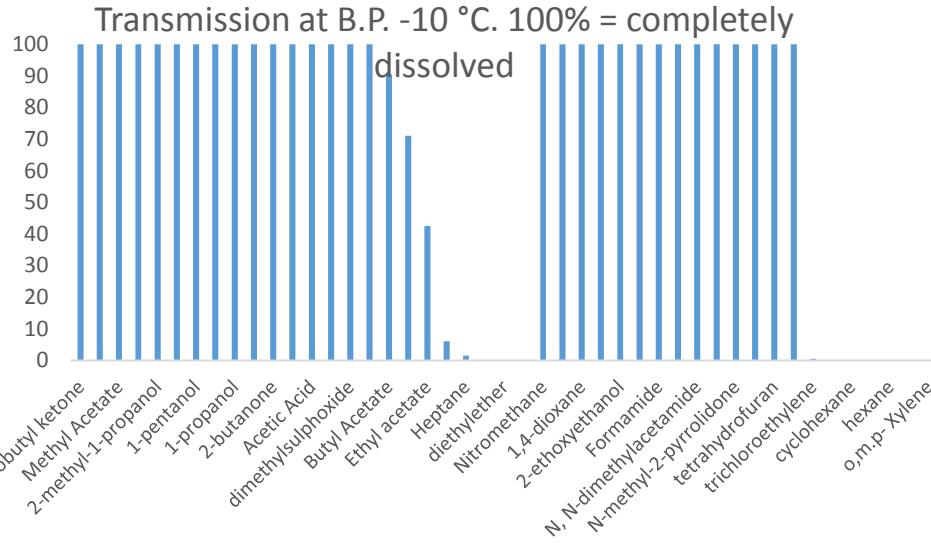
Particle attributes



Bulk attributes

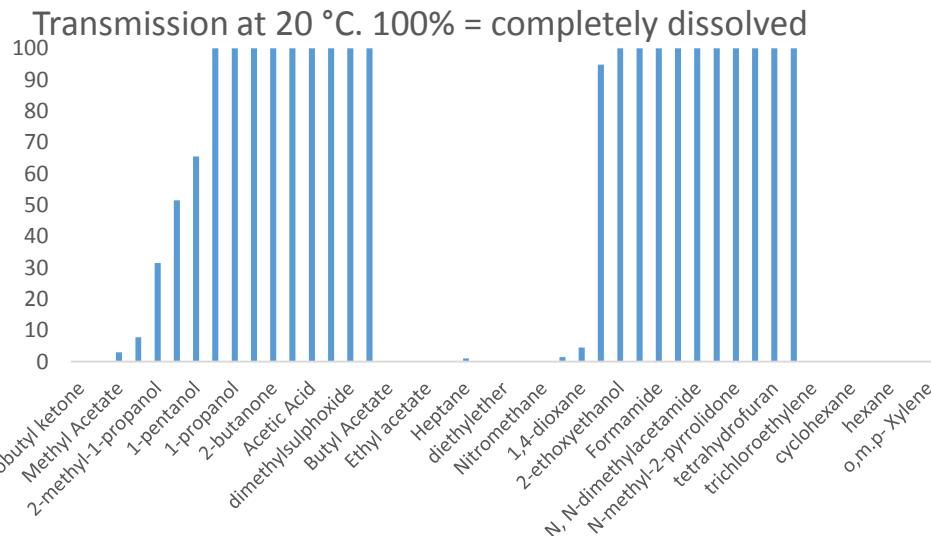


Stage 2: Solvent Screen



Description

- Assess solubility from library of solvents
- Broad range of solvent types and functionality



Methodology

- 50 g/L of API mixed with solvent
- Dissolution evaluated at 3 temperatures:
 - 20 °C
 - B.P. – 10 °C
 - Mid point



Selection Criteria for solvent screen

Parameter	Design space
Transmission at B.P. – 10 °C	> 95 %
Transmission at 20 °C	< 95 %
ICH Class	3 or 2

- 11 solvents out of 54 fall within design space and carried on to next stage

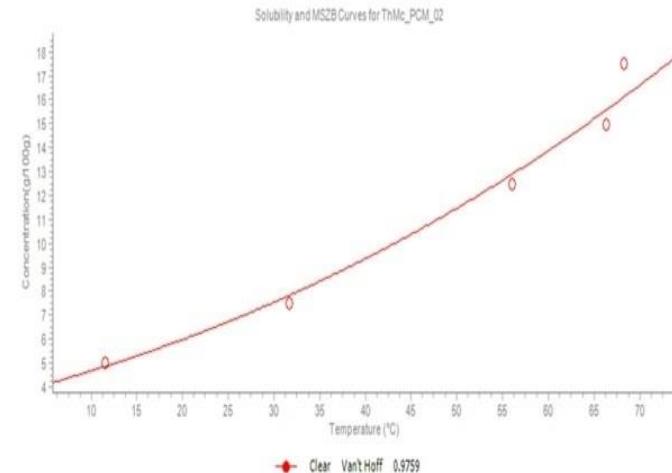
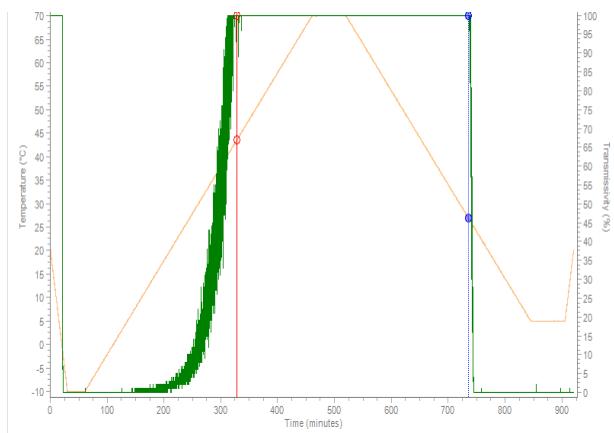
Stage 3: Solvent Selection

Description

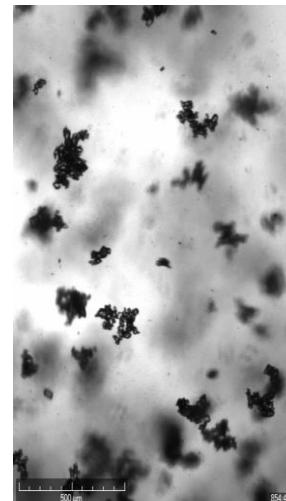
- Assess T- dependence
- Chemical and physical stability assessed

Methodology

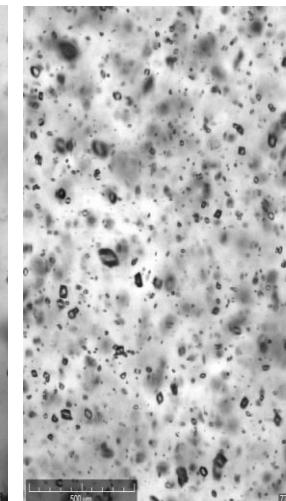
- Concentrations 2.5 to 20 wt%
- $T = 5 \text{ }^{\circ}\text{C}$ to $(\text{B.P.} - 10) \text{ }^{\circ}\text{C}$
- Slow heating ramp ($0.1 \text{ }^{\circ}\text{C}/\text{min}$)
- T cycling avoided
- Imaging used



High
agglomeration



Low
agglomeration



Fouled



Non-
fouled

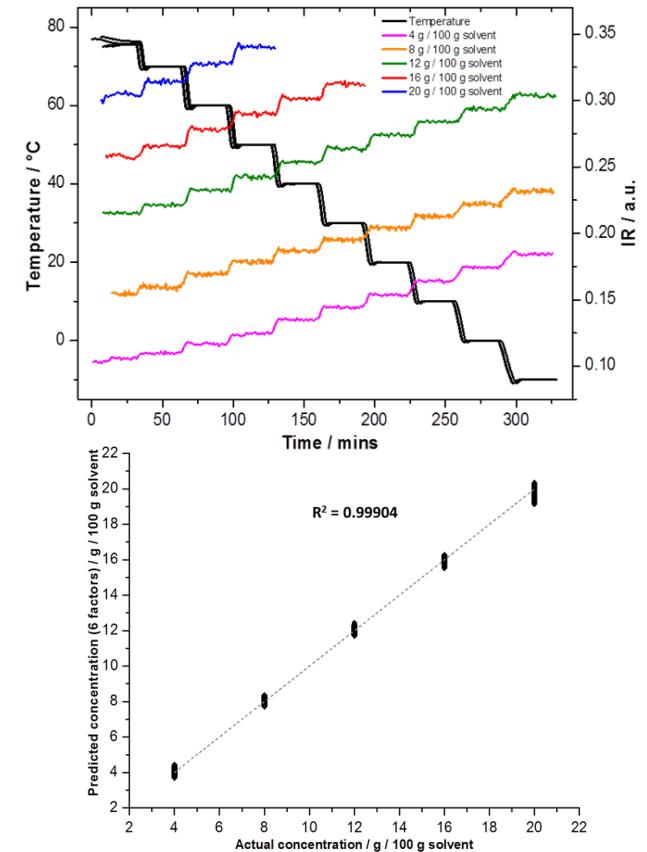
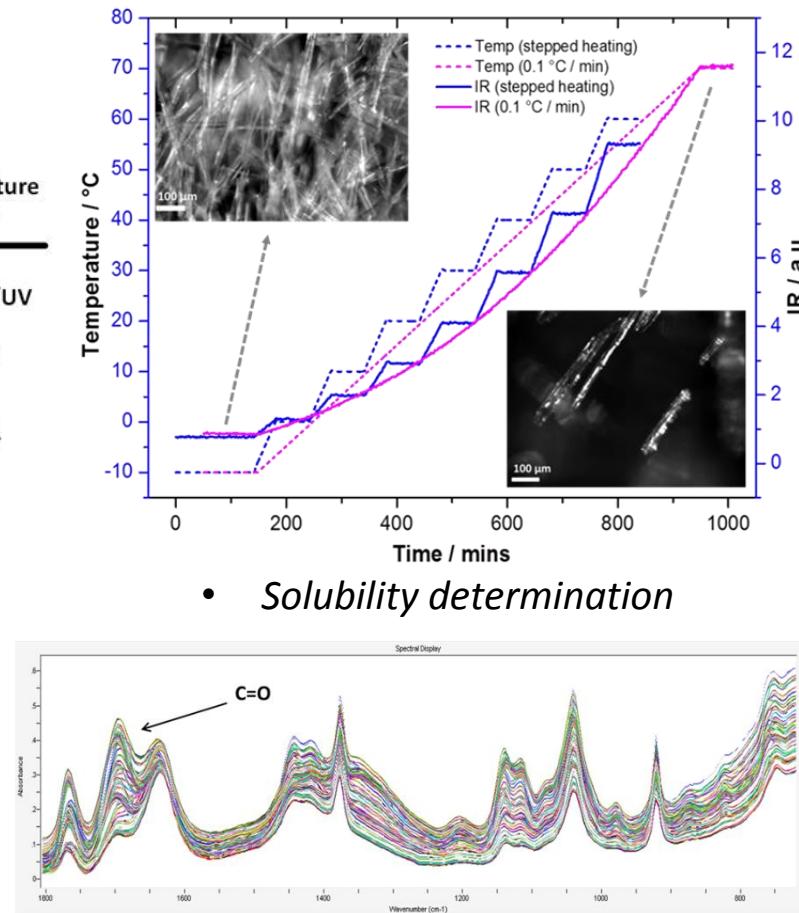
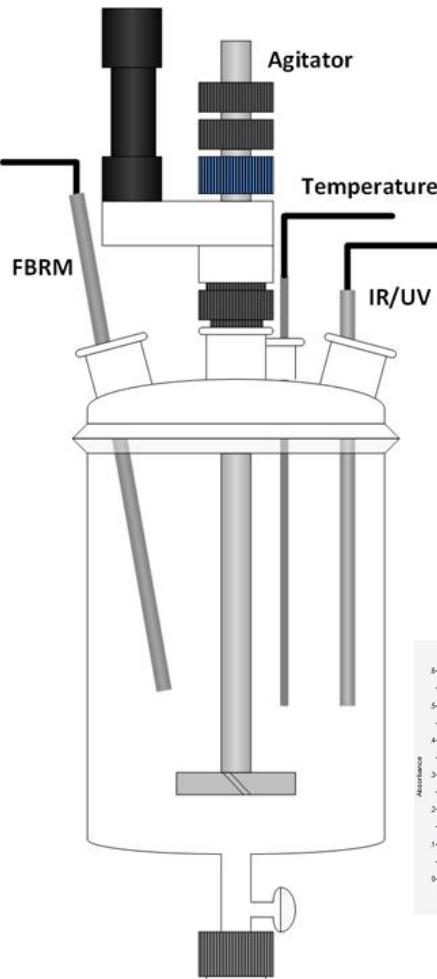


Stage 3: Solvent Selection

Parameter	Design space	Chosen solvent
Upper temperature	$\leq 90 \text{ } ^\circ\text{C}$	80 $^\circ\text{C}$
Lower temperature	$\geq 5 \text{ } ^\circ\text{C}$	5 $^\circ\text{C}$
Yield	$\geq 90 \text{ \%}$	90 $\%$
Solid fraction	10 to 25 % w/w	17 %
Metastable zone width	$> 5 \text{ } ^\circ\text{C}$	20 $^\circ\text{C}$
Form and chemical stability at elevated temp.	$> 24 \text{ hr}$	$> 24 \text{ hr}$
Agglomeration	Low to none	Low to none
Fouling	None	None

- Only 1 solvent out of 11 from previous stage met design space criteria:
 - 3-methyl-1-butanol (iso-amyl alcohol)

Stage 4. In-line monitoring of crystallisation e.g. spectroscopic approaches



- *Temperature dependent calibration using PLS modelling*

Stage 5: System understanding

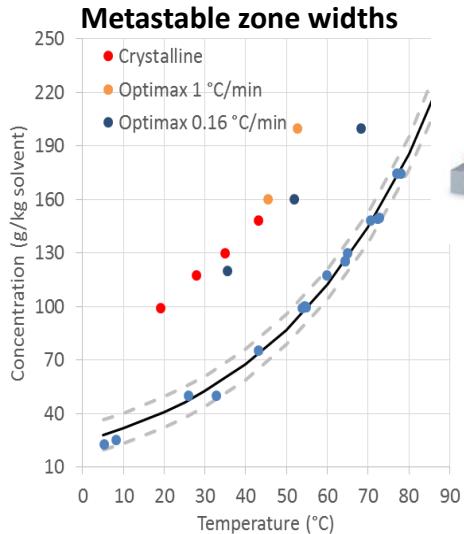
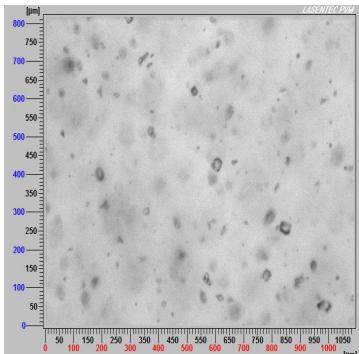
Description

- ID process conditions for desired performance.
- ID limits
- Inform platform selection, mixing, etc.

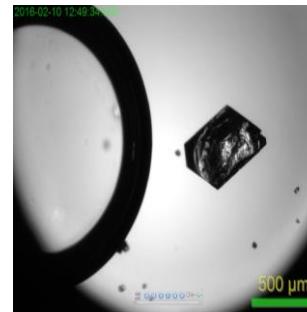
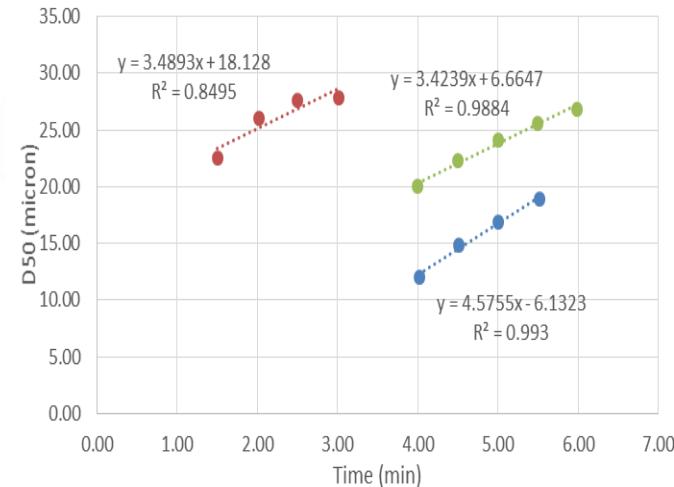
Methodology

- Range of tests developed to assess:
 - Metastable zone
 - Secondary nucleation
 - Growth rate
 - Fouling
 - Agglomeration

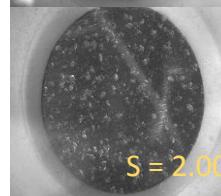
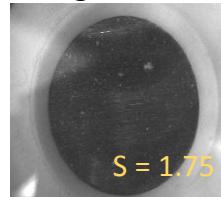
Agglomeration



Growth rates. Bulk and single crystal



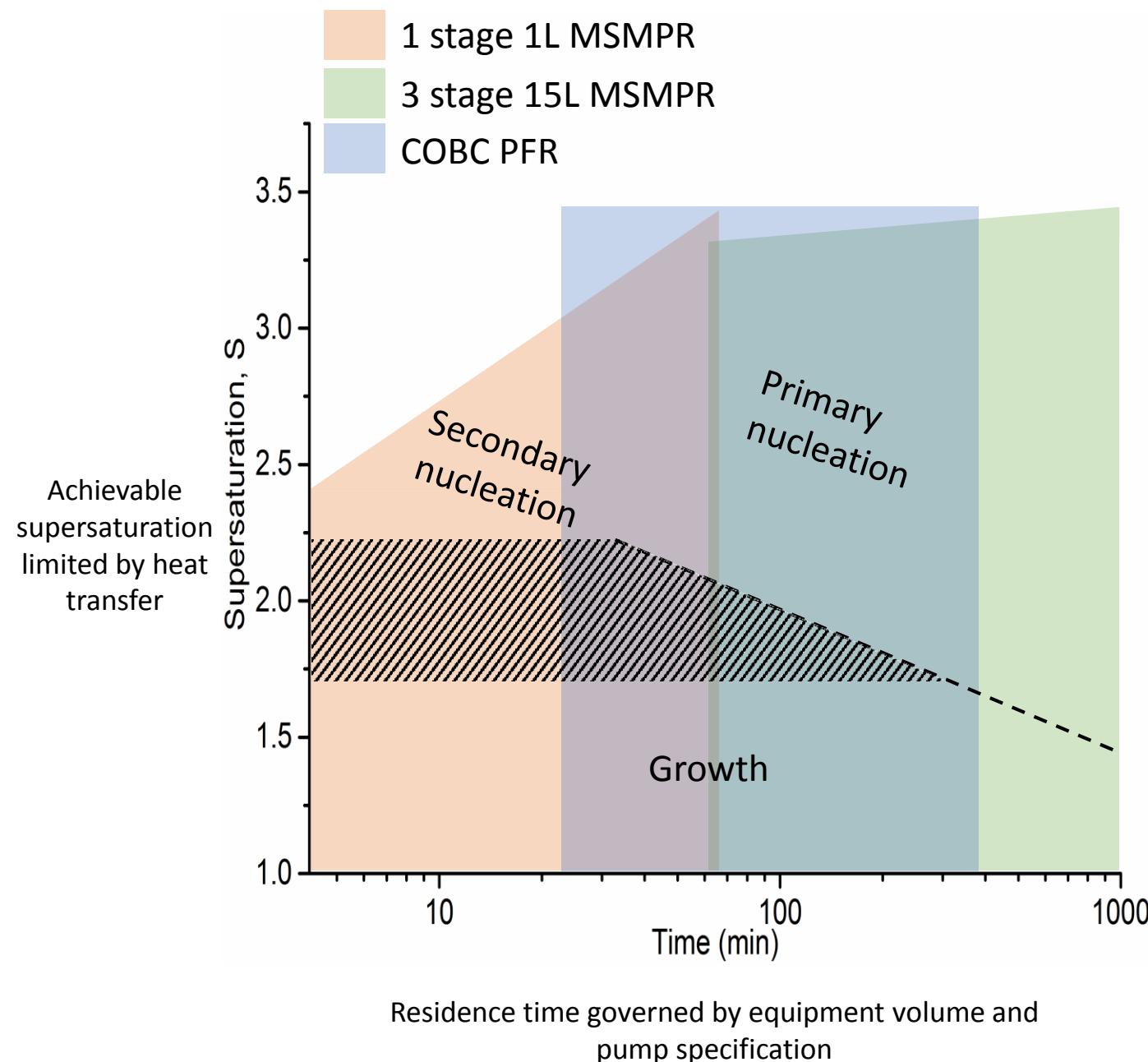
Fouling induction times



Stage 5: System understanding

Parameter	Chosen solvent
Metastable zone width	22 to 35 °C
Min. supersaturation for secondary nucleation	$S = 1.7$ to 2.2
Growth rate	Max 3 $\mu\text{m}/\text{min}$
Agglomeration	Low to none
Fouling induction time	$S = 1.75$: 278 min $S = 2.00$: 107 min

Stage 5: System understanding



From system understanding tests:

- 1. Primary nucleation** observed at:
 - 40 min at $S=2.2$
 - 107 min at $S=2.0$
 - 278 min at $S=1.75$
- 2. Secondary nucleation** observed at $S=2.2$ but not at $S=1.7$

Couple system understanding and crystalliser characterisation to select suitable platform(s)

Stage 6: Process understanding

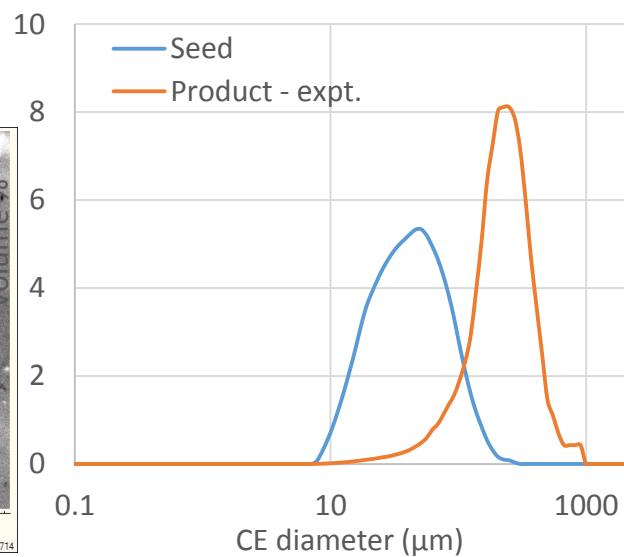
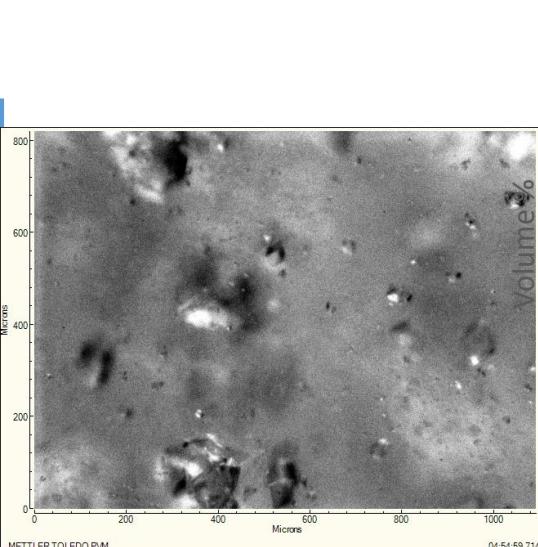
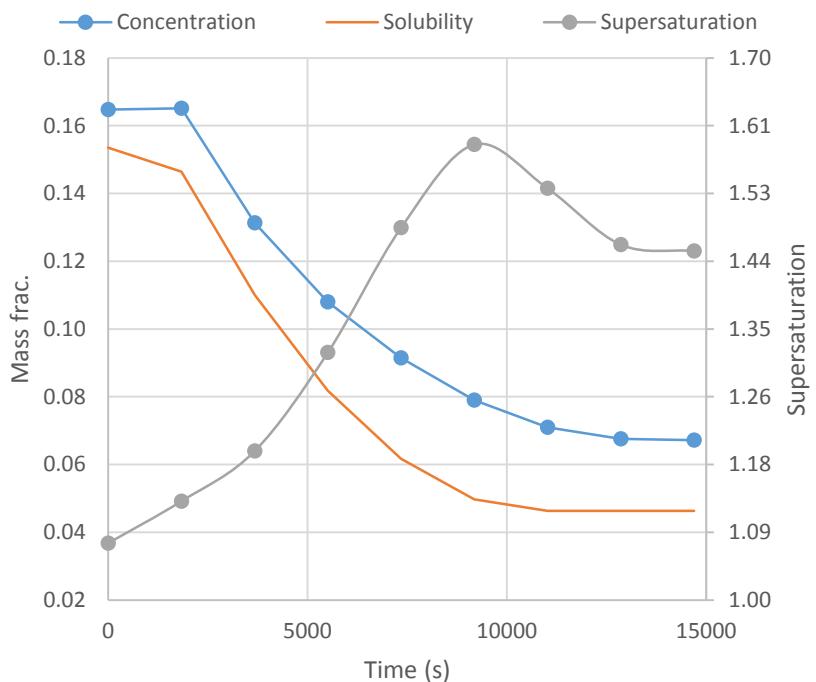


Description

- Experimental DoE coupled with PBE to establish design space

Methodology

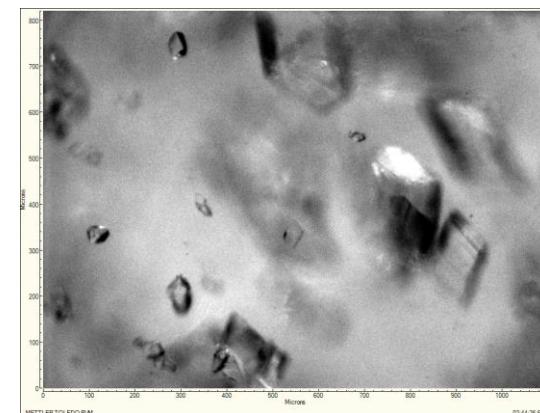
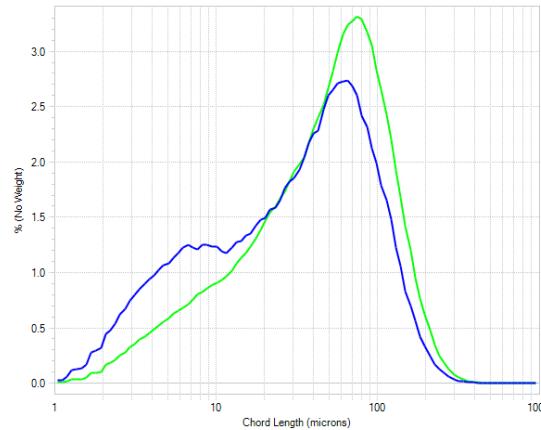
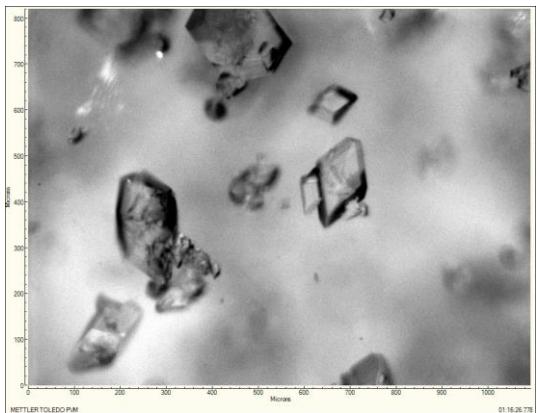
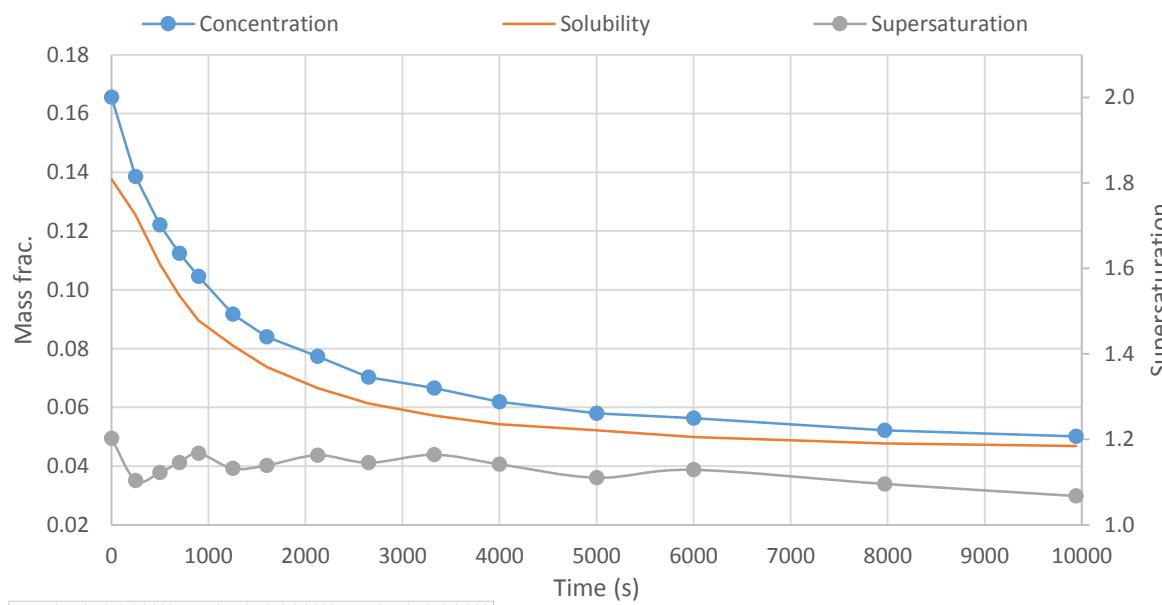
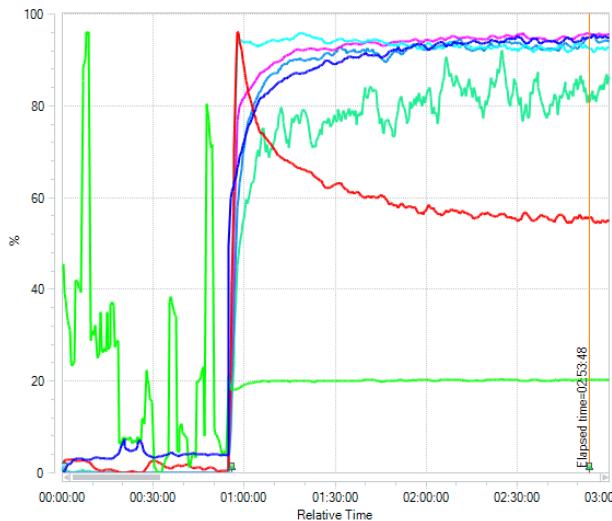
- Batch seeded cooling experiments used as basis for parameter estimation
- Covering a range of seed mass, cooling rate and power input



Expt.	Seed mass (g)	Cooling rate (°C/min)	Power input (W/kg)
1	0.95	0.50	0.023
2	4.73	0.50	0.023
3	0.95	0.17	0.023
4	0.95	0.50	0.053
5	4.73	0.50	0.053
6	2.84	0.35	0.053

Stage 6: Process understanding

- Experiments also performed under supersaturation control to minimise likelihood of nucleation
- Using ReactIR signal as feedback
- Temperature offset 8 °C ($S = 1.2$)

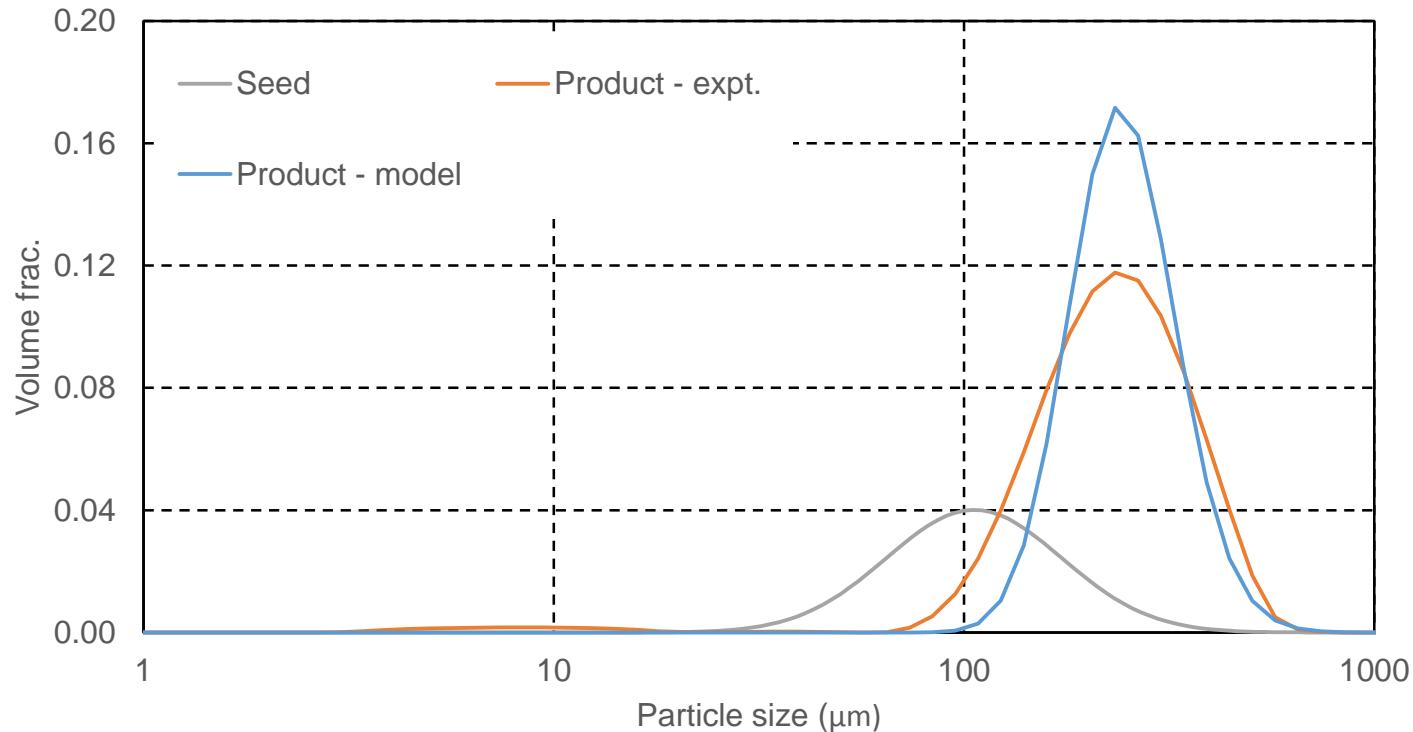


Stage 6: Process understanding

- Parameter estimation - power law growth model

Model Parameter	Final Value	Initial Guess	Lower Bound	Upper Bound	Confidence Interval			95% t-value	Standard Deviation
					90%	95%	99%		
Crystallizer_MSMPR001 Activation energy ("PCA_cry")	0	0	0 *	0 *					
Crystallizer_MSMPR001 Growth rate constant ("PCA_cry")	0.00036478	0.00036478	1×10^{-5}	0.001	0.004745	0.005719	0.00773	0.06378 **	0.002782
Crystallizer_MSMPR001 Order with respect to supersaturation ("PCA_cry")	4.12663	4.12663	1	5	5.978	7.205	9.738	0.5727 **	3.505
Reference t-value (95%):								1.70557	

Expt. 8 - PSD comparison



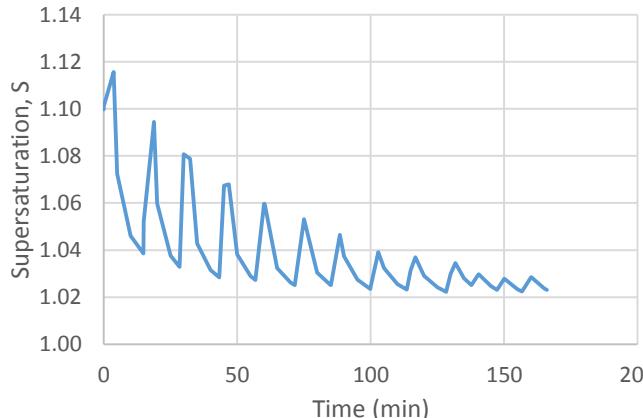
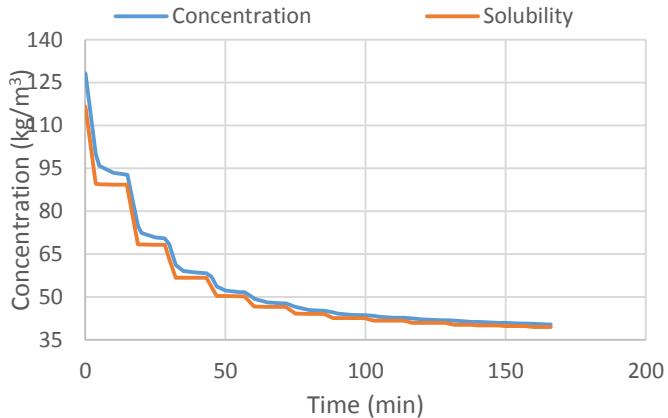
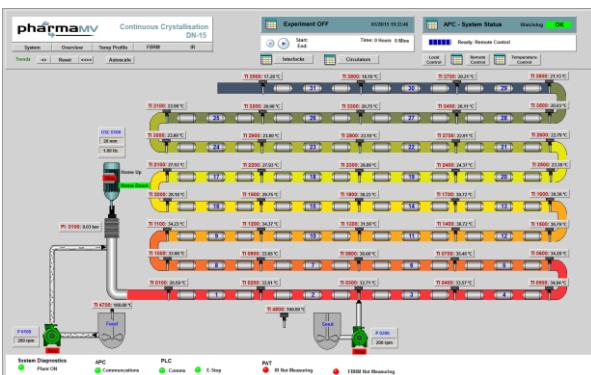
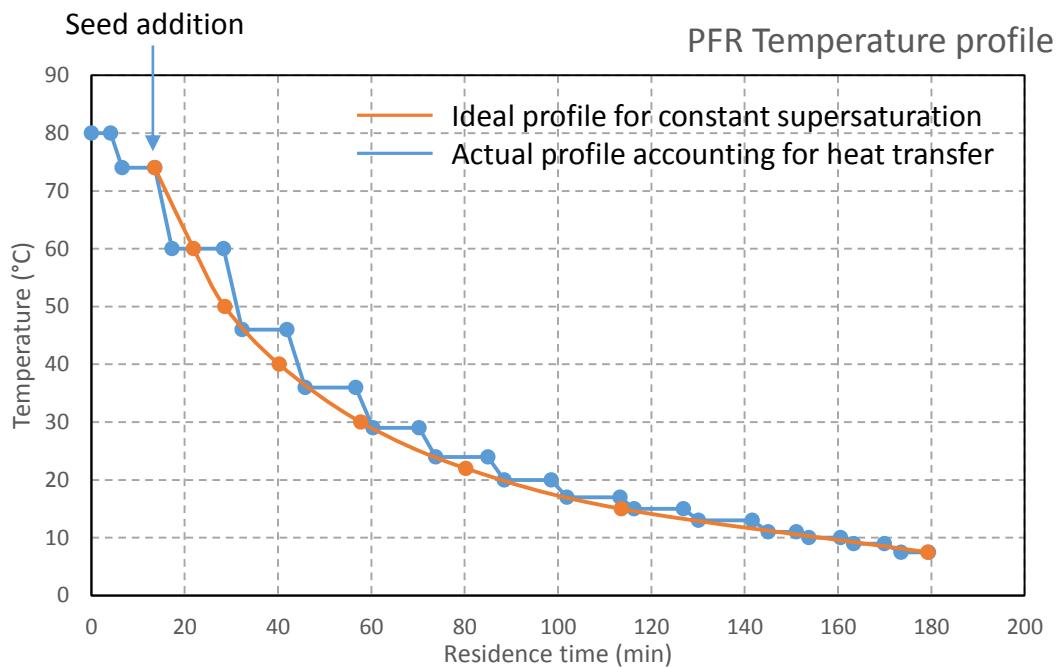
Stage 7: Proof of concept

Description

- Design continuous crystallisations to deliver specific particle size targets

Methodology

- Combine PBE model with heat transfer models to determine T profile and seed loading to meet target size
- Continuous crystallisations performed in modular skid mounted units configurable as PFR or MSMPR



Example PFR:

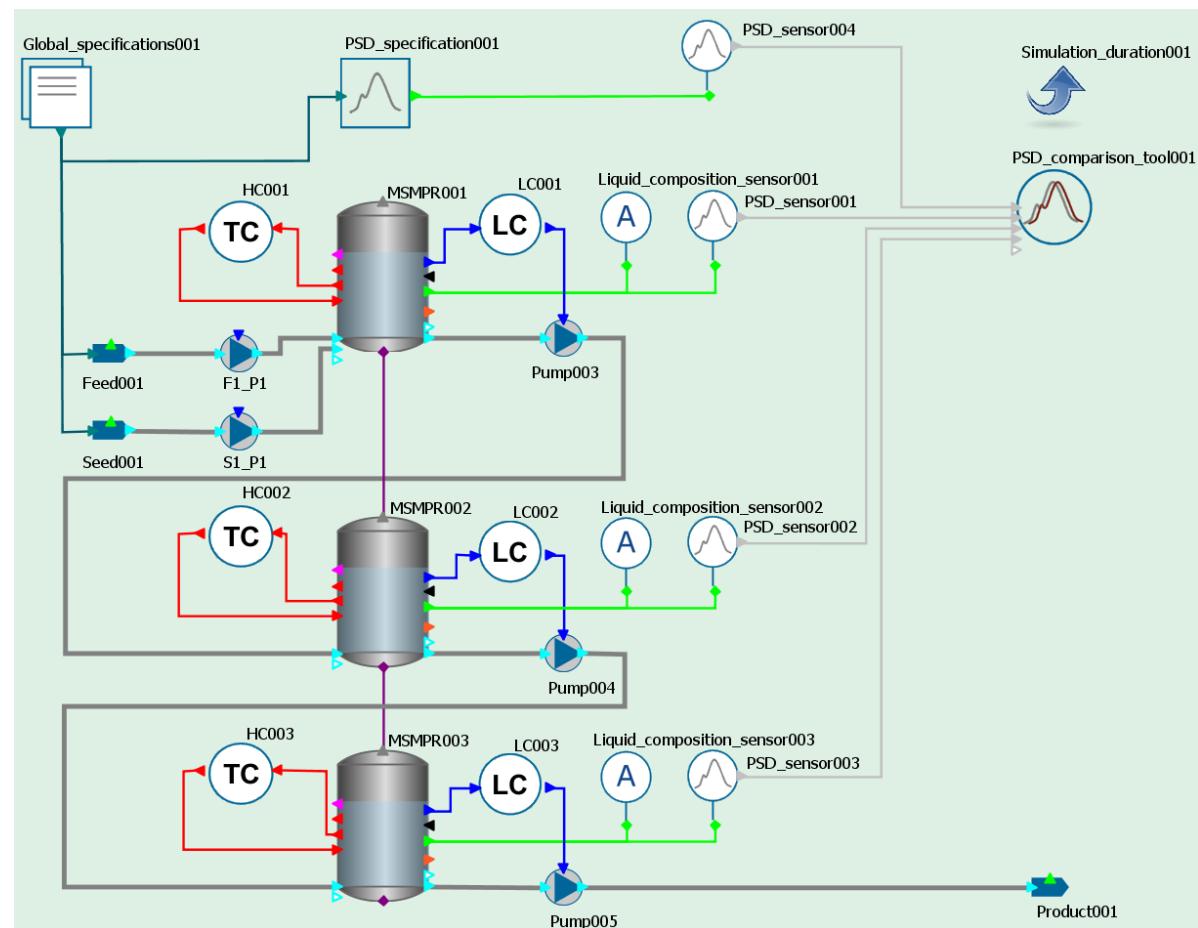
- Target: $D_{50} \sim 67 \mu\text{m}$, span ~ 1.5 , 3.5 kg crystal mass
- Temperature profile to maintain $S = 1.2$ converted to COBC profile
- 6.1 % seed loading, 166 min residence time, 1180 min operating time (excluding start-up)

Stage 7: Proof of concept

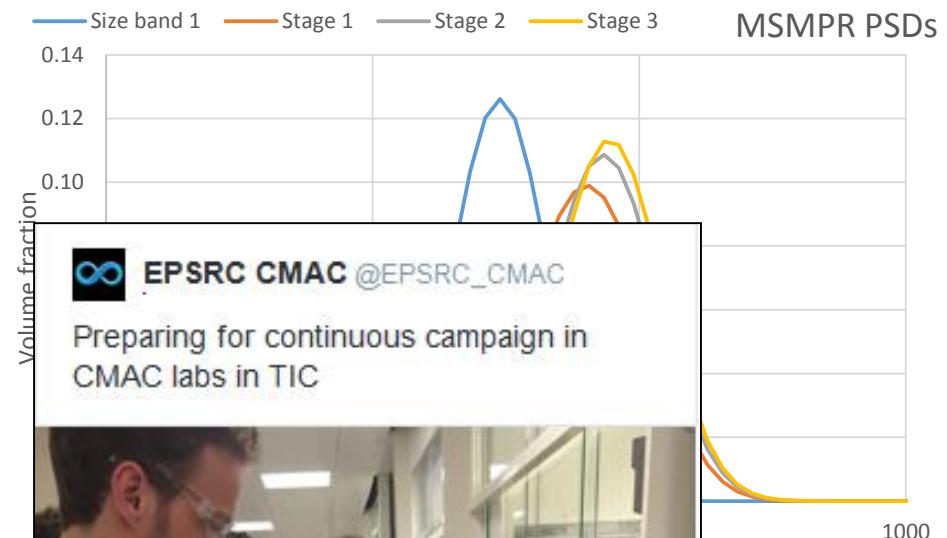
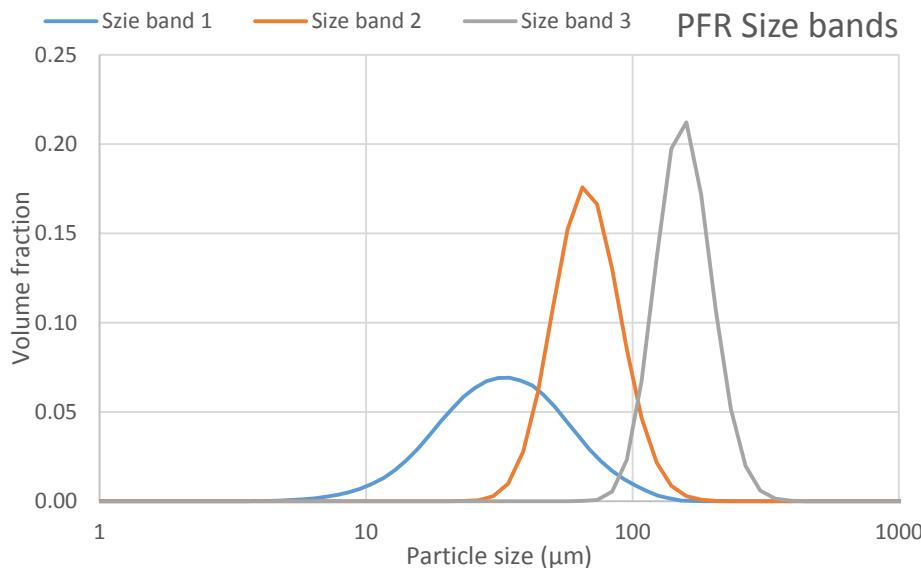
Example MSMPR:

Target: D₅₀ ~ 77 µm, span ~1.22, 2.5 kg crystal mass

- 3 stage MSMPR using 2 L vessels
- Stage temperatures: 63.8, 48.3 and 32.5 °C (keeps S < 1.35)
- 7.1 % seed loading, 172 min residence time, 980 operating time (excluding start-up)

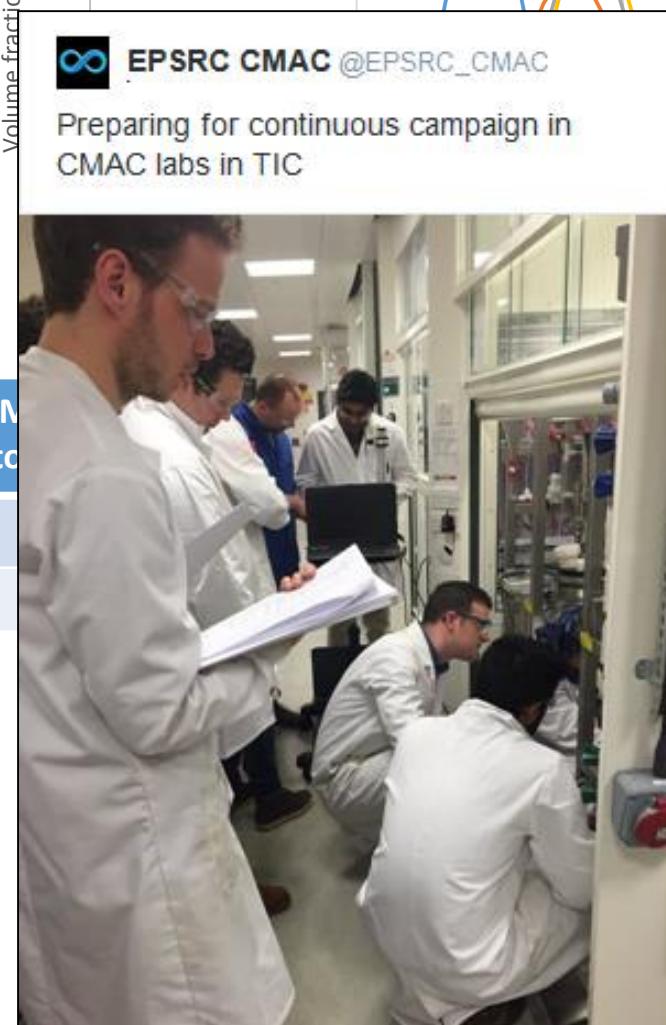


Stage 7: Proof of concept - overview



	Size band 1 total (kg)	Size band 2 total (kg)	Size band 3 total (kg)	Not total
Isoamyl alcohol	40.95	30.64	51.07	
Paracetamol	7.71	5.73	9.55	

Campaigns under way for 4 weeks,
w/c commencing 18th April

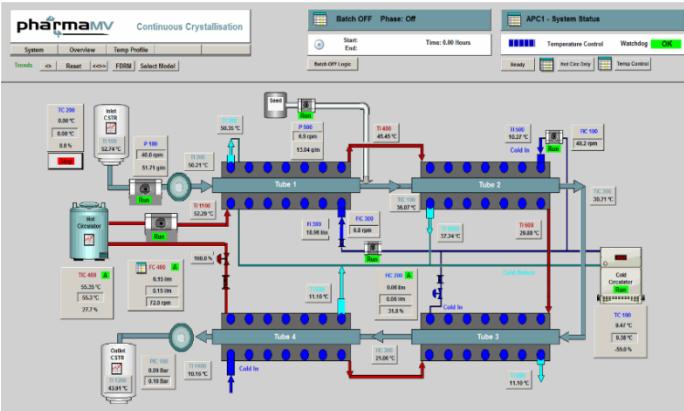


28.95 kg
4.50 kg
ent): 56 L
dispersant): 6 L

Continuous Crystallisation Case Studies

Basic Automation

Cambridge Reactor “Rattlesnake”



Systems set up with:

- Feed and seed pumps
- Circulators and temperature sensors
- FTIR and FBRM PAT instruments
- Industrial Programmable Logic Controllers
- Industrial PCs with PharmaMV software

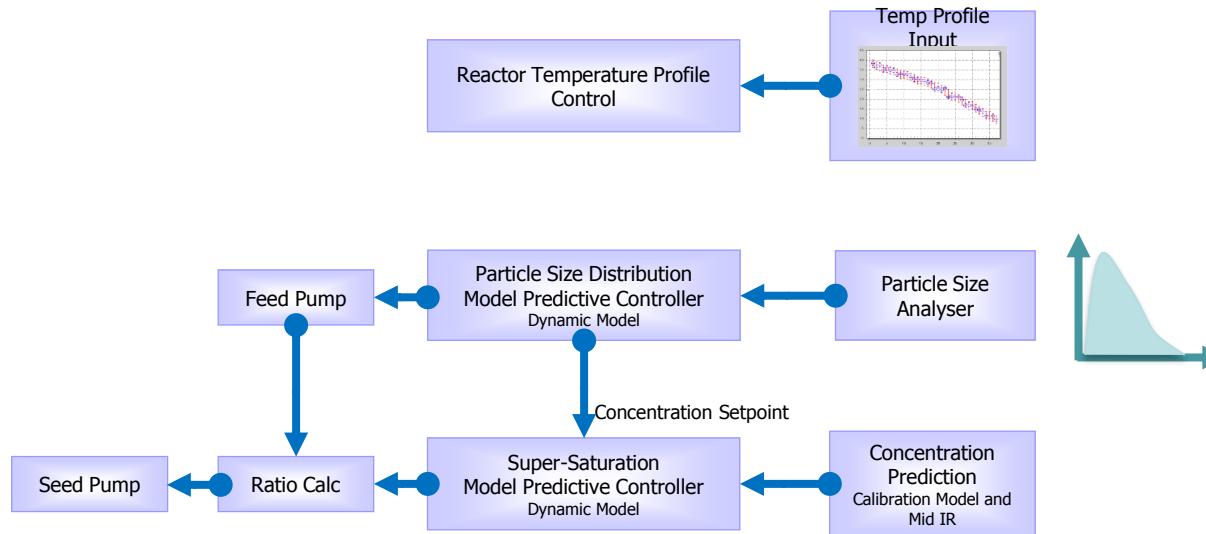
Nitech DN-15



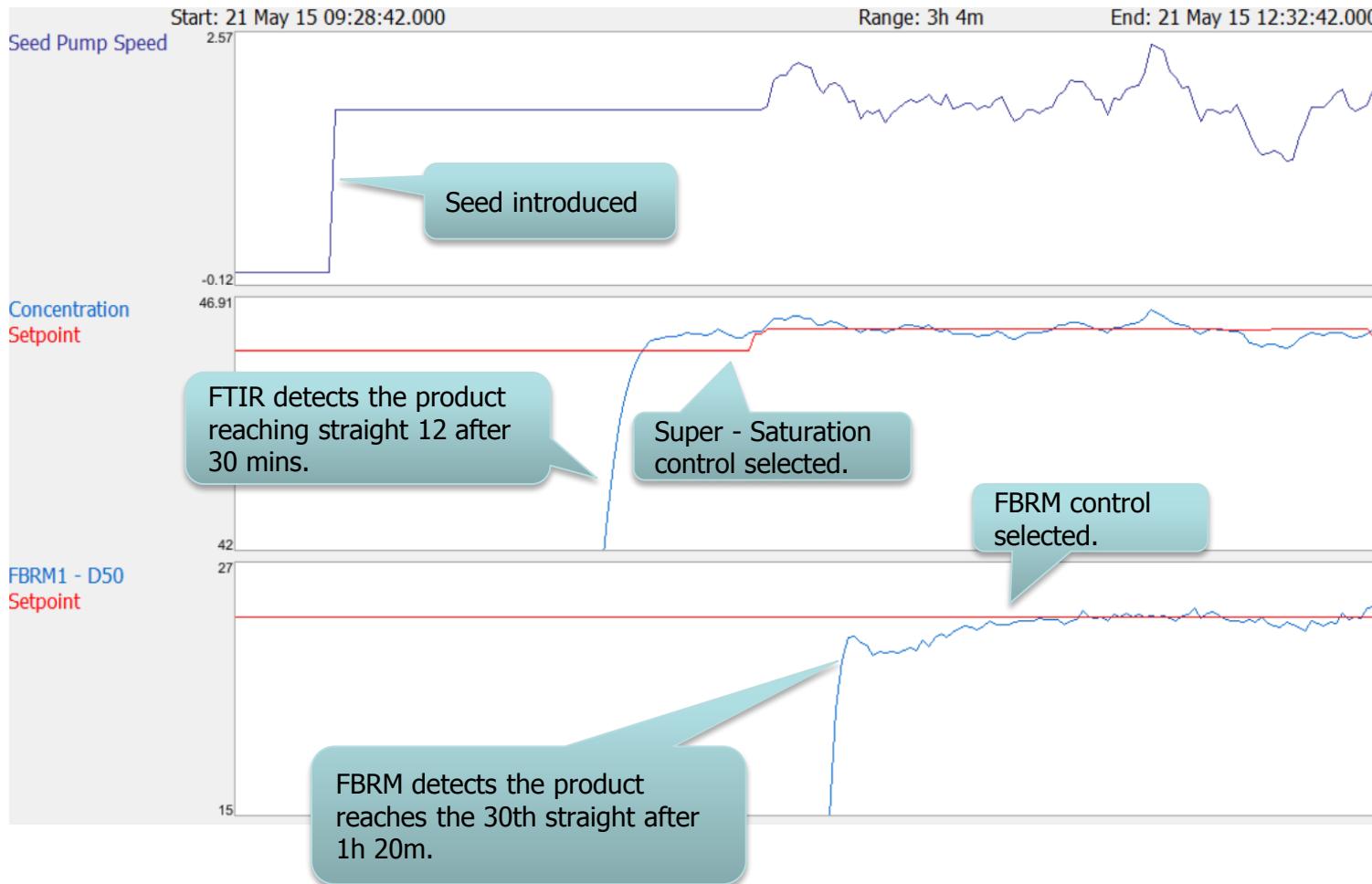
APC for Continuous Crystallisation

Transferrable Control Strategy

- The solution consists of three model-predictive controllers.
 - **Temperature Profile Controller:** Maintains the temperature profile at the optimum. The profile is not adjusted in real-time.
 - **Super-Saturation Control:** Controls super-saturation mid-way through the reactor by adjusting seed loading to FTIR derived concentration.
 - **Particle Size Control:** Adjusts super-saturation levels based on FBRM results (D50: PSD Median).



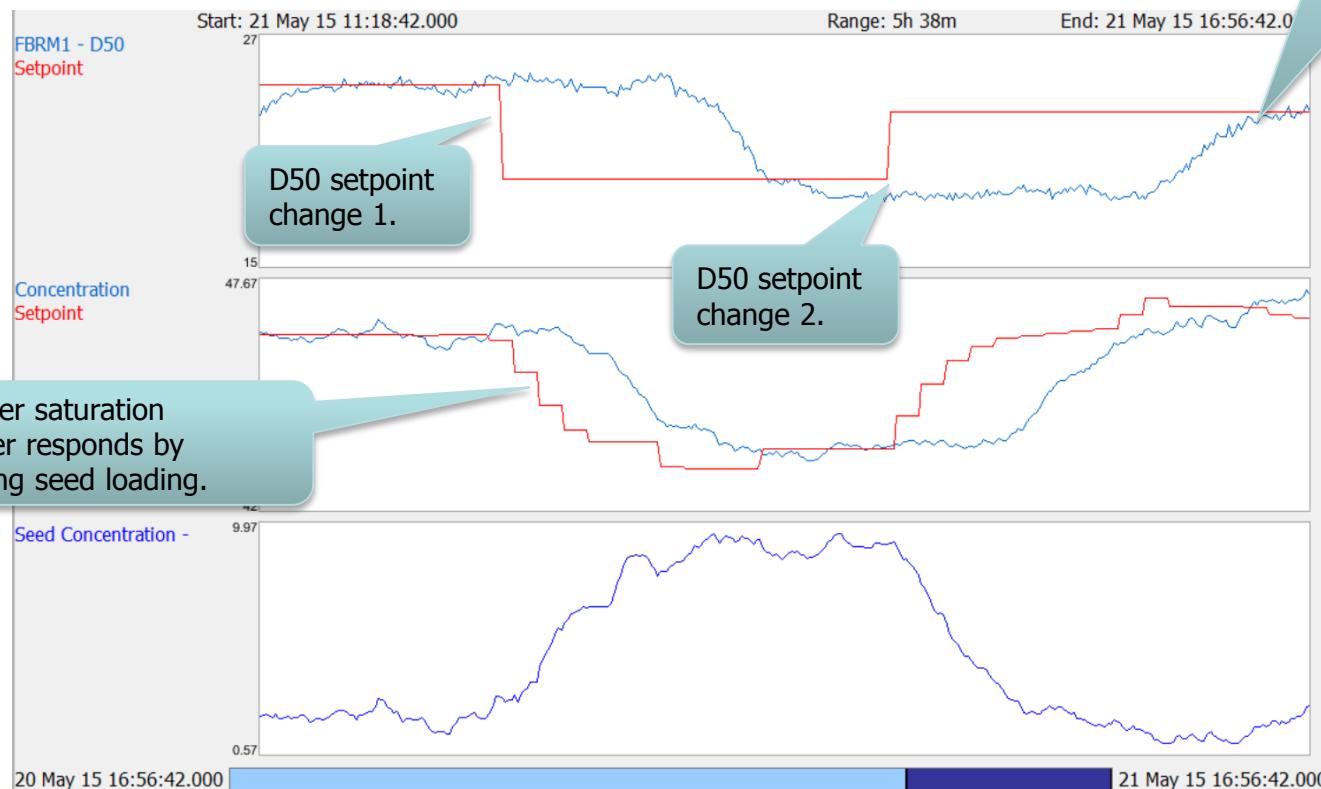
APC for Continuous Crystallisation: Concentration and FBRM Based Control – Start Up (DN 15)



APC for Continuous Crystallisation

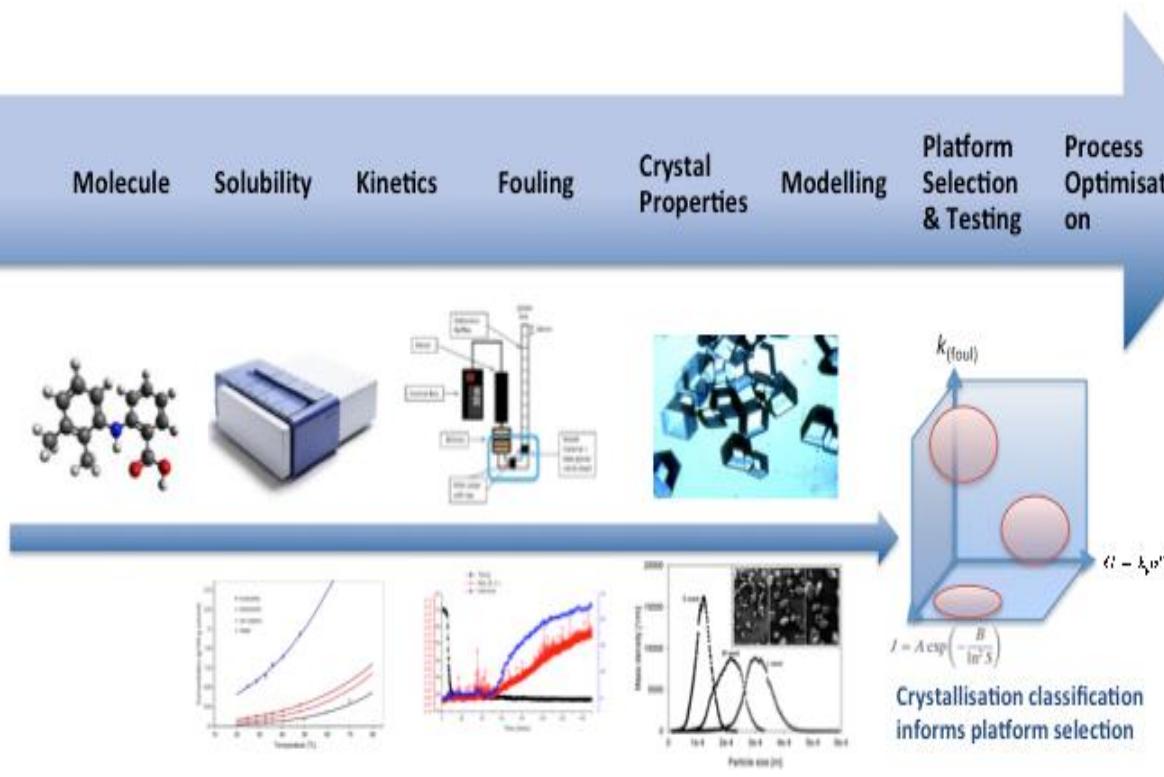
D50 Setpoint change demonstration (DN 15)

- To evaluate the APC system's performance, two D50 setpoint changes were applied during a continuous run.



Exploiting Informatics

- Utilise ELN to accumulate systematic data from different systems
- Complement mechanistic models with statistical tools



CrystEngComm

COMMUNICATION



[View Article Online](#)
[View Journal](#) | [View Issue](#)

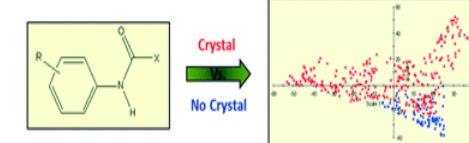
A random forest model for predicting the crystallisability of organic molecules†

Cite this: *CrystEngComm*, 2015, 17, 4272

Received 4th December 2014,
Accepted 16th February 2015

A random forest model has for the first time enabled the prediction of the crystallisability (crystals vs. no crystals) of organic molecules with ~70% accuracy. The predictive model is based on calculated molecular descriptors and published experimental crystallisation propensities of a library of substituted acylanilides.

$J = A \exp\left(-\frac{B}{\ln S}\right)$
Crystallisation classification informs platform selection



Predicting Crystallisability Of Organic Molecules using Random Forest

Applied also to solubility, nucleation, fouling, agglomeration, polymorphism, solvate formation



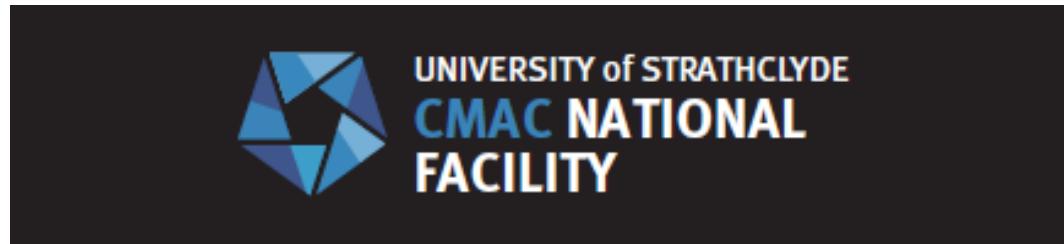
Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation



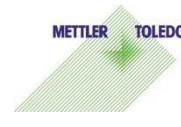
Acknowledgements

Cameron Brown, Thomas McGlone, Humera Siddique, Ian Houson, Naomi Briggs
Vishal Raval

Fraser Mabbott, Stephanie Yerdelen, Sebastian Davidson , Bilal Ahmed, Nazer Rajoub, Scott McPhee,
Jan Sefcik, Chris Rielly, Joop ter Horst, Alison Nordon, Chris Price,
Sara Ottoboni, Clarissa Forbes



Ewan Mercer
John Mack
Karolina Krzemieniewska
Mihai Rascu



GSK



AstraZeneca



NOVARTIS



CRD CAMBRIDGE REACTOR DESIGN

