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Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

CMAC: A National Research Centre in Continuous Manufacturing and Crystallisation

Prof Alastair J. Florence,

EIPG Scientific Symposium, Technology Advances Impacting Pharmaceutical Industry, 17 April 2016

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Engineering and Physical Sciences Research Council

Opportunities for Continuous Manufacturing

- Adoption of Lean Manufacturing Principles
  - Avoid challenges of large batch by controlled steady-state continuous processes
- Growing levels of interest across pharma – demand for better solutions
- Benefits include:
  - **Greater control over product quality** – improved purity, more predictable scale-up
  - **Lower costs** – capex, opex, working capital
  - **Sustainability** – less waste, "greener chemistry", lower CO_2 footprint
  - **Greater responsiveness** – speed to market, reduced stock outs, adding capacity
  - **Enables** the manufacture of more complex products

But, many challenges and no complete solution exists - better understanding required

Community Recommendations

J. Pharm Sci. 104(3), 781–791, 2015

Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Workup, and Isolation of Drug Substance May 20–21, 2014 Continuous Manufacturing Symposium

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Need to Develop:

- Flow chemistry toolbox
- More selective chemistries
- Modular equipment (lab-scale / standardization)
- Modelling & control methods across operations
- Means to manage change (catalyst / fouling)
- Workflows for process design
- Culture: inputs from across organisation; multidisciplinarity
- Skills development
- Disseminate examples of CM
- Engage with regulators
- Economic case for CM

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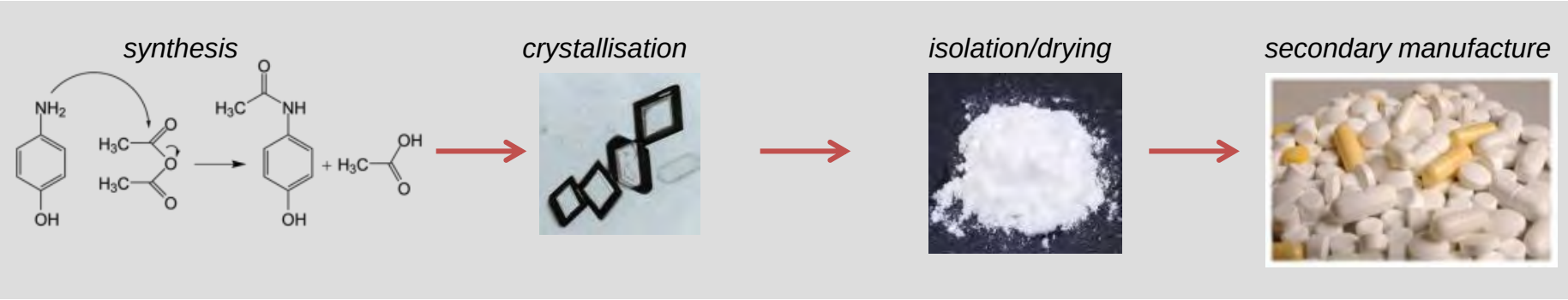
Collaborative Centre Scope: from synthesis to formulated product



Focus on Improving Particulate Based Products, Processes and Supply Chains

Develop tools and know how to exploit continuous manufacturing to deliver:

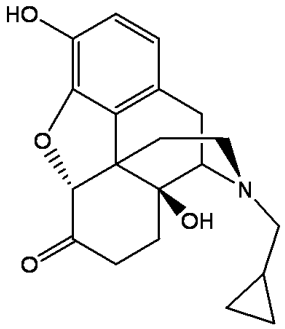
Consistent Particles

Better Particles

Novel Particles

So what's the problem with crystallisation?

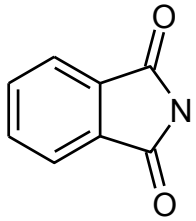
….molecules show complex physical form behaviour



Naltrexone

62 crystallisations from 31 solvents:

- 34 distinct solid forms identified
- 3 polymorphs & 27 solvates



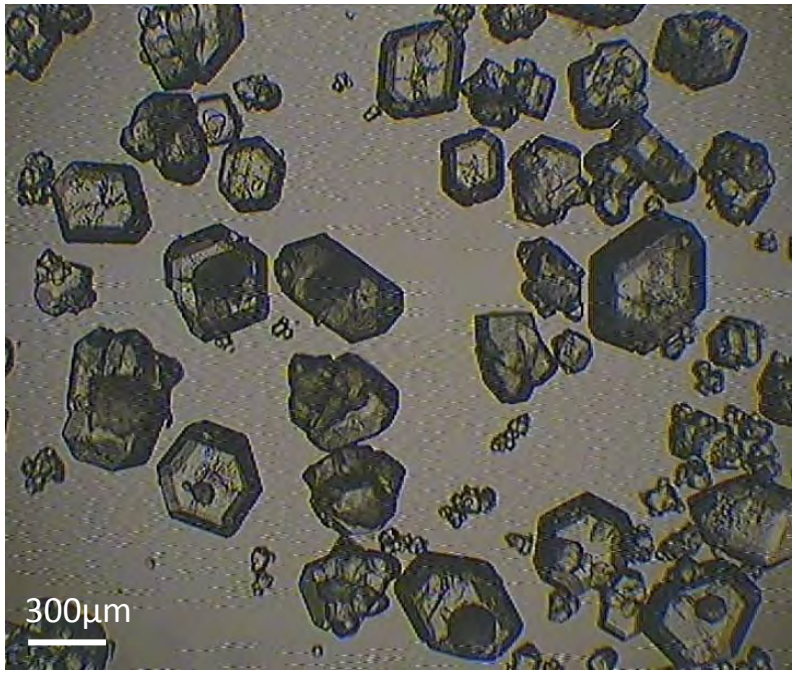
Phthalimide

> 500 crystallisations from 67 solvents:

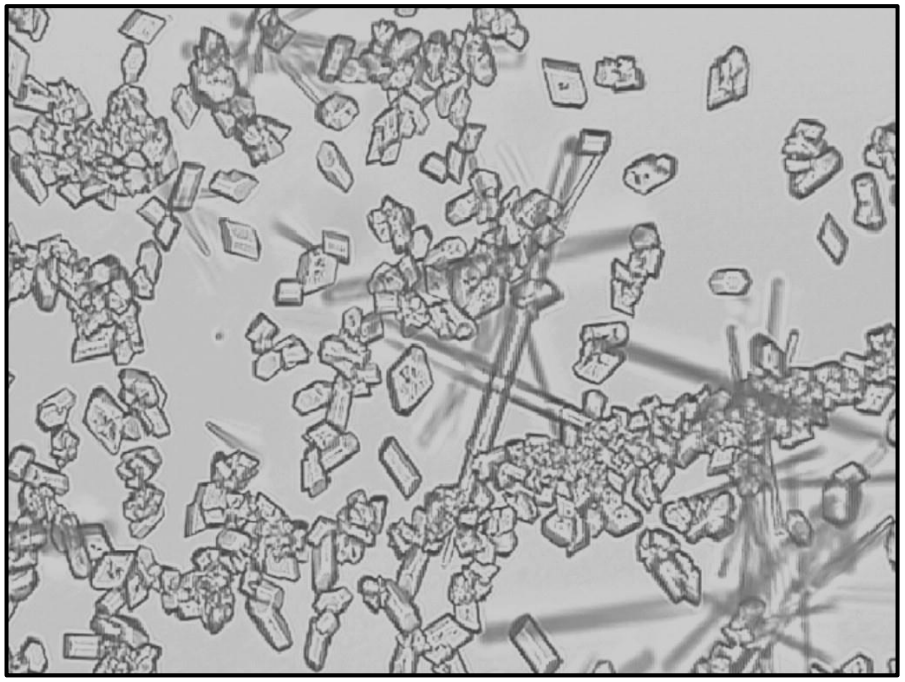
- only 1 solid form identified

Need to produce only the required form – phase diagram can be complex

…as well as Complex Transformation Processes



Fines in crystallisation of α form of L-glutamic acid – Variable filtration time

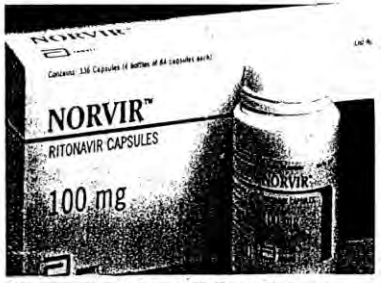


Mixture of carbamazepine forms II and III due to in situ transformation – variable dissolution rates

Supersaturation, secondary nucleation and transformation impact on uniformity and control as well as cost of quality

Can Lead to Problems with Performance e.g. Polymorphic form

Manufacturing problems hit Abbott's HIV drug ritonavir



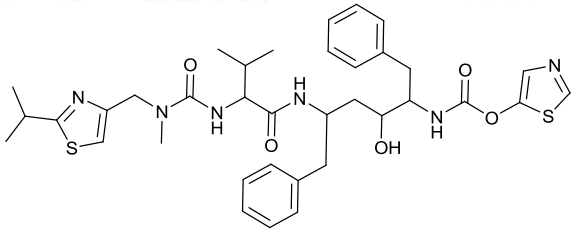
Capsules unlikely to be available from mid-August

Capsules of Abbott Laboratories' protease inhibitor Norvir (ritonavir) are likely to become unavailable by the middle of August. The company has a problem with the manufacture of the anti-HIV capsules which it cannot resolve at present.

The problem relates to "undesirable" crystal formation. Abbott says that a series of recent production batches of Norvir capsules failed the approved test for dissolution, and were not released for marketing. Investigation of the reason for the failure showed the presence of a new crystalline form of ritonavir which affects the way it dissolves, and possibly its absorption. Retained samples from a number of marketed batches of capsules were examined and there was no evidence of the unwanted crystalline form.

Mr Mark Haywood (managing director, Abbott Laboratories) said that teams were working round the clock to try to resolve the issue, but at present the company had no idea why the problem was occurring.

THE PHARMACEUTICAL JOURNAL (VOL 261) August 1, 1998



A more stable polymorphic form appeared in product – Had to be withdrawn and reformulated

- "After two-and-a-half years of closely monitored…formulation manufacturing, we encountered a new form of ritonavir, a crystal form... we had manufactured about 240 batches of ritonavir and none of those batches had ever failed a dissolution test."

Polymorph	Solubility (mg / mL) in Ethanol/Water Ratio		
	99/1	90/10	75/25
Form I	90	234	170
Form II	19	60	30

Uncontrolled change in forms can impact on performance – bioavailability ….though also processing

Despite all of the advances, problems still occur

In February of 2011, production of **Duragesic** (Fentanyl transdermal patch) was stopped when "microscopic crystallization" was found during the manufacturing of the Durasegic 100 µg/hr patches.

PRODUCT: Piperacillin and **Tazobactam** for Injection, USP
REASON FOR RECALL Crystallization: Potential to exhibit precipitation/crystallization in IV bag or IV line upon reconstitution.

PRODUCT Leucovorin Calcium Injection, USP, Sterile liquid, single use vials, 10mg/mL;
REASON FOR RECALL Presence of Particulate matter:complaints of visible crystalline particulates.

Crystallisation - Multiple Objectives

Require crystallisation process to deliver:

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

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


AIChE

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

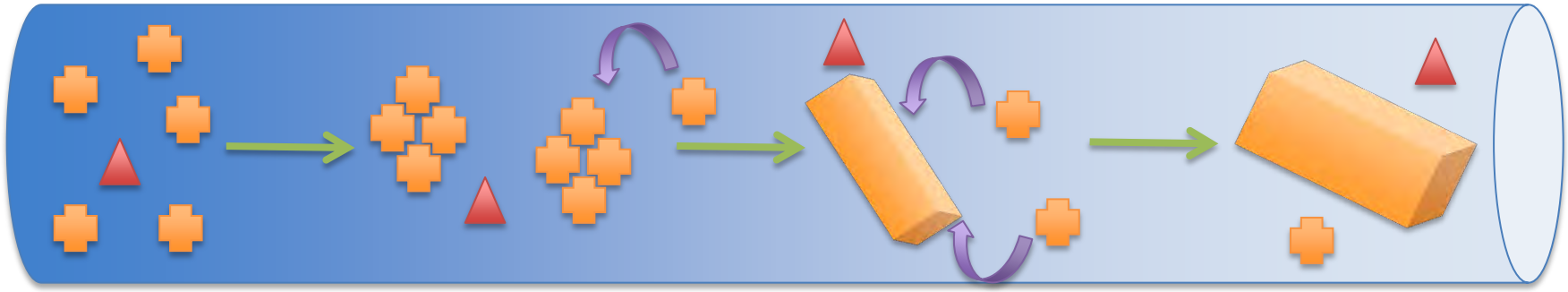
DOI 10.1002/aic.11555
Published online June 3, 2008 in Wiley InterScience (www.interscience.wiley.com).

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

- **Combine product *and* process understanding to develop process**

An Ideal Scenario….

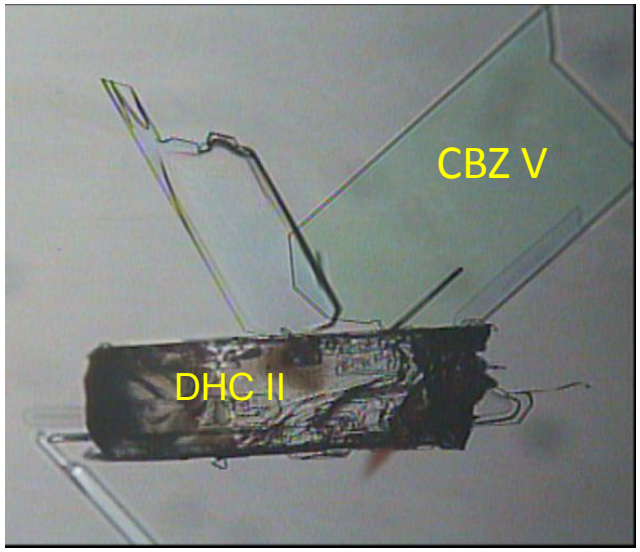
- **Produce consistent number, form and size of nuclei then control rate of growth (avoiding further nucleation and agglomeration and/or attrition)**

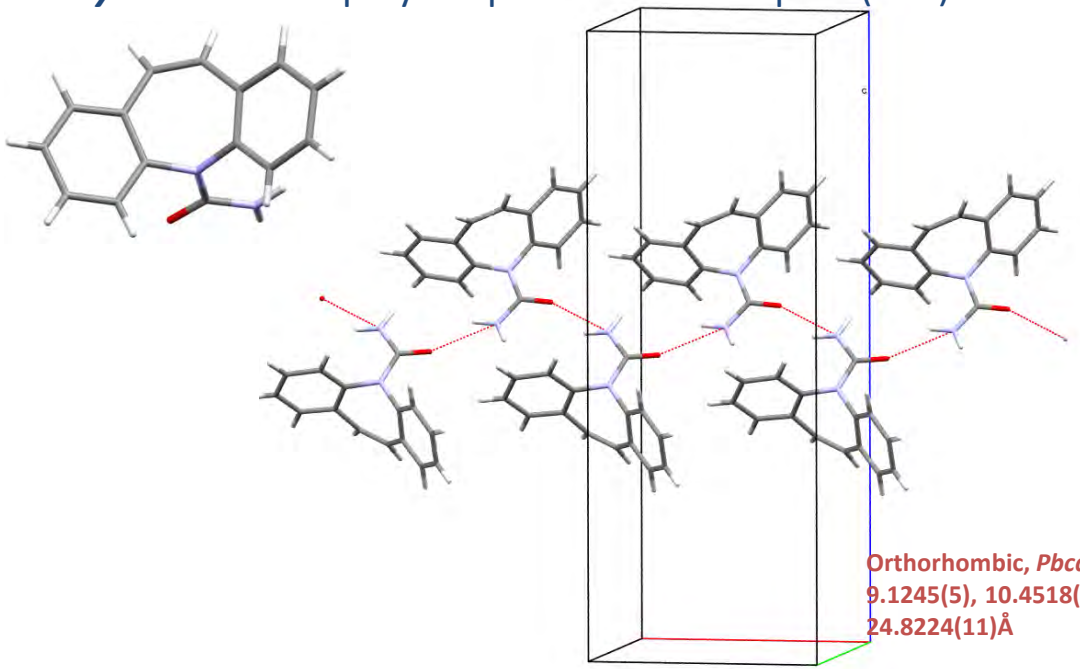


- **All molecules exposed to same environment → controlled transformation kinetics → product consistency → product performance**
- **Continuous processing allows ability to separate out stages and deliver close control over each step**

Accessing New Crystal Structures….

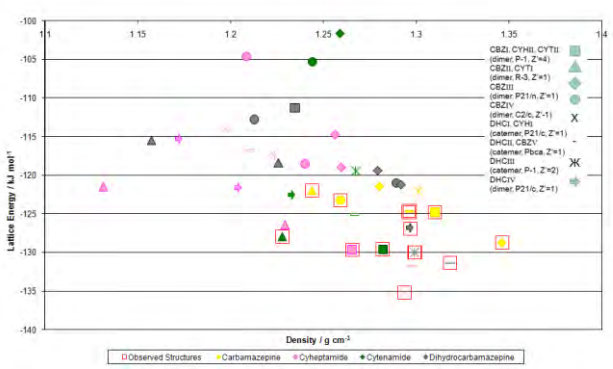
10,11-Dihydrocarbamazepine (DHC) form II crystal used as isostructural, heteromolecular seed (template) for crystallisation of ***predicted but previously unobserved*** polymorph of carbamazepine (CBZ)





Orthorhombic, *Pbca*, *a*, *b*, *c* = 9.1245(5), 10.4518(5), 24.8224(11)Å

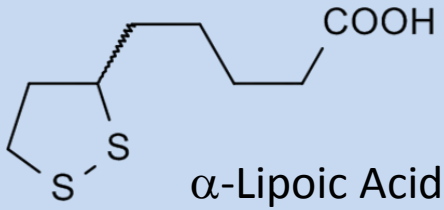
J-B. Arlin, L. S. Price, S. L. Price and A. J. Florence, *Chem. Commun.*, 2011, 47, 7074-7076



"Predicted unobserved" structures are not necessarily 'false' hits
Challenge for experimentalists to identify conditions for formation

Getting The Right Form

Improving stability through co-crystallisation

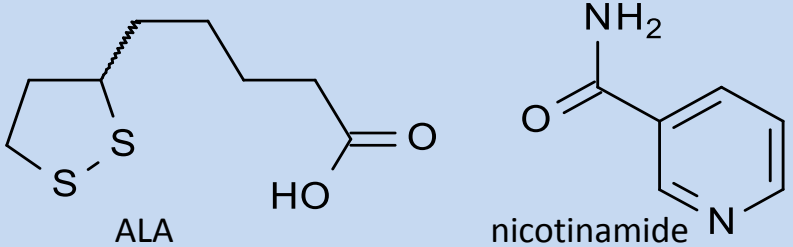


α-Lipoic Acid

- Anti-oxidant used as a nutritional supplement
- Unstable when exposure to heat and light
- Prone to polymerisation > 40°C

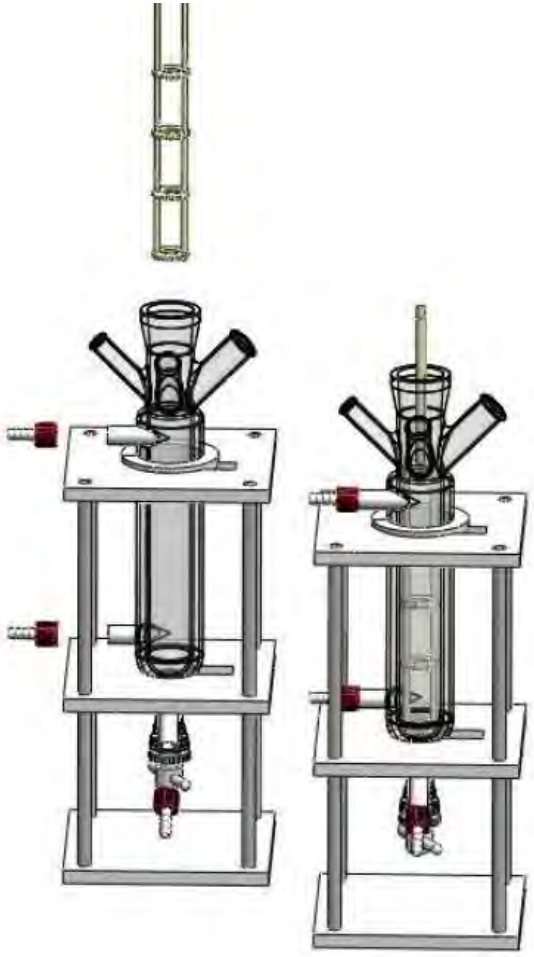
1:1 ALA:nicotinamide co-crystals obtained from small scale screen

Co-crystal has enhanced thermal stability



	Original purity	After 30 minutes at 60°C	80°C
ALA	99%	61%	18%
Co-crystal	**99%**	**99%**	**99%**

Scale-Up - Batch OBC



Co-crystallisation scaled-up in 500 mL batch OBC to obtain data prior to moving to COBR:

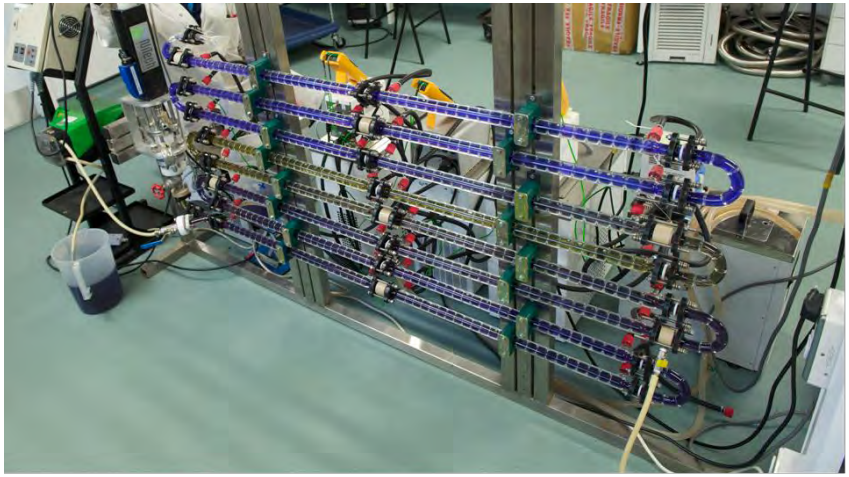
- Suitable solvent system
- Cooling profile
- Starting concentration
- Oscillatory mixing conditions
- Solvent system
- Cooling profile

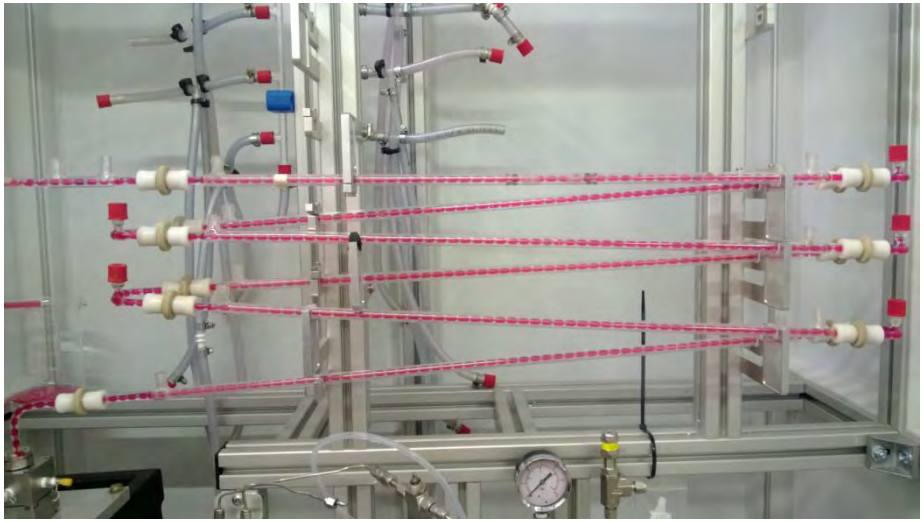
Ternary phase diagram to confirm co-crystal domain

COBC in the Lab

Typical Ranges for Lab Setup

- volume = 1 – 5L (<10, 10, 15 mm ID)
- flow rates = 50 - 250 mL/min (15mm ID)
- agitation = 1-3 Hz & 10-30 mm (typical range)
- residence times = 10 – 300 min
- T-zones = as many as required
- Thermocouples inserted to control T





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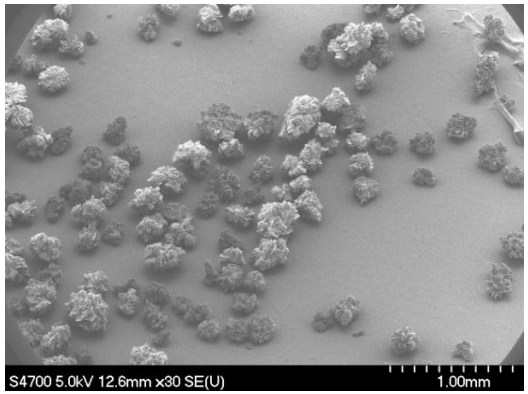
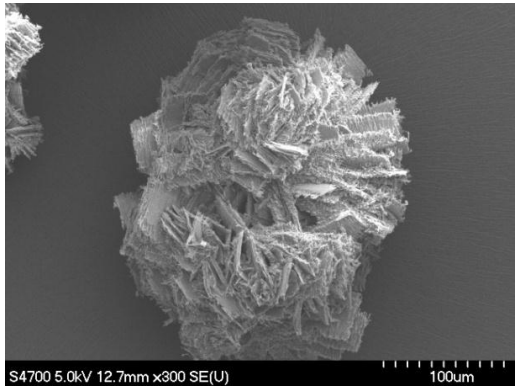
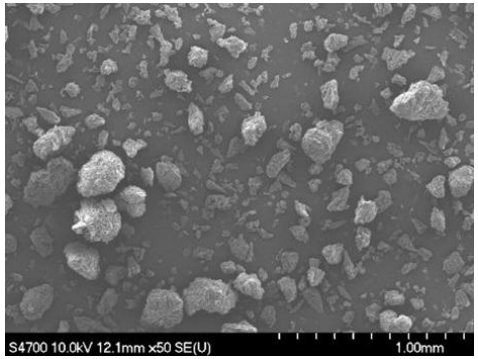
Scale-up of co-crystallisation process from 0.3g (vial) → 30g (OBC)→ 1kg (COBC).

SEM

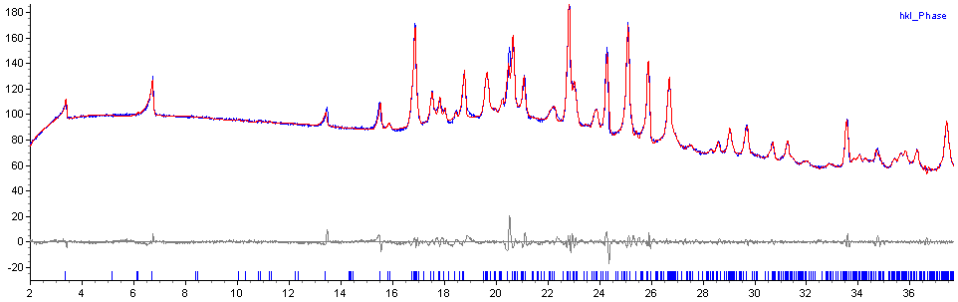






vs. batch

XRPD



Phase pure co-crystal product
Consistent particle size

Pawley fit to XRPD data from reclaimed sample of co-crystals (*a*, *b*, *c* (Å) = 26.44762, 5.31036, 34.27961; β (°) = 90.524, Rwp = 4.120)

HPLC: purity increased to 99.03% (from 97.4%) after co-crystallisation

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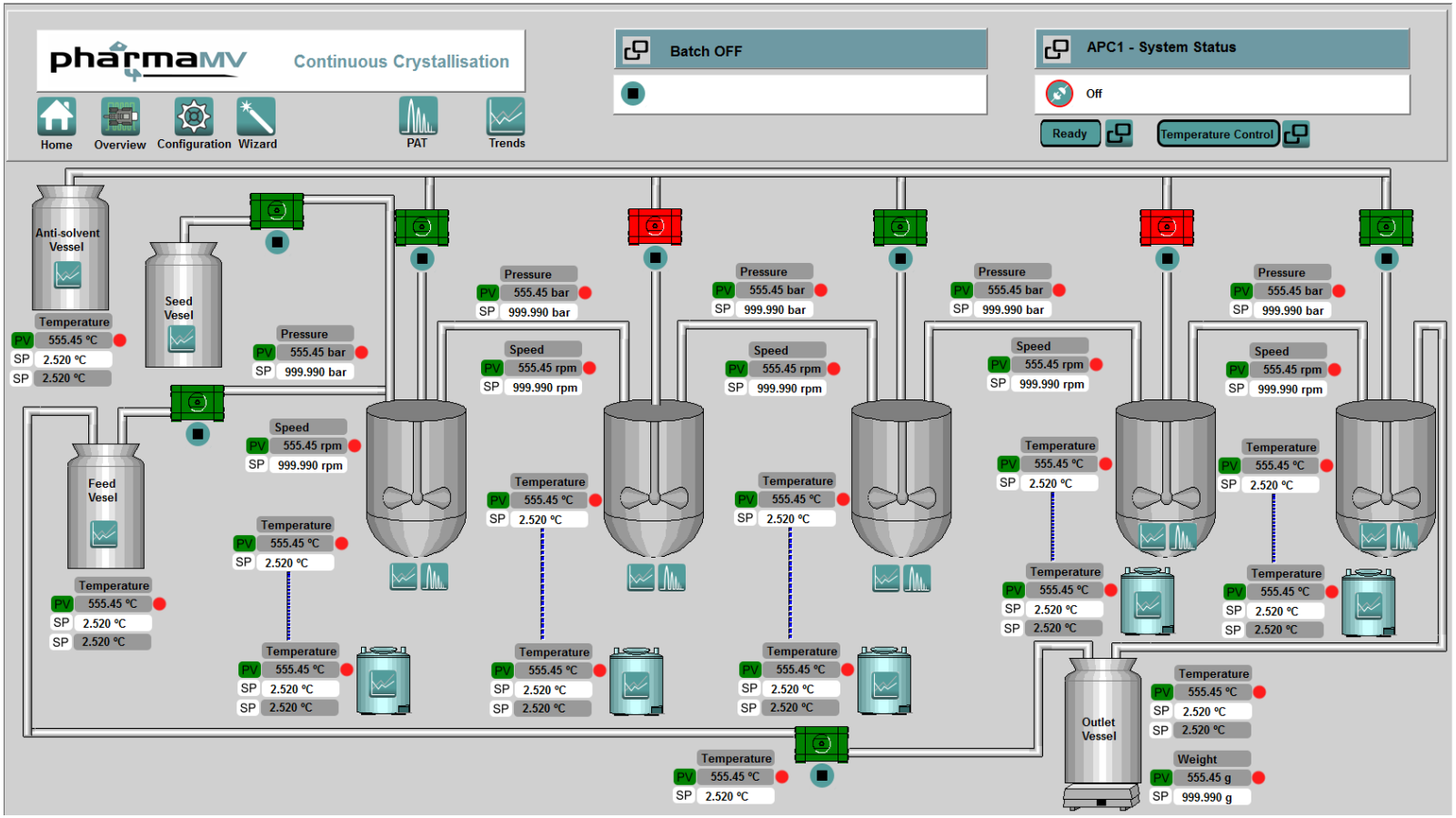
Novel Automated PAT Enabled Process Platforms

Controlling properties through continuous processing



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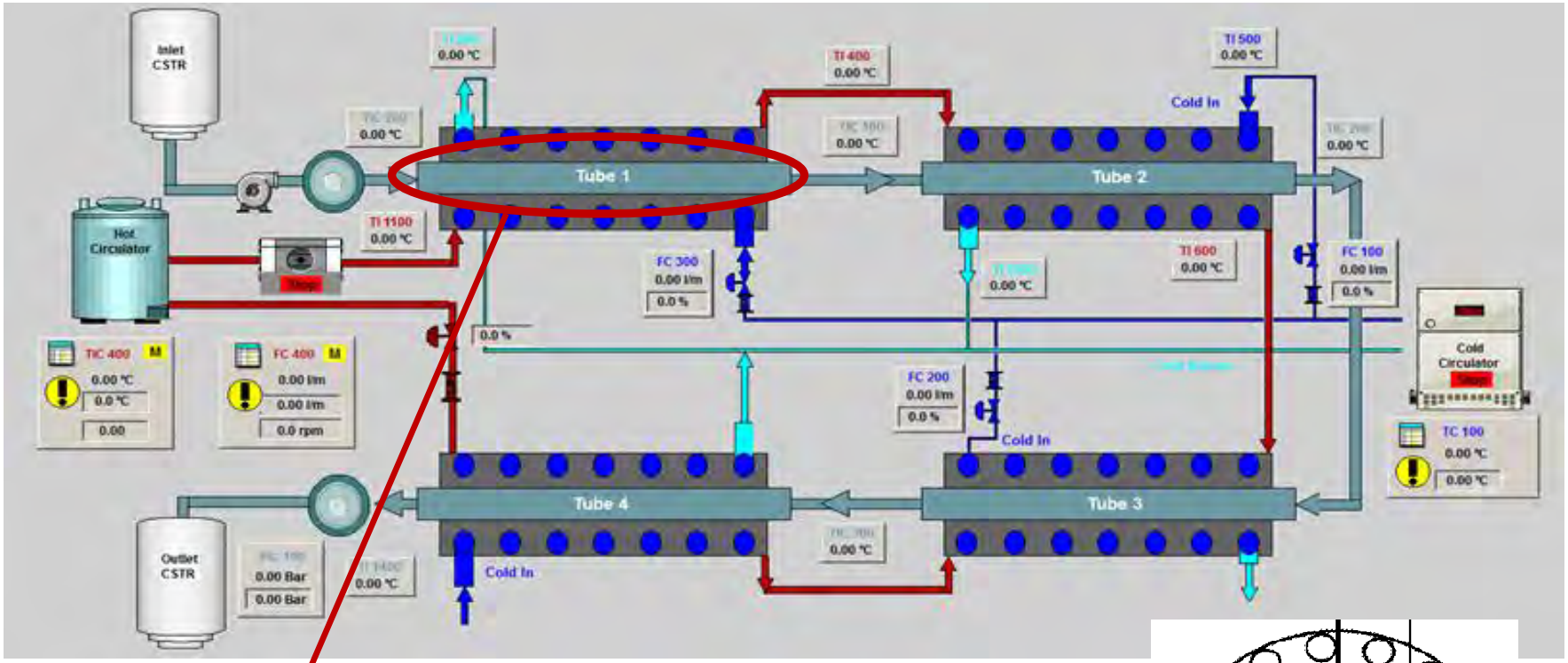
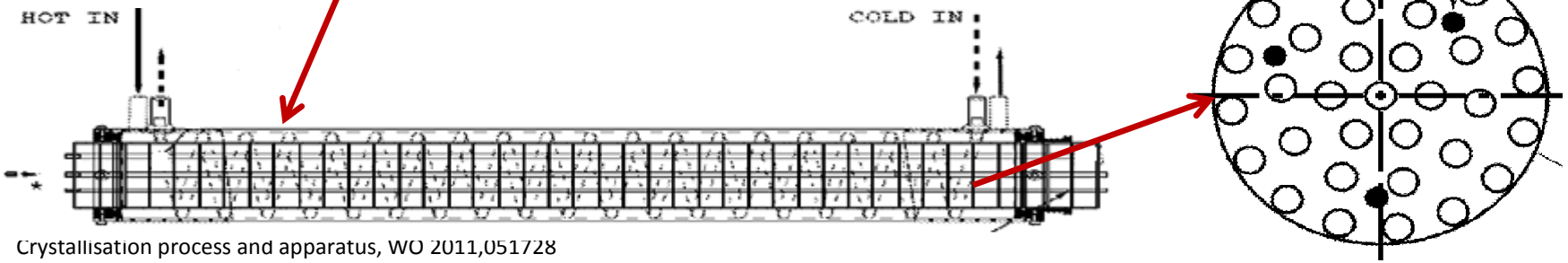
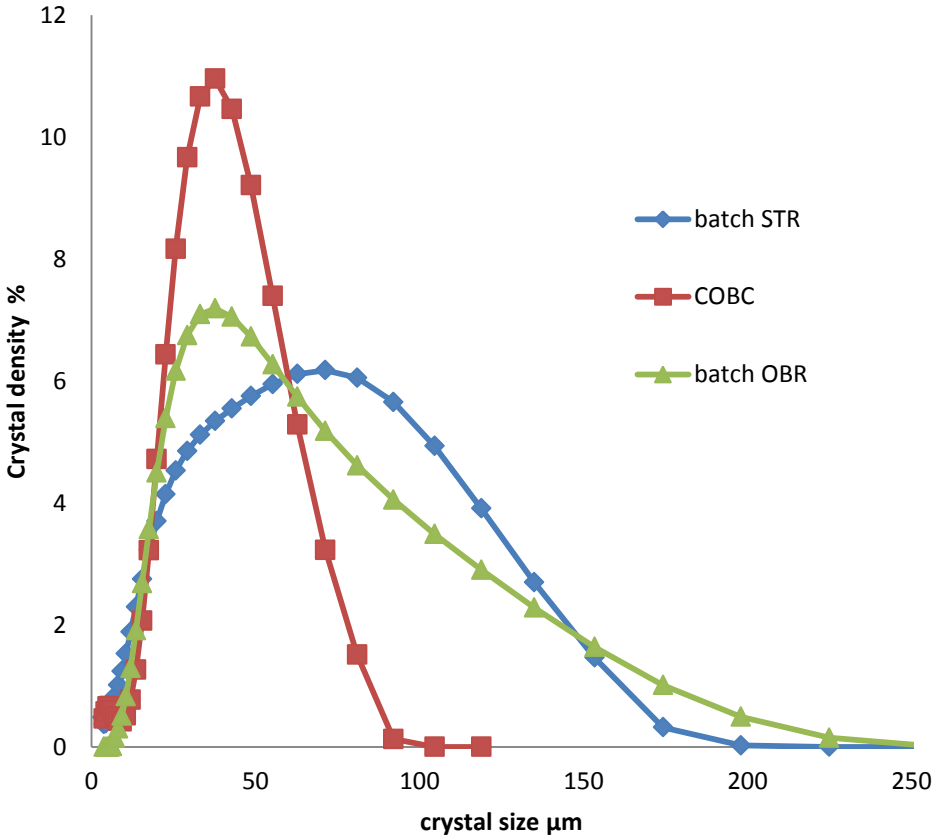
CRD Rattlesnake: COBR





Crystallisation process and apparatus, WO 2011,051728

Lactose: Batch vs Continuous Crystallisation



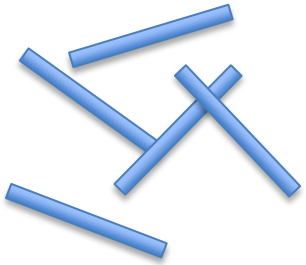
Crystalliser	Residence time	RPM/Reo
STR	2.5	500
MF-OBC	2.5	300
COBC	2.5	300

Crystalliser	Mean particle size	Yield %
STR	71.2	27.9
MF-OBC	37.6	31.2
COBC	37.6	37.3

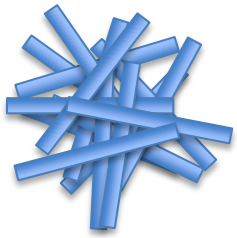
Getting The Right Form

Manipulating properties through continuous agglomeration

Dealing with poor powder flow



Particles (10s μm)



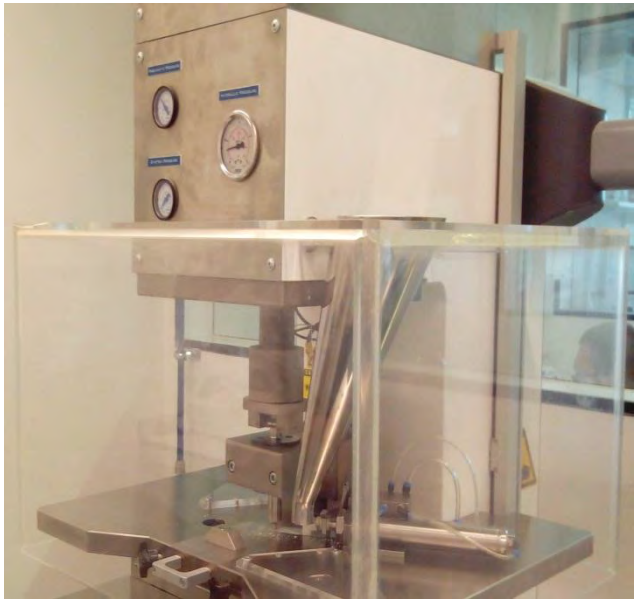
Loose aggregates (100s μm)

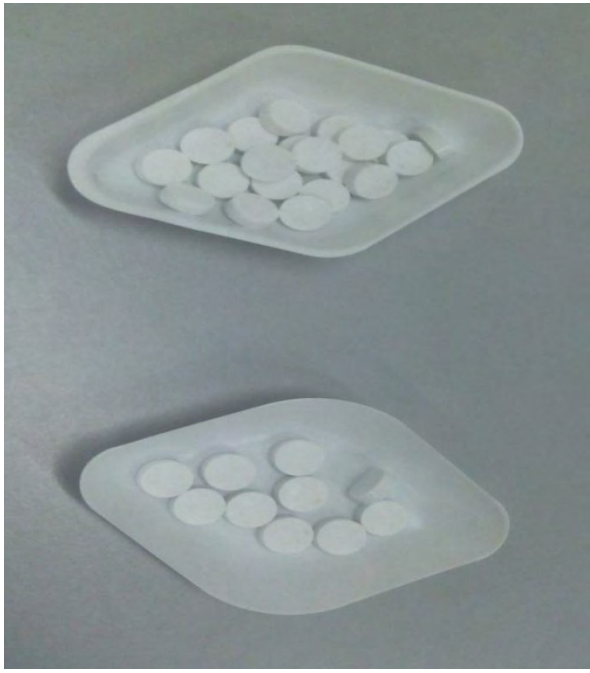
Intergrown, spherical agglomerates (100-1000 μm)

Transform ‘difficult’ particles into well behaved granules

Getting The Right Form

Manipulating properties through continuous agglomeration





- Granular API form of aspirin
- 500 μm
- Significantly improved flow properties
- Suitable for direct compression

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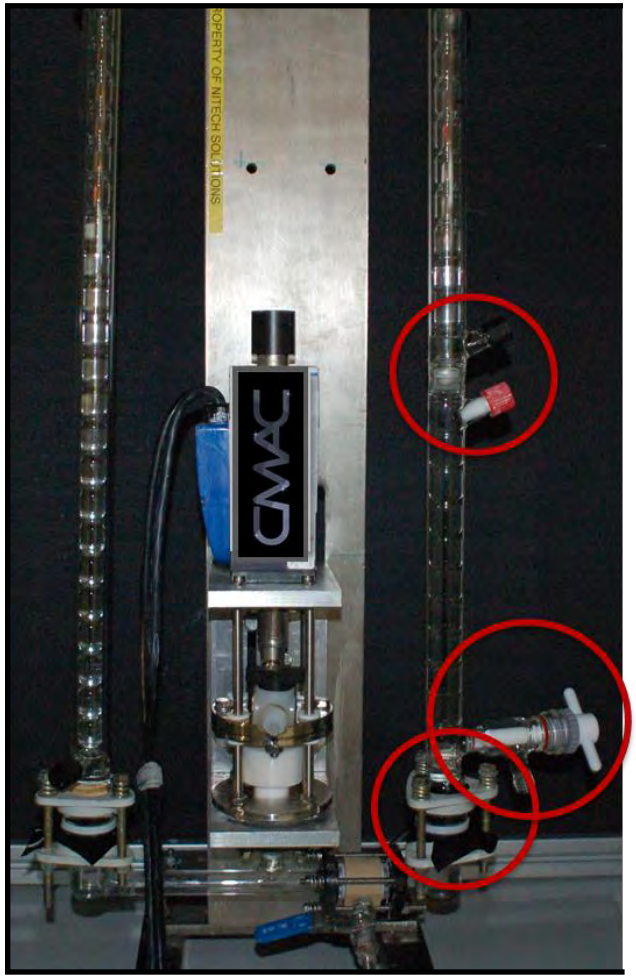
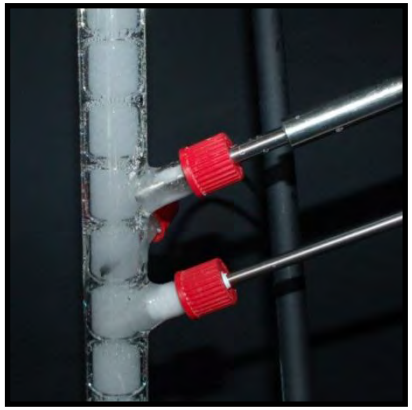
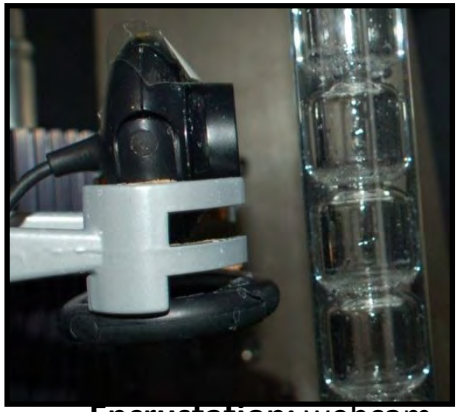
Getting The Right Technology

Manipulating properties through structural and process understanding





Nucleation: Inline FBRM and UV



Encrustation: webcam focused on interbaffle zone

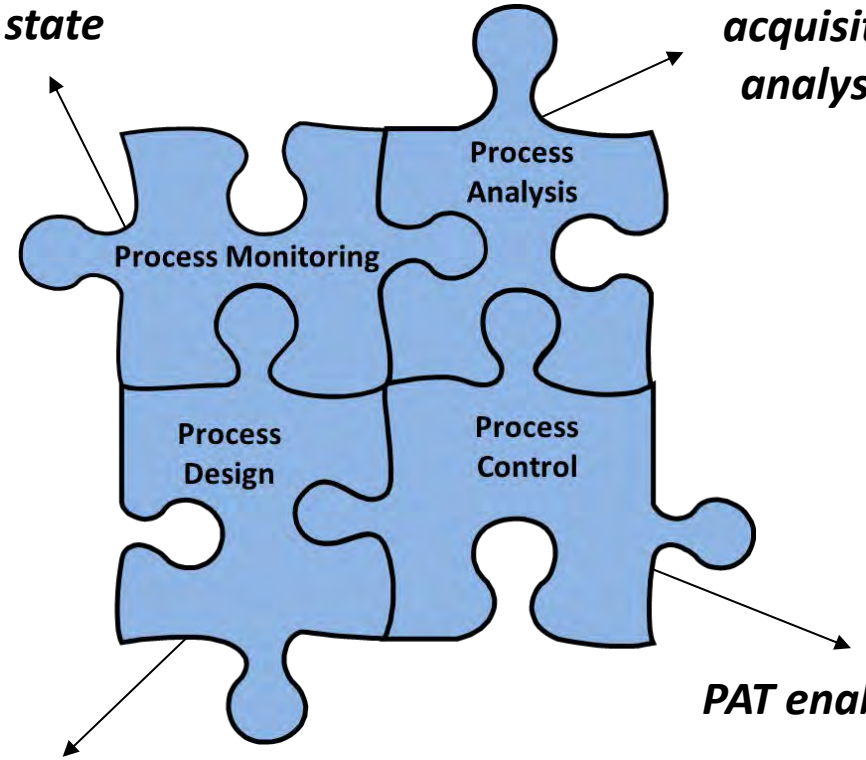
Implement real time PAT feed back for supersaturation control over crystallisations

Scott Glass
PERCEPTIVE ENGINEERING LTD
METTLER TOLEDO
CLAIRET SCIENTIFIC LIMITED
ABB

Exploiting PAT Routinely

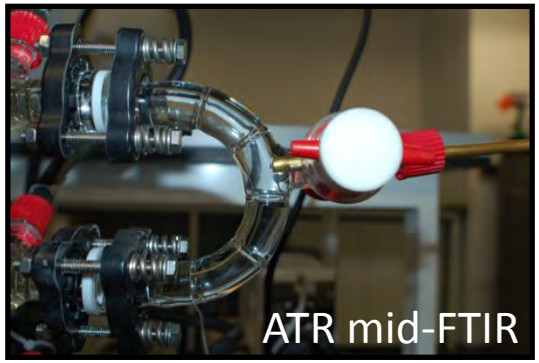
Identify steady state

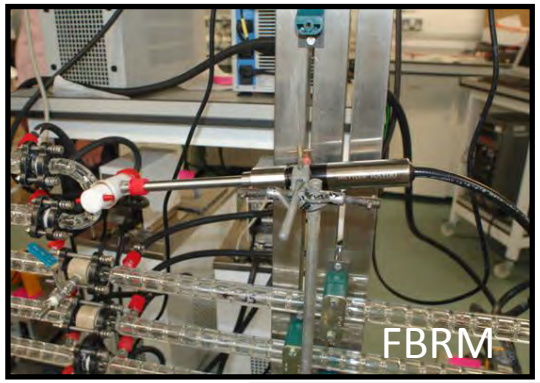
Multivariate data acquisition and analysis tools

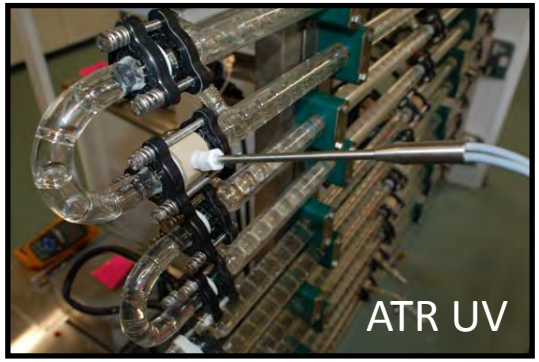


PAT enabled control

Design for Quality: CQA / CPP

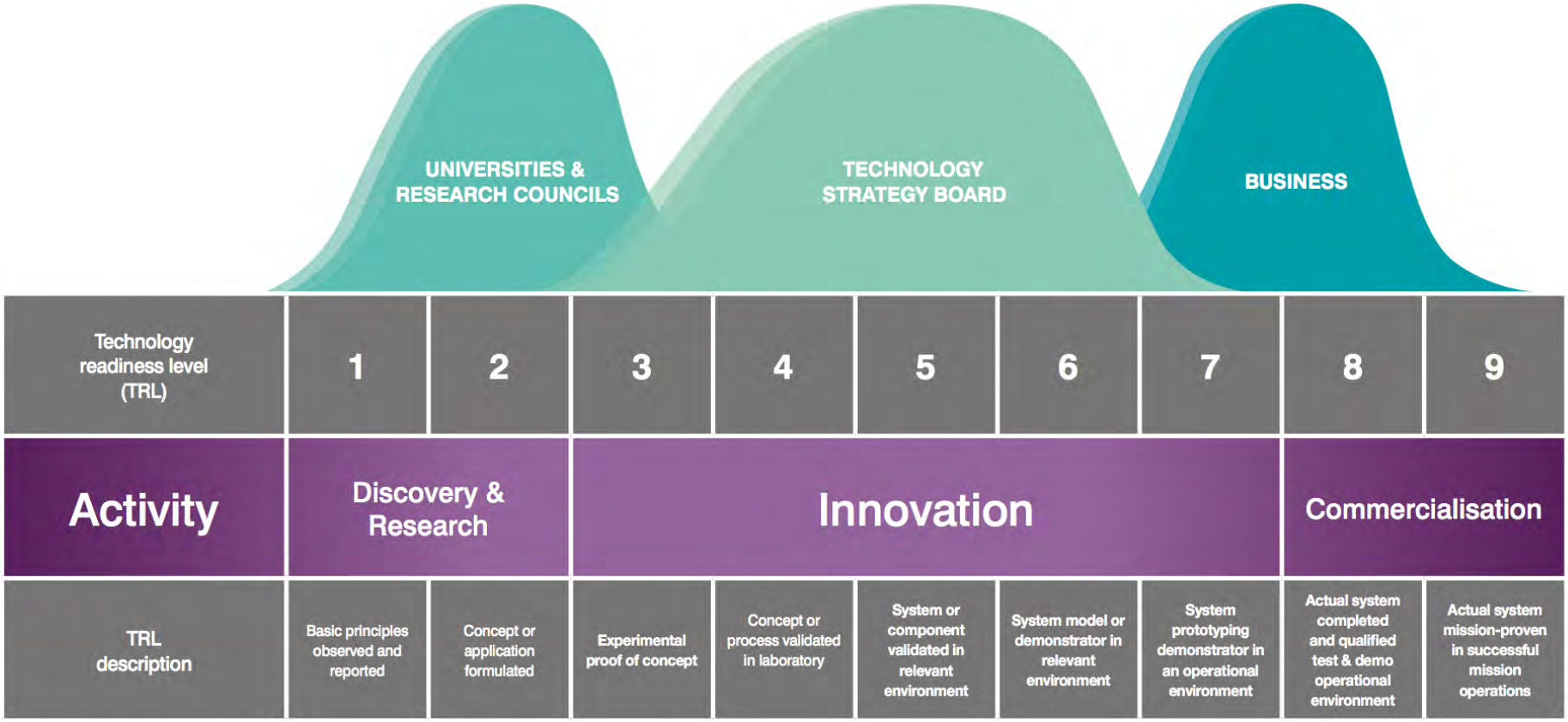






Progress Needs Joined Up Approach Across Innovation System

from research to implementation



Source: The NASA-developed Technology Readiness Level model[17]

UK TSB High Value Manufacturing Strategy, 2012-2015

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- £16M new facility – government, industry and university support
- Located in the Technology Innovation Centre
- Open access ethos
- Room for academic and industry researchers to co-locate (currently ~60)
- State of the art processing and analytical labs:
  - Continuous processing platforms
  - Suite of PAT enabled control capabilities
  - Surface and amorphous materials analysis
  - Substance and product testing

See: www.cmac.ac.uk

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Acknowledgements

Research

Lihua Zhao, Ian Houson,
Vishal Raval, Naomi Briggs,
Thomas McGlone, Nazeer Rajoub,
Humera Siddique, Cameron Brown

Jan Sefcik, Anna Jawor-Baczynska,
Ulrich Schacht
Blair Johnston, Andrea Johnston,
Rajni Bhardwaj

David Littlejohn, Alison Nordon,
Laura Palmer, Jaclyn Dunn

Iain Oswald, Robert Young

Cambridge Reactor Design,
Nitech, Mettler Toledo,
Avantium, AM Technology

NiTech SOLUTIONS
METTLER TOLEDO
CRD CAMBRIDGE REACTOR DESIGN
AVANTIUM crystallization systems
gsk GlaxoSmithKline
AstraZeneca
NOVARTIS

Funding
Scottish Funding Council, EPSRC Centre for Innovative Manufacturing, TSB, GSK, AstraZeneca, Novartis