Development of Continuous Crystallisations in an Oscillatory Baffled Crystalliser

Prof Alastair J. Florence, University of Strathclyde, 6th June 2013
EPSRC Centres for Innovative Manufacturing

Centres *co-created* with industry to address their long-term manufacturing challenges and/or emergent market opportunities.

**Pre-Competitive Collaboration**
Partnership approach to meet the challenges of continuous manufacturing and crystallisation

**Drivers for Change**
Technology, Economic, Regulatory
A large multi-disciplinary team to meet the challenges of our demand-led scope

Prof Umit Bititci, Strathclyde
Prof Lee Cronin, Glasgow
Prof Alastair Florence, Strathclyde
Prof Sir Mike Gregory, Cambridge
(Dr Jag Srai)
Prof Gavin Halbert, Strathclyde
Prof David Littlejohn, Strathclyde
(Dr Alison Nordon)
Prof Zoltan Nagy, Loughborough/Purdue
Prof Xiongwei Ni, Heriot-Watt
Prof Colin Pulham, Edinburgh
Prof Chris Rielly, Loughborough
Dr Jan Sefcik, Strathclyde
Prof Chick Wilson, Bath

Establish Centre culture and open collaborative ethos
Aim to bring in additional UK and international expertise as required e.g. through ICON projects, new funding

Also support Doctoral Training Centre
45 PhD studentships; 4 year studentships, training across 7 leading UK Universities
Origins – A Demand-Led Scope

Manufacturing 2020
- UK based
- Off the grid
- Affordable
- Close to customer
- Complete quality by design
- Better understood
- Automated
- On demand
- Next gen lean
- As routine as batch
- Efficient
- Consistent
- Higher quality
- Safe
- Robust
- All in
- Making different things
- Faster
- Cheaper
- Cleaner
- More complex
- Sustainable
- Simpler
- Local
- Outsourced
- More traceable
- More regulated
- More transferable
- Tailored
The formation (crystallisation) and processing of particles is a key step
- Particle – imparts stability & dictates physical properties
- e.g. PSD impacts downstream filtration, flow, milling, segregation, content uniformity....
- Deliver consistent particles via continuous operation at steady state

- Select approaches based on understanding of product and process properties
- Deploy as component of continuous end-to-end or hybrid batch-continuous approaches

- Also operations and supply chain – Dr Jag Srai, Cambridge
Building Continuous Processing Capability

- *Laboratory-scale*, modular systems
- Synthesis to formulated product

- Develop & test modules across Centre, characterise and develop/integrate control
Establish Methodologies for Solution Crystallisation

- Collect information to guide most appropriate approach to continuous process development.
- Accelerate progress – guided by compound physical props to right technical solution.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Solubility</th>
<th>Kinetics</th>
<th>Fouling</th>
<th>Crystal Props</th>
<th>Modelling</th>
<th>Platform Selection &amp; Testing</th>
<th>Process Optimisation</th>
</tr>
</thead>
</table>
| • Mol Props  
• Purity  
• Stability  
• Compatibility  | • Solvent system  
• Cooling profile  
• Morphology  | • Nucleation (1st and 2nd)  
• Growth  
• Agglomeration  
• Attrition  | • Supersaturation  
• Cooling  
• Fluid dynamics  
• MOC  | • e.g. hardness  
• Form, BCS/DCS  
• Purity, Morphology  
• Defects, surface  | • Empirical  
• 1st principles  
• Direct design/statistical models  | • COBR  
• MSMPR  
• Other  
• STR...  
• PAT  | • PAT enabled  
• Closed loop feedback control  |

Crystallisation classification informs platform selection

\[ k_{(foul)} \]

\[ G = k_f \omega^n. \]
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 responses so compromises often required
- Delivering consistency brings significant advantages
- **Combine product and process understanding to achieve desired outcome**
Controlling Solution Crystallisation

1. Nucleate particles
2. Grow particles and de-supersaturate solution e.g. controlled cooling profile

- Supersaturation a key parameter:
  Nucleation (primary and secondary), growth, shape, CSD, agglomeration..

- Move beyond empirical to PAT/model based control

- Apply to continuous

Potential Issues

- Fines in crystallisation of metastable polymorph ($\alpha$ form) of L-glutamic acid
- Uncontrolled growth on reactor walls (encrustation/ fouling) in an agrochemical crystallisation
- Fouled transflectance PAT probe

Define optimal operating conditions to deliver desired outcome and avoid uncontrolled nucleation, encrustation plus oiling out, phase transformations, attrition, agglomeration/deagglomeration
Availability of Technologies is Key (lessons from flow chemistry)

One of the hindrances to the examination of continuous processes in the laboratory has, in the past, been the dearth of off-the-shelf continuous reactors. The fact that chemists had to set up their own continuous process equipment put off many from going down this pathway. However, as new equipment, particularly microreactors, has become available not only in stainless steel and Hastelloy but also in glass, more and more chemists are taking the plunge and looking at the advantages of continuous processing.

Where are we in terms of lab-scale equipment for continuous crystallisation?
Continuous Crystallisation Technologies
Are the right technologies available and accessible?

**Crystallisers**
- Multistage MSMPR
- COBC
- Taylor Couette
- ACR - CoFlore™
- ATR
- STFR
- Spinning disk reactor
- Impinging Jet
- Electrospray
- Spray drying
- Extrusion
- Microfluidics (polymorphs/co-crystals)

**Seeding / Non-seeded** – control nucleation, growth surface

**PAT** – particle size/FBRM, imaging; concentration/MIR, ATR-UV, Raman, Solid form/Raman

**Process Models** – understanding and real time control (CFD, PBE, MPC)

**Filtration/Drying** – isolate dry, finely divided, free flowing powder

**Scale-Down** – implement earlier in the lab
Oscillatory Baffled Reactors - OBR

Well studied for range of applications: e.g. Ni (Heriot-Watt), Mackley (Cambridge), Harvey (Newcastle), Ristic (Sheffield)

- Uniform, efficient and controllable vortex mixing - $f$(oscillation; baffles; geometry)
- Decouples mixing from net flow
- High specific surface area - rapid heat transfer
- Flexible operating conditions
- Scalable
- Reduced shear compared with stirred tank - attrition
- Plug flow reactor suitable for slower processes including crystallisation
COBC in the Lab

Typical 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)
- residence times = 10 – 60 min
- T-zones = as many as required
- Thermocouples inserted to control T
- Other PAT for solid and solution phase
COBR - Operation

Considerations for success:

- Net flow and oscillatory conditions - ensure optimal mixing in given tube diameter
- Near plug flow RTD
- Efficient heat and mass transfer
- Effective dispersion/suspension of particles
- Reactor sized on the basis of required residence time for process
- Final geometry/configuration determined by the throughput requirement
- Scale-up principle to maintain geometric ratios and oscillatory and net flow Reynolds numbers.

- Development approach to utilise batch OBR as 1st step to continuous
COBR DN15 – Residence Time Distribution Measurement

Characterising the DN15 COBR

Residence time distribution experiments to assess plug flow

- $E_\theta$ curves calculated for tracer experiments under a range of conditions for DN15 (flow, oscillation, length, mean residence time up to 1hr)
- Identify operating conditions with acceptable (near plug flow) conditions ($D/uL < 0.2$)
- Minimal axial dispersion in plug flow required for narrow PSD
Characterising DN15 COBR
Basic Cooling Profile

- Further work to improve heating/cooling to achieve smooth T-profiles
- Smooth profile along reactor length - consistent growth rates of particles, minimise defects/strain, optimise impurity rejection...
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

Selected parameters for cooling crystallisation:

- 1:1 IPA-hexane
- Oscillation conditions
  - Frequency/amplitude - 1 Hz / 25 mm
- Cooling from 40 – 2.5 °C over 60 mins
- ~70% yield
Continuous Cooling Crystallisation in the COBC

COBC: 15 mm ID jacketed
  length: 25 m
  Volume: 4.2 L
Flow rate: 71 mL/min
Cooling: stepped, linear profile, 40-2.5°C
Residence time: 1 hour (2.5 RT to steady-state)
Oscillation: 1Hz, 30mm
Run Time: 2 x 5 hr trials (2.5hrs @ steady-state)
Total solid produced: > 1.6kg (330g/hr)
Yield: ~70% (w/w)
Slurry collected: filtered and dried
Scale-up of co-crystallisation process from 0.3g (vial) → 30g (OBC)→ 1kg (COBC).

**SEM**

**XRPD**: Pawley fit of bulk powder to SX structure

Pawley fit to XRPD data from reclaimed sample of co-crystals \((a, b, c\ (\text{Å}) = 26.44762, 5.31036, 34.27961; \beta (^\circ) = 90.524, \text{Rwp} = 4.120)\)

**HPLC**: purity increased to 99.03% (from 97.4%) after co-crystallisation
Unseeded L-glutamic acid

Continuous Oscillatory Baffled Crystalliser (COBC)

Results for MB OBC; Frequency 2Hz Amplitude, 20mm

<table>
<thead>
<tr>
<th>Conc. (g/L)</th>
<th>Cooling Profile</th>
<th>1°C/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rapid cooling</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>α</td>
<td>β</td>
</tr>
<tr>
<td>30</td>
<td>α</td>
<td>β</td>
</tr>
<tr>
<td>40</td>
<td>α</td>
<td>β</td>
</tr>
</tbody>
</table>

α-LGA produced in the COBC

Encrustation in a COBC glass straight

Blockage in COBC collar
Maximise similarity between batch and continuous crystallisations
- Minimise the differences in material requirements and hydrodynamics
- Enable direct transfer of conditions
Moving Fluid Batch OBC

- Screening system for COBC – assess physical properties of system
- Efficient process development prior to continuous implementation
- Fluid oscillation effected via membrane – prevent contamination from unjacketed straight
- PAT incorporation
- Imaging (nucleation and encrustation assessment)
Image Analysis – ML-OBC

Identify impact of process conditions (supersaturation, heat transfer, mixing, flow, materials of construction) on nucleation and fouling.

Nucleation

Encrustation
Nucleation & Encrustation Monitoring – Imaging
Assess nucleation, growth and fouling kinetics

- Identify conditions that lead to loss of control
- In this case – for single device, seeding approach selected
Continuous seeded Crystallisation of β L-Glutamic Acid.

<table>
<thead>
<tr>
<th>Seed loading.</th>
<th>Growth Soln.</th>
<th>High (40mg/g)</th>
<th>Low (18mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (0.37mg/g)</td>
<td><strong>No Encrust.</strong> Pure β LGA 7hr run (5 RT) Size: 240μm</td>
<td><strong>No Encrust.</strong> Pure β 8hr run (6 RT) Size: 90μm</td>
<td></td>
</tr>
<tr>
<td>Low (0.1mg/g)</td>
<td>Encrust., Blockage, 4hr run (3 RT) α and β LGA Size:240μm</td>
<td><strong>No Encrust.</strong> Minor fouling Pure β LGA 8hr run (6 RT) Size :70μm</td>
<td></td>
</tr>
</tbody>
</table>
Controlling Each Stage of Process

Utilise different units for continuous nucleation (high supersaturation, $S$) and continuous growth (low supersaturation, $S$)
Summary

- Create the right particle first time – particle attributes – what do we want to make?
- Limitations of OBR in terms of physical parameters (max solids loading, viscosity, gas...)
- Proven toolbox of platforms to meet needs of different processes
- Early understanding of process and product is vital
- Encrustation – care over supersaturation – need to confirm over long running times
- Combined control of nucleation and growth feasible
Acknowledgements

Research
Lihua Zhao, Vishal Raval
Naomi Briggs
Thomas McGlone
Jan Sefcik, Ulrich Schacht
David Littlejohn, Alison Nordon
Iain Oswald, Robert Young

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