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

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Overview

1. Development of a Testbed for Continuous Crystallisation
2. DN15 COBC Characterisation
3. Application of COBC for L-Glutamic Acid Crystallisation
Control and Understand

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

Oscillatory Baffled Crystallisers (OBC’s)

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

Stationary Baffles

Baffle string

Oscillatory Baffled Mixing
Traditional OBC Approach from Batch to Continuous

**Batch**

- Define crystallisation conditions

**Continuous**

- Continuous production of API
- Encrustation, Blockages
- Exclusively metastable polymorph isolated

**Model Compound**: L-Glutamic Acid
Batch vs Continuous

Differences between Batch OBC and COBC

- Net flow
- Vessel diameter
- Baffle material
- Baffle geometry
- Shear rates
- Heat transfer

Q. How to maximise similarity between Batch and Continuous?
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
Quantify the extent of fouling under a range of process conditions to identify how to encrustation may be monitored/reduced/eliminated.

Nucleation in the bulk ($\beta$ - LGA)  
Nucleation on the wall ($\alpha$ - LGA)
Images converted to 8-bit grey scale and Image J software used for analysis.

1) Background subtraction
2) Select region of interest
3) Calculate mean grey scale
4) Plot response against time

Induction time at various supersaturations
System Characterisation

Key Factors:
Heat/Mass Transfer, Flow, Mixing, Shear

Control over heat transfer
Differences between Batch OBC and COBC
Baffle geometry
Baffle material
Shear rates
Vessel diameter

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

Schematic of imperfect pulse technique
Dimensionless RTD curves calculated from a range of conditions.
## Continuous Seeded Crystallisation of β L-Glutamic Acid

### Seed Suspension PSD

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Supersaturation for Controlled Growth</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Particle size [μm]</th>
<th>Volume [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>100</td>
<td>0.3</td>
</tr>
</tbody>
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### Seed Loading and Growth Solution

<table>
<thead>
<tr>
<th>Seed Loading</th>
<th>Growth Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (0.37mg/g)</td>
<td>No Encrust. Pure β LGA 7hr run (5 RT) Size: 240μm</td>
</tr>
<tr>
<td>Low (0.1mg/g)</td>
<td>Encrust., Blockage, 4hr run (3 RT) α and β LGA Size: 240μm</td>
</tr>
<tr>
<td>High (40mg/g)</td>
<td>No Encrust. Pure β 8hr run (6 RT) Size: 90μm</td>
</tr>
<tr>
<td>Low (18mg/g)</td>
<td>No Encrust. Pure β LGA 8hr run (6 RT) Size : 70μm</td>
</tr>
</tbody>
</table>

### SEM of β LGA Product

- Size: 240μm

### Microscopy of β LGA Product

- Size: 240μm

### Diagram

- Growth Solution Pumped through bellow
- Hot seed suspension pumped into COBC
- Seeding port

### Temperature and Concentration

- Saturated
- Supersaturated
- Controlled Growth

### Supplementary Information

- Continuous Seeded Crystallisation of β L-Glutamic Acid
- Microscopy of β LGA product
- SEM of β LGA product
• Traditional moving baffle batch OBC doesn’t appear to provide the correct information for scaling to continuous OBC

• The development of an 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
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)
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