Developing Pharmaceutical Continuous Crystallization Processes - Knowledge & Gaps

Chris Price on behalf of the IMI team
Product Development
Innovative Manufacturing Initiative
Move from Batch, to End to End Continuous Processing

Reaction → Extraction → Reaction → Reaction → Reaction

The power of PAT:
At line HPLC

Final intermediate
API

The moment when the final reagent flow commences final intermediate is consumed and API product is formed

Extraction → Distillation → Crystallisation → Isolation
Task: Provide a multi-product, scalable, continuous particle formation & purification system delivering consistent API suitable for direct formulation.

<table>
<thead>
<tr>
<th>Purity Chem &amp; Phase</th>
<th>Batch produced NCE A is recrystallized for phase control &amp; is very pure. NCE A forms many solvates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle Attributes</td>
<td>Particle size distribution, crystal habit, bulk properties suitable for direct formulation</td>
</tr>
<tr>
<td>Process Understanding</td>
<td>Suitable for a QbD filing using on / at line process monitoring &amp; control</td>
</tr>
<tr>
<td>Consistency</td>
<td>Consistent attributes over extended process duration over a range of scales</td>
</tr>
<tr>
<td>Multi product</td>
<td>Applicable to most NCEs without major equipment redesign</td>
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</table>
So what does 100 years of continuous crystallization teach us?

- To minimise encrustation operate at low supersaturation
- Slow growth delivers purification
- Suppress nucleation, to make large particles for easy separation
- Scale up / down is difficult
- Successful design requires an extensive data set collected at scale
- Operation at small scale is very challenging
How about continuous precipitation

- Potential to deliver fine particles
- Operate at high supersaturation to get high nucleation rates and minimal growth
- Delivers little purification
- Favours extreme crystal habits (needles / filaments)
- Large variations in special distribution of supersaturation make scale up difficult
- Risk of nucleating a meta-stable phase of polymorphic materials which then transforms during isolation
Ideas to take forwards

- Minimise encrustation by operating at low supersaturation
- Obtain purification by slow growth

Manipulate nucleation rate independently of supersaturation to achieve target size

How?
Technical design aspects to consider

- Selection of appropriate crystallizer
- Mass/energy balances
- Residence time
- Crystal suspension
- Optimal supersaturation and mixing
- Nucleation
- Crystal growth rate
- Representative Off-take
- Encrustation
- Mean crystal size (L50) and crystal size distribution (CSD)
- Production rate
- Crystallizer volume

PRODUCT WITH CONTROLLED
Purity
Size distribution
Habit
Form
Consistency
NCE A Purification

Crystallization achieves significant purification but a few impurities need to be controlled.

Control strategy:
Control input quality
Starting materials
Reaction conditions

Monitor reactions by on-line assay

Control crystallization conditions.
Solvates concerns dominate NCE A crystallization development.

Batch DOE
To find level of MEK in MIBK to get yield & avoid MEK solvate.

Low MEK concentration form unsolvated crystals

MEK > ca 15% tend to form MEK solvate.
Impact of Supersaturation on Crystal habit

Decreasing Supersaturation

Faces with high growth rate dependence on supersaturation

Decreasing Supersaturation
 Particle Size Control - NCE A

API for oral products

L_{50} = 22\mu m

API for inhaled products

L_{50} = 10\mu m

L_{50} = 4\mu m
NCE A Crystallization Process Understanding

Strategy based on identification of process parameters and understanding their impact on process performance

Feed solvent ratio
Vols MIBK per vol MEK

API concentration in feed stream

Residence time in first crystallizer (mins)

Temperature of first crystallizer (°C)

Residence time in second crystallizer (mins)

Temperature of second crystallizer (°C)

Range evaluated (knowledge space)
Proven Acceptable Range (design space)
Normal Operating Range (control space)
Risk of forming MEK solvate
Risk of line blockage due to solubility limit
Scaling-up Continuous Crystallization

Images showing equipment for continuous crystallization at different scales:
- 2 g/h
- 10 g/h
- 40 g/h
- 400 g/h
Consistency across scales – reliable scale-up

2008
Plant Campaign
L10 = 3.8 μm
L50 = 12.7 μm
L90 = 24.3μm

2005
Lab POC
L10 = 3.4 μm
L50 = 12 μm
L90 = 26 μm
Consistency of purity and assay

Unqualified imp NGT 0.15%
Spec limit 0.3%
Encrustation was a significant issue during early stages of process development. Operating at low supersaturation minimises the problem. Building a cleaning procedure into the process has made long term operation possible.
A Success ....
But is it applicable to other NCEs

- NCE A
  - Combined cooling & anti-solvent crystallization
- NCE B
  - Isothermal anti-solvent crystallization to produce a hemi-hydrate
- NCE C
  - Reactive & cooling crystallization
- NCE D
  - Cooling crystallization of material which tends to oil dreadfully
- NCE E
  - Combined cooling & anti-solvent crystallization

A, C & D run at plant scale for extended periods > 12 days
B & E run at lab POC scale for >30 hours
Filter & wash API to remove impurities and leave wet in a non-solvent to allow drying without agglomeration / granulation.

A semi batch approach has been demonstrated a pilot scale using the FIMA, a combined centrifuge and dryer.

This necessitates the accumulation of a charge of product crystal slurry which is held for at least the duration of the isolation cycle.
Manipulating nucleation rate independently of growth rate allows control of the product particle size, operating at low supersaturation minimises encrustation, delivers purity & less extreme crystal habits.

Operation with a high crystal surface area of small crystals allows a high mass of API to be crystallized per unit volume of solution even at low supersaturation. Thus the equipment is small compared with the conventional continuous crystallizers.

Making small organic crystals of similar density to their mother liquors avoids hydrodynamic constraints encountered in conventional continuous crystallizer design.

Artificially enhancing rather than suppressing nucleation allows us to avoid compound specific crystallizer design.

Proven for cooling, anti-solvent and reactive crystallization

Particle sizes are typical of APIs and are controlled.
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<td>Cooling, anti-solvent &amp; reactive crystallizations of 5 different NCEs each with their own challenges run at scale for meaningful duration</td>
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So what about the gaps?

**Nucleation**
- This approach requires a high secondary nucleation rate at very low supersaturation. There are several ways to do this well but our understanding is incomplete. There is more opportunity to improve the approach with a deeper understanding.

**Isolating the particles for direct formulation**
- Individual 2-20μm particles of API tend to have poor powder properties. Harvesting them as granules and incorporating “functional excipients” seems attractive.

**Linking continuous primary & secondary manufacture**
- An attractive future state
Secondary Processing
Benefits - Batch vs continuous approach- potential to streamline

Continuous processing can help avoid this.
Possible to have raw materials to product in minutes/ hours
Online analysis/parametric release required but continuous facilitates this
…“fault handling utilizes an integrated fault diagnosis system (MSPC) to allow fault-tolerant control”….

*i.e.* only stop when there is a real risk to quality.