Enabling Technologies for the Continuous Manufacturing of APIs: Continuous Crystallization

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Crystallization Process Development

- Process Goals
  - Purity
  - Yield
  - Average Size and Size Distribution
  - Correct Polymorph or Pseudopolymorph
  - Shape
Road Map for Pharmaceutical Manufacturing

Paradigm shifts in manufacturing and quality envisioned

Blue Sky Vision: Continuous Manufacturing

Quality by Design

Traditional Manufacturing

Disconnected process steps

Past

Current

Process steps and their impact understood

Seamlessly integrated and well characterized processes

＞ 2020
Novartis-MIT Blue Sky Vision
Integrated Continuous Manufacturing: A radical transformation

→ the ultra LEAN Manufacturing

From start of chemical synthesis through final pharmaceutical dosage form
Our Definition of “Continuous” (ultra QbD)

- Flow
- Integration (end to end)
- Systems approach
- Integrated control strategy
Novartis-MIT Center for Continuous Manufacturing

- Phase 1 June 2007-May 2012
- Phase 2 June 2012—June 2017
- 60 MIT students and post-docs
- 20 Novartis staff and 12 MIT Professors from Chemical Engineering, Chemistry, and Mechanical Engineering
- Most research performed in each professor’s lab
- Dedicated facility for translational work.
MIT Continuous Manufacturing Facility
MIT Pilot Plant

VIDEO

Courtesy of NVS-MIT Center
Tablets Produced in Integrated Process
Batch Versus Continuous Crystallization

- **Continuous Crystallization**
  - Built in flexibility for control
  - Does not necessarily discharge at equilibrium conditions
  - Lower cost
  - CSD is broad
  - Polymorph Control?

- **Batch Crystallization**
  - Cleaning done between each batch
  - Simplicity of equipment
  - Narrower size distribution
  - Higher cost
Novartis-MIT Center for Continuous Manufacturing

- Important task: demonstration of end-to-end continuous manufacturing platform
- Used to gain experience about integration and control
- Involves multiple reactions, workup steps, crystallizations
- Each crystallization presented unique challenges
Example 1: Optimization via Modeling of MIT Pilot Plant MSMPR

VIDEO

Courtesy of NVS-MIT Center
Example 1: Optimization via Modeling of MIT Pilot Plant MSMPR
Example 1: Optimization via Modeling of MIT Pilot Plant MSMPR
Model for Multistage MSMPR

Population Balance: Conservation equation for the number of crystals in a population

\[ G_i \tau_i \frac{dn_i}{dL} + n_i = n_{i-1} \]  \hspace{1cm} (1)

\( n_i \): population density at stage \( i \)
\( \tau_i \): residence time at stage \( i \)
\( L \): crystal size
\( G_i \): crystal growth rate at stage \( i \)
\( B^0 \): nucleation rate

Mass Balance

\[ M_{T,i} = \rho_s \ k_v \int L^3 \ n_i \ dL = (C_{i-1} - C_i) \]  \hspace{1cm} (2)

\( M_{T,i} \): Suspension density at stage \( i \)
\( C \): steady state solute concentration
\( \rho_s \): crystal density
\( k_v \): volume shape factor

Crystal Growth

\[ G = k_g \left( \frac{C - C_s}{C_s} \right)^g \]  \hspace{1cm} (3)

\( C_s \): equilibrium concentration
\( k_g, g, k_b, b \): model parameters to be estimated

Nucleation

\[ B^0 = k_b \left( \frac{C - C_s}{C_s} \right)^b \]  \hspace{1cm} (4)
Kinetics Parameter Estimation

a) Convert the experimental values of CSD into Population Density

b) Find the values of k_g, g, k_b, and b that minimize the objective function \( \Phi \) :

\[
\min_{\theta} \quad \Phi(\theta) = \sum_{0}^{L_{\text{max}}} \left[ (n_{\text{exp}} - n_{\text{calc}}(L))^2 \right]
\]

Subject to equations (1) to (4)

where \( \theta = [k_g, g, k_b, b] \)
Modeling Work for Crystallization of Intermediate

- Modeled how changing temperature and residence time of each stage affects purity and yield.
Example 2: Tight Control of Continuous Aliskiren Reactive Crystallization

C11 (SPP-100 FREE BASE) + C12(FUMARIC ACID) → ALISKIREN (SPP-100) SALT

Reaction Scheme:

\[ \text{C11 (SPP-100 FREE BASE)} + \text{C12(FUMARIC ACID)} \rightarrow \text{ALISKIREN (SPP-100) SALT} \]
UV control of fumaric acid addition

C13 crystallization is very sensitive to fumaric acid/C11 ratio

Molar Ratio of fumaric acid/C11

% C13 (mass/mass)
Feed forward control

Dilute drug substance → Water absorption column → UV flowcell

Fumaric acid feed → Reactive crystallization → Filter & wash

Independent (wild) feed $F_A$ → Controlled feed $F_B$

$R = \frac{F_B}{F_A}$

Solvent dilution → Density flowcell → Silicon dioxide

Drum dryer → Vacuum dryer

Extrusion/ molding
UV control of fumaric acid addition

- Tightly controlled Fumaric Acid addition by the control system can reach high yield with satisfactory crystal properties.
Example 2: Summary

Starting from Isolated Freebase to final API

- Continuous process - effectively telescoped into 2 steps (15 L pilot-plant scale crystallizer), 8 hours total residence time
- First stage: simultaneous reaction and crystallization
- Second stage: further growth and nucleation
- Process Yield of 97%
- Conti. Process results in significantly shorter processing time compared to batch
Example 3: Control of Polymorphism in Continuous Crystallization

- There are limited studies on polymorphism in continuous crystallization.

- Polymorphism impacts product bioavailability and manufacturability.

- There are fundamental differences when moving from batch to continuous crystallization process:
  - Residence time distribution
  - Secondary nucleation
  - Seeding Efficacy
  - Steady state vs. Equilibrium
  - No solvent mediated transformation
Case study: L-glutamic acid

- Polymorphism: α form (metastable), β form (stable)
- Solvent: Water
- Characterization: polymorph ratio (Raman, XRD), solute concentration (FTIR)

(a) α form
(b) β form
Studying the possibility to control polymorphism via manipulating stage temperature and residence time
- Residence time = 60 min, Temp = 25°C → α form specific
- Polymorph specific MSMPR observed for the first time

*Mass Ratio= α form/ (α form + β form)*
Control of steady state polymorphism

- Effect of temperature and residence time on polymorphism:

<table>
<thead>
<tr>
<th>τ (min)</th>
<th>T=25°C</th>
<th>T=45°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ML conc. (g/kg solvent)</td>
<td>28.60</td>
<td>22.36</td>
</tr>
<tr>
<td>Polymorphism</td>
<td>α form</td>
<td>α form</td>
</tr>
</tbody>
</table>

Metastable Form

Low Temp
Short RT

Stable Form

High Temp
Long RT

Metastable form

Stable form
Efficacy of seeding on Polymorphism

Experimental Design:

- Single stage MSMPR (T = 25°C, $\tau = 60$min) → the unseeded steady state contains pure $\alpha$ form

- $\beta$ polymorph seed added during startup:

<table>
<thead>
<tr>
<th>Seed type</th>
<th>$\beta$ form</th>
<th>$\beta$ form</th>
<th>$\beta$ form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seed mass</td>
<td>5% to $M_{Teq}$</td>
<td>50% to $M_{Teq}$</td>
<td>100% to $M_{Teq}$</td>
</tr>
<tr>
<td>Final form</td>
<td>$\alpha$ form</td>
<td>$\alpha$ form</td>
<td>$\alpha$ form</td>
</tr>
<tr>
<td>$\tau_{washout}$</td>
<td>$4\tau$</td>
<td>$7\tau$</td>
<td>$9\tau$</td>
</tr>
</tbody>
</table>

- Seeding is unable to alter the steady state polymorphism, the seeds are removed in several residence time
Example 4: Heterogeneous Crystallization on Patterned Excipients

Advantages:

**Manufacturing process**
- Streamlined downstream processing
- Control over crystallization kinetics through heterogeneous nucleation
- API properties masked by the excipient to simplify downstream process development

**API-excipient composite particles**
- Widely tunable chemical, physical, and mechanical properties
- Potential to enhance API bioavailability
- Potential to control drug release profile
- Applicable to multiple API forms
Controlling API nucleation by tuning the nanopore shape

Polymer surfaces with nanopores of various shapes and sizes were fabricated by Nanoparticle Imprint Lithography (NpIL), as well as Nanoimprint lithography (NIL).
Aspirin: Crystal orientation suggests nucleation of (011) & (100) from the ledge

Crystal orientation verified by XRD

Why not (002) & (100)?
Nucleation of mefenamic acid in anisole on HPMC surfaces

<table>
<thead>
<tr>
<th>Hetero-nucleant Type</th>
<th>Induction time ($\tau$, h)</th>
<th>Error (h)</th>
<th>Linearity (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A ($60^\circ$ and $120^\circ$)</td>
<td>9.6</td>
<td>0.1</td>
<td>0.99</td>
</tr>
<tr>
<td>Type B ($80^\circ$ and $100^\circ$)</td>
<td>13.6</td>
<td>0.3</td>
<td>0.98</td>
</tr>
<tr>
<td>Type C ($90^\circ$)</td>
<td>8.8</td>
<td>0.1</td>
<td>0.99</td>
</tr>
<tr>
<td>no polymer</td>
<td>42.7</td>
<td>0.8</td>
<td>0.99</td>
</tr>
<tr>
<td>no pattern</td>
<td>15.8</td>
<td>0.3</td>
<td>0.96</td>
</tr>
<tr>
<td>spheres</td>
<td>36.5</td>
<td>0.7</td>
<td>0.95</td>
</tr>
</tbody>
</table>

![Images of HPMC surfaces with different nucleation types]

![Graph showing Ln(P) vs. Time (h) for different nucleation types]

![Structures of mefenamic acid, anisole, and HPMC]

![Chemical structures of mefenamic acid, anisole, and HPMC]
Publication List


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- Novartis Pharma
Thank you!

Questions?
Back-up
Polymorph transformation in MSMPR

**Single Stage MSMPR: 25°C, \( \tau = 2\text{hr} \)**

- **Seeding condition:** 100% \( MT_{eq} \) \( \beta \) seed
- **Polymorph transform:** \( \beta \rightarrow \alpha \)

![Graph showing concentration vs. time for MSMPR](image)

- Pure \( \beta \) form
- \( \alpha \) crystal found
- State transition

Legend:
- ML Conc.
- Beta form
- Alpha form
Polymorph dynamic simulation

Case Study objectives:
• Study the effect of seeding
• Effect of process parameters (residence time, temperature) on steady state polymorphism and stability

Simulation methodology:
• Population balance equations (partial integro-differential equations)
• Mass balance between liquid and solids
• Method of characteristics solves PDE at steady state
• Obtain steady state yield and polymorphism
Simulation case 1: seeding efficacy

- Single stage MSMPR, T = 25°C and \( \tau = 60\) min

- Regardless of the seeding conditions, steady state polymorphism remains unchanged (stable S.S.)
Polymorph dominance at different $\tau$ was studied (25°C):

- Negligible $\beta$ stable form at S.S. for $\tau<400$ mins
- To reach $>50$wt% stable form at S.S., $\tau>800$ mins (13 hrs)
Implications from polymorph simulations

- Dynamic simulation can be used to determine the S.S. polymorphism and the S.S. stability
  - Further investigate effect of temperature and residence time
  - May be difficult to obtain desired form at short residence time (>13hrs in the case of the commercial β L-glutamic acid)

- Design MSMPR system to achieve desired polymorph (β form) while reducing total residence time:
  - Continuous seeding from MSMPR cascade