A Decade’s Experience Delivering Clinical and Commercial Supplies using Fully Continuous Hot Melt Extrusion

Session V: Continuous Processing and Enhanced Process Control: The Realization of QbD
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March 2016
Presentation Overview

- Brief introduction to hot melt extrusion (HME)
- Merck’s HME history
- HME processing options: batch vs. continuous
- Compare/contrast to continuous blending/compression
- Use of PAT for HME in development (RTDs) & production (waste gate)
- Process development for HME
  - Use of development data to establish relationship between process parameters & responses
  - Use of modeling to predict process responses
- Control strategy definition for HME
- Batch definition for HME
- Summary & conclusion
- Acknowledgements
Hot Melt Extrusion (HME) Overview

- Hot melt extrusion applications:
  - Generating amorphous solid dispersions
  - Solubility enhancement
  - Food effect mitigation
  - Controlled release
  - Taste masking
  - Abuse-deterrence
Abbott acquires Knoll Pharma from BASF ($6.9B; 2001)

Warner Lambert HME product Rezulin approved (1997)

Abbott files sNDA for Kaletra (2005)

First modern HME at legacy MRK (2003)

Small scale GMP HME at MRK (2005)

HME production facilities qualified at MRK (2011)

First NDA filed using HME (2012)

Noxafil tablets US approval (2013)

Belsomra US approval (2014)

GrisPeg Approved (1975)

Merck HME Products

*former Merck product
HME Processing Options

- **Upstream Process:**
  - Continuous feeding of individual components
  - Pre-blending then feeding

- **Downstream Process:**
  - Milling, Blending, Direct Compression
  - Encapsulation
  - Injection Molding/Direct Shaping
  - Spheronization

- Wide spectrum of options between fully independent unit operations and fully continuous process
HME Upstream Processing: Batch vs. Continuous & Decision to Preblend

- Technical & cost considerations for choosing the upstream process
  - API/polymer feeding trials →
    - Low Tg/highly compressible materials are challenging to feed robustly over long periods of time
    - Preblending = easier feeding
  - Cost analysis of pre-blending versus individual feeding
    - Low-medium volume products were typically cost neutral
    - High volume products benefit from individual feeding
## HME vs. Continuous Blending/Compression

<table>
<thead>
<tr>
<th>Similarities to Traditional Continuous Manufacturing</th>
<th>Differences from Traditional Continuous Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residence time distributions leveraged for process development</td>
<td>HME has potential failure modes at each end of the residence time distribution range – inadequate mixing &amp; degradation</td>
</tr>
<tr>
<td>PAT utilized for process monitoring/control</td>
<td>Control strategy definition may be different for HME – process responses such as Tmelt used</td>
</tr>
<tr>
<td>Batch definition is a key consideration when defining the process</td>
<td>A combination of batch &amp; continuous unit operations may make up the process train</td>
</tr>
</tbody>
</table>
PAT Platform for HME – Inline NIR

- NIR signal transmitted through extrudate at exit of extruder
- Online readout of formulation composition every ~5 sec
- Used to detect and isolate bad product during routine production
- Used to measure \textit{Residence Time Distributions (RTDs)} during process development
Use of PAT During Development – RTD Measurement

![Graph showing RTD measurements for 18mm and 27mm data and models.](image)

<table>
<thead>
<tr>
<th>Scale (mm)</th>
<th>18</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass flow rate (kg/hr)</td>
<td>7.0</td>
<td>23.7</td>
</tr>
<tr>
<td>Screw speed (rpm)</td>
<td>380</td>
<td>380</td>
</tr>
<tr>
<td>Mean residence time (s)</td>
<td>25.7</td>
<td>26.7</td>
</tr>
<tr>
<td>StDev residence time (s)</td>
<td>5.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Lag time (s)</td>
<td>16.7</td>
<td>15.0</td>
</tr>
<tr>
<td>&quot;Mixers in series&quot;</td>
<td>3.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Time constant (s)</td>
<td>8.8</td>
<td>12.0</td>
</tr>
</tbody>
</table>
Use of PAT During Development – RTD Measurement and Scale Independent Responses

**Median Residence Time (s)**

- **Mass Flow Rate (kg/hr)**
  - 300
  - 350
  - 400
  - 450

- **Screw Speed (rpm)**
  - 200
  - 250
  - 300

**Median Screw Rotations**

- **Mass Flow Rate (kg/hr)**
  - 300
  - 350
  - 400
  - 450

- **Screw Speed (rpm)**
  - 150
  - 200
  - 250

**Extruder Screw Fill (%)**

- **Mass Flow Rate (kg/hr)**
  - 15
  - 20
  - 25

- **Screw Speed (rpm)**
  - 15
  - 20

**Screw Fill vs. Specific Feed Rate (kg/hr/rpm)**

- **Screw Fill (%)**
  - 30
  - 40
  - 50
  - 60

- **Specific Feed Rate (kg/hr/rpm)**
  - 0.03
  - 0.06
  - 0.09
  - 0.12

- **Median Residence Time (s)**

- **Median Screw Rotations**

- **Extruder Screw Fill (%)**

- **Screw Fill vs. Specific Feed Rate (kg/hr/rpm)**
Use of PAT During Production: Waste Gate Control

**HME Control Strategy** - PAT control of hot melt extrusion waste gate based upon % drug loading (wt/wt)

- **Risk Mitigated**
  - Mitigates risks to composite assay and content uniformity failure within the final coated tablets
Fault detected and out of spec material diverted to waste

API Flow was too high despite flow set-point. Thus, lowered flow set-point until API flow was back under control.
PAT for HME – Benefits/Drivers

- **Real time quantitative monitoring and detection of process upsets**
  - Verification of composition/uniformity of extrudate
  - Detect pre-mix uniformity, segregation or preferential sticking issues (or other disturbances – feeder noise, process drift, Pressure fluctuations in liquid feeds)
  - Quality control: isolation of off-specification material

- **“Flying Blind” during mass feeder refills**
  - Mass feeders feed at last known conditions during refills
  - Feeders may need to re-tune for raw material lot changes

- **Enhance understanding of process dynamics**
  - Start up/Shut down
  - Time to reach steady state

- **Provide additional information for residence time distribution (RTD)**
  - Help understand process fingerprint and enable scale-up
  - Design process to get desired quality with fixed feeder performance

- **Holistic/Quality by Design approach for quality assurance**
  - Option to include as part of process control strategy
  - Support continued process verification through monitoring
HME Process Development – Linking Quality to Process

Conceptual Representation of Extrusion Process Space:
↑ Throughput & or ↓ Energy = Molecular Dispersion Not Achieved
↑ Energy & or ↓ Throughput = Decomposition

- Process Unstable: Insufficient Dampening
- Design Space
- Chemical Decomposition
- Residence Times Trigger Scale-Up
- Single Phase Mixture Not Achieved
HME Process Development – Linking Quality to Process

### Process Input Parameters
- Barrel/Die/Screw Configuration
- Feed Rate
- Screw Speed
- Barrel Temp Profile

### Scale Independent Response Parameters
- Specific Mechanical Energy
  - Residence Time Distribution
- Product Temperature Profile
  - Mixing Cycles
  - Product Temperature ($T_{\text{melt}}$)
  - Cooling Rate

### Quality Attributes
- Chemical stability
- Phase/form stability
  - Processability
- Moisture content
Control Strategy Definition for HME

- **Option #1:** Use of process parameters
  - Scale dependent, proven acceptable ranges easily defined

<table>
<thead>
<tr>
<th>Unit Operation</th>
<th>In Process Control</th>
<th>Process Parameter Range</th>
<th>Material Attribute</th>
<th>Test Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot melt extrusion</td>
<td></td>
<td></td>
<td><strong>Screw speed</strong> 150 – 450 rpm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Barrel temperature</strong> 140 – 200 °C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Material Throughput</strong> 10 – 45 kg/hr</td>
<td><strong>Every batch</strong></td>
</tr>
</tbody>
</table>

- **Option #2:** Use of process response(s)
  - Scale independent, design space needs to be established

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<thead>
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<tr>
<td>Hot melt extrusion</td>
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<td><strong>Screw speed</strong></td>
<td><strong>Every batch</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Barrel temperature</strong>, and <strong>screw speed</strong> to meet melt temperature and NIRS API concentration measurement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Material Throughput</strong> 138 ≤ T_{melt} ≤ 213°C and <strong>API concentration (20% ±2% wt/wt)</strong></td>
<td><strong>Every batch</strong></td>
</tr>
</tbody>
</table>

HME Process Development – Relationship Between Parameters & Responses

- \( T_{\text{melt}} = f (\text{barrel temperature}, \text{screw speed}, \text{feed rate}, \text{screw design}, \text{die}) \)

Product Melt Temperature \( T_{\text{melt}} \) (°C)

Specific feed rate = \( \frac{\text{(mass flow rate)}}{\text{(screw speed)}} \)

- \( T_{\text{melt}} \) is only a function of barrel temperature, screw speed, and feed rate once screw design & die type are selected for the process

- Represents design space and translates product attribute back to process parameters
HME Process Development: Modeling of HME via SCC’s Ludovic

- 1D HME process simulation at 27mm scale, 24kg/hr and 380rpm using Ludovic
  - product temperature changes with screw axial position
  - majority of residence time is spent in the fully filled mixing (kneading block) sections

Modeling moves us from measuring only inlet and outlet to process understanding.

Twin Screw Course Pharma Edition : March 30, 2016 – Princeton, NJ
Batch Size Definition for HME

- Batch size definition could be based on upstream or downstream processing depending on limiting factor(s)
- Individual feed processing will be based on downstream limitations
- Using pre-blends, an extrusion batch can be 1 pre-blend or multiple pre-blends (same process, same control strategy)
- DOM in all cases is the first addition of API to the “batch” – i.e. if 7 pre-blends = 1 HME batch, DOM = API addition to pre-blend #1
Batch Size Definition for HME - Example

- Pre-blending = 365 kg in an 1800 L tote (based on pre-blend bulk density)
- HME = 1-X pre-blends - extruded, kibbled, & vacuum transferred to 1800 L totes
- Milling = ≤ 650-675 kg in an 1800 L tote (based on kibbled HME bulk density)
Conclusions

• Hot melt extrusion has been utilized for continuous mixing for many years
  – Extent of CP utilized should be balance of technical risks and business benefits

• Enhanced process understanding obtained through QbD development enables attribute based design space
  – First-principles and statistical process modeling contributes to this understanding

• PAT such as in-line transmission NIR leads to stronger process development and process control

• Time interval between new technology lab installation and approved products often takes a decade or more
  – Teams like FDA’s Emerging Technology Team and MHRA’s Innovation Office have the opportunity to reduce this cycle time
Acknowledgements

People
• Alanna Cleary
• Luke Schenck
• Mike Eglesia
• Mike Lowinger
• Colton Bower

Teams
• Hot Melt Extrusion Technology Development Team
• MK-4305 Pharm Working Group
• MK-0859 Pharm Working Group