Hot melt extrusion and its use in the manufacturing of pharmaceutical dosage forms

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Modeling of the extrusion process and prediction of scale-up and transfer behaviour

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Presentation outline

- Modeling strategy
- Simulation of hot melt extrusion process
- 1D simulation case study
- Transfer technology (i.e. “scale-up”)
- Summary
Why modeling?

- Limited availability and cost of API’s
  - Evaluate alternate machine configurations
  - Evaluate process variables (virtual DOE)
- Obtain data not otherwise available
- Troubleshoot problems
- Scale-up
Simulation strategy

- Several options available
  - 3D modeling
  - Response surface methodology
  - 1D modeling
3D modeling

3D finite element modeling
2D flow analysis network

- Rigorous treatment
- Accurate, detailed
- Limited to unit ops
- Resource intensive
Response surface methodology

- Rigorous treatment
- Accurate
- Limited extrapolation
- Resource intensive

Image courtesy Bernhard Van Lengerich, with permission
1D simulation

- Approximations
- Versatile
- Cost effective
- Integrated cross-section

Image courtesy Mahesh Gupta (Peldom), with permission
Modeling basis

- Extruders *cannot* differentiate between pharma polymers and "traditional" thermoplastics
  - API’s that do not melt are no different than filled thermoplastic compounds.
  - Pharma solid dispersion is no different than polymer alloy.

- The extruder can only detect viscosity, degree-of-fill, pressure, etc...
Modeling basis

- Hot melt extruder geometry is identical to “traditional” polymer machinery – from the perspective of the melt in the screw channel (intermeshing, co-rotating Erdmenger self-wiping profile).
- Hot melt extrusion applications can use existing modeling and simulation tools available for “traditional” polymer processing.
- Interpretation of results is critical to the successful use of these tools...
Modeling challenge

Complex geometry + Complex rheology

Precludes comprehensive treatment of complete process
1D simulation example

$T_F = \text{Feed temperature of melt}$

$T_B = \text{Inner barrel surface temperature}$

Density, Specific Heat = constant, independent of melt temp.

Melt viscosity = strong function of temperature and shear rate
Mass, momentum balance

\[ q = AN + \frac{B}{\eta} \cdot \frac{dp}{dz}, \quad 0 < z < L \]

\( q = \) Volumetric melt flow (assumed uniform melt density)
\( N = \) Screw rotation speed
\( A, B = \) Characteristic for each screw component, function of \((z)\)
Melt viscosity = strong function of temperature and shear rate
Energy balance

\[ q \frac{dT}{dz} = C\phi\eta N^2 - DU (T - T_B), \quad 0 < z < L \]

\( \phi = \) Screw fill level
\( U = \) Heat transfer coefficient between melt and barrel
\( T_B = \) Inner barrel surface temperature
\( C, D = \) Known functions of geometry and physical properties
Calculate $p(z)$ and $T(z)$, $0 < z < L$

Assumes $p, T$ are function of $z$ only

$T = “cross-section average temperature”$
Solving balance equations

Boundary condition 1  \[ p = p_{\text{DIE}} \] at  \[ z = L \]

Boundary condition 2  \[ T = T_F \] at  \[ z = 0 \]

Problems:
A,B = Complex function of (z), different for each screw component
\( P(z) \) = Function of viscosity (strong function of temperature)
\( T(z) \) = Function of screw fill level (\( \phi = 1 \) if \( p > 0 \), \( \phi < 1 \) if \( p = 0 \))
Alternative solution

Divide each screw component into **computational elements**

- More subdivisions assigned to “active” screw types
- \( N = \) total number of computational elements
All coefficients, processing variables are a function of $(z)$

**Continuous Variables**

- $p(z), 0 < z < L$
- $T(z), 0 < z < L$

**Discrete Point Values**

- $p_i, i = 0, 1, 2, \ldots, N$
- $T_i, i = 0, 1, 2, \ldots, N$
Alternative solution

Boundary condition 1  \[ p_N = p_{\text{DIE}} \]

Boundary condition 2  \[ T_0 = T_F \]

\[
q = A_i N + \frac{B_i}{\eta_i} \cdot \frac{\Delta p_i}{\Delta z_i}, \quad \text{for } i = 1, 2, 3, \ldots N
\]

\[
q \frac{\Delta T_i}{\Delta z_i} = C_i \phi_i \eta_i N^2 - D_i U_i (T_i - T_B), \quad \text{for } i = 1, 2, 3, \ldots N
\]
Iteration procedure – step 1

Assume temperature profile $T_i$, $(i = 0, 1, 2, \ldots N)$
Iteration procedure – step 2

Compute pressure drop through die/orifice ($P_{DIE}$)
Iteration procedure - step 3

Pressure equation solved from $i = N-1$ to $i = 1$

Initial condition at $i = N$

Compute viscosity at assumed T

Compute screw fill level
Iteration procedure – step 4

Step 4: Temperature equation solved from $i = 1$ to $i = N - 1$

Initial condition at $i = 0$

Based on computed screw fill level
Compare computed results

Computed $T(z)$ compared to assumed $T(z)$

If $T$, $P$ profiles are within specified tolerance criteria

✔ Iteration ends

✔ Compute residence time, power, etc.
Compare computed results

Computed $T(z)$ compared to assumed $T(z)$
If $T$, $P$ profiles *do not* meet specified tolerance criteria
  ✓ Assume new temperature profile
  ✓ Repeat calculations until convergence
Simulation case study

- 34mm lab-scale extruder
  - Leistritz LSM34, L/D = 35
  - 300 rpm screw speed
  - 12.5 kg/hr feed rate

- Raw materials ‘pre-granulated’
  - Polymer
  - Plasticizer
  - Surfactant
  - API
Define geometry

- Machine type
  - Free volume
  - Available power
  - Geometric parameters
- Feeding and venting positions
- Screw configuration
- Die geometry
Select an Extruder from the list.

Click on an extruder to enable the Shaft selection tab. Double-click to jump directly to shaft selection.
Define materials

- Polymers
  - Solid state thermal and physical properties
  - Melt thermal and rheological properties
  - Rheological model

- Solid additives
  - Solid state thermal and physical properties
  - Non-melting “inert” filler as API placebo
  - Rheological model

- Liquid additives
  - Plasticizing effect
Material Editor

Materials Database: Pharma Materials

ID: 3  Access: Open  Modified: 10/17/09

Materials Database Tools

Name
Pharma Materials  Update

New...  Add New Material...

Delete...  Backup...

Restore...
Define extrusion process

- Screw speed
- Feed position
- Feed temperature
- Feed rate
- Temperature profile
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**Processing Conditions**

- **Polymers:** CI-991 Placebo
- **State:** Solid
- **Throughput Rate:** 12.5 kg/h
- **Screw Speed:** 300.0 rpm
- **Head Pressure:** 10.00 bar

**Barrel Set Temperature Profile**

1. FEED 3.5D
2. MAIN 3.5D
3. MAIN 3.5D
4. MAIN 3.5D
5. MAIN 3.5D
6. MAIN 3.5D
7. MAIN 3.5D
8. MAIN 3.5D
9. VENT 3.5D
10. MAIN 3.5D

**Feed Port**

- **Feed Temperature:** 25.00 °C
- **Feed Pressure:** 0 bar

**Position:** 29.0 / 91.0 mm

**Processing Conditions data verification status:** OK
Analyze results

- Specific energy
- Discharge temperature
- Discharge pressure
- Residence time
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge Temperature</td>
<td>187.2 °C</td>
</tr>
<tr>
<td>Head Pressure</td>
<td>10.0 bar</td>
</tr>
<tr>
<td>Average Residence Time</td>
<td>36.8 s</td>
</tr>
<tr>
<td>Unmelted Polymer at Exit</td>
<td>0.0 %</td>
</tr>
<tr>
<td>Torque per Shaft</td>
<td>17.3 N·m</td>
</tr>
<tr>
<td>Mechanical Power Input</td>
<td>1.09 kW</td>
</tr>
<tr>
<td>Specific Energy Input</td>
<td>0.087 kW·h/kg</td>
</tr>
<tr>
<td>Viscous Dissipation</td>
<td>0.55 kW</td>
</tr>
<tr>
<td>Heat Transfer to Barrel</td>
<td>-0.30 kW</td>
</tr>
<tr>
<td>Units System</td>
<td>International System of Units (SI)</td>
</tr>
</tbody>
</table>

**12.5 kg/h @ 300 rpm**

**Head Temperature:** 187.2 °C

**Pressure Rise:** 10.0 bar

**Fill Factor:** 36.0 %

**Melting Length:** 2.65 D

**Model:** JKS
Calibration of model

- Practical use of 1D simulation requires “calibration” of model results using empirical coefficients to match actual process data
  - Melting
  - Specific energy
  - Melt temperature
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Axial profiles

- Degree-of-fill
- Melting
- Pressure
- Temperature
- Specific energy
- Residence time
- Viscosity
- Mixing
Mechanical Power Input

Power (kW)
Correlation of results

Extrusion Parameters → Key System Parameters → Product Quality Attributes

- **Machine Parameters**
  - Free Volume
  - Screw Configuration
  - Die Geometry

- **Process Parameters**
  - Screw Speed
  - Feed Rate
  - Barrel Temperature

- **Specific Energy**
  - Mechanical
  - Thermal
  - Melt Temperature
  - Residence Time Pressure

- **Physical Properties**
  - Crystallinity
  - Morphology
  - Bioavailability

- **Rheology**
  - Mol. weight
  - Mw Distribution

- **Other**
  - Dissolution
  - Color

Ref: Bernhard Van Lengerich, PhD Thesis, Technical University of Berlin
Scale-up

- Lab-scale process from 34mm machine was transferred to 50mm production line
  - Leistritz ZSE50 extruder, L/D=36
  - Volume difference = 4X = 50 kg/hr
  - Production machine different $D_o/D_i$
- Product requirement = 100% amorphous
- API has extreme thermal sensitivity, degradation level not to exceed lab scale
Melt Viscosity

Viscosity (kPAs)

- Viscosity decreases significantly from approximately 0.24 to 0.14 kPAs.

Diagram shows a linear decrease in melt viscosity along the length of an extruder.
Prediction of position where melting is completed = 547.5mm
Material temperature where melting is completed = 136 °C
Melt residence time can be identified (23 sec)
### Summary

**12.5 kg/h @ 300 rpm**

- **Discharge Temperature:** 187.2 °C
- **Head Pressure:** 10.0 bar
- **Average Residence Time:** 36.8 s
- **Unmolten Polymer at Exit:** 0.0%
- **Torque per Shaft:** 17.3 N·m (14.1% max torque)
- **Mechanical Power Input:** 1.09 kW (14.1% max power)
- **Specific Energy Input:** 0.087 kW·h/kg (0.09 kW·h/kg net)
- **Viscous Dissipation:** 0.55 kW (3.1% on tip gaps)
- **Heat Transfer to Barrel:** -0.30 kW

**Units System:** International System of Units (SI)

**Model:** JKS

### Summary

**50.0 kg/h @ 300 rpm**

- **Discharge Temperature:** 184.2 °C
- **Head Pressure:** 10.0 bar
- **Average Residence Time:** 48.2 s
- **Unmolten Polymer at Exit:** 0.0%
- **Torque per Shaft:** 71.2 N·m (7.9% max torque)
- **Mechanical Power Input:** 4.47 kW (7.9% max power)
- **Specific Energy Input:** 0.089 kW·h/kg (0.09 kW·h/kg net)
- **Viscous Dissipation:** 1.97 kW (1.7% on tip gaps)
- **Heat Transfer to Barrel:** -0.68 kW

**Units System:** International System of Units (SI)

**Model:** JKS

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*Image of a software interface showing results of extrusion testing.*
Prediction of position where melting is completed = 920mm
Material temperature where melting is completed = 135 °C
Melt residence time can be identified (33.6 sec)
Summary

- Commercial process successfully launched
  - Lower discharge temperature and narrower RTD than lab-scale process (also lighter color)
  - Different extruder geometry and screw design
  - Specific energy same as lab-scale

- Product specifications (crystallinity, degradation products, dissolution) can be correlated with specific energy, residence time and thermal history
1D process simulation for hot melt extrusion applications is commercially available and provides a cost-effective tool to probe deeper inside the extruder.

- Expensive and scarce API’s (kg quantities)
- Scale-up (translation between OEM machinery)
- Product and process optimization

These simulation tools can be used to model both solid dispersion and controlled release oral solid dosage forms.
Summary

- Rheological characterization for polymer/API compositions remains a challenge for any simulation/modeling technique
Thank You!