Hot Melt Extrusion Processing for the Pharmaceutical Industry

Dr Rod Bottom
Sales Account Manager, Process-Pharma

Rod.Bottom@thermofisher.com
Topics

• Introduction
  • Challenges in pharmaceutical formulation development
  • Overview of melt extrusion
  • Solid dispersions
  • Examples of HME polymers

• Laboratory and production scale extruders
  • Minilab
  • Pharmalab

• Process Analytics for Hot Melt Extrusion
  • QBD and PAT
  • NIR for PAT
  • Feasibility example
  • Process mastercurve example

• Conclusions and questions
What is your challenge today?

- Limited by your API
- Poor solubility
- Taste masking
- New delivery methods
- New dosage concepts
- New capsule materials
Biopharmaceutics Classification Scheme

Class II
- Low Solubility
- High Permeability

Class I
- High Solubility
- High Permeability

Class IV
- Low Solubility
- Low Permeability

Class III
- High Solubility
- Low Permeability

Permeability: 90%

Solubility: 0.1 mg/ml
Why use Hot Melt Extrusion technology?

- different applications: sustained release, solubility enhancement, taste masking
- anhydrous process, no solvents
- simple process (limited number of process steps, single step?)
- short residence time
- different dosage forms (depending on shape of the die and downstream processing equipment): tablets, granules, pellets, films, ...
- continuous process (high throughput)
- in-line monitoring possibilities
- co-extrusion (e.g. manufacturing of high-precision medical devices)
The Melt Extrusion Process

Feeding → Compounding/Extrusion → Downstreaming
Examples of some screw elements

• For nearly all mixing applications a well dispersed and well distributed mixture is required.

• Distributive mixing can be achieved by splitting and reorienting the flow repeatedly

• Dispersive mixing can be achieved by passing the mixture through small regions of intense deformation.
What are we doing by Melt Extrusion?

- Polymeric thermoplastic carrier
- Drug
- Plasticiser
- Filler etc.

...we are preparing a solid dispersion
## Binary Solid Dispersions by Melt processing

**Extrudate**

<table>
<thead>
<tr>
<th>Extrudate is a:</th>
<th>Solid crystalline suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymer Phase</td>
<td>A</td>
</tr>
<tr>
<td>Drug Phase is</td>
<td>C</td>
</tr>
<tr>
<td>Appearance</td>
<td>Opaque</td>
</tr>
<tr>
<td>A DSC will find</td>
<td>Tg + Fp</td>
</tr>
<tr>
<td>Expected stability</td>
<td>Thermodynamically stable</td>
</tr>
</tbody>
</table>
Solid Dispersion – Characterisation

Global characterisation tools

- DSC/MTDSC/TGA
- PXRD
- NIR/IR/Raman
- SS-NMR

Localised characterization tools

- Scanning probe & imaging based techniques (e.g. AFM, SEM, LTA, PT-MS)
- IR/Raman imaging
Hot melt extrusion polymers

- Polymers
  - e.g. methacrylate polymers, cellulose derivatives, PEO, PEG, PVA, waxes, lipids, PVP, copovidone, PEG/PVA graft polymers, poloxamer, PVAc, EVA, silicone, PVP/VA
  - requirements:
    - thermoplastic behaviour
    - suitable Tg
    - high degradation temperature
    - low toxicity
- Plasticisers
  - e.g. triethyl citrate, PEG, dibutyl sebacate, propyleneglycol, diethyl phtalate, dibutyl phtalate, glycerol monostearate, ...
  - reduce Tg and melt viscosity to improve workability and flexibility of polymer
  - smooth surface of extrudate (no sharkskinning, stick/slip effect)
Hot melt extrusion polymers

Example of some BASF polymer properties
Equipment for hot melt extrusion

Formulation Development
Proof of concept

Small amount of compounds

HAAKE MiniLab

Formulation & Process
Development, Clinical Trial,
Full Production

Easy handling & cleaning,
track record

PRISM PHARMALAB
The MiniLab

HAAKE MiniLab – suitable e.g. for

- Proof of concept studies
- Creating specimen for drug delivery systems
- Your advantages of a Micro Compounder

- Substantial cost savings for proof of concept studies due to compounding of small quantities of ingredients (5 ml)
- Understanding of material characteristics by documenting structural changes via integrated viscosity measurement
- Flexible process conditions for different materials by
  - Using conical counter or co-rotating screws
  - Automatic bypass operation for extrusion/recirculation
  - Force feeder especially for continuous powder feeding
Pharma MiniLab for small scale production

**HAAKE Pharma MiniLab**

- Allows you e.g. to produce clinical trial samples for e.g. phase 1 when only a few grams of clinical material is needed
- No time delay due to long process development on a larger twin screw extruder
- The characteristics of our GMP Version are
  - Without backflow channel
  - Force feeder for powder and small pellets
  - Stainless steel materials without painted parts
  - Password protected controls
Equipment for hot melt extrusion

Formulation Development
Proof of concept

Small amount of compounds

HAAKE MiniLab

Formulation & Process Development, Clinical Trial, Full Production
Easy handling & cleaning, track record

PRISM PHARMALAB
Pharmalab 16 and Pharma 24 Extrusion Lines

• 16 and 24mm parallel twin screw extruders
• Output 5-20 Kg/hour
• Multiple feeding ports
• Fully configurable screws
• Complete line of post-extrusion ancillary systems
Pharmalab 16 Hot Melt Extruder

Pharmalab 16 HME
Process development studies
Producing samples for Clinical Trials

Advantages of a Pharmalab HME
Substantial cost savings for process development from compounding of samples (from 200g)

Significant time savings from ability to process multiple samples in succession.

Flexible process configurations for different materials from segmented screws and barrels.

Opportunities for multiple feed streams to minimise use of expensive API.

Special feeding accessories for difficult to handle ingredients.
QbD (Quality by Design) and PAT (Process Analytical Technologies) - The Link

QbD is included in FDA’s *Pharmaceutical CGMP Initiative for the 21st Century - a Risk Based Approach*

**Quality-by-Design**

- **Raw Materials**
- **Weighing Feeding**
- **Extrusion**
- **Downstreaming**
- **Product**

• **Development:** PAT supports RA to identify the risks
• **Manufacturing:** PAT helps to monitor quality on critical process points
Likely Question to be answered by PAT ihn HME

- Solid Dispersion
  - Modification of Drug:
    - Modification I
    - Modification II...
  - Drug stage:
    - crystalline or amorphous?
  - Impurities
    - Exist?
    - Which?
    - Concentration?
  - Moisture Content
  - Homogeneity
  - Interactions, or modifications during processing
On-line, In-line, At-line, Off-line…?

- **In-line**
- **On-line**
- **At-line** beside the line simultaneously
- **Off-line** in separate lab later
Reasons for NIR as PAT for Melt Extrusion

- **Speed**: Answers in seconds / real-time information
- No offline-sampling, no sample preparation, no reagents or disposables (other techniques require making solutions or otherwise preparing a sample)
- Multiple analyses per scan (API content, moisture, ...)
- Provides physical and chemical picture of the process
- High instrument precision, good signal/noise ratio
- Non invasive, non destructive (Sample and process are not influenced by the measurement)
- Ease of use
- Rugged and robust
- Adaptable to fibre optics (Instrument and sample can be hundreds of meters apart)
Near Infrared

- NIR spectral information is useful in many industries but usually needs to be processed by a computer.

- NIR analysers are simple to use and do not require a chemist or scientist, only an operator.
  - Vibrational spectroscopy is made easy.
  - Push-button solutions for Near IR analysis.
  - One of the reasons Near IR succeeds in process where others fail.
Sampling Points on the Extruder

NIR probe at the extruder end

NIR probe in feeder hopper and liquid feeding system

NIR probe at the spheronization and compression
Custom Probe

- Custom reflectance probe commissioned to fit the standard thread (1/2”-20 UNF) on outlet of continuous extruder
Pharma 16 HME Twin-screw extruder with coupled ThermoFisher Antaris MX FT-NIR spectrometer
Feasibility Study

- Base mix of Kollidon (polyvinyl acetate/polyvinyl pyrrolidone) and lactose
- Drug blend added at 10% increments
- Extruder run at 140°C
- Six readings taken at each concentration change – several readings required before mixture stabilised
Spectra Raw Materials – Room Temperature

- Raw material powders scanned with probe at room temperature

![Graph showing the spectra of raw materials.

- Drug blend
- Kollidon
- Lactose

Wavenumbers (cm⁻¹)
Second Derivative Spectra Raw Materials

Drug blend
Kollidon
Lactose

Cal Range 6772-6584 cm\(^{-1}\)
NIR Spectra of Extrudate

Region of interest
Expanded Second Derivative Spectra Extrudate

- lac-koll 5
- lac-koll 6
- 10% drug 3
- 10% drug 4
- 20% drug 5
- 20% drug 6
- 30% drug 5
- 30% drug 6
- 40% drug 5
- 40% drug 6
- 50% drug 5
- 50% drug 6

Wavenumbers (cm⁻¹)

Log(1/R)

10% Drug Blend
0% Drug Blend
20% Drug Blend
30% Drug Blend
40% Drug Blend
50% Drug Blend
PLS Regression

Corr. Coeff.: 0.99
RMSEC: 2.22%
PLS Range: 6772-6584 cm\(^{-1}\)
Factors: 2
Process Mastercurve...by Similarity Match
Screw speed impacts product

Screwspeed set from 100 rpm to 400 rpm

Impact on NIR-Signal
Throughput matters less

Impact on NIR-Signal

Feeder empty
Temperature impacts product

Impact on NIR-Signal

Temp. 160°C ↗ 180°C

Temp. 180°C ↓ 140°C
One NIR-Mastercurve to monitor the whole process

- Monitor one Mastercurve only instead of $xx$ different curves.
- Only when the Similarity Match shows an alert is the analysis of other curves necessary.
Conclusions

• Hot Melt Extrusion provides pharmacists with new possibilities for formulation development

• Systems are available for producing materials at very early stage right up to full scale production

• Process Analytics can provide valuable real-time date to help control and maintain product quality and develop robust production processes.
• Questions?