Investigation into Different Types of Solid Dispersions Obtained at Grams Scale Twin Screw Melt Extrusion

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Introduction

- Drug Delivery Systems
  - Absorption enhancement
  - Controlled release
  - Targeting

- Solid dispersion
  - Absorption/dissolution enhancement technology especially for poorly water soluble drugs

- Melt Extrusion
  - One of the key technologies for solid dispersion preparation
  - Challenge: to reduce the amount of materials for formulation/process development....  “Small Scale Extruder”
“The dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method.”

W. L. Chiou and S. Riegelman
Journal of Pharmaceutical Sciences, 1971
Solid Dispersion (in this study)

“The dispersion of one or more active ingredients in inert carriers or matrixes at solid state prepared by the melting (fusion), solvent, or melting-solvent method.”
Solid Dispersion Types

2 Phases
- Eutectic Mixture
- Solid Crystal Suspension
- Amorphous Precipitation
- Glass Suspension (A/A)
- Glass Suspension (C/A)

1 Phase
- Glass Solution (Glassy Solid Solution)
- Solid Solution

Compound/Complex Formations
- Acid-Base Reaction
- Inclusion Compound
- Cocrystal
- Coamorphous

Crystaline
Amorphous
Molecularly dispersed

Active Ingredient
Carrier/2nd Active Ingredient

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Small Scale Extrusion
Small Scale Extrusion

Mixing in Extruder

DSM Xplore Pharma Micro Extruder

- Barrels; Vertical, separation type, 2/5 mL changeable, max 450 °C, in 20 min from 20 °C to 150 ± 2 °C
- Screws; Co-rotating, conical shape, tip length adjustable, 0 to 250 rpm
- Feeder; vertical, Water-cooling
- Easy to fill, easy to clean, fast operation

Objectives:
Evaluation of the capability for mixing and for solid dispersion preparation (all the types!)

Modifications from:
Dipersive Mixing

Continuous Mode

Recirculation Mode

Effect of screw speed on median particle size of NaCl in continuous mode

Effect of process time on median particle size of NaCl in recirculation mode

0.5 g NaCl + 4.5 g polymer
Barrel temp.: 120-130°C

0.5 g NaCl + 4.5 g polymer
Barrel temp.: 120-130°C
Screw speed: 200 rpm
Distributive Mixing

Content uniformity of NaCl after 1 min recirculation of three polymers

Formula: 0.5 g NaCl + 4.5 g polymer
Barrel temperature: 120-130°C
Screw speed: 200 rpm
NaCl content: electrical conductivity meter,
20mg/sample, mean ± s, n=10
Solid Dispersion: 3 Model Cases

2 Phases
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Crystalline
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Example #1
Glass Solution

- **Formulation**
  - Carbamazepine:Soluplus = 10:90
  - Carbamazepine:Kollidon VA64 = 10:90
  - Carbamazepine:Eudragit E PO = 10:90

- **Process**
  - 5 g of Material
  - Recirculation mode
  - Barrel: 160°C
  - Screw: 200 rpm
  - Process time: 1 min
Example #1
Glass Solution

DSC

Heat Flow

Temperature (°C)

0 20 40 60 80 100 120 140 160 180 200

CBZ-VA Extrudate
CBZ-EPO Extrudate
CBZ-SP Extrudate
VA
EPO
SP
CBZ

XRPD

Intensity

2 theta (°)

5 10 15 20 25 30 35 40 45 50

CBZ-VA Extrudate
CBZ-EPO Extrudate
CBZ-SP Extrudate
VA
EPO
SP
CBZ
Example #1
Glass Solution

Dissolution of carbamazepin from crystalline, physical mixture and extrudate

0.1N HCl, 900 mL, 37 °C, paddle 50 rpm, 50 mg drug/vessel, mean± s, n=3
Example #2
Solid Crystal Suspension

• Formulation
  – Griseofulvin:Mannitol = 25:75

• Process
  – 5 g of Material
  – Recirculation mode
  – Barrel: 170°C
  – Screw: 200 rpm
  – Process time: 15 min
Example #2
Solid Crystal Suspension

DSC

Heat Flow

Temperature (°C)

-20 0 20 40 60 80 100 120 140 160 180 200 220

GFV-Mannitol Extrudate
α-Mannitol
GFV

XRPD

Intensity

2 theta (°)

5 10 15 20 25 30 35 40 45 50

GFV-Mannitol Extrudate
α-Mannitol
GFV
Example #2
Solid Crystal Suspension

Particle size distribution of griseofulvin measured with LASER diffractometry
Example #2
Solid Crystal Suspension

Dissolution of griseofulvin from crystalline, physical mixture and extrudate

- ▲ GFV-Mannitol Extrudate
- □ GFV-Mannitol Physical Mixture
- ○ GFV

water, 900 mL, 37 °C
paddle 50 rpm,
3 mg drug/vessel
mean± s, n=3

Dissolution of griseofulvin from crystalline, physical mixture and extrudate
Example #3
Cocrystal

• Formulation
  – Carbamazepine:Nicotinamide = 1:1 mol

• Process
  – 5 g of Material
  – Recirculation mode
  – Barrel: 170°C
  – Screw: 200 rpm
  – Process time: 1 min
### Example #3
Cocrystal

#### DSC

- Heat Flow
- Temperature (°C)
- CBZ-NIC Extrudate
- NIC
- CBZ

#### XRPD

- Intensity
- 2 theta (°)
- CBZ-NIC Extrudate
- NIC
- CBZ
Dissolution of carbamazepin from crystalline, physical mixture and extrudate

- **CBZ-NIC Extrudate**
- **CBZ-NIC Physical Mixture**
- **CBZ**

0.1N HCl, 900 mL, 37 °C paddle 50 rpm, 25 mg drug/vessel mean ± s, n=3
<table>
<thead>
<tr>
<th>SD Types</th>
<th>Formulae</th>
<th>Process</th>
<th>DSC (Drug/Carrier)</th>
<th>XRPD (Drug+Carrier)</th>
<th>Dissolution</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eutectic Mixture</td>
<td>Ibuprofen:Poloxamer 188 = 30:70</td>
<td>60°C, 200 rpm , 1min</td>
<td>C/C (2 Tm)</td>
<td>C+C</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
</tr>
<tr>
<td>Solid Crystal Suspension</td>
<td>Griseofulvin:Mannitol =25:75</td>
<td>170°C, 200 rpm , 15min</td>
<td>C/C (2 Tm)</td>
<td>C+C</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
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<tr>
<td>Amorphous Precipitation</td>
<td>Naproxen:Eudragit EPO:Mannitol=25:25:50</td>
<td>170°C, 200 rpm , 1min</td>
<td>A/C (1 Tg + 1 Tm)</td>
<td>A+C</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
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<tr>
<td>Glass Suspension (C/A)</td>
<td>CBZ:Soluplus/Eudragit EPO/Kollidon VA64 =70:30</td>
<td>160°C, 200 rpm , 1min</td>
<td>C/A (1 Tm + 1 Tg)</td>
<td>C+A</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
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<tr>
<td>Glass Suspension (A/A)</td>
<td>Indomethacin/Citric Acid=50:50</td>
<td>160°C, 200 rpm , 1min</td>
<td>A/A (2 Tg)</td>
<td>A</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
</tr>
<tr>
<td>Glass Solution</td>
<td>CBZ:Soluplus/Eudratig EPO/Kollidon VA64 =10:90</td>
<td>160°C, 200 rpm , 1min</td>
<td>M/A (1 Tg)</td>
<td>A</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
</tr>
<tr>
<td>Solid Solution</td>
<td>Griseofulvin:PEG6000 =5:95</td>
<td>160°C, 200 rpm , 1min</td>
<td>M/C (1 Tm)</td>
<td>A+C</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
</tr>
<tr>
<td>CCF (Acid-Base)</td>
<td>Naproxen:Eudragit EPO=50:50</td>
<td>100°C, 200 rpm , 1min</td>
<td>M/A (1 Tg)</td>
<td>A</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
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<tr>
<td>CCF (Inclusion compound)</td>
<td>Indomethacin:HP-beta-CD=50:50</td>
<td>173°C, 200 rpm , 1min</td>
<td>M/A (1 Tg)</td>
<td>A</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
</tr>
<tr>
<td>CCF (Cocrystal)</td>
<td>CBZ:Nicotinamide =1:1 mol</td>
<td>170°C, 200 rpm , 1min</td>
<td>New C (1 Tm)</td>
<td>New C (1 Tm)</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
</tr>
<tr>
<td>CCF (Coamorphous)</td>
<td>Indomethacin:Naproxen =1:1 mol</td>
<td>170°C, 200 rpm , 1min</td>
<td>A (1 Tg)</td>
<td>A</td>
<td>Confirmed</td>
<td><img src="emoji" alt="Smiley" /></td>
</tr>
</tbody>
</table>

C: crystalline, A: amorphous, M: molecularly dispersed, CBZ: carbamazepin, CCF: compound/complex formation
Conclusion

- The DSM Xplore Pharma Micro Extruder is capable to realize dispersive and distributive mixing with representative pharmaceutical polymers.

- The extruder achieved to prepare all eleven types of solid dispersion at 5 g scale.

- The extruder is an effective tool for pharmaceutical development especially for special formulations from early development stage.
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