Twin-screw melt granulation of a thermally labile drug

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Objectives

*Twin-screw melt granulation offers many advantages over continuous wet granulation and roller compaction.*

- To investigate the effect of formulation and process variables on the physicochemical properties of granules
  - Formulation variables: binder type
  - Process variables: screw profile, barrel temp, screw speed and feed rate
- To understand the mechanisms and physicochemical changes during granulation
Presentation outline

1. Introduction of melt granulation and gabapentin (GABA), a thermally labile drug with poor compaction property

2. Selection of thermal binder and effect of thermal binder on the properties of GABA granules

3. Effect of processing conditions on the properties of GABA granules

4. Conclusions and future studies
Twin-Screw Melt Granulation

Granulation by TSE

Wet granulation

Melt granulation

- Continuous manufacturing
- On-line and real time monitoring of product quality
- Short granulation time and wider processing window
- Reduction in binder (solution) level
- Uniform distribution of formulation components
- Less undesired physicochemical changes

- Use low-melting or thermoplastic materials as binders
- Energetic materials/explosives; powder metallurgy
- Improved flow and flow properties than roller-compacted granules
Nucleation mechanism of melt granulation: Depend on particle size and viscosity of binder

**Distribution**
- Binder with low melt-viscosity
- Molten binder is distributed onto the surfaces of solid particles
- Nuclei are formed by collision between the wetted particle

**Immersion**
- Thermoplastic binder with high melt viscosity
- Adhesion of solid particles onto the surface of molten binder particles

Gabapentin (GABA) as a “Model drug”

Goal of the study

• Identify formulation and process to (1) Improve compactability of gabapentin and (2) minimize processing-induced chemical degradation of gabapentin

Gabapentin as a “model drug” for melt granulation

• High-dose, poorly compressible drug
• Poor thermal stability
• Current commercial process: fluidized-wet or high-shear wet granulation. Gradual increase in the impurity content during the shelf life has been an real issue.
• During wet granulation, GABA is solubilized in binder solution. The presence of polymeric binders prevent GABA from recrystallize during drying. The solubilized GABA undergoes significant degradation during the storage.
# Properties of Gabapentin

<table>
<thead>
<tr>
<th>Properties</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Anti epileptic</td>
</tr>
</tbody>
</table>
| **Description**     | White to off-white, crystalline solid  
Form II, the most stable form, is used in this study                                                                                       |
| **MW**              | 171.24 g/mol                                                                                                                             |
| **Melting point**   | 162-166°C                                                                                                                                |
| **pKa**             | 3.7 (carboxylate), 10.7 (amine)                                                                                                           |
| **BCS class**       | BCS class III (high solubility and low permeability)                                                                                       |
| **Solubility**      | pH-dependent solubility; soluble in water (100 mg/mL)                                                                                     |
| **Particle size**   | 6.1 μm (d10), 55.24 μm (d50), 215.64 μm (d90)                                                                                               |
| **Others**          | Crystalize rapidly, amorphous GABA could not be prepared                                                                                  |

The chemical structure of Gabapentin is shown in the diagram. The USP39 NF34 Gabapentin and the PubChem link are provided for further reference.
Degradation pathway in solution & solid state: lactamization (GABA-L)

- Gabapentin degrades to a cyclic lactam via an intramolecular cyclization reaction triggered by a nucleophilic attack of the COOH group by the N of the amino group, followed by a dehydration reaction.
- The degradation reaction is irreversible.
- USP specification of Gaba-lactam: NMT 0.4%
GABA undergoes lactamization upon melting

Dehydration due to degradation (~10.5% w/w)

Overlap between melting and degradation

Tm ~ 174°C
The experiment from DSC and Hot stage PLM confirm that Gabapentin is immiscible with binders.

Preliminary study: binder selection
Miscibility between GABA and binders

- Hydrophilic binder: PEG 8000
- Hydrophobic binder: Glycerol behenate (Compritol)
- Thermoplastic polymer: HPC ELF (Klucel)

wt% hydroxypropyl groups: 53-81
Too good miscibility of GABA and binders is not desired!

- Hold at 80°C
  - PEG (Tm ~60°C)

- Hold at 100°C
  - Compritol (Tm ~70°C)

- Hold at 140°C
  - HPC (Tg ~0°C, soften at 100-140°C)
80% GAGB and 20% binder;
Feed rate 10 g/min, Screw speed 100 rpm

<table>
<thead>
<tr>
<th>Binders</th>
<th>Zone 1</th>
<th>Zone 2</th>
<th>Zone 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GB-PEG8000</td>
<td>80°C</td>
<td>80°C</td>
<td>40°C</td>
</tr>
<tr>
<td>GB-Compritol</td>
<td>90°C</td>
<td>90°C</td>
<td>60°C</td>
</tr>
<tr>
<td>GB-HPC ELF</td>
<td>120°C</td>
<td>120°C</td>
<td>70°C</td>
</tr>
</tbody>
</table>

Leistritz nano 16
Open-end discharge
SEM Images of Granules

GABA+PEG/1000 X

GABA+Compritol/1000 X

GABA+HPC/1000 X
Melt granulation significantly improves compaction properties. HPC is the most effective.

- Mill the granule and collect the granule between 20-60 mesh (250-850 μm) → mix with 1% Mg stearate → compress into tablet
Degradation of GABA granules upon storage
USP specification for GABA-L: NMT 0.4%

Induction-sealed HDPE bottles, desiccated
Degradation of gabapentin
USP specification for GABA-L: NMT 0.4%

- Higher barrel temperature led to higher level of degradant
- At the same temperature: HPC ELF-based granule shown higher % GABA-lactam than Compritol and PEG 8000-based granules
Particle size reduction during melt granulation

GABA in HPC ELF based formulation has the smallest particle size → high mechanical stress resulted in breakage of drug crystals and amorphization → highest impurity

<table>
<thead>
<tr>
<th>Param. 3 Opt. concentration</th>
<th>µm</th>
<th>µm</th>
<th>µm</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.72</td>
<td>63.12</td>
<td>116.13</td>
<td>33.47</td>
<td></td>
</tr>
<tr>
<td>7.57</td>
<td>42.88</td>
<td>96.49</td>
<td>25.69</td>
<td></td>
</tr>
<tr>
<td>4.69</td>
<td>21.41</td>
<td>49.06</td>
<td>26.51</td>
<td></td>
</tr>
<tr>
<td>1.57</td>
<td>10.45</td>
<td>41.90</td>
<td>30.75</td>
<td></td>
</tr>
</tbody>
</table>

- Gabapentin drug substance
- Compritol-GABA granules
- PEG8000-GABA granules
- HPC-GABA granules

Acetone
Chloroform
Development of granule structure during the granulation along screw profile
20% HPC EXF + Gabapentin
Change in gabapentin particle size along screw (EXF2-4)

- Sample the granules from each zone
- Disperse in acetone in order to dissolve HPC
- Measure the particle size of gabapentin

Gradual decrease in GABA particle size

[Graph showing particle size distribution across zones]
Melt rheology of binders

- Melt viscosity of HPC ELF (pseudoplastic) >> melt viscosity of PEG 8000 and Compritol (Newtonian fluid).

- The high viscosity of HPC melt during granulation resulted in high shear stress that led to significant particle size reduction.
When granules were stored in open containers, slower degradation at higher humidity – due to crystallization of amorphous GABA

Effect of processing variables: screw speed, feed rate, and screw profile

- Move kneading element further down stream
- Remove some narrow pitch conveying element to lower the torque
The effect of screw speed and feed rate on GABA extrudate size

- **5 g/min**
- **7.5 g/min**
- **10 g/min**

**Screw Speeds:**
- 100 rpm
- 150 rpm
- 200 rpm
- 300 rpm
Effect of screw speed and feed rate on the level of GABA-L

- Degradant content increases with increasing feed rate and decreasing the screw speed (increasing specific rate)
Impurity increases as degree of fill of conveying elements prior to kneading elements increases.

\[ KW \text{ (applied)} = \frac{KW \text{ (motor rating)} \times \%\text{torque} \times \text{rpm} \times 0.97}{\text{Max. rpm}} \]

\[ \text{Specific energy} = \frac{KW \text{ (applied)}}{\text{Feed rate} \left(\frac{\text{kg}}{\text{hr}}\right)} \]

\[ \%\text{Fill} = \frac{\text{Feed rate} \times 100}{(\text{Cross section area} \times \text{Pitch length} \times \text{rpm} \times \text{Density})/2} \]

**IMPURITY VS SPECIFIC MECHANICAL ENERGY**

**IMPURITY VS DEGREE OF FILL**

\[ y = 0.0042x + 0.0263 \]

\[ R^2 = 0.7966 \]
GABA particle size of GABA in extrudates: highest vs. lowest degree of fill

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fill Degree</th>
<th>GABA Drug Substance</th>
<th>Granule, 5 g/min, 300 rpm</th>
<th>Granule, 10 g/min, 100 rpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (μm)</td>
<td>21.54</td>
<td>19.90</td>
<td>13.29</td>
<td>12.99</td>
</tr>
<tr>
<td>50% (μm)</td>
<td>52.94</td>
<td>59.76</td>
<td>113.29</td>
<td>123.16</td>
</tr>
<tr>
<td>90% (μm)</td>
<td>116.29</td>
<td>123.16</td>
<td>201.14</td>
<td>202.49</td>
</tr>
<tr>
<td>Cpt. conc.</td>
<td>34.14</td>
<td>20.19</td>
<td>20.19</td>
<td>20.24</td>
</tr>
</tbody>
</table>

Density distribution graph showing the particle size distribution for GABA in extrudates for different fill degrees and production parameters.
Effect of shear stress on %GABA-L

Relation between %GABA-L (A) and shear stress (B) generated along the screw profile during melt granulation.
DSC and ATR-FTIR of melt granules processed at different degrees of fill

DSC profiles of GABA granules processed at different degree of fill compared with physical mixture and Amorphous GABA

- Decreasing in T_m and ΔH
- No recrystallization signal detected

ATR-FTIR spectra of melt granules processed at different degree of fill compared with physical mixture, GABA, and HPC

- No FT-IR peak shift
Polymorphic transformation of GABA when processed with a more aggressive screw design

- GB Form II transformed to GABA Form III with an aggressive screw design

**FTIR spectra of GABA granules compared with GABA**
- 10 g/min, 100 rpm (30°KB)
- 10 g/min, 100 rpm (60°KB)

**XRD patterns of GABA granules compared with physical mixtures**
- Physical mixture

**Key Points**
- Torque ~ 700 G.m (30°KB)
- Torque ~ 1300 G.m (60°KB)
More compressible GABA granules at higher degree of fill

Compressibility of the granules processed at different degree of fill

Correlation between tensile strength of the tablet compressed at 100 MPa, as a function of degree of fill
Ongoing studies

1. Evaluate split feeding to minimize drug degradation while improving the compaction properties of GABA granules
2. Quantify the thermal and mechanical stress during melt extrusion
3. More advanced technique to characterize binder distribution
Conclusions

- From improving the compaction properties perspective, hydroxypropyl cellulose, a thermoplastic polymer, is more effective than low melting point waxes such as PEG 8000 and Compritol.

- High melt viscosity of HPC resulted in more chemical degradation during processing and upon storage.

- Both the size of the granules coming off the extruder and the impurity of GABA correlate better with the degree of fill (or specific rate) than the specific mechanical energy.

- Processing parameters (screw speed and feed rate) should be optimized to achieve the balance between improving GABA compressibility but also minimizing GABA degradation.
Acknowledgements

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Abbe Haser

Tony Listro

Charlie Martin
Augie Machado
Brian Haight
Backup slides
Melting and lactamization of GABA under hot-stage PLM

- 25°C
- 174°C
- 176°C (with bubble)
- 180°C
- 183°C
- 184°C
Studying HPC of different particle size

80% Gabapentin + 20% Binders

- HPC ELF : D50 ~ 160 μm
- HPC EXF : D50 ~ 50 μm
- Spray-dried HPC : D50 ~ 10 μm

80% GAGB and 20% binder
Feed rate 10 g/min, Screw speed 100 rpm
Effect of HPC particle size on GABA granule size

![Bar chart showing the effect of HPC particle size on GABA granule size](chart.png)
Effect of HPC particle size on compaction profiles of granules

- **Physical mixture**: Small particle size of binder improve the compressibility of drug
- **Melt granules**: binder particle size does not have effect on the compressibility of drug
Effect of HPC particle size on the degradation of GABA

Smaller particle size of HPC $\rightarrow$ more degradation

No significant difference in particle size reduction after melt granulation