“Measure Often, Produce Once:”

A case study of the effect of binder type on dry granulation and tablet compression properties in a model formulation

Anshul Gupte, Ph.D.
Associate Director, Pharmaceutical Development
Metrics Contract Services
April 30, 2015
Purpose

To compare the impact of roller compaction processing parameters and resulting tableting properties using dry granulation binders.
Methodology

● Model formulation with four components:
  ➢ API (30% drug load),
  Disintegrant (Crospovidone)
  Binder: 1) Avicel® DG, 2) Avicel PH 101 + Di-calcium phosphate, 3) Kollidon® VA-64 Fine
  Lubricant (Magnesium stearate)

● Roller compaction processing parameters (varied):
  ➢ Ribbon thickness, roller force, roller speed

● Roller compaction parameters (not varied):
  ➢ Mill speed (90 rpm) and granulator screen (0.8 mm)

● Compression force (not varied)
# Formulation

**Figure 2: List of Ingredients in the formulation**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
<th>% w/w</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intra-Granular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Mag. Stearate</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Avicel DG</td>
<td>64.0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Avicel PH 101)</td>
<td>N/A</td>
<td>48.0</td>
<td>58.0</td>
</tr>
<tr>
<td>Di-Calcium Phosphate</td>
<td>N/A</td>
<td>16.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Kollidon VA-64 Fine</td>
<td>N/A</td>
<td>N/A</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>Extra-Granular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mag. Stearate</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
## Roller Compaction
### Materials, Parameters, Levels

<table>
<thead>
<tr>
<th>Materials</th>
<th>Process Parameters</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel® DG [ADG]</td>
<td>Roll Force</td>
<td>6, 12, 18 kN/cm</td>
</tr>
<tr>
<td></td>
<td>Granulator screen</td>
<td>0.8 mm</td>
</tr>
<tr>
<td>Avicel® PH-101 and Di-calcium phosphate [PADCP]</td>
<td>Ribbon thickness</td>
<td>2, 3, 4 mm</td>
</tr>
<tr>
<td></td>
<td>Granulator mill speed</td>
<td>90, 120 rpm</td>
</tr>
<tr>
<td>Kollidon® VA-64 Fine [KVA 64]</td>
<td>Roll speed</td>
<td>2, 4, 8, 12 rpm</td>
</tr>
</tbody>
</table>
Manufacturing Process Flow
Results
Granules/Fines vs. Roll force at roll gap of 2 mm

Granules/Fines (Granules defined as 60 mesh and over and Fines as below 60 mesh)

Roll Force (kN)

Avicel DG
Avicel +DCP
Kollidon VA-64 Fine
Granules/Fines vs. Roll force at roll gap of 3 mm

Granules/Fines (Granules defined as 60 mesh and over and Fines as below 60 mesh)

Roll Force (kN)

<table>
<thead>
<tr>
<th>Roll Force</th>
<th>Avicel DG</th>
<th>Avicel +DCP</th>
<th>Kollidon VA-64 Fine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.6</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>18</td>
<td>1.6</td>
<td>1.6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Avicel DG

Avicel +DCP

Kollidon VA-64 Fine
Principle component (PC) analysis – scores plot
Principle component (PC) analysis - scores plot
Principle component (PC) analysis – loading plot

Granules/Fine Ratio

- ADG
- PADCP
- KVA64
- Roll Force (kN)
- Ribbon Thickness (mm)
- Roll Force (kN)*Ribbon Thickness (mm)
- Roll Force (kN)*Roll Speed (RPM)
- Ribbon Thickness (mm)^2

X-Variables (Granule/Fine ratio, PC-6, B0W:3.08359...
Principle component (PC) analysis – loading plot

Disintegration Time

Weighted regression coefficients

X-Variables (Disintegration time, PC-5, B0W:1.8104...
Principle component (PC) analysis - loading plot

Tablet Breaking force

X-Variables (Tablet breaking force, PC-5, B0W:5.20...
Conclusions

• Present investigation showed sensitivity of selected binders to studied design variables and their interaction effects within subjected design space.

• Better granulation and tableting properties can be arranged in following descending order: KVA64 > PADCG > ADG

• KVA-64 fine blends exhibited the highest proportion of granules/fines.
  • Ratio was inversely proportional to the roller gap.
Conclusions

● Tablet hardness was inversely proportional to roller compaction force; the hardest tablets produced used KVA-64 fine blends.

● Study shows value of examining the correlation between a dry granulation binder and the roller compaction parameters in order to create a working design space.
Questions?