Blending in pharmaceutical industry

Importance and challenges

Marketta Uusi-Penttilä

Nootdorp, 05 April 2016
Mission Aspen Oss

Aspen Oss supplies complex Active Pharmaceutical Ingredients (APIs) of very high quality worldwide with an excellent customer service. Based on this value proposition our customers are able to build and maintain a sustainable position in the world of the pharmaceutical business.

Our high level technology is developed over many years by our highly motivated and knowledgeable staff and business partners. Teamwork is and has been a key success factor in these developments.

We act in a respectful manner towards society and environment. Safety, compliance and labor satisfaction are essential to support our business.
History of Aspen Oss

1923: Organon

1971: Diosynth/ Akzo Nobel

2005: Organon and Diosynth Integrated business

2007: Schering-Plough and Organon

2009: Schering-Plough and MSD

2013: Aspen Pharma and API Operations MSD
Aspen Pharma

Top 10 generic pharmaceutical companies based on sales

Global ranking on worldwide generic pharmaceutical sales in 2014 (Sales in USD\textcurrency billion)

- Aspen stands with ~10 000 employees at the 6th place in the world of the largest generic pharmaceutical companies.
- Aspen has 26 manufacturing facilities in 18 locations on six continents. With a market value of >$ 12 billion.
- Core business: Pharmaceuticals and APIs: >150 countries.
Drug product

Drug product
- Tablets
- Capsules

Drug product = API + Excipients

API = Active Pharmaceutical Ingredient
Ingredient that is biologically active

Excipients = inactive ingredients in drug product
Drug product (tablet)

Excipients = inactive ingredients in drug product

- **Transport** the active drug to the site in the body where the drug is intended to exert its action, in the right concentration, and at the right rate
- Improve **processability** and **handling**
- Help the drug to **disintegrate** into particles small enough to reach the bloodstream more quickly
- Protect the product's **stability** so it will be at maximum effectiveness at time of use
- Make the product **taste** and **look** better
### Drug product

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
<th>Amount (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>API</td>
<td>500.0</td>
</tr>
<tr>
<td>Starch, pregelatinized</td>
<td>Diluent (filler), disintegrant, binder</td>
<td>75.0</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>Diluent (filler)</td>
<td>66.0</td>
</tr>
<tr>
<td>Povidone</td>
<td>Disintegrant, binder</td>
<td>2.5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>Disintegrant</td>
<td>5.9</td>
</tr>
<tr>
<td>Potassium sorbate</td>
<td>Antimicrobial preservative</td>
<td>0.6</td>
</tr>
<tr>
<td>Granulation from above</td>
<td></td>
<td>650.0</td>
</tr>
<tr>
<td>Alginic acid</td>
<td>Binder, disintegrant</td>
<td>15.0</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>Glidant</td>
<td>0.4</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>666</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
<th>Amount (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRSP (Drospirenone)</td>
<td>API</td>
<td>3</td>
</tr>
<tr>
<td>EE (Ethinyl estradiol)</td>
<td>API</td>
<td>0.03</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>Diluent (filler)</td>
<td></td>
</tr>
<tr>
<td>Corn starch</td>
<td>Diluent (filler), disintegrant, binder</td>
<td></td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>Diluent (filler), disintegrant, binder</td>
<td></td>
</tr>
<tr>
<td>Povidone</td>
<td>Disintegrant, binder</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100-200</td>
</tr>
</tbody>
</table>

Round tablets of 120 – 700 mg are easy to handle and produce
How pharmaceutical products are made

Typical flowsheet for tablet and capsule manufacturing, which comprise more than 80% of domestic pharmaceutical products.
How pharmaceutical products are made

Typical flowsheet for tablet and capsule manufacturing, which comprise more than 80% of domestic pharmaceutical products.
How pharmaceutical products are made

Typical flowsheet for tablet and capsule manufacturing, which comprise more than 80% of domestic pharmaceutical products.
API
Homogeneity of API

Last steps of API production process

Final precipitation/crystallization
  → filtration
    → drying

  → particle size reduction
    → homogenization by dry mixing
        → drum filling

One substance, same particle size distribution in each drum!
Main challenges/issues

- Fine particle size of API (d50 <20 µm) to improve bioavailability
- Poor flowability
- Segregation when particle size distribution is very wide/bimodal
- Difficulty to characterize the quality of mixing using an efficient, precise and non-destructive procedure
Particle size distribution per drum without homogenization
Particle size distribution per drum without homogenization

Production issue during drum 9
Drug product
Content uniformity

Is this pill OK?

Does every tablet contain the appropriate amount of API?

USP test <905> for content uniformity

=> ensure that the amount of drug substance in each individual tablet is the same
Content uniformity challenge

10 million tablets of 100 mg
1 mg API / tablet
1000 kg drug product powder of which
10 kg API

10 million tablets of 100 mg
1 µg API / tablet
1000 kg drug product powder of which
10 g API
Content uniformity – typical dose

Birth control pills - dose of API per tablet:

- 15 µg ethinyl estradiol + 60 µg gestodene
- 20 µg ethinyl estradiol + 150 µg desogestrel
- 20 µg ethinyl estradiol + 3000 µg drospirenone:
- 50 µg ethinyl estradiol + 1000 µg norethindrone
- 1.5 mg estradiol + 2.5 mg nomegestrol acetate

Paracetamol 500 mg per tablet
Particle size – 1 µg API per tablet

1 million API particles for 1 million tablets
=> 1 API particle per tablet with mean particle size of 114 µm

10 million API particles for 1 million tablets
=> 10 API particle per tablet with mean particle size of 53 µm

100 million API particles for 1 million tablets
=> 100 API particle per tablet with mean particle size of 11 µm

1000 million API particles for 1 million tablets
=> 1000 API particles per tablet with mean particle size of 1 µm

Improved content uniformity
Figure 5. Estimated number of particles in a single tablet versus dose.
Content uniformity

Maximum mean particle diameter and coefficient of variation which assures 99% probability to pass content uniformity test

<table>
<thead>
<tr>
<th>Particle diameter coefficient of variation, C (%)</th>
<th>0.1 µg</th>
<th>1 µg</th>
<th>10 µg</th>
<th>100 µg</th>
<th>1 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.36</td>
<td>18.0</td>
<td>38.8</td>
<td>83.6</td>
<td>180.0</td>
<td>388.0</td>
</tr>
<tr>
<td>20</td>
<td>7.15</td>
<td>15.4</td>
<td>33.2</td>
<td>71.5</td>
<td>154.0</td>
<td>332.0</td>
</tr>
<tr>
<td>40</td>
<td>4.62</td>
<td>9.95</td>
<td>21.4</td>
<td>46.2</td>
<td>99.5</td>
<td>214.0</td>
</tr>
<tr>
<td>60</td>
<td>2.44</td>
<td>5.27</td>
<td>11.3</td>
<td>24.4</td>
<td>52.7</td>
<td>113.0</td>
</tr>
<tr>
<td>80</td>
<td>1.16</td>
<td>2.49</td>
<td>5.37</td>
<td>11.6</td>
<td>24.9</td>
<td>53.7</td>
</tr>
<tr>
<td>100</td>
<td>0.523</td>
<td>1.13</td>
<td>2.43</td>
<td>5.23</td>
<td>11.3</td>
<td>24.3</td>
</tr>
<tr>
<td>120</td>
<td>0.236</td>
<td>0.508</td>
<td>1.10</td>
<td>2.36</td>
<td>5.08</td>
<td>11.0</td>
</tr>
<tr>
<td>140</td>
<td>0.109</td>
<td>0.235</td>
<td>0.506</td>
<td>1.09</td>
<td>2.35</td>
<td>5.06</td>
</tr>
<tr>
<td>160</td>
<td>0.0521</td>
<td>0.112</td>
<td>0.242</td>
<td>0.521</td>
<td>1.12</td>
<td>2.42</td>
</tr>
<tr>
<td>180</td>
<td>0.0259</td>
<td>0.0558</td>
<td>0.120</td>
<td>0.259</td>
<td>0.558</td>
<td>1.20</td>
</tr>
<tr>
<td>200</td>
<td>0.0134</td>
<td>0.0288</td>
<td>0.0621</td>
<td>0.134</td>
<td>0.288</td>
<td>0.621</td>
</tr>
</tbody>
</table>
Main challenges/issues for blend and content uniformity

- Fine particle size of API (d50 <20 µm) to improve bioavailability
- Poor flowability
- How to mix tiny proportions of predominantly minute particles within a matrix of much larger ingredients?
- Multiple ingredients of various particle sizes beyond the active pharmaceutical ingredients
- Particle shape, density, and cohesiveness vary
- Ingredients from different vendors may behave differently due to their particle size and shape and other factors, and their tendency to form aggregates.
- Segregation during tabletting, drum filling, transport, …
- Difficulty to characterize the quality of mixing as it is difficult to accurately measure the mixture composition using an efficient, precise and non-destructive procedure
Root causes of blend or product content uniformity problems

1) Non-optimum blending
2) Sampling error
3) Segregation
4) Loss of component
5) Analytical error
Some solutions to content uniformity issues

• Correct choice of API particle size to promote blend uniformity

• Correct choice of excipients to promote blend uniformity

• Active pre-blend ("ordered mixture")
  – first blend the active with a portion of a suitable “carrier” excipient
  – progressively blend with increasing amounts of the remaining components

• Issues with segregation can be reduced by matching the particle size and density of the active drug substance with excipients
Correct choice of API particle size to promote blend uniformity

Experimental and simulated percent of intended potency profiles of drug-excipient blends made with either the smaller particle size drug and the larger particle size drug. Geometric means of 6.1 and 18.5 µm. The intended potency was 10µg.

<table>
<thead>
<tr>
<th>percent of intended range</th>
<th>Number of unit doses within the given percent of intended range</th>
<th>Smaller 6.1 µm</th>
<th>simulated</th>
<th>Larger 18.5 µm</th>
<th>simulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>86-90</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>90-94</td>
<td></td>
<td>5</td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>94-98</td>
<td>5</td>
<td>13</td>
<td></td>
<td>483,249</td>
<td></td>
</tr>
<tr>
<td>98-102</td>
<td>59</td>
<td>1,000,000</td>
<td></td>
<td>20</td>
<td>313,436</td>
</tr>
<tr>
<td>102-106</td>
<td>59</td>
<td>16</td>
<td></td>
<td>145,337</td>
<td></td>
</tr>
<tr>
<td>106-110</td>
<td>59</td>
<td>7</td>
<td></td>
<td>45,337</td>
<td></td>
</tr>
<tr>
<td>110-114</td>
<td>59</td>
<td>1</td>
<td>9,744</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Correct choice of API particle size to promote blend uniformity

\[
d_{97.7} = d_{50} \cdot e^{2 \left( \ln \left( \frac{d_{50}^3}{1000} \right) \right) - \frac{6D}{\pi \rho} \left( \frac{C_v}{100} \right)^2 - 4.5}.
\]

- \(d_i\) Particle diameter of the API (\(\mu\)m)
- \(D\) dose (mg)
- \(C_v\) coefficient of variation of the dose
- \(\rho\) Density of the drug (g/cm\(^3\))

Effect of particle size on content uniformity

- Batches with a low variability (actual data)
- Batches with a high variability (actual data)
Effect of particle size on content uniformity

99% probability for passing content uniformity criteria

\[ \rho_g = (d_{90}/d_{50})^{0.78} \]

Blending in pharmaceutical industry – Importance and challenges

- Every tablet must contain the appropriate amount of API
- Fine particle size of API (d50 <20 µm) to improve bioavailability
- Choice of excipients to improve blending and drug product performance
- Segregation of powder during processing (tabletting) & transport
Thank you!

Acknowledgements

Organon, Diosynth, Schering-Plough, MSD and Aspen colleagues