Considerations in Excipients

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Drug Product Quality

Multiple Manufacturers

SUPAC Formulation(s)

Further Development Formulation(s)

Clinical Trial Formulation(s)

Development Formulation(s)

ANSA Approval

Supplements

NDA Approval

Safety and Efficacy

Pharmacokinetics (PK)

Abbreviated New Drug Application

Scale-up and post-approval changes

New Drug Application
# Excipients

<table>
<thead>
<tr>
<th>Lamictal</th>
<th>Teva lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>lamotrigine</td>
<td>lamotrigine</td>
</tr>
<tr>
<td>lactose</td>
<td>lactose monohydrate</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>magnesium stearate</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>microcrystalline cellulose</td>
</tr>
<tr>
<td>povidone</td>
<td>povidone</td>
</tr>
<tr>
<td>sodium starch glycolate</td>
<td>sodium starch glycolate</td>
</tr>
<tr>
<td>FD&amp;C yellow #6 (100mg), ferric oxide yellow (150mg), and FD&amp;C blue #2 aluminum lake (200mg)</td>
<td>FD&amp;C yellow #6 (100mg), ferric oxide yellow (150mg), and FD&amp;C blue #2 aluminum lake (200mg)</td>
</tr>
<tr>
<td>-</td>
<td>colloidal silicon dioxide; pregelatinized starch</td>
</tr>
</tbody>
</table>
Biowaivers and BCS

• Biowaiver – waiver of need to demonstrate in vivo BE based on in vitro BE

• Apply biowaivers to less risky drugs, but which are those?!?

• Biopharmaceutics Classification System (BCS)
  – Based on solubility and intestinal permeability
  – Class 1 = high solubility and high permeability
  – Class 3 = high solubility and low permeability

  • Class 3 biowaivers: Excipients should not modulate drug absorption

The percent approval of different classes of BCS drugs listed on WHO EML from 2000 to 2011

Excipient Effects

- Class 3 Biowaivers: Excipients should not modulate drug absorption

Study 1

• Cimetidine and acyclovir – BCS class 3 drugs
• 14 common excipients
• Three capsule formulations for each drug
• In vivo evaluation (2 capsules as single dose)
  – Fasted, single-dose, four-way crossover bioequivalence study (n=24) in healthy human volunteers
• Oral liquid used as reference product
• Average BE analysis to determine impact of excipients
Study 1

Two 4 way crossover BE study in healthy subjects

Study 1A

Cimetidine
BCS Class III

3 Test capsules:
3 excipients in each capsule

Reference:
commercial oral Solution

Study 1B

Acyclovir
BCS Class III

3 Test capsules:
3 excipients in each capsule

Reference:
commercial oral suspension
Study 2

4 way cross over BE study: Cimetidine

- CimTest-A: < 45mg HPMC
- CimTest-B: < 40mg Mag Stearate
- Commercial Cimetidine oral solution
- Reference Solution: Oral solution without sorbitol

V-blender

Turbula mixer
<table>
<thead>
<tr>
<th>Excipient</th>
<th>Recommended maximum allowable amount for a class 3 biowaiver (mg)</th>
<th>Maximum excipient amount studied here (mg)</th>
<th>Typical excipient amount (when present) in an IR tablet or capsule with a total weight of 300mg</th>
<th>Maximum amount (mg) in Inactive Ingredient Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline Cellulose</td>
<td>Qualitatively same and quantitatively v similar</td>
<td>600</td>
<td>100mg (20%-90%)</td>
<td>1385.3</td>
</tr>
<tr>
<td>Hydroxypropyl Methyl Cellulose</td>
<td>Qualitatively same and quantitatively v similar</td>
<td>40</td>
<td>10mg (2%-5%)</td>
<td>444.4</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate</td>
<td></td>
<td>50</td>
<td>4.5mg (0.5%-2.5%)</td>
<td>51.69</td>
</tr>
<tr>
<td>Corn Starch</td>
<td></td>
<td>900</td>
<td>150mg (25%-75%)</td>
<td>1135</td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td></td>
<td>200</td>
<td>12mg (4%)</td>
<td>876</td>
</tr>
<tr>
<td>Colloidal Silicon Dioxide</td>
<td></td>
<td>40</td>
<td>1.5mg (0.1%-1%)</td>
<td>100</td>
</tr>
<tr>
<td>Dibasic Calcium Phosphate</td>
<td></td>
<td>600</td>
<td>150mg (25%-75%)</td>
<td>635.5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td></td>
<td>100</td>
<td>10mg (2%-5%)</td>
<td>340</td>
</tr>
<tr>
<td>Lactose</td>
<td></td>
<td>900</td>
<td>240mg (80%)</td>
<td>1020</td>
</tr>
<tr>
<td>Povidone</td>
<td></td>
<td>70</td>
<td>7.5mg (0.5%-5%)</td>
<td>240</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td></td>
<td>80</td>
<td>6mg (1%-3%)</td>
<td>72</td>
</tr>
<tr>
<td>Pregelatinized Starch</td>
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<td>200</td>
<td>150mg (5%-75%)</td>
<td>435.8</td>
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<tr>
<td>Croscarmellose Sodium</td>
<td></td>
<td>120</td>
<td>37.5mg (0.5%-25%)</td>
<td>180</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td></td>
<td>40</td>
<td>7.5mg (0.25% to 5%)</td>
<td>400.74</td>
</tr>
</tbody>
</table>
Conclusions and Limitations

• 12 out of 14 were found to be non-problematic: should be no more than quantities studied

• HPMC and microcrystalline cellulose: should be qualitatively the same and quantitatively similar to reference product

• It is possible that other BCS class 3 drugs have properties that differ from cimetidine and acyclovir to render those drugs susceptible to other excipient influences that cause modified drug absorption.

• [T]he greatest concern would appear to be a drug that depends on an uptake transporter that an excipient inhibits by virtue of the excipient having molecular structure similarity to the transporter's pharmacophore or recognition site.
Commentaries

  – results obtained by Vaithianathan et al. should not be extrapolated to other drugs
Summary Slide

• Excipient monographs
  – Need for excipient understanding regarding biowaiver scenarios
  – Pediatric applications
    • https://b pca.nichd.nih.gov/collaborativeefforts/initiatives/Pages/index.aspx