Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs

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Topics

• BCS Class 3 excipient study

• Reply to “On the effect of common excipients on the oral absorption of class 3 drugs”
Drug Product Quality

- Multiple Manufacturers
- SUPAC Formulation(s)
- Further Development Formulation(s)
- Clinical Trial Formulation(s)
- Development Formulation(s)
- ANDA Approval
- Supplements
- NDA Approval
- Safety and Efficacy
- Pharmacokinetics (PK)

Abbreviated New Drug Application
Scale-up and post-approval changes
New Drug Application
Biopharmaceutics Classification System

- Biopharmaceutics Classification System

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Class 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Solubility</td>
<td>Low Solubility</td>
</tr>
<tr>
<td>High Permeability</td>
<td>High Permeability</td>
</tr>
</tbody>
</table>

- **Class 3**
  - High Solubility
  - Low Permeability

- **Class 4**
  - Low Solubility
  - Low Permeability

- **High Solubility**: highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 – 6.8
- **High permeability**: extent of absorption in humans is determined to be $\geq 85\%$ of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose
- **Biowaiver** – waiver of need to demonstrate *in vivo* BE based on *in vitro* BE
- **Apply biowaivers to less risky drugs**, but which are those?!?
BCS Based Biowaivers

• Biowaivers: Waiver of *in vivo* bioavailability (BA) and/or bioequivalence (BE) studies

• BCS Class 1 drugs
  – biowaivers acceptable
  – commonly performed

• Are BCS Class 3 drugs good candidates for biowaivers?
  – If dissolution of Class 3 compounds is very rapid *in vivo* (~oral solution), bioavailability is controlled by permeation process

• BCS class 3 drugs constitute almost:
  – 25% of drugs marketed in USA
  – 40% of orally administered drugs on the WHO Model List of Essential Medicines

• Extending biowaivers to class 3 drugs can reduce development costs and reduce human drug exposure
Excipient Effects

• US FDA and EMA allow biowaivers of BCS class 3 drugs:
  – For excipients that are not known to affect bioavailability, BCS class 3 biowaivers require that excipients be qualitatively the same and quantitatively very similar

• BCS Class 3 drugs: site-dependent absorption properties
Top 20 excipients in BCS Class 3 drugs

- Magnesium Stearate
- Microcrystalline Cellulose
- Lactose
- Starch
- Sodium Starch Glycolate
- Silicon Dioxide
- Povidone
- Pregelatinized Starch
- Hydroxypropylmethyl Cellulose
- Opadry
- Crospovidone
- Talc
- Calcium Phosphate
- Citric Acid
- Sucrose
- Methyl Cellulose
- Titanium Dioxide
Study 1A and 1B

- Objective: to assess the impact of very large amounts of 14 commonly used excipients on BCS class 3 drug absorption in humans

Two 4 way crossover BE study in healthy subjects

**Cimetidine**
- BCS Class III
- 3 Test capsules: 3 excipients in each capsule
- Reference: commercial oral Solution

**Acyclovir**
- BCS Class III
- 3 Test capsules: 3 excipients in each capsule
- Reference: commercial oral suspension
Test capsule formulations with 100mg cimetidine per capsule

<table>
<thead>
<tr>
<th>formulation</th>
<th>Excipient 1</th>
<th>Excipient 2</th>
<th>Excipient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CimTest-1</td>
<td>Microcrystalline Cellulose (300mg)</td>
<td>Hydroxypropyl-methyl Cellulose (45mg)</td>
<td>Sodium Lauryl Sulfate (25mg)</td>
</tr>
<tr>
<td>CimTest-2</td>
<td>Corn Starch (450mg)</td>
<td>Sodium Starch Glycolate (100mg)</td>
<td>Colloidal Silicon Dioxide (20mg)</td>
</tr>
<tr>
<td>CimTest-3</td>
<td>Dibasic Calcium Phosphate (300mg)</td>
<td>Sodium Lauryl Sulfate (25mg)</td>
<td>Crospovidone (50mg)</td>
</tr>
</tbody>
</table>

Passed QC testing, although not all very rapidly dissolving (although at least rapidly dissolving).
Test capsule formulations with 100mg acyclovir per capsule

<table>
<thead>
<tr>
<th>formulation</th>
<th>Excipient 1</th>
<th>Excipient 2</th>
<th>Excipient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcyTest-1</td>
<td>Microcrystalline Cellulose (300mg)</td>
<td>Hydroxypropyl-methyl Cellulose (45mg)</td>
<td>Sodium Lauryl Sulfate (25mg)</td>
</tr>
<tr>
<td>AcyTest-2</td>
<td>Lactose (450mg)</td>
<td>Povidone (35mg)</td>
<td>Stearic Acid (40mg)</td>
</tr>
<tr>
<td>AcyTest-3</td>
<td>Pregelatinized Starch (100mg)</td>
<td>Croscarmellose Sodium (60mg)</td>
<td>Magnesium Stearate (40mg)</td>
</tr>
</tbody>
</table>

Passed QC testing, although all were (only) rapidly dissolving.
Cimetidine mean profiles
## Cimetidine BE analysis

<table>
<thead>
<tr>
<th>Formulation (vs CimTest-2)</th>
<th>Cmax point estimate</th>
<th>Cmax 90% CI</th>
<th>AUCt point estimate</th>
<th>AUCt 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CimTest-1</td>
<td>90.6</td>
<td>81.0-101.3</td>
<td>90.9</td>
<td>84.9-97.2</td>
</tr>
<tr>
<td>CimTest-3</td>
<td>101.5</td>
<td>90.8-113.4</td>
<td>95.0</td>
<td>88.8-101.6</td>
</tr>
<tr>
<td>Solution</td>
<td>75.2</td>
<td>67.3-84.1</td>
<td>81.1</td>
<td>75.8-86.8</td>
</tr>
</tbody>
</table>

HPMC: retards drug release?

Reference oral solution contains sorbitol: increase gastrointestinal transit time?
Sorbitol effect

Fig. 4. Mean plasma concentrations of ranitidine in 24 healthy volunteers after administration of 150 mg ranitidine solution with addition of 0 (closed circle), 1.25 (triangle), 2.5 (square), and 5 Gm (diamond) of sorbitol.

Acyclovir mean profiles

Same formulation and same effect for AcyTest-1
## Acyclovir BE analysis

<table>
<thead>
<tr>
<th>Formulation (vs suspension)</th>
<th>Cmax point estimate</th>
<th>Cmax 90% CI</th>
<th>AUCt point estimate</th>
<th>AUCt 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcyTest-1</td>
<td>82.7</td>
<td>72.1-94.9</td>
<td>91.7</td>
<td>80.4-104.7</td>
</tr>
<tr>
<td>AcyTest-2</td>
<td>102.9</td>
<td>89.7-118.1</td>
<td>97.4</td>
<td>85.3-111.2</td>
</tr>
<tr>
<td>AcyTest-3</td>
<td>87.1</td>
<td>75.9-99.9</td>
<td>87.6</td>
<td>76.7-99.9</td>
</tr>
</tbody>
</table>

HPMC: retards drug release?

High magnesium stearate with Turbula mixer cause over-lubrication?)
Study 1 Conclusions

• Fourteen excipients were evaluated
• Most excipients did not appear to impact BCS class 3 drug permeability
• CimTest-1 and AcyTest-1 exhibited lower exposure, probably due to HPMC impact on dissolution
• AcyTest-3 exhibited low exposure, probably due to magnesium stearate impact on dissolution
• The commercial cimetidine solution exhibited low exposure, perhaps due to level of sorbitol
Study 2

14 Excipients

Study 1A: cimetidine
- No impact: SLS, corn starch, sodium starch glycolate, colloidal silicon dioxide, dibasic calcium phosphate, and crospovidone.
- Indeterminate: microcrystalline cellulose
- Reduced AUC and Cmax: HPMC-90mg* (with microcrystalline cellulose), sorbitol

Study 1B: acyclovir
- Reduced AUC and Cmax: HPMC-90mg (with microcrystalline cellulose), magnesium stearate-80mg (with pregelatinized starch and croscarmellose sodium)
- No impact: SLS, lactose, povidone, and stearic acid.
- Indeterminate: microcrystalline cellulose, pregelatinized starch, and croscarmellose sodium

*In study 1A, the HPMC-containing capsule did not fail either AUC or Cmax, but did exhibit a lower AUC and Cmax similar to its counterpart formulation in study 1B.
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
## Prototype Study 2 Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Formula</th>
<th>Excipient</th>
<th>% Dissolved in 15 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>CimTest-A-10mg</td>
<td>Cimetidine (100mg); Microcrystalline cellulose (300mg); Sodium lauryl sulfate (25mg)</td>
<td>HPMC: 10mg (2.3%)</td>
<td>92.9 ± 3.3</td>
</tr>
<tr>
<td>CimTest-A-20mg</td>
<td></td>
<td>HPMC: 20mg (4.5%)</td>
<td>89.5 ± 2.8</td>
</tr>
<tr>
<td>CimTest-A-45mg</td>
<td></td>
<td>HPMC: 45mg (9.5%)</td>
<td>38.6 ± 8.1</td>
</tr>
<tr>
<td>CimTest-A-75mg</td>
<td></td>
<td>HPMC: 75mg (15%)</td>
<td>23.5 ± 3.6</td>
</tr>
<tr>
<td>CimTest-B-20mg</td>
<td>Cimetidine (100mg); Pregelatinized starch (100mg); Crosscarmellose sodium (60mg)</td>
<td>Mag st: 20mg (7.1%)</td>
<td>94.5 ± 2.4</td>
</tr>
<tr>
<td>CimTest-B-40mg</td>
<td></td>
<td>Mag st: 40mg (13.3%)</td>
<td>60.2 ± 3.2</td>
</tr>
<tr>
<td>CimTest-B-40mg-L</td>
<td></td>
<td>Mag st: 40mg (8%) + Lactose: 200mg</td>
<td>60.0 ± 5.0</td>
</tr>
<tr>
<td>CimTest-B-40mg-T</td>
<td></td>
<td>Mag st: 40mg (13.3%): turbular mixer</td>
<td>29.0 ± 5.1</td>
</tr>
</tbody>
</table>

**Note:**
- CimTest-B-40mg-L: 40mg (8%) + Lactose: 200mg
- CimTest-B-40mg-T: 40mg (13.3%): turbular mixer

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![V-blender](image)

**V-blender**

![Turbula mixer](image)

**Turbula mixer**
In Vitro Dissolution

- All capsules were very rapidly dissolving in media of pH 1.2, 4.5, and 6.8.
- CimTest-A contained 20mg HPMC (plus two others)
- CimTest-B contained 20mg magnesium stearate (plus two others)
Mean Cimetidine Profiles

![Graph showing mean cimetidine profiles for different solutions over time](image_url)
Cimetidine Average BE Results

<table>
<thead>
<tr>
<th>Formulation (vs reference)</th>
<th>$C_{\text{max}}$ point estimate</th>
<th>$C_{\text{max}}$ 90% CI</th>
<th>$\text{AUC}_{0-t}$ point estimate</th>
<th>$\text{AUC}_{0-t}$ 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CimTest-A</td>
<td>122.1</td>
<td>109.4–136.2</td>
<td>112.2</td>
<td>104.4–120.6</td>
</tr>
<tr>
<td>CimTest-B</td>
<td>105.0</td>
<td>94.1–117.2</td>
<td>105.2</td>
<td>97.9–113.0</td>
</tr>
<tr>
<td>Commercial solution</td>
<td>86.9</td>
<td>77.9–97.0</td>
<td>100.2</td>
<td>93.2–107.7</td>
</tr>
<tr>
<td>Excipient</td>
<td>Recommended maximum allowable amount for a class 3 biowaiver (mg)</td>
<td>Maximum excipient amount studied here (mg)</td>
<td>Typical excipient amount (when present) in an IR tablet or capsule with a total weight of 300mg</td>
<td>Maximum amount (mg) in Inactive Ingredient Database</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<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>50</td>
<td>50</td>
<td>4.5mg (0.5%-2.5%)</td>
<td>51.69</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>900</td>
<td>900</td>
<td>150mg (25%-75%)</td>
<td>1135</td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>200</td>
<td>200</td>
<td>12mg (4%)</td>
<td>876</td>
</tr>
<tr>
<td>Colloidal Silicon Dioxide</td>
<td>40</td>
<td>40</td>
<td>1.5mg (0.1%-1%)</td>
<td>100</td>
</tr>
<tr>
<td>Dibasic Calcium Phosphate</td>
<td>600</td>
<td>600</td>
<td>150mg (25%-75%)</td>
<td>635.5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>100</td>
<td>100</td>
<td>10mg (2%-5%)</td>
<td>340</td>
</tr>
<tr>
<td>Lactose</td>
<td>900</td>
<td>900</td>
<td>240mg (80%)</td>
<td>1020</td>
</tr>
<tr>
<td>Povidone</td>
<td>70</td>
<td>70</td>
<td>7.5mg (0.5%-5%)</td>
<td>240</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>80</td>
<td>80</td>
<td>6mg (1%-3%)</td>
<td>72</td>
</tr>
<tr>
<td>Pregelatinized Starch</td>
<td>200</td>
<td>200</td>
<td>150mg (5%-75%)</td>
<td>435.8</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>120</td>
<td>120</td>
<td>37.5mg (0.5%-25%)</td>
<td>180</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>40</td>
<td>40</td>
<td>7.5mg (0.25% to 5%)</td>
<td>400.74</td>
</tr>
</tbody>
</table>
Conclusions

14 Excipients

Study 1A: cimetidine
- No impact: SLS, corn starch, sodium starch glycolate, colloidal silicon dioxide, dibasic calcium phosphate, and crospovidone.
- Indeterminate: microcrystalline cellulose
- Reduced AUC and Cmax: HPMC-90mg* (with microcrystalline cellulose), sorbitol

Study 2: cimetidine
- No impact: magnesium stearate-40mg, as well as pregelatinized starch and croscarmellose sodium
- Increased Cmax: HPMC-40mg (with microcrystalline cellulose)
- Reduced Cmax: sorbitol

Study 1B: acyclovir
- Reduced AUC and Cmax: HPMC-90mg (with microcrystalline cellulose), magnesium stearate-80mg (with pregelatinized starch and croscarmellose sodium)
- No impact: SLS, lactose, povidone, and stearic acid.
- Indeterminate: microcrystalline cellulose, pregelatinized starch, and croscarmellose sodium
Conclusions

• Fourteen commonly used excipients in IR solid oral dosage forms were evaluated
• 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
Topics

• BCS Class 3 excipient study

• Reply to “On the effect of common excipients on the oral absorption of class 3 drugs”
Extrapolation to other drugs?

• Currently, FDA and EMA only allow BCS class 3 biowaivers when IR formulations are qualitatively the same and quantitatively very similar.

• “[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.”

• We continue to conclude that the 12 common excipients need not be qualitatively the same nor quantitatively very similar to reference, but rather, simply be not more than the quantities studied in our manuscript for cimetidine and acyclovir, and potentially other class 3 drugs with similar properties.