Review of GI physiology and use of biorelevant media

PQRI Workshop
Bethesda 2012

Prof. Dr. Jennifer Dressman
„An IVIVC can only be as good as the data used to produce it!“

*With respect to the dissolution side, this means designing an appropriate dissolution test*
Finding the right dissolution test…..

- What factors influence release from drug products?
  - The properties of the drug
  - The quality and design of the drug product
  - The conditions under which the test is run
Finding the right dissolution test.....

**Hypothesis:**
the closer the dissolution test conditions to the physiology, the better the chances of predicting *in vivo* performance
Finding the right dissolution test…..

THREE important considerations:

1) **WHERE** in the GI tract is drug released from the dosage form

2) **HOW LONG** does the dosage form have to release the drug

3) **COMPOSITION** of the fluids into which drug is released
Finding the right dissolution test…..

1) **WHERE** in the GI tract is drug released from the dosage form? This will vary with the drug product e.g.
   
   1) Immediate release dosage forms
   2) Enteric coated dosage forms
   3) Extended release dosage forms
   4) Pulsatile delivery…..

The site(s) of release and/or % released at each site of release are often also dependent on whether the dosage form is given before or after a meal, so the dissolution test should reflect the dosing conditions
Finding the right dissolution test…..

1) **HOW LONG** does the dosage form have to release the drug?

- The drug must be released before or at its site(s) of absorption, otherwise release will not result in absorption. So it is important to understand the permeability of the drug at various points in the gut.

- The passage of the dosage form through the stomach depends on **unit size** and **prandial state**.
Finding the right dissolution test.....

1) **HOW LONG** does the dosage form have to release the drug?

In the **fasted state**, motility in the upper GI tract is cyclical and passage is size-independent.
Finding the right dissolution test…..

1) **HOW LONG** does the dosage form have to release the drug?

In the **fed state**, passage of bigger units may be considerably delayed.
Finding the right dissolution test…..

1) **HOW LONG** does the dosage form have to release the drug?

These effects can lead to huge differences in the plasma profiles.
**Finding the right dissolution test.....**

**COMPOSITION** of the fluids into which drug is released

The foods and drinks we consume, gastric juices, bile, pancreatic juices, bacterial fermentation as well as water re-uptake all combine to influence the composition of the GI fluids at various points in the gut.
Solubility of Dipyridamole (µg/ml) in buffers and human aspirates

<table>
<thead>
<tr>
<th>pH</th>
<th>Solubility (µg/ml)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 5</td>
<td>60</td>
<td>(Kohri et al. IJP 1992)</td>
</tr>
<tr>
<td>pH 6</td>
<td>13</td>
<td>(Kohri et al. IJP 1992)</td>
</tr>
<tr>
<td>pH 7</td>
<td>5</td>
<td>(Kohri et al. IJP 1992)</td>
</tr>
<tr>
<td>HIF fasted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH 6.7</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>HIF fed 30</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>HIF fed 60</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td>HIF fed 120</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>HIF fed 180</td>
<td>254</td>
<td></td>
</tr>
</tbody>
</table>
**Solubility of Ketoconazole (µg/ml) in buffers and human aspirates**

- pH 5 ~90 (Esclusa-Diaz et al. IJP 1996)
- pH 6 ~13 (Esclusa-Diaz et al. IJP 1996)
- pH 6.5 6.9 (Poelma JPP 1991)
- **HIF fasted** (pH 6.7) 28.8
- **HIF fed** 30 and HIF fed 60 (pH 6.5) 873
- **HIF fed** 120 (pH 5.8) 989
- **HIF fed** 180 (pH 4.9) 476
For weak bases and acids, solubility is highly dependent on pH.

Gastric pH is usually low.

Intestinal pH is usually near neutral.
Solubilization by mixed micelles in the bile

- **Hydrophobic core**
- **Hydrophilic shell**

**Cholesterol**

**Water-soluble portion**

**Bile salt**

**Lecithin**

**All lipid-soluble**

Important for lipophilic drugs
Finding the right dissolution test…..

COMPOSITION of the fluids into which drug is released

The foods and drinks we consume, gastric juices, bile, pancreatic juices, bacterial fermentation as well as water re-uptake all combine to influence the composition of the GI fluids at various points in the gut.

Not only the drug, but also the excipients, can have dissolution/release characteristics that are dependent on the composition.
GI-appropriate media composition and volume: „biorelevant“ dissolution media

1. Fasted state
   - Stomach:
     - FaSSSGF: simulates reduced surface tension in the stomach
   - Small intestine:
     - FaSSIF to simulate basal bile secretion in upper SI

Vertzoni et al. EJPB 2005,
Dressman et al. Pharm.Res. 1998
In vitro simulation of the gastric contents: **preprandial** (FaSSGF)

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCl</td>
<td>q.s. pH 1.6</td>
</tr>
<tr>
<td>Pepsin</td>
<td>0.1 g</td>
</tr>
<tr>
<td>Sodium Taurocholate</td>
<td>80 µM</td>
</tr>
<tr>
<td>Lecithin</td>
<td>20 µM</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>34.2 mM</td>
</tr>
<tr>
<td>Distilled Water</td>
<td>q.s. 1,000 ml</td>
</tr>
</tbody>
</table>

In vitro simulation of the small intestine contents: preprandial (FaSSIF-V2)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maleic acid</td>
<td>19.12 mM</td>
</tr>
<tr>
<td>Sodium taurocholate</td>
<td>3 mM</td>
</tr>
<tr>
<td>Lecithin</td>
<td>0.2 mM</td>
</tr>
<tr>
<td>NaCl</td>
<td>68.62 mM</td>
</tr>
<tr>
<td>NaOH</td>
<td>34.80 mM</td>
</tr>
<tr>
<td>Distilled Water</td>
<td>qs 500 ml</td>
</tr>
</tbody>
</table>

- pH: 6.5
- Osmolality: 180 ± 10 mOsm
- Buffer Capacity: 10 ± 2 mEq/L/pH unit

E. Jantratid, Pharm Res 2008
Simulation of the fed state in the upper GI tract
GI-appropriate media composition and volume: „biorelevant“ dissolution media

2. Fed State

- **Stomach:**
  - FeSSGF: Milk BUFFER pH 5 combination to simulate gastric conditions after a standard breakfast

- **Small intestine:**
  - „FeSSIF-V2“ to simulate postprandial bile secretion, lipolysis products, increased buffer capacity and osmolality in upper SI after food intake

E. Jantratid, Pharm Res 2008
**in vitro simulation of the gastric contents:** postprandial (*FeSSGF*)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>17.12 mM</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>29.75 mM</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>237.02 mM</td>
</tr>
<tr>
<td>Milk: Buffer</td>
<td>1:1</td>
</tr>
<tr>
<td>NaOH/HCl</td>
<td>q.s. pH 5</td>
</tr>
</tbody>
</table>

This medium has a pH of 5, Osmolality 400 mOsmol/kg, buffer capacity 25 mmoLE/l/ΔpH

E. Jantratid, Pharm Res 2008
**in vitro simulation of the small intestinal contents: postprandial (FeSSIF-V2)**

<table>
<thead>
<tr>
<th>Sodium taurocholate</th>
<th>10 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lecithin</td>
<td>2 mM</td>
</tr>
<tr>
<td>Glycerol monooleate</td>
<td>5 mM</td>
</tr>
<tr>
<td>Sodium oleate</td>
<td>0.8 mM</td>
</tr>
<tr>
<td>Maleic acid</td>
<td>55 mM</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>81.65 mM</td>
</tr>
<tr>
<td>NaCl</td>
<td>125.5 mM</td>
</tr>
<tr>
<td>Distilled Water</td>
<td>qs 1 Liter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pH</th>
<th>5.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality</td>
<td>390 ± 10 mOsm</td>
</tr>
<tr>
<td>Buffer Capacity</td>
<td>25 mEq/L/pH unit</td>
</tr>
</tbody>
</table>

E. Jantratid, Pharm Res 2008
Application of media to predicting food effects: Danazol

Aqueous solubility: 1µg/ml
Dose: 200 mg
pKa: neutral
log P: 4.53

D:S 200 liters
H₂O
20 liters
FaSSIF
6 liters
FeSSIF
Danatrol dissolution profiles in various media at 100 rpm
Danazol's food effect reflects its dissolution characteristics

Plasma profiles of danazol after administration in the fasted (○) and fed (●) state (from Charman et al.)
GI-appropriate media composition and volume: "biorelevant" dissolution media

Making life easier:

Using "instant" powders to make the biorelevant media

source: Biorelevant.com
Designing an appropriate Dissolution Test

- Classify the drug substance according to BCS
- Choose appropriate media composition and volume
- Choose an appropriate apparatus
- Consider the hydrodynamics
- Determine whether de-aeration of the medium is necessary
- Choose an appropriate test duration
Designing an appropriate Dissolution Test

- Classify the drug substance according to BCS
- Choose appropriate media composition and volume
- Choose an appropriate apparatus
- Consider the hydrodynamics
- Determine whether de-aeration of the medium is necessary
- Choose an appropriate test duration
Designing an appropriate Dissolution Test

- Notes on Media composition and volume

1) for *highly soluble* drugs in IR dosage forms, media composition should be simple e.g. aqueous buffer
2) for *less soluble* drugs, consider biorelevant media
3) if the drug is poorly soluble but highly permeable, sink conditions may be generated in the GI tract and could be considered for dissolution
4) if the drug is poorly soluble and has low/moderate permeability, use of sink conditions for dissolution will likely lead to overprediction of absorption.
5) Some dosage forms are far more prone to composition effects than others e.g. *enteric coated dosage form* compared to *osmotic pump*. 

Designing a Dissolution Test

- Classify the drug substance according to BCS
- Choose appropriate media composition and volume
- Choose an appropriate apparatus
- Consider the hydrodynamics
- Determine whether de-aeration of the medium is necessary
- Choose an appropriate test duration
Dissolution apparatus

- **USP* Apparatus I/II**
  - one vessel/unit
  - basket/paddle
  - volume: 500-1000 ml

Useful when one or two media will be employed
- Less suitable for IVIVC with MR dosage forms, since IVIVC may not be possible if release testing is performed in a single medium
- Also unsuitable for lipid dosage forms due to poor dispersion of the lipid

*USP 26 United States Pharmacopoeia*
Application of the fed state media to lipid-based formulations; paddle

Dissolution in the paddle method resulted in very poor release from the formulation due to inadequate dispersion.
Dissolution apparatus

- USP Apparatus III (BioDis)
  - series of cylinders with sieves at each end
  - volume per cylinder: 200-250 ml
  + Enables simulation of passage through the GI tract in one test
  + adjustment of dip-rate combined with sieve size can achieve emulsification of lipid dosage forms

*USP - United States Pharmacopoeia*
Application of the biorelevant media to lipid-based formulations in the BioDis

In the BioDis, the formulation dissolved best in FeSSGF and the profile in this medium matched the absorption profile well.

Jantratid et al., EJPB 2008
**Application of biorelevant media in the BioDis to MR dosage form performance**

<table>
<thead>
<tr>
<th>Segment of the GI tract</th>
<th>pH-gradient preprandial</th>
<th>Residence time (min)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>blank medium</td>
<td>pH</td>
</tr>
<tr>
<td>Stomach</td>
<td>Blank FaSSGF</td>
<td>1.6</td>
</tr>
<tr>
<td>Duodenum/ Jejunum</td>
<td>Blank FaSSIF-V2</td>
<td>6.5</td>
</tr>
<tr>
<td>Jejunum/ Ileum</td>
<td>Blank Half-FaSSIF</td>
<td>7.0</td>
</tr>
<tr>
<td>Distal Ileum</td>
<td>FaSSIF-sans</td>
<td>7.5</td>
</tr>
<tr>
<td>Colon</td>
<td>SCoF</td>
<td>5.8</td>
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Case example: Mesalamine products

- These products are used for the therapy of Crohn‘s disease and ulcerative colitis in Europe
  - Claversal®; Salofalk®
    - Eudragit L coating (dissolves at pH > 6,0)
  - Pentasa®
    - Microgranulate with an Ethylcellulose coating
    - Release is diffusion driven
  - Granustix®
    - Eudragit L coating (dissolves at pH > 6,0) AND diffusion driven release
Case example: Mesalamine products

Pentasa and Granustix: Release sites in GI tract based on BioDis results

Salofalk and Claversal: Release sites in GI tract based on BioDis results
Summary

To come up with the „right“ dissolution test for generating an IVIVC, one needs to consider
the drug‘s properties (solubility, permeability etc.)
the mechanism of release of the dosage form
dosage form dimensions
the excipient properties
dosing conditions in the *in vivo* study

With this information, it should be possible to generate an *in vitro* profile that closely reflects the *in vivo* release profile
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