Theme: Emerging Regulatory Initiatives

Dissolution Testing and Specifications for BCS I & III drugs in Immediate Release Products

The Future of in In-Vivo Predictive Dissolution methods

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• Deanna Mudie, Ph.D.  Postdoctoral Fellow, U-M
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What is it we can’t do today,…..

……….. but if we could, would revolutionize our business?

Joel Barker, Futurist

A better dissolution test!

Our hypothesis is:
Meaningful in vitro test methods and comprehensive computational tools that accurately reflect the in vivo environment will make more accurate assessment of oral dosage form performance possible.
Human physiology is complex

So, in vivo dissolution is complex

So, *in vivo* predictive dissolution testing is complex

Potential rate-determining steps in drug absorption

Gastric emptying
\[ \frac{dM_e}{dt} = k_{ge} M_s \]

Disintegration

50 mL + glass of water (240 mL)

Dissolution in stomach
\[ \frac{dM_d}{dt} = \left( \frac{D}{h_{eff}} \right) A \left( C_s - C_b \right) \]

Absorption
\[ \frac{dM_a}{dt} = k_a C_b \]

GI Residence Time

50 – 100 mL

pH change?

Dissolution in intestine
\[ \frac{dM_d}{dt} = \left( \frac{D}{h_{eff}} \right) A \left( C_s - C_b \right) \]
Standard Compendial Tests for “Oral Bioperformance”

• ~1950: Disintegration Test
• ~1970: Dissolution Apparatus 1 (rotating basket)
• ~1980: Dissolution Apparatus 2 (paddle)

Since 1980 – not much new
Some Critical Material Attributes (CMA) and Critical Processing Parameters (CPP) Affecting “In Vivo” Dissolution (CQA):

**GI Environmental Factors**
- pH
- Buffer species (HCO_3^-)
- Buffer concentration (10-15mM HCO_3^-)
- GI fluid hydrodynamics
- Intestinal motility
- Fluid Volume
- Viscosity
- Bile salts
- etc.

**Drug Properties:**
- Solubility
- pKa (acids and bases)
- Ksp, CSC (Cocrystals)
- Particle size
- Intestinal Permeability
- Partition coefficient
- Surfactant solubilization
- Precipitation propensity, kinetics
- etc.

**Formulation Properties:**
- API particle size
- API size distribution
- Drug release mechanism
- Disintegration mechanism
- Manufacturing Method
- Processing effects
- Excipient
  - Function
  - Performance
  - Amount, Grade
- Dosage form aging
- etc.
There is a lot of information on GI fluid content...


**GI Environmental Factors**

- pH
- Buffer species (HCO₃⁻)
- Buffer concentration (10-15mM HCO₃⁻)
- GI fluid hydrodynamics
- Intestinal motility
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- etc.

**Table 2.** Literature Values for Concentrations of Some Major Components of Fluid in the Fasted and Fed Stomach and Small Intestine

<table>
<thead>
<tr>
<th>Component</th>
<th>Stomach</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasted mean</td>
<td>7.3±2</td>
<td>6.7±7.6</td>
<td>8.9±33</td>
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<td>Stomach mean</td>
<td>6.7±10</td>
<td>6.4±8</td>
<td>8.9±33</td>
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<tr>
<td>Fasted median</td>
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</table>
Dissolution Testing: The Future

• Need to transition to multiple dissolution methodologies for different purposes (eg: fit for purpose dissolution methodologies)
  • Quality control (eg: Good, Fast, and Cheap; appropriate for material and process control)
  • In Vivo Predictive (eg: QbD purposes: CMA, CPP, CQA assessment; not necessarily Fast or Cheap)

Need to “take into account” buffer, buffer capacity, drug pKa, drug solubility, pH, pH changes, hydrodynamics, absorption, etc.

• Need to consider BCS Class in selecting appropriate dissolution methodologies from several options
  • Current compendial methods (eg: Apparatus I, II, IV)
  • Multicompartment systems: Gastrointestinal Simulators (eg: GIS, ASD)
  • Multiphase systems: (eg: Biphasic)
  • Other variations, future developments

Need to “take into account” drug pKa (acid(a), base (b), neutral (c)), solubility, buffer, buffer capacity, pH, pH changes, absorption, etc.
Physiological dissolution “systems” explored to date

Multicompartment systems (stomach + intestine)
- Artificial Stomach and Duodenum (ASD)
- Gastrointestinal Simulator (GIS)
- pH dilution method (single beaker)

Two-phase dissolution apparatus (dissolution + absorption)
- Simultaneous dissolution and partitioning in single compartment containing two phases (water:organic)
- Membrane systems

Combination systems
- Multicompartment + Two phase
- USP 4 + Two-phase
Some other physiological dissolution “systems”

- Flow-through systems (hydrodynamically realistic?)
  - USP 4 (flow-through)

- Artificial Dynamic GI System, TIM-1 (TNO)
- Stress test apparatus
- Dissolution/Permeation system (uses Caco-2 cells)
- Disintegration apparatus
Intestinal Water Content


Liquid contents of the: stomach (Fig. 3A), small bowel (Fig. 3B), multiple intensity projection image of individual small bowel water pockets, colour coded and extracted from images (Fig. 3C).

Mean Gastric Volume before and after 240 mL
\[ t_{1/2} = 13 \text{ min} \]

Mean Total Intestine Water Content before and after 240 mL
\[ V_{\text{mean}} \sim 40-80 \text{ mL} \]

Small Intestine water pocket size and volume (before 240 mL)
Stomach and intestine: Two-compartment dissolution apparatus

- Several publications in literature describing Artificial Stomach-Duodenum (ASD)
- Used in pharmaceutical industry
- Used to compare with *in vivo* bioavailability values

Relative bioavailability estimation of carbamazepine crystal forms

Gastrointestinal System (GIS)

Physiologic pH, volumes, buffers, surfactants may be used.

Adjustable parameters:
- pH
- Buffer species
- Buffer capacity
- Stomach emptying rate
- Duodenal emptying rate
- "Secretion rate"

Measurable parameters:
- Total amount/conc.
- Amount dissolved
- pH

Drug = propranolol (BCS Class I)

Stomach

- Initial: 50 mL
- pH=2.0
- 250 mL H₂O
- Final: 50 mL

Duodenum

- Initial: 50 mL
- pH=6.5
- 0.1M PO₄
- Maintained at 50 mL

Jejunum

- Intestinal “Secretion”

Stomach Emptying Rate $t_{1/2}$

1 mL/min

1 mL/min

Adjusted
Propranolol (BCS I) in GIS system

- pKa ~ 9.6
- Dose: 10-90 mg
- Solubility: 33 mg/mL
- Human Pe = 2.9x10^{-4} cm/s
- BCS Class I

Stomach half-emptying time = 5 min

Effect of stomach emptying time on rate of appearance of dissolved drug in Duodenum + Jejunum compartments

GIS dissolution + GastroPlus Simulation
(dissolved duodenum+jejunum compartments used as input into Gastroplus)

Propranolol (BCS I)
Metoprolol (BCS I)

Advantages & disadvantages of two-compartment systems

**Advantages**

- Sequentially exposes drug to gastric followed by intestinal media
  - Differing media properties in stomach and intestine (e.g. pH, lipid & bile salt concentrations) can affect dissolution
- Captures *in vivo* gastric-emptying rates and flow rates
  - Can vary to simulate effect on dissolution

**Disadvantages**

- Assumes dissolved drug is proportional to drug in plasma
Why care about “absorption”

Two-phase system application/characterization

- Withdraws dissolved drug from aqueous medium
- Can help maintain physiological aqueous drug concentration in physiologically realistic volume of liquid (e.g., 50-100 mL)

Dissolution/Permeation (D/P)
Scaling parameters for physiological relevance of two-phase (eg: octanol:water) system

It is possible (under some circumstances) to achieve similar \textit{in vitro} and \textit{in vivo} mass transport rates

\[ k_p = \left( \frac{A_I}{V_a} P_I \right)_{\text{in vitro}} \approx k_a = \left( \frac{A}{V} P_{eff} \right)_{\text{in vivo}} \]

- Modify vessel diameter \((A_I)\) & volume \((V_a)\)
- Adjust in vitro dose (MT) as needed

\[ \left( \frac{M_T}{V_a} \right)_{\text{in vitro}} = \left( \frac{\text{Dose}}{75 ml} \right)_{\text{in vivo}} \]

Comparison of ibuprofen (200 mg) in vivo and in two phase system

Wagner J.G et al., *J. Pharm. Biopharm*, 1984, 12, 4; Eller M.G. et al., *Biopharm & Drug Dis*, 1989, 10, 269-278

Dissolution and partitioning of 200 mg Ibuprofen tablets 150 ml pH 6.3 50 mM phosphate buffer, 77 rpm, 150 ml 1-octanol, A = 63 cm²
Ibuprofen (600 mg) absorption in humans

- Single dose, 600 mg Ibuprofen
- Taken with 200 ml water
- 24 fasted healthy volunteers
- Average input into plasma determined by deconvolution

USP Predictions for 600 mg Ibuprofen (10mM, pH=6.8)
GIS Predictions for 600 mg Ibuprofen (10mM, pH=6.8)
Scaled two phase apparatus predicted to describe in vivo input into plasma for Ibuprofen tablets

<table>
<thead>
<tr>
<th>Input variable</th>
<th>Value(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/V</td>
<td>80.1/V cm⁻¹</td>
</tr>
<tr>
<td>Vₐ</td>
<td>150 ml</td>
</tr>
<tr>
<td>Pᵢ</td>
<td>28 X 10⁻⁴ cm/s</td>
</tr>
<tr>
<td>Dose</td>
<td>600 * 2 mg</td>
</tr>
<tr>
<td>S</td>
<td>25 s⁻¹</td>
</tr>
<tr>
<td>Buffer concentration</td>
<td>10 mM</td>
</tr>
<tr>
<td>Buffer pKₐ</td>
<td>6.8</td>
</tr>
<tr>
<td>So</td>
<td>0.068 mg/ml</td>
</tr>
<tr>
<td>Drug pKₐ</td>
<td>4.4</td>
</tr>
<tr>
<td>rₒ</td>
<td>11.5 or 20 μm</td>
</tr>
<tr>
<td>Drug Dₜ</td>
<td>7.5 X 10⁻⁶ cm²/s</td>
</tr>
<tr>
<td>Drug ρ</td>
<td>1.1 g/cm³</td>
</tr>
<tr>
<td>Viscosity</td>
<td>0.007 cm²/s</td>
</tr>
</tbody>
</table>
Solubility & Absorption rate determined dissolution

Assumes:

\[ k_a = 5 \text{ h}^{-1} \]

\[ (A/V) = 3.5 \text{ cm}^{-1} \]

10 mM phosphate buffer pH=6.8
Potential types of In vivo Predictive Dissolution (IPD) methods

- **Intestinal**
  - USP apparatus

- **Gastric**
  - Intestinal

- **GIS (ASD) multi-compartment apparatus**

- **Abs**
  - Intestinal

- **Gastric-Two phase apparatus**

- **Two-phase apparatus**

- **Gastric**
  - Intestinal
# BCS Subclasses and Dissolution Testing for IR Dosage Forms

## Table I. BCS Subclassification and Dissolution Testing for Immediate-Release Dosage Forms

<table>
<thead>
<tr>
<th>BCS subclassification</th>
<th>Solubility at pH 2</th>
<th>Solubility at pH 6.8</th>
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</tr>
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<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
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<td>&gt;85% dissolution in 15 min; 30 min, F2 &gt;50, pH=6.8</td>
</tr>
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<td>IIA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Low</td>
<td>High</td>
<td>High</td>
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<td>IIC&lt;sup&gt;c&lt;/sup&gt;</td>
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References:
Conclusions: In vivo Predictive Dissolution

• A mechanistic approach to method selection and development is the path toward In Vivo Predictive Dissolution (IPD).

• Gastric emptying and absorption are key components to make *in vitro* dissolution more *in vivo* predictive, especially for BCS 2&4 drugs.

• Mechanistic analyses of *in vitro* transport are essential to design and scale potential IPD apparatuses.

• Relevant physiological parameters are crucial to *in vivo* transport analyses and need to be further studied and applied.

• The applicability of new IPD methodologies to better predict in vivo performance should be “validated” with *in vivo* data.

• If we follow this path, we will do dissolution better 10 years from now.