Opportunities for Regulatory Relief via In Vitro Dissolution

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June 10, 2015
Topics

• Current issues with in vitro dissolution
• IVIVC, IVIVR, and biopharmaceutic risk
• Deconvolution IVIVR method
• BCS Class 2 (for weakly basic drugs)
• BCS Class 3 excipient considerations
Two of the Most Common Complaints about In Vitro Dissolution

• Too sensitive (i.e. over discrimination)
• Not sensitive enough (i.e. not discriminating enough)

• Opportunities
  – Regulatory relief
  – Methods development/validation/standardization of more challenging dissolution problems (e.g. BCS class 2)
Complications

• Attaining complete dissolution and sink conditions
  – Enhanced drug solubility (e.g. via additional surfactant) tends to reduce dissolution test sensitivity.

• Same EVERYTHING across dose strengths
  – Historical tendency to prefer the same test methods and same specs, even though different doses can result in a fundamental change in the dissolution problem.

  • A higher dose may dissolve slower or to a lesser extent, than lower dose.
Roles of In Vitro Dissolution

• Product development tool
• QC test
• Clinically relevant assessment tool [a/k/a in vivo performance test]
  – Meaning?
• A measure of in vivo dissolution
  – As assessed by deconvolution of PK profile when absorption is dissolution-limited?
Meaning of “In Vivo Performance”

- In vivo dissolution (profile)
- In vivo absorption (profile)
- In vivo pharmacokinetic profile
- Sensitive to efficacy or safety

- Sure, all related, but lack of clarity is a barrier.
- Do we want in vitro dissolution to predict first-pass metabolism?
- We have to be careful about what we expect of in vitro dissolution. Lack of clarity detracts from reliable utility of in vitro dissolution.
- IVIVR – in vitro dissolution – in vivo absorption relationship
  - Absorption = dissolution + permeation
Beyond In Vitro Dissolution Science: Status Quo and the Confidence Game

• Organizations will often not pursue approaches that lack utility in drug development or lack high regulatory certainty.

• Status quo
  – Stakeholder know current strength/limitations of in vitro dissolution
  – Budget
    • No requirement for “biostudies with several formulations”

• Uncertain elements
  – Budget
  – Acceptable role of modeling and simulation
Novel In Vitro Dissolution Methods

• Two major elements
  – Apparatus and operating conditions
  – Media

• Apparati
  – Compendial
  – Two or more “lumen” compartments (e.g. stomach and duodenum per ASD model)
  – Systems with “absorption compartment” (e.g. biphasic systems to mimic absorption during dissolution for low solubility drugs to avoid “too much” surfactant)
Biopharmaceutic Risk

• Is an IVIVC/IVIVR possible or even likely for a BCS 1 IR tablet?
• ... a BCS 2 IR tablet?
• ... a BCS 3 IR tablet?
• ... a BCS 4 IR tablet?

• Is it possible to understand how dissolution contributes to the absorption kinetics?
Biopharmaceutic Risk

• For a SUPAC change, a IR tablet of a BCS Class 2 drug demonstrates rapid in vitro dissolution (including being in spec). Is a biowaiver possible?

• For a SUPAC change, a ER tablet of a BCS Class 2 drug demonstrates in vitro dissolution in spec. Is a biowaiver possible?
## Categories of IVIVC/IVIVR

<table>
<thead>
<tr>
<th>Category</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convolution (FDA Level A)</td>
<td>A</td>
</tr>
<tr>
<td>Deconvolution</td>
<td>B</td>
</tr>
<tr>
<td>Deconvolution (but only linear)</td>
<td>C</td>
</tr>
<tr>
<td>– USP Level A</td>
<td>D</td>
</tr>
<tr>
<td>Summary parameters</td>
<td></td>
</tr>
<tr>
<td>Point estimates</td>
<td></td>
</tr>
<tr>
<td>Rank order</td>
<td></td>
</tr>
</tbody>
</table>

Selection of IVIVC Approach

interested in drug absorption

interested in overall pharmacokinetics

Level AA (deconvolution-based)

Level AAA (convolution-based)
Deconvolution IVIVR

• Application of the nonlinear, deconvolution-based model to the in vitro-in vivo relationships
  – metoprolol
  – piroxicam
  – ranitidine
  \[ F_a = \frac{1}{f_a} \left( 1 - \frac{\alpha}{\alpha - 1} (1 - F_d) + \frac{1}{\alpha - 1} (1 - F_d)^\alpha \right) \]

• Hypothesis: Factor(s) controlling overall absorption kinetics and dosage form performance can be elucidated from IVIVR.
• Only requires one formulation.
• Early formulation development.
Model Development

solid dosage form
  ↓
dissolution
  ↓
solution in GIT
  ↓
permeation
  ↓
drug in plasma
Model

\[ F_a = \frac{1}{f_a} \left( 1 - \frac{\alpha}{\alpha - 1} (1 - F_d) + \frac{1}{\alpha - 1} (1 - F_d)^\alpha \right) \]

- \( F_a \) is the fraction of the total amount of drug absorbed at time \( t \),
- \( f_a \) is the fraction of the dose absorbed at \( t = \) infinity,
- alpha is the ratio of the first-order apparent permeation rate coefficient (\( k_{p,app} \)) to the first-order dissolution rate coefficient (\( k_d \)), and
- \( F_d \) is the fraction of drug dose dissolved at time \( t \).
Model Assumptions

• Only dissolution and permeation
  – first-order dissolution ($k_d$)
    • $F_{d \text{ in } \text{ vitro}} = F_{d \text{ in } \text{ vivo}} = F_d$
  – first-order permeation ($k_p$)

• Assumptions in the determination of $F_a$
Alpha

\[ \alpha = \frac{k_{\text{app}}^p}{k_d} \]

- **large alpha**: dissolution rate-limited absorption
- **small alpha**: permeation rate-limited absorption
- **alpha = 1**: mixed rate-limited absorption
Theoretical IVIVRs

\[ F_a = \frac{1}{f_a} \left( 1 - \frac{\alpha}{\alpha - 1} \left(1 - F_d \right) + \frac{1}{\alpha - 1} \left(1 - F_d\right)^\alpha \right) \]
Metoprolol Dissolution Profiles

\[ f_2 = 19.1 \quad \rho_m = 0.80 \]
Metoprolol Plasma Profiles

The graph illustrates the plasma concentration (ng/ml) of metoprolol over time (hr) for different metabolizer rates: fast, medium, and slow. The data points are represented by symbols:

- **•** Lopressor
- **○** fast
- **▲** medium
- **△** slow

The x-axis represents time in hours (0 to 24), and the y-axis represents metoprolol plasma concentration in ng/ml (0 to 100 ng/ml). The graph shows a decrease in metoprolol concentration over time for all metabolizer rates.
Metoprolol IVIVRs

fraction metoprolol dissolved vs. fraction metoprolol absorbed

- Lopressor
- fast
- medium
- slow
## Metoprolol Absorption Kinetics

<table>
<thead>
<tr>
<th></th>
<th>fa</th>
<th>alpha</th>
<th>k_d (hr⁻¹)</th>
<th>k_p app (hr⁻¹)</th>
<th>t_win (hr⁻¹)</th>
<th>phi</th>
<th>k_p (hr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopressor</td>
<td>0.923 (0.025)</td>
<td>0.0877 (0.0328)</td>
<td>9.24 (0.12)</td>
<td>0.810 (0.268)</td>
<td>1.89 (0.16)</td>
<td>0.852 (0.063)</td>
<td>0.648 (0.248)</td>
</tr>
<tr>
<td>Fast</td>
<td>0.962 (0.024)</td>
<td>0.0743 (0.0178)</td>
<td>8.34 (0.48)</td>
<td>0.619 (0.139)</td>
<td>2.25 (0.56)</td>
<td>0.930 (0.042)</td>
<td>0.591 (0.138)</td>
</tr>
<tr>
<td>Medium</td>
<td>0.882 (0.034)</td>
<td>0.0995 (0.0181)</td>
<td>4.02 (0.17)</td>
<td>0.400 (0.068)</td>
<td>1.88 (0.26)</td>
<td>0.846 (0.045)</td>
<td>0.330 (0.048)</td>
</tr>
<tr>
<td>Slow</td>
<td>0.885 (0.030)</td>
<td>0.648 (0.103)</td>
<td>1.63 (0.11)</td>
<td>1.05 (0.16)</td>
<td>2.67 (0.36)</td>
<td>0.736 (0.066)</td>
<td>0.778 (0.153)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.910 (0.015)</td>
<td>-</td>
<td>-</td>
<td>0.759 (0.098)</td>
<td>2.22 (0.18)</td>
<td>0.830 (0.031)</td>
<td>0.609 (0.085)</td>
</tr>
</tbody>
</table>

Hypothesis

• Modest changes in dissolution have no in vivo consequence for IR dosage forms whose overall absorption is not dissolution controlled.
  – When can bioequivalence studies be waived for IR products that exhibit modest differences in dissolution?
  – Is a dissolution method acceptable if two IR products are bioequivalent, but exhibit modest differences in dissolution?
Piroxicam Dissolution Profiles

\[ f_2 = 23.4 \quad \rho_m = 0.66 \]
Piroxicam IVIVRs

fraction piroxicam dissolved vs fraction piroxicam absorbed

- *Feldene*
- *fast*
- *medium*
- *slow*
# Piroxicam Absorption Kinetics

<table>
<thead>
<tr>
<th></th>
<th>( f_a )</th>
<th>alpha</th>
<th>( k_d ) (hr(^{-1}))</th>
<th>( k_p^{\text{app}} = k_p ) (hr(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast</td>
<td>0.949 (0.018)</td>
<td>0.896 (0.138)</td>
<td>8.10 (0.60)</td>
<td>7.26 (1.12)</td>
</tr>
<tr>
<td>Medium</td>
<td>0.893 (0.020)</td>
<td>1.54 (0.24)</td>
<td>4.66 (0.10)</td>
<td>7.17 (1.10)</td>
</tr>
<tr>
<td>Feldene</td>
<td>0.896 (0.019)</td>
<td>3.42 (0.84)</td>
<td>3.13 (0.20)</td>
<td>10.7 (2.6)</td>
</tr>
<tr>
<td>Slow</td>
<td>0.819 (0.022)</td>
<td>6.50 (2.17)</td>
<td>1.75 (0.05)</td>
<td>11.3 (3.8)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.892 (0.011)</td>
<td>-</td>
<td>-</td>
<td>9.00 (1.14)</td>
</tr>
</tbody>
</table>

Ranitidine Dissolution Profiles

\[ f_2 = 32.1 \quad \rho_m = 0.44 \]
Ranitidine Plasma Profiles

Graph shows the concentration of ranitidine in plasma over time for different groups:
- **Zantac** (black circles)
- **Fast** (white circles)
- **Medium** (black triangles)
- **Slow** (white triangles)

The y-axis represents the ranitidine plasma concentration (μg/L), while the x-axis represents time (hr). The data points indicate the concentration levels at various time intervals.
Ranitidine IVIVRs

![Graph showing fraction of ranitidine dissolved vs fraction of ranitidine absorbed. The graph includes data points for Zantac, fast, medium, and slow dissolution rates.]
### Ranitidine Absorption Kinetics

<table>
<thead>
<tr>
<th></th>
<th>( f_a )</th>
<th>alpha</th>
<th>( k_d ) (hr(^{-1}))</th>
<th>( k_p^{\text{app}} ) (hr(^{-1}))</th>
<th>( t_{\text{win}} ) (hr(^{-1}))</th>
<th>phi</th>
<th>( k_p ) (hr(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast</td>
<td>0.502</td>
<td>0.0646</td>
<td>10.4 (1.4)</td>
<td>0.680 (0.095)</td>
<td>2.00 (0.17)</td>
<td>0.361</td>
<td>0.113 (0.030)</td>
</tr>
<tr>
<td>Zantac</td>
<td>0.520</td>
<td>0.0943</td>
<td>6.18 (0.30)</td>
<td>0.583 (0.108)</td>
<td>2.10 (0.20)</td>
<td>0.399</td>
<td>0.227 (0.041)</td>
</tr>
<tr>
<td>Mediam</td>
<td>0.541</td>
<td>0.0964</td>
<td>5.33 (0.29)</td>
<td>0.514 (0.100)</td>
<td>2.50 (0.34)</td>
<td>0.419</td>
<td>0.206 (0.036)</td>
</tr>
<tr>
<td>Slow</td>
<td>0.517</td>
<td>0.156</td>
<td>3.94 (0.64)</td>
<td>0.613 (0.075)</td>
<td>2.14 (0.16)</td>
<td>0.374</td>
<td>0.233 (0.031)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.520</td>
<td>-</td>
<td>-</td>
<td>0.597 (0.047)</td>
<td>2.18 (0.12)</td>
<td>0.389</td>
<td>0.225 (0.017)</td>
</tr>
</tbody>
</table>
### IVIVR Analysis and Permeability

<table>
<thead>
<tr>
<th>drug</th>
<th>$P$ (cm/sec) $\times 10^6$</th>
<th>$k_p$ (pred) $(hr^{-1})$</th>
<th>$k_p$ (obs) $(hr^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>piroxicam</td>
<td>91.3 $(\pm 1.2)$</td>
<td>3.49 $(\pm 0.05)$</td>
<td>9.00 $(\pm 1.14)$</td>
</tr>
<tr>
<td>metoprolol</td>
<td>10.7 $(\pm 0.3)$</td>
<td>0.410 $(\pm 0.011)$</td>
<td>0.609 $(\pm 0.085)$</td>
</tr>
<tr>
<td>ranitidine</td>
<td>0.425 $(\pm 0.058)$</td>
<td>0.0163 $(\pm 0.0022)$</td>
<td>0.225 $(\pm 0.017)$</td>
</tr>
</tbody>
</table>
Summary

• The factor(s) controlling overall absorption kinetics and dosage form performance can be elucidated from in vitro dissolution - in vivo absorption relationships.
  – kinetic importance of dissolution
  – $f_2$ criteria (or other metrics)
  – connection to Caco-2 permeability
Lamotrigine

- Antiepileptic drug
- BCS Class 2
  - BCS class 2b
- pKa = 5.7 (weakly basic)
<table>
<thead>
<tr>
<th>pH</th>
<th>Dose Strength (mg)</th>
<th>$C_s$ (mg/mL)</th>
<th>$D_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>200</td>
<td>1.09 ± 0.01</td>
<td>0.733</td>
</tr>
<tr>
<td>4.5</td>
<td>200</td>
<td>2.53 ± 0.08</td>
<td>0.316</td>
</tr>
<tr>
<td>6.8</td>
<td>200</td>
<td>0.210 ± 0.007</td>
<td>3.80</td>
</tr>
</tbody>
</table>

Dose number ($D_0$) employed a nominal volume of 250mL.
The percent approval of different classes of BCS drugs listed on WHO EML from 2000 to 2011

## BCS Class 3 excipient considerations: common excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Recommended maximum allowable amount for a class 3 biowaiver (mg)</th>
<th>Typical excipient amount (when present) in an IR tablet or capsule with a total weight of 300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline Cellulose</td>
<td>Qualitatively the same and quantitatively very similar to reference product</td>
<td>100mg (20%-90%)</td>
</tr>
<tr>
<td>Hydroxypropyl Methyl Cellulose</td>
<td>Qualitatively the same and quantitatively very similar to reference product</td>
<td>10mg (2%-5%)</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate</td>
<td>50</td>
<td>4.5mg (0.5%-2.5%)</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>900</td>
<td>150mg (25%-75%)</td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>200</td>
<td>12mg (4%)</td>
</tr>
<tr>
<td>Colloidal Silicon Dioxide</td>
<td>40</td>
<td>1.5mg (0.1%-1%)</td>
</tr>
<tr>
<td>Dibasic Calcium Phosphate</td>
<td>600</td>
<td>150mg (25%-75%)</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>100</td>
<td>10mg (2%-5%)</td>
</tr>
<tr>
<td>Lactose</td>
<td>900</td>
<td>240mg (80%)</td>
</tr>
<tr>
<td>Povidone</td>
<td>70</td>
<td>7.5mg (0.5%-5%)</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>80</td>
<td>6mg (1%-3%)</td>
</tr>
<tr>
<td>Pregelatinized Starch</td>
<td>200</td>
<td>150mg (5%-75%)</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>120</td>
<td>37.5mg (0.5%-25%)</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>40</td>
<td>7.5mg (0.25% to 5%)</td>
</tr>
</tbody>
</table>

Vaithianathan S, et al. Mol Pharmaceutics, in press. DOI: 10.1021/acs.molpharmaceut.5b00154
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