GastroPlus: Mechanistic Deconvolution and the Future Role of Physiological Modeling in IVIVC

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Can we find a mathematical input function that allows us to use the \textit{in vitro} release data (on the left) to predict the \textit{in vivo} plasma concentration-time data (on the right)?

If we generate such a function, can we use that function to predict the plasma concentration-time for different formulations with different \textit{in vitro} release-time profiles?
What is the purpose of an IVIVC?

• IVIVC can be used for many purposes:
  
  – To reduce regulatory burden (IVIVC in lieu of additional \textit{in vivo} experiments)
  
  – To reduce cost burden associated with bioequivalence trials
  
  – For dissolution method development:
    • Which \textit{in vitro} method best correlates with a deconvoluted \textit{in vivo} profile?
  
  – For formulation design:
    • How do I develop my formulation to produce an \textit{in vitro} dissolution rate that will achieve bioequivalence?
**Step 1: Deconvolution in GastroPlus with traditional methods**

- Determine the *in vivo* bioavailability (F% - NOT dissolution or absorption) from plasma concentration data

- Traditional options:
  - **Model-dependent:**
    - Based on mass balance among PK compartments
      - Wagner-Nelson, Loo-Riegelman
  - **Model-independent:**
    - Based on theory of linear systems analysis
      - Numerical deconvolution
Drawbacks to using the traditional methods for deconvolution

• Output?
  – Amount of drug reaching central compartment vs. time (systemic availability or F%)
  – Does not tell us anything about how it got there:
    • Was it all absorbed and some lost to first pass extraction?
    • Was only some of it absorbed with little or no first pass extraction?
    • Was the in vivo release/dissolution anything like the in vitro experiment?

• Assumptions:
  – Drug obeys one-, two, or three-compartment open model
    (limitation – does not consider drug’s true distribution)
  – First-order absorption
    (limitation – not realistic)
  – No saturable (nonlinear) absorption or clearance
    (limitation – what if drug is substrate for enzymes/transporters?)
  – Terminal oral plasma concentration-time points independent of absorption
    (limitation – what about colonic absorption?)
**Step 1: Deconvolution in GastroPlus with Mechanistic Absorption method**

- **Inputs** (in addition to the data required for the traditional methods):
  - Physiological parameters
  - Drug properties (solubility, $\text{Peff}$, $\log P$, $\text{pKa}$, etc.)

- **Outputs**:  
  A model that combines all available *in silico*, *in vitro* and *in vivo* information and provides:
  - *in vivo* dissolution, absorption and bioavailability vs. time profiles
  - Description of site-dependent absorption
  - Description of tissue contributions to first pass extraction

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**Deconvolution**

*in vivo* dissolution vs. time along the gut—NOT F!
Formulation vs. Bioavailability

- Total amount dissolved
  - Deconvoluted profile from the GastroPlus mechanistic approach
- Total amount absorbed
- Total amount into portal vein
- Total amount into systemic circulation (bioavailability)
  - Deconvoluted profile from traditional methods
Absorption and first pass extraction?

Difference between traditional and mechanistic deconvolution?
**Difference between traditional and mechanistic deconvolution?**

![Diagram](image)

- **Fa**
- **FDp** (not Fa!)
- **F**

**Absorption**

**Metabolism**

**Bioavailability**

* Mechanistic

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Mechanistic Absorption Deconvolution: “Deconvolute Then Correlate”

Fit the *in vivo* release profile (*using single or double Weibull function or Z-Factor*) for each formulation used in IVIVC.

Find one correlation function to best fit *in vivo* vs. *in vitro* release profiles across all formulations used in the IVIVC.

Find the *in vivo* dissolution vs. time profile that best fits the plasma concentration-time data once absorption and PK are well-established from IR (and IV, if available) doses.

Deconvoluted *in vivo* dissolution vs. time profile obtained using the Weibull function (single or double).

![Weibull Controlled Release Profile](image)

*File: Weibull Controlled Release Profile*

- **Comments:**
- **Parameters:**
  - *Time scale* (h): 1.7592
  - *Shape* (b): 1.7592
  - *Location* (a): 0.7706
  - *Scale* (c): 1.7962

*File loaded from:*

- **Results:**
  - *R^2*: 0.9994
  - Akaike Information Criterion (AIC) = 17.3418
  - Schwarz Criterion (SC) = 17.338

*Simulations Plus, Inc.*
Step 2: Correlation

- Find the correlation between the deconvoluted *in vivo* release and *in vitro* dissolution profiles:
  - Linear
  - Power function
  - 2nd order polynomial
  - 3rd order polynomial

*Now, THAT’S information a formulator can really use!*
Flexibility of the Weibull Function?

- The first step is optimization of *in vivo* release profile in a form of a Weibull function.
- GastroPlus offers single- and double-Weibull function for optimization of *in vivo* release profile, which cover wide variety of release profile shapes.
Step 3: Convolution

- Predict the plasma concentration-time profile using the IVIVC and *in vitro* dissolution curve:
  - Internal validation: use the formulations involved in the development of the IVIVC
  - External validation: use the formulations NOT involved in the development of the IVIVC

- Acceptance criteria:
  - Internal validation:
    - $\leq 15\%$ absolute prediction error (PE) for $C_{\text{max}}$ and $\text{AUC}$ of each formulation
    - $\leq 10\%$ mean absolute prediction error (PE) for $C_{\text{max}}$ and $\text{AUC}$
  - External validation:
    - $\leq 10\%$ absolute prediction error (PE) for $C_{\text{max}}$ and $\text{AUC}$
Modeling Controlled Release Formulations in GastroPlus

Fig. 1. Schematic representations of different MR technologies: (A) multi-unit membrane-coated pellets, (B) Oros®, (C) GeoMatrix®.
Let’s build the IVIVC...

Select from a number of methods for comparison.

Run the deconvolution first to analyze the *in vivo* vs. *in vitro* profile.
Status Window displays the statistical information for fitted IVIVC

Automatically generate the IVIVC with different functions
Is it valid?

Status Window displays validation statistics of the convolution.

Select any combination of records for which *in vitro* data is available to use in convolution:

- Examine internal predictability
- Examine external predictability
- Predict the Cp-time profile for a new formulation
Using Test and Reference Product Data to Identify the Target \textit{in vitro} Dissolution Profile

- Predict the performance of a new Test product before the first clinical study assuming the \textit{in vitro release} = \textit{in vivo release}:
  - IVIVC: $y = x$
- \textit{Run the study and fail bioequivalence! Now what?} We need to know the true \textit{in vivo} release rate using mechanistic deconvolution.
  
  Step 1: Deconvolute the Reference product’s \textit{in vivo} release to identify the target profile
  
  Step 2: Design new formulation which can match the target \textit{in vivo} release profile

Is there something I can do to predict how well the new formulation (Test2) will match the target \textit{in vivo} profile before running the next clinical study?

- Use IVIVC built on our current test formulation
What are we trying to do before our first bioequivalence trial?
Umm... what happens if we fail?
Use IVIVC built on our current test formulation

Deconvoluted *in vivo* release:

The Reference profile (in red) is what we need to match with our next (Test2) product.
OK… we have an IVIVC. Now what?

• We have our Test product IVIVC (even though it’s only a single formulation):
  
  \[ y = ax^b \]

• Now that we have an idea how our Test product behaves \textit{in vivo}, we can identify the target \textit{in vitro} dissolution for our 2\textsuperscript{nd} Test product:
  
  – \( y = \) the deconvoluted \textit{in vivo} release of the Reference
  
  – Let’s solve for “x”
The in vitro dissolution target for the next Test product (Test2)

Our Test product(s) correlation:

\[ y = ax^b \]

The Reference product’s deconvoluted profile (red curve above)

This is based on the assumption that Test and Test2 would have the same IVIVC
Design the formulation and dissolution method

Test Modifications:
RPM
Volume
pH
Polymer matrix
Particle Size Distribution
Excipients
Multi-stage dissolution
Use of In Vitro–In Vivo Correlation to Predict the Pharmacokinetics of Several Products Containing a BCS Class I Drug in Extended Release Matrices

Tahseen Mirza • Srikanth A. Bykadi • Christopher D. Ellison • Yongsheng Yang • Barbara M. Davit • Mansoor A. Khan

Table V Internal Validation Statistics of Pharmacokinetic Parameters (C<sub>max</sub> and AUC) from Actual Experiments

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC actual ng/ml*h</th>
<th>AUC predicted ng/ml*h</th>
<th>Percent error</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; actual ng/ml</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; predicted ng/ml</th>
<th>Percent error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference fast release 100 mg</td>
<td>504.23</td>
<td>469.9</td>
<td>−6.81%</td>
<td>34.37</td>
<td>31.96</td>
<td>−7.01%</td>
</tr>
<tr>
<td></td>
<td>607</td>
<td>603</td>
<td>−5.96%</td>
<td>34.37</td>
<td>35.14</td>
<td>2.15%</td>
</tr>
<tr>
<td>Reference extended release 200 mg</td>
<td>1,129.32</td>
<td>1,027.86</td>
<td>−8.98%</td>
<td>61.35</td>
<td>57.28</td>
<td>−6.63%</td>
</tr>
<tr>
<td></td>
<td>1,446</td>
<td>1,297</td>
<td>−10.26%</td>
<td>61.35</td>
<td>57.03</td>
<td>−7.11%</td>
</tr>
<tr>
<td>Reference extended release 50 mg</td>
<td>243.52</td>
<td>256.96</td>
<td>5.52%</td>
<td>12.77</td>
<td>14.32</td>
<td>12.13%</td>
</tr>
<tr>
<td></td>
<td>353</td>
<td>343</td>
<td>−2.85%</td>
<td>12.77</td>
<td>13.14</td>
<td>2.63%</td>
</tr>
</tbody>
</table>

*Predicted by numerical convolution, AUC calculated at 20 h (fast), 24 h (200 mg) and 24 h (50 mg)

*Predicted through Gastroplus® model, AUC calculated at 30 h (fast), 48 h (200 mg) and 48 h (50 mg)
IVIVC for BCS Class II (F = 66%)

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Research Article

Developing In Vitro–In Vivo Correlation of Risperidone Immediate Release Tablet

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Abstract. The present study was aimed to predict the absorption profile of a risperidone immediate release tablet (IR) and to develop the level A in vitro–in vivo correlation (IVIVC) of the drug using the gastrointestinal simulation based on the advanced compartmental absorption and transit model implemented in GastroPlus™. Plasma concentration data, physicochemical, and pharmacokinetic properties of the drug were used in building its absorption profile in the gastrointestinal tract. Since the fraction absorbed of risperidone in simulation was more than 90% with low water solubility, the drug met the criteria of class II of the Biopharmaceutics Classification System. The IVIVC was developed based on the model built using the plasma data and the in vitro dissolution data in several dissolution media based on the Japanese Guideline for Bioequivalence Studies of Generic Products. The gastrointestinal absorption profile of risperidone was successfully predicted. A level A IVIVC was also successfully developed in all
### Table IV. Percent Prediction Error (PE) for Cmax and AUC of Reference Tablet

<table>
<thead>
<tr>
<th>Dissolution Media</th>
<th>Cmax (ng/ml)</th>
<th>PE (%)</th>
<th>AUC (ng h/mL)</th>
<th>PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate buffer pH 4 (50 rpm)</td>
<td>10.28</td>
<td>-6.55</td>
<td>60.77</td>
<td>-5.08</td>
</tr>
<tr>
<td>Phosphate buffer pH 1.2 (50 rpm)</td>
<td>10.27</td>
<td>-6.45</td>
<td>60.77</td>
<td>-5.08</td>
</tr>
<tr>
<td>Phosphate buffer pH 6.8 (50 rpm)</td>
<td>9.94</td>
<td>-3.01</td>
<td>60.74</td>
<td>-5.03</td>
</tr>
<tr>
<td>Water</td>
<td>10.33</td>
<td>-7.07</td>
<td>60.77</td>
<td>-5.08</td>
</tr>
<tr>
<td>Phosphate buffer pH 6.8 (100 rpm)</td>
<td>9.51</td>
<td>1.41</td>
<td>60.70</td>
<td>-4.96</td>
</tr>
</tbody>
</table>

### Table V. Percent Prediction Error (PE) for Cmax and AUC of Test Tablet

<table>
<thead>
<tr>
<th>Dissolution Media</th>
<th>Cmax (ng/ml)</th>
<th>PE (%)</th>
<th>AUC (ng/mL)</th>
<th>PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate buffer pH 4 (50 rpm)</td>
<td>10.26</td>
<td>0.48</td>
<td>60.77</td>
<td>3.23</td>
</tr>
<tr>
<td>Phosphate buffer pH 1.2 (50 rpm)</td>
<td>10.19</td>
<td>1.16</td>
<td>60.77</td>
<td>3.23</td>
</tr>
<tr>
<td>Phosphate buffer pH 6.8 (50 rpm)</td>
<td>10.09</td>
<td>2.13</td>
<td>60.75</td>
<td>3.26</td>
</tr>
<tr>
<td>Water</td>
<td>10.35</td>
<td>-0.39</td>
<td>60.77</td>
<td>3.23</td>
</tr>
<tr>
<td>Phosphate buffer pH 6.8 (100 rpm)</td>
<td>9.88</td>
<td>4.15</td>
<td>60.73</td>
<td>3.29</td>
</tr>
</tbody>
</table>
IVIVC for BCS Class III?

In Vitro–In vivo Correlation (IVIVC) Models for Metformin after Administration of Modified-Release (MR) Oral Dosage Forms to Healthy Human Volunteers

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deconvolution approach. The basic convolution level A model, which used in vitro dissolution as the in vivo input, had %PE values as high as 103%. Using an extended convolution approach, which modeled the absorption of metformin using a Hill function, a level A IVIVC model with %PE as low as 11% was developed. In conclusion, the current work indicates that level C and A IVIVC models with good internal predictability may be developed for a permeability- and absorption window-limited drug such as metformin.

Summary

- Applied correctly, IVIVCs can save substantial resources when registering products changes (i.e., biowaivers) or to assist with formulation design activities.

- Traditional IVIVC methods determine the in vivo input rate to the systemic circulation (i.e., F% vs. time – not absorption and not dissolution!)

- The GastroPlus Mechanistic Absorption method allows you to separate *in vivo* dissolution of your formulation from absorption & first pass extraction:
  - Best estimate of the true *in vivo* dissolution/release of your product.

- And finally, DDDPlus™ lets you design hypothetical formulations and experimental conditions to help aid in dosage form design and *in vitro* dissolution experiment design.
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**Controlled Release Technologies**

- **Gastric release:**
  - Unreleased drug remains in stomach

- **Integral tablet:**
  - Unreleased drug remains in tablet – moves from one compartment to the next (e.g., erosion tablet, pulsed, multi-layer systems)

- **Dispersed:**
  - Unreleased drug disperses among compartments (e.g., beads)

\[ U = \text{unreleased} \quad D = \text{drug in solution} \]
Enteric Coated Tablet
- the whole tablet stays in stomach for the period of stomach transit time
- after leaving stomach the dissolution continues as for IR formulation

Enteric Coated Capsule
- the small enteric coated pellets can get distributed throughout the GI tract
- the pellets start leaving stomach immediately at the rate calculated as “1/transit time”
- Only the pellets that already left stomach will start dissolving (dissolution as for IR formulation)

Controlled Release Technologies

Enteric coating – not user specified pH range

\( U = \text{unreleased} \quad D = \text{drug in solution} \)