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 *in vitro* release data (on the left) to predict the *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 *in vitro* release-time profiles?

**IVIVC**

\[ F(t) = f(D(t)) \]
What is the purpose of an IVIVC?

- IVIVC can be used for many purposes:
  - To reduce regulatory burden (IVIVC in lieu of additional in vivo experiments)
  - To reduce cost burden associated with bioequivalence trials
  - For dissolution method development:
    - Which in vitro method best correlates with a deconvoluted in vivo profile?
  - For formulation design:
    - How do I develop my formulation to produce an 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?*)

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**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, Peff, logP, 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
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

Difference between traditional and mechanistic deconvolution?

Absorption and first pass extraction?
**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)
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 AUC of each formulation
    - $\leq 10\%$ mean absolute prediction error (PE) for $C_{\text{max}}$ and AUC
  - External validation:
    - $\leq 10\%$ absolute prediction error (PE) for $C_{\text{max}}$ and 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®.

Figure from Michel et al, European Urology Supplements 4 (2005) 15-24
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 \textit{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 in vivo, we can identify the target in vitro dissolution for our 2nd Test product:
  – \( y = \) the deconvoluted 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
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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**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)

**Enteric Coated Tablet**
- The whole tablet stays in the 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 the 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)

**Enteric coating – not user specified pH range**

U = unreleased  D = drug in solution