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

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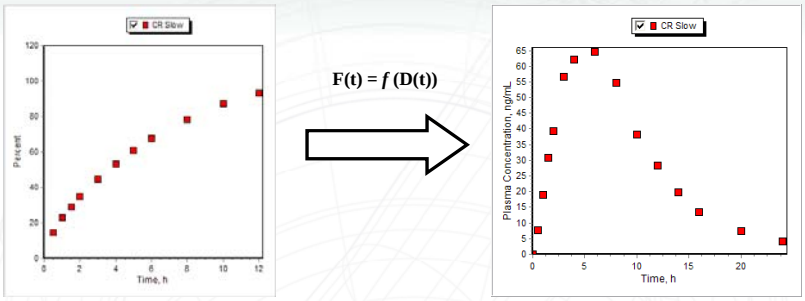
IVIVC



- 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?

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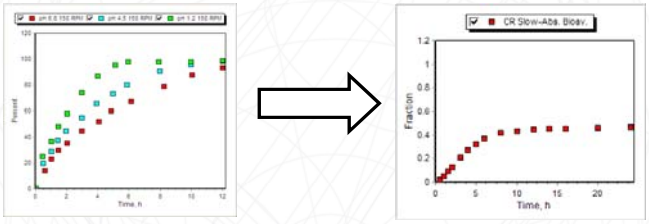
What is the purpose of an IVIVC?

- 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?

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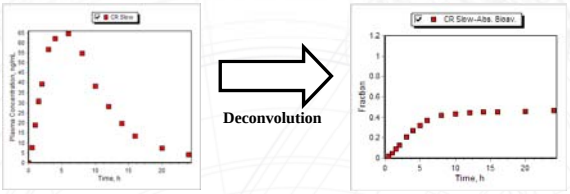
Step 1: Deconvolution in GastroPlus with traditional methods



- 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

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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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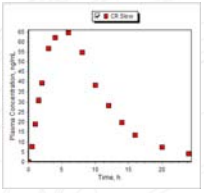
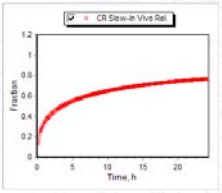
Step 1: Deconvolution in GastroPlus with Mechanistic Absorption method



Deconvolution



***in vivo* dissolution vs. time along the gut– NOT F!**

- 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

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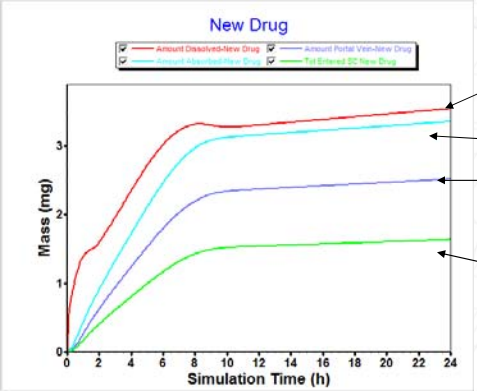
Formulation vs. Bioavailability



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

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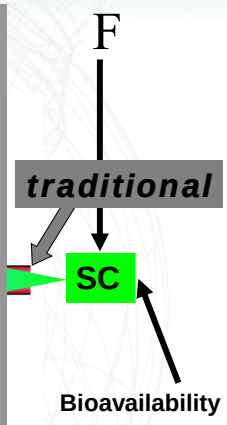
Difference between traditional and mechanistic deconvolution?

Absorption and first pass extraction?



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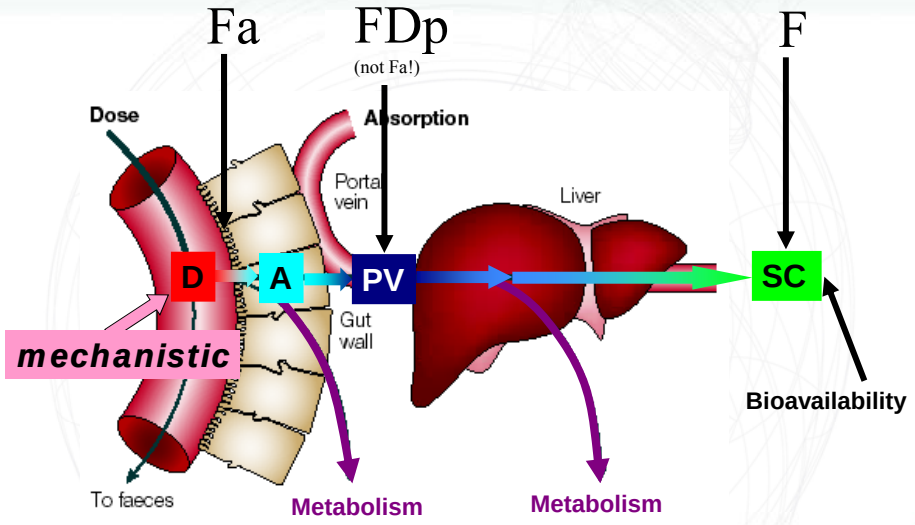
Difference between traditional and mechanistic deconvolution?



* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

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Mechanistic Absorption Deconvolution: "Deconvolute Then Correlate"

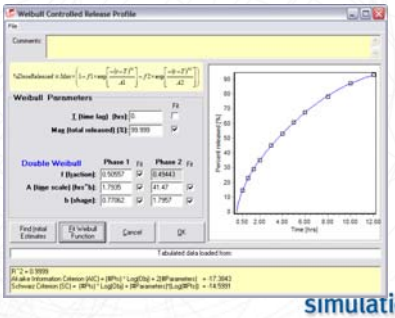
Fit the *in vivo* release profile (*using single or double Weibull function or Z-Factor*) for each formulation used in IVIVC

⇒

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)



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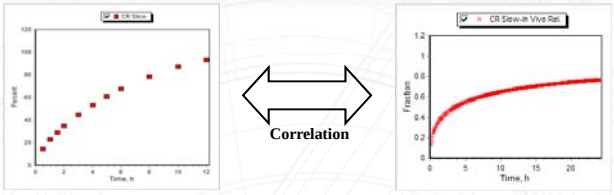
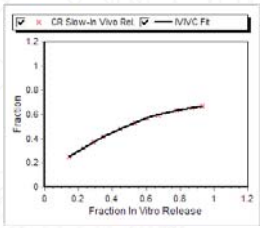
Step 2: Correlation



- 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!

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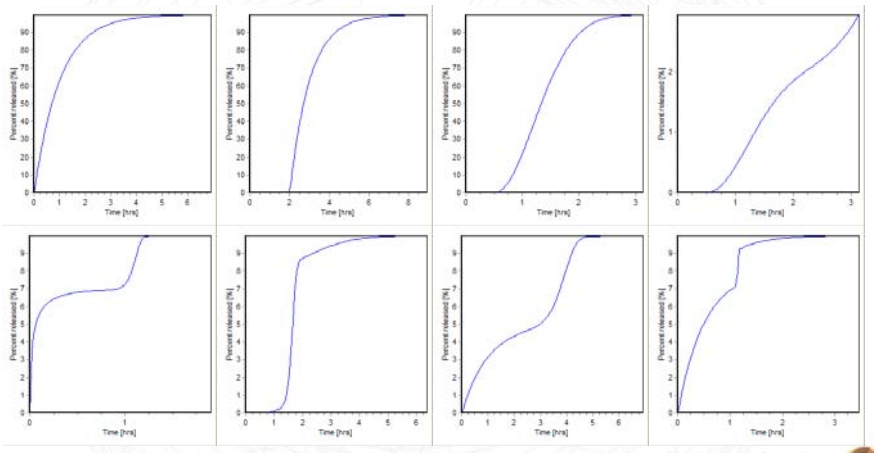
Flexibility of the Weibull Function?

- 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



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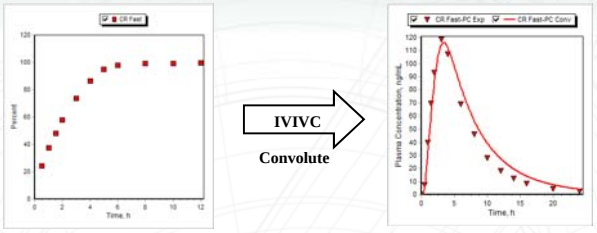
Step 3: Convolution



- 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:
    - ≤ 15% absolute prediction error (PE) for C_{max} and AUC of each formulation
    - ≤ 10% mean absolute prediction error (PE) for C_{max} and AUC
  - External validation:
    - ≤ 10% absolute prediction error (PE) for C_{max} and AUC

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Modeling Controlled Release Formulations in GastroPlus

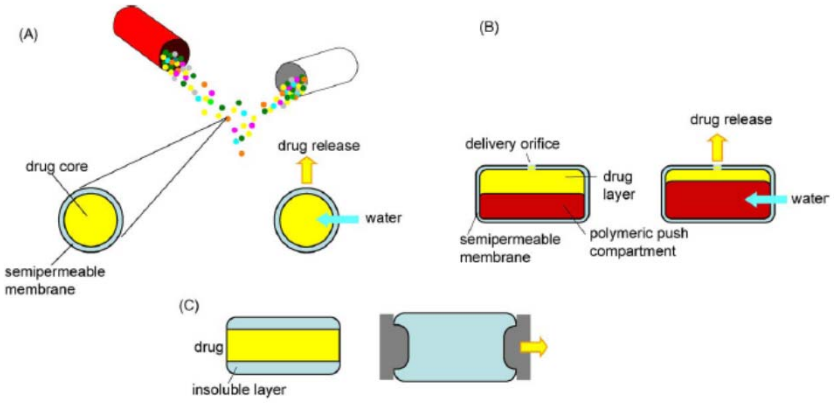

Fig. 1. Schematic representations of different MR technologies: (A) multi-unit membrane-coated pellets, (B) Oros®, (C) GeoMatrix®.

Figure from Michel et al, European Urology Supplements 4 (2005) 15-24

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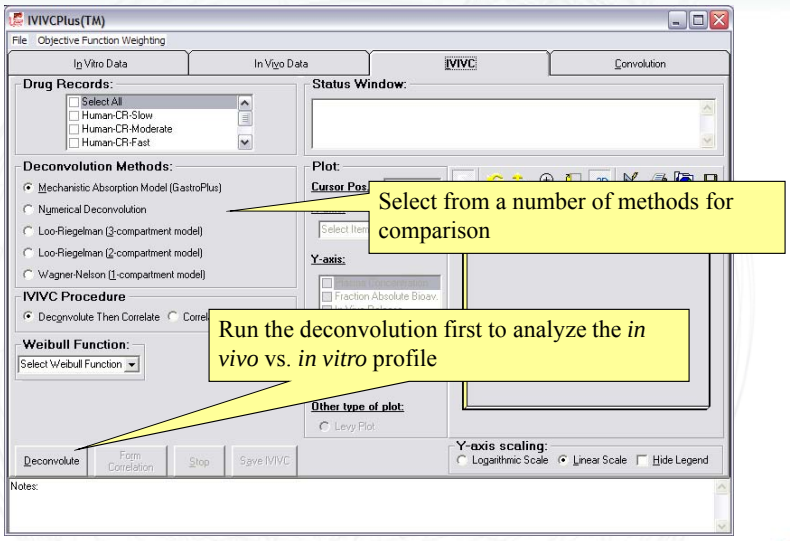
Let's build the IVIVC…



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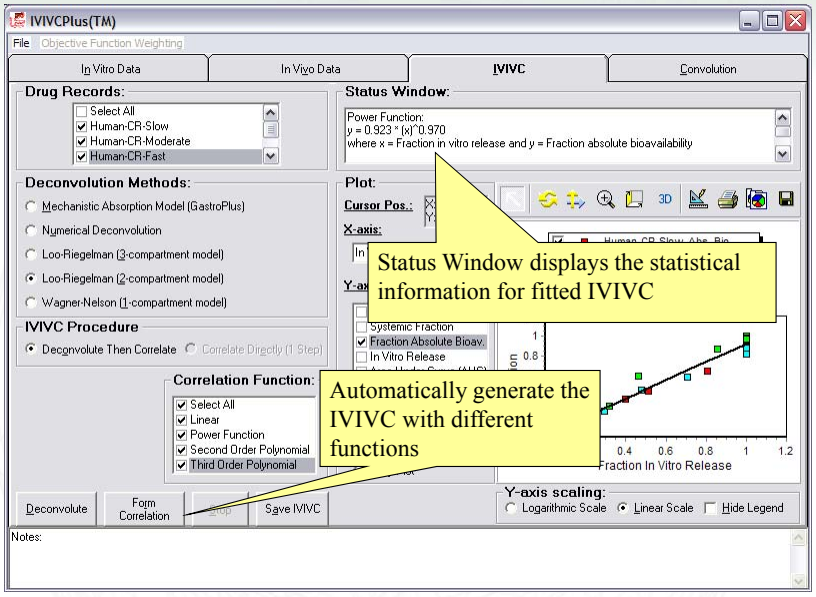

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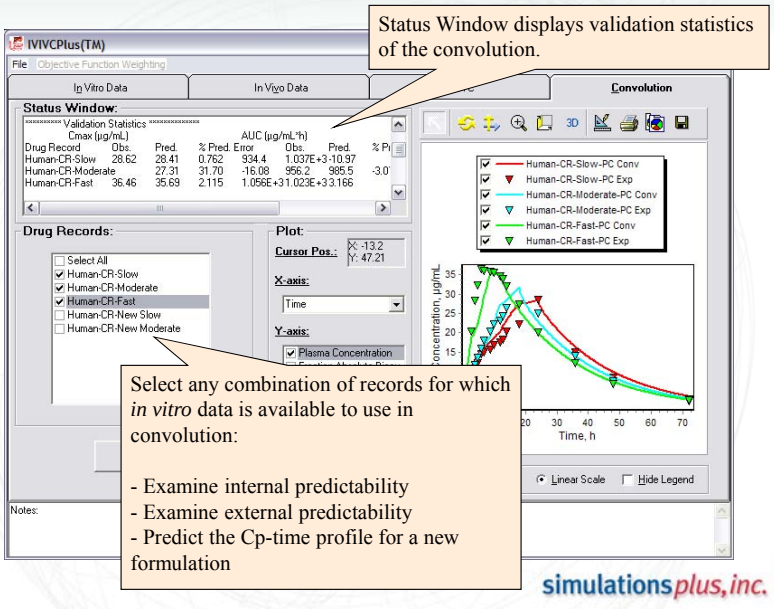
Is it valid?



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Using Test and Reference Product Data to Identify the Target *in vitro* Dissolution Profile

- Predict the performance of a new Test product before the first clinical study assuming the *in vitro release = in vivo release*:
  - IVIVC: y = x
- *Run the study and fail bioequivalence! Now what*? We need to know the true *in vivo* release rate using mechanistic deconvolution.

Step 1: Deconvolute the Reference product's *in vivo* release to identify the target profile

Step 2: Design new formulation which can match the target *in vivo* release profile

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

- Use IVIVC built on our current test formulation

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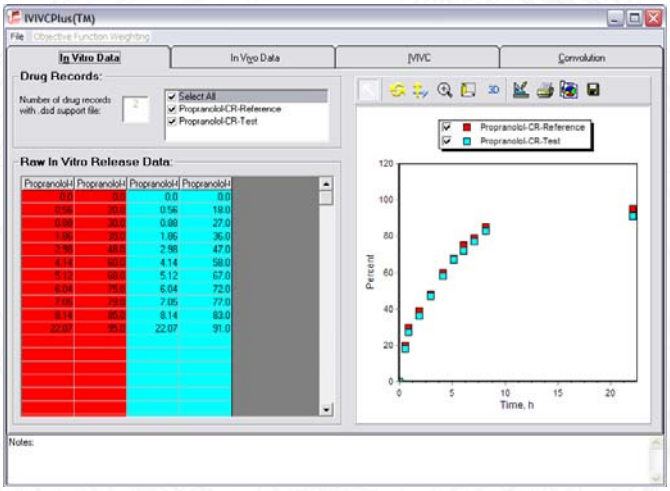
What are we trying to do before our first bioequivalence trial?



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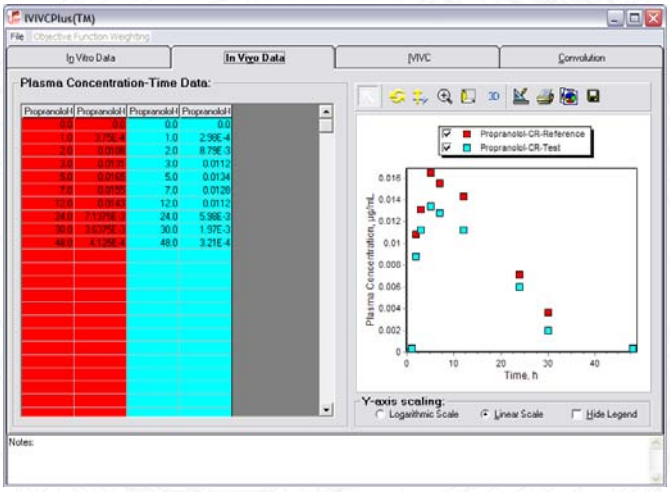
Umm… what happens if we fail?



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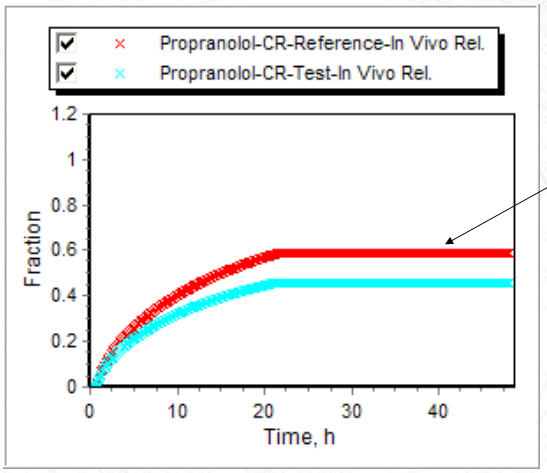
Use IVIVC built on our current test formulation



Deconvoluted *in vivo* release:

The Reference profile (in red) is what we need to match with our next (Test2) product

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OK… we have an IVIVC. Now what?

- We have our Test product IVIVC
  (even though it's only a single formulation):

  $$y = ax \wedge b$$

- 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"

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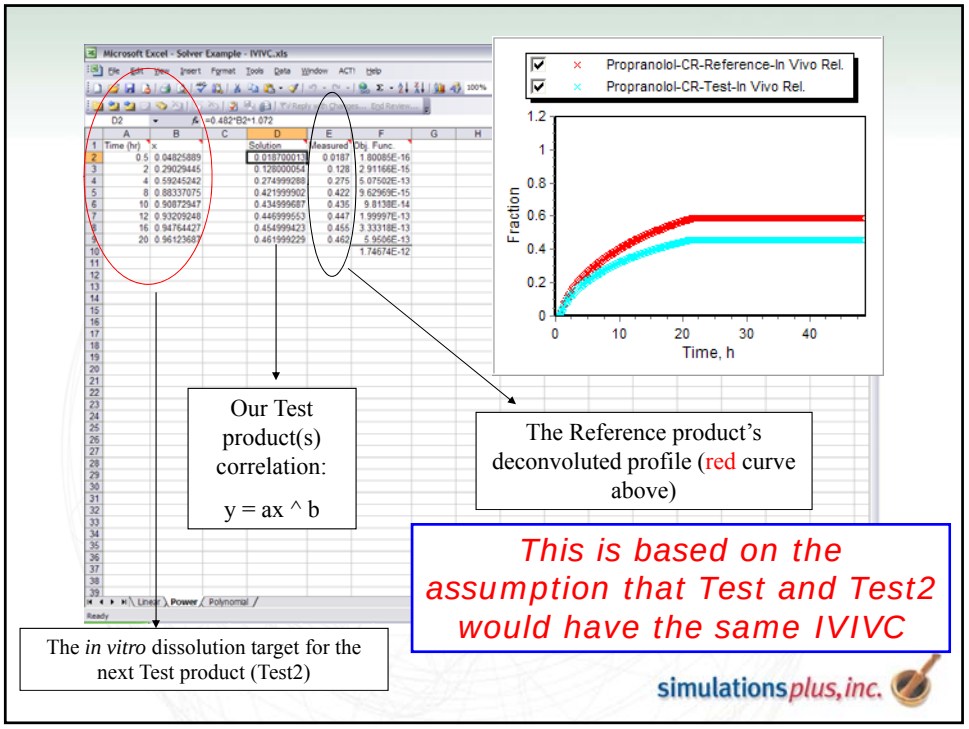
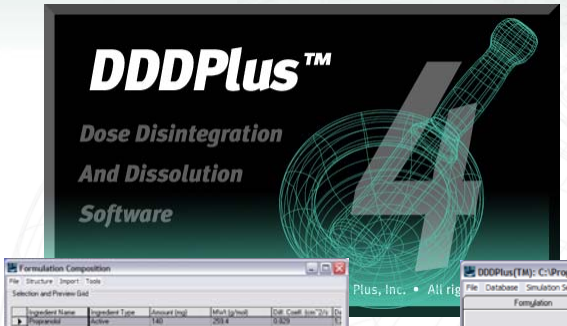
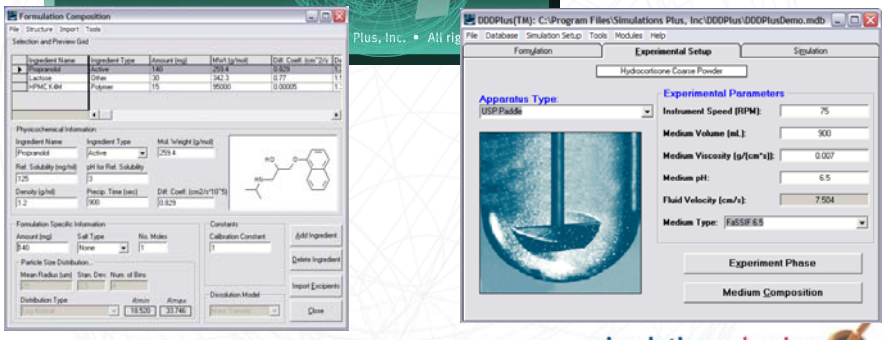


Design the formulation and dissolution method



Test Modifications:

RPM
Volume
pH
Polymer matrix
Particle Size Distribution
Excipients
Multi-stage dissolution



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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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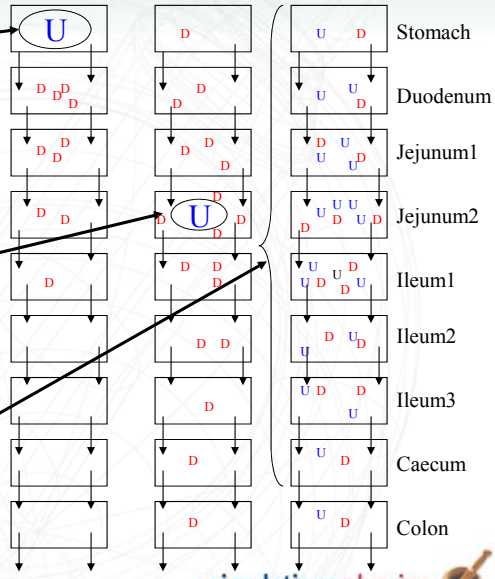
Controlled Release Technologies

- 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 = unreleased **D = drug in solution**

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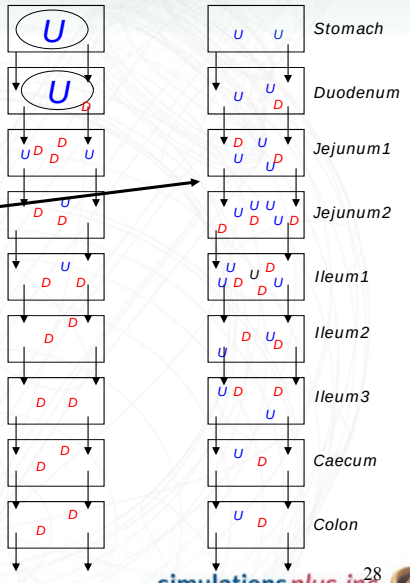
Controlled Release Technologies

- 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)



Enteric coating – not user specified pH range

U = unreleased ***D = drug in solution***

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