GastroPlus®

Part II: Mechanistic IVIVCs and Virtual BE trial simulations

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Lecture Agenda

- Mechanistic deconvolutions
- Virtual bioequivalence trials
- Synergy between DDDPlus™ and GastroPlus®

Research Collaboration Agreement with the FDA (2014-19)

- 5-year collaborative project with the FDA Office of Testing and Research on the utility of GastroPlus™ Mechanistic Absorption Modeling (MAM) and IVIVCs to predict complex absorption characteristics
  - Goal is to facilitate drug product development by decreasing regulatory burden through modeling & simulation

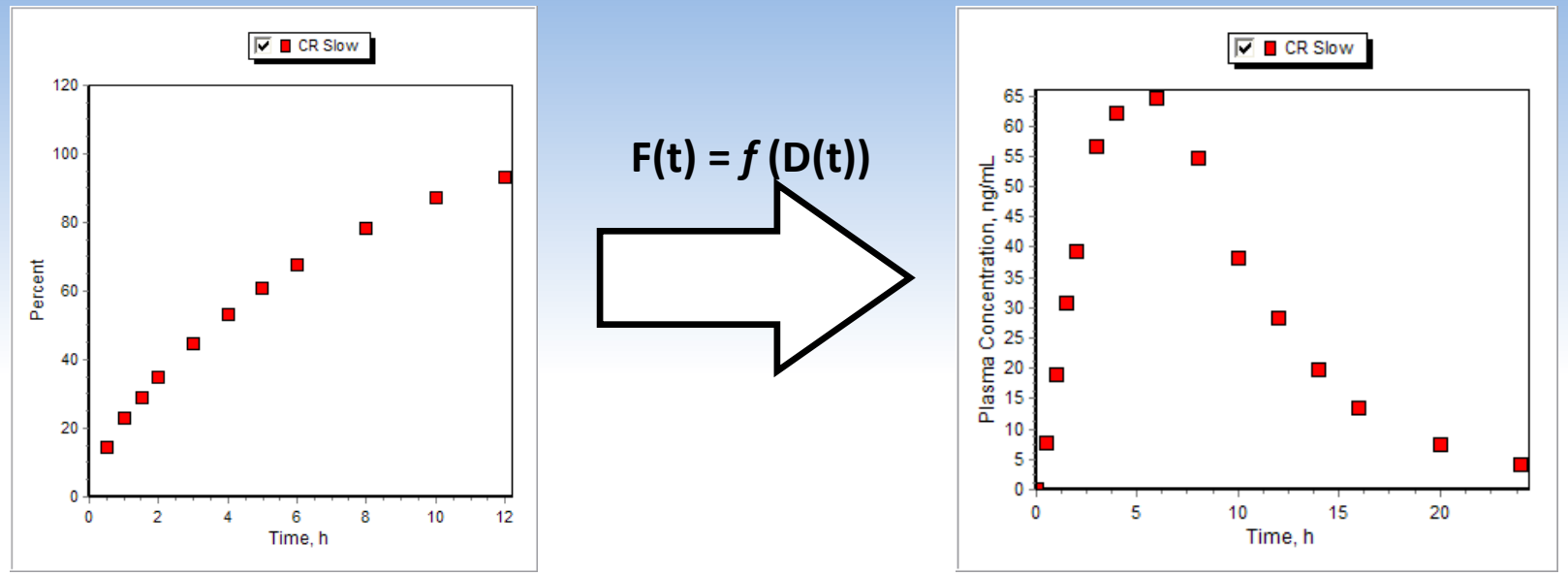
What is an *In Vitro - In Vivo* Correlation (IVIVC)?

- Working definition:

> "A predictive mathematical treatment describing the relationship between an *in vitro* property of a dosage form (e.g., the rate or extent of drug release) and a relevant *in vivo* response (e.g., plasma concentration-time data)"

FDA Guidance for Industry Extended Release Solid Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations (1997)

What is an *In Vitro - In Vivo* Correlation (IVIVC)?

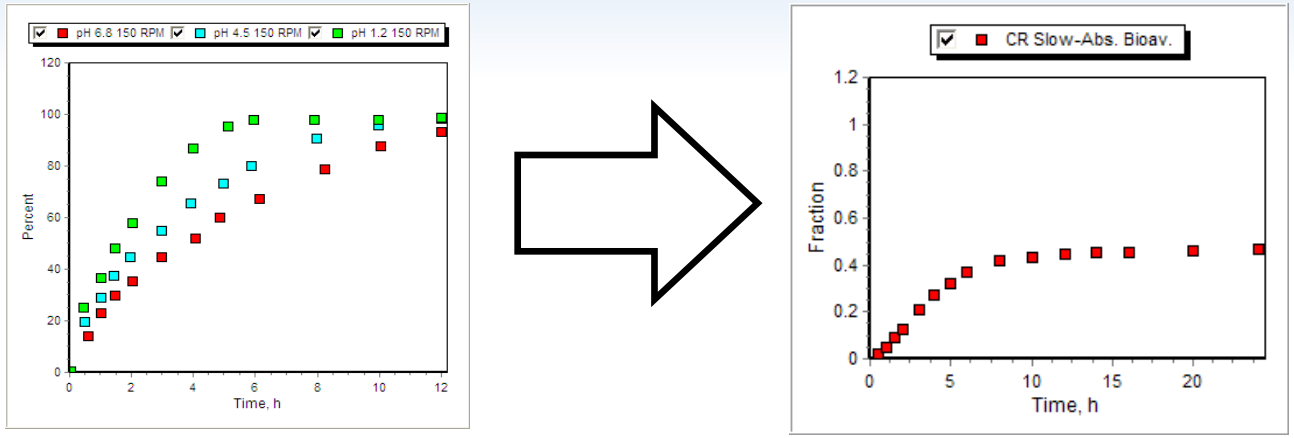


- Can we find a mathematical function that allows us to correlate the *in vitro* release data (on the left) with the *in vivo* plasma concentration-time data (on the right)?

- 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?

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?
  - Establish dissolution specifications
    - What is the acceptable variability in key parameters before we are no longer bioequivalent?

IVIVC Categories

- Level A:
  - Point-to-point relationship between *in vitro* dissolution and *in vivo* input rate (can be linear or non-linear)
- Level B:
  - Correlation based on statistical moment analysis (*in vitro* dissolution time correlated with MRT)
- Level C:
  - Single point relationship between a dissolution parameter (e.g., t50%) and pharmacokinetic output (e.g., Cmax, AUC)

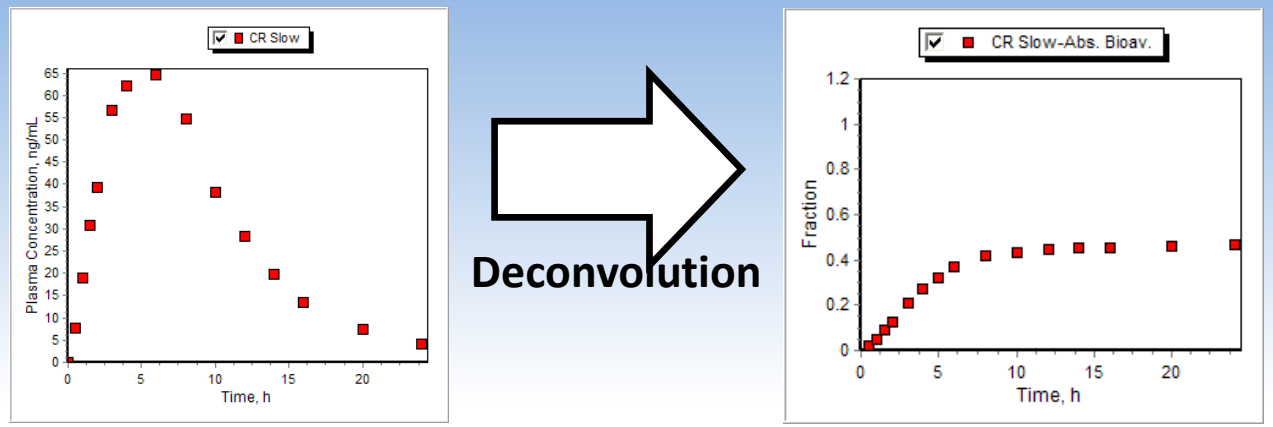
IVIVC and the Biopharmaceutical Classification System

Class	Solubility	Permeability	IVIVC?
I	High	High	Possible, if ***dissolution is rate limiting*** step
II	Low	High	Possible, if *in vitro* & *in vivo* dissolution are similar
III	High	Low	Limited, since ***absorption is rate limiting*** step
IV	Low	Low	Not expected (unless dissolution is identified as limiting step)

IVIVC – Level A

- Inputs:
  - *in vitro* dissolution data from batches tested *in vivo*
    - Compendial methods
  - *in vivo* $C_p(t)$ profiles for reference formulations
    - IV, solution or IR doses – for building / calibrating the PK model
  - *in vivo* $C_p(t)$ profiles after CR dose
- Outputs:
  - Step 1 ("deconvolution"): to derive the *in vivo* input rate
  - Step 2 ("correlation"): point-to-point correlation between *in vitro* dissolution and *in vivo* input rate (bioavailability or dissolution *vs* time)

Step 1: Deconvolution in GastroPlus with Traditional Methods



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

- Traditional options:

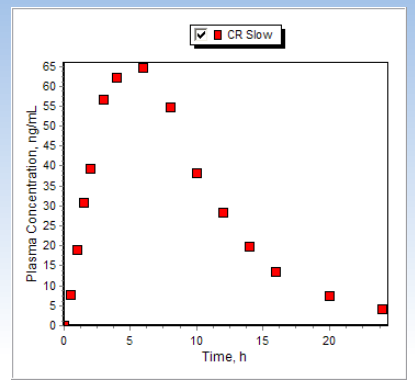
  - Model-dependent:
    - Based on mass balance among PK compartments
      - Wagner-Nelson, Loo-Riegelman

  - Model-independent:
    - Based on theory of linear systems analysis
      - Numerical deconvolution

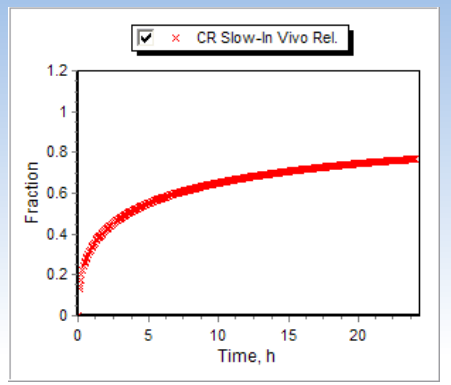
Drawbacks to Using the Traditional Methods for Deconvolution

- 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



Deconvolution



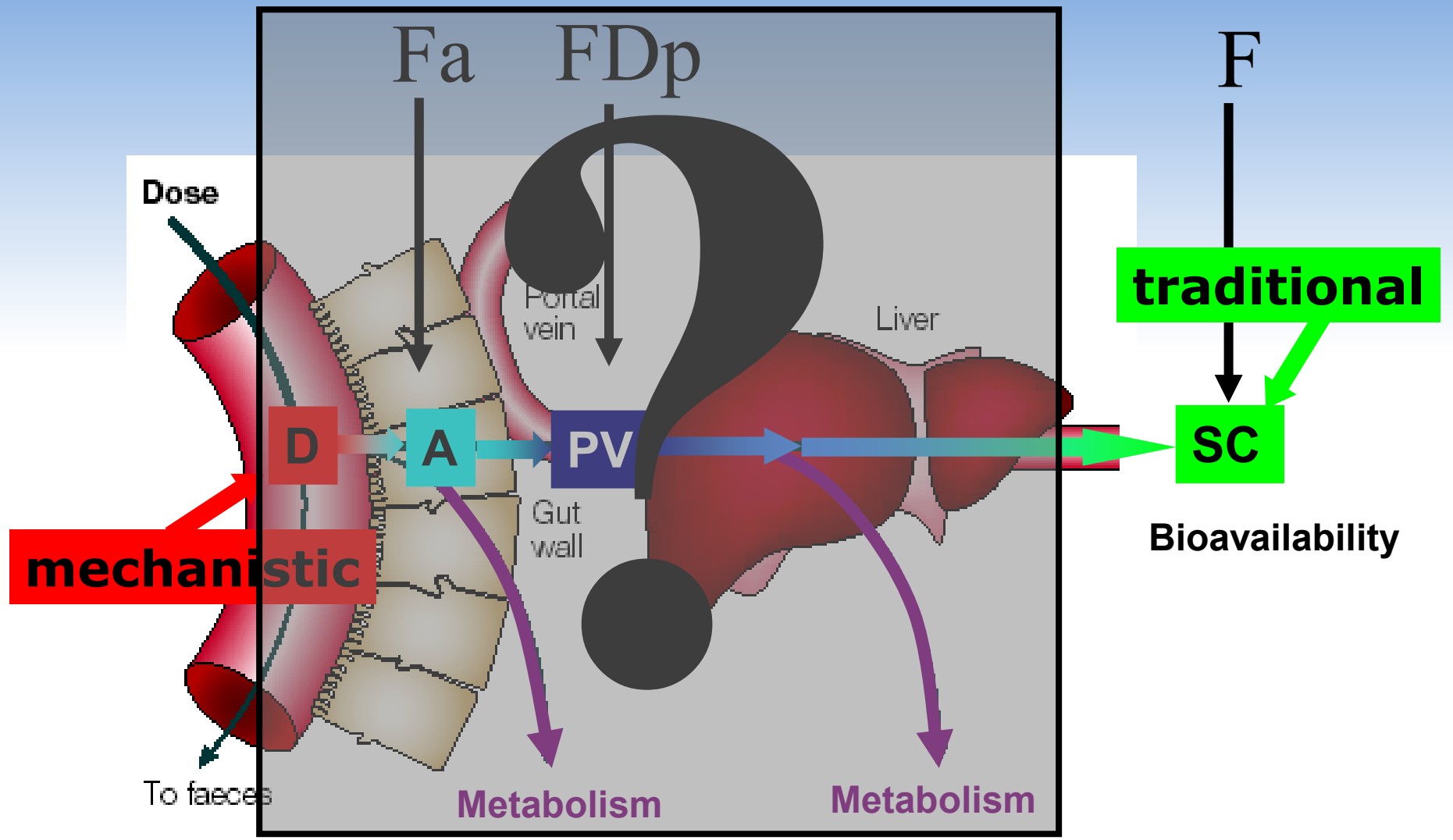
***in vivo* dissolution vs. time along the gut– NOT F%!**

- Inputs (in addition to the data required for the traditional methods):
  - Physiological parameters
  - Drug properties (solubility, Peff, logP, pKa, etc.)

- Outputs:

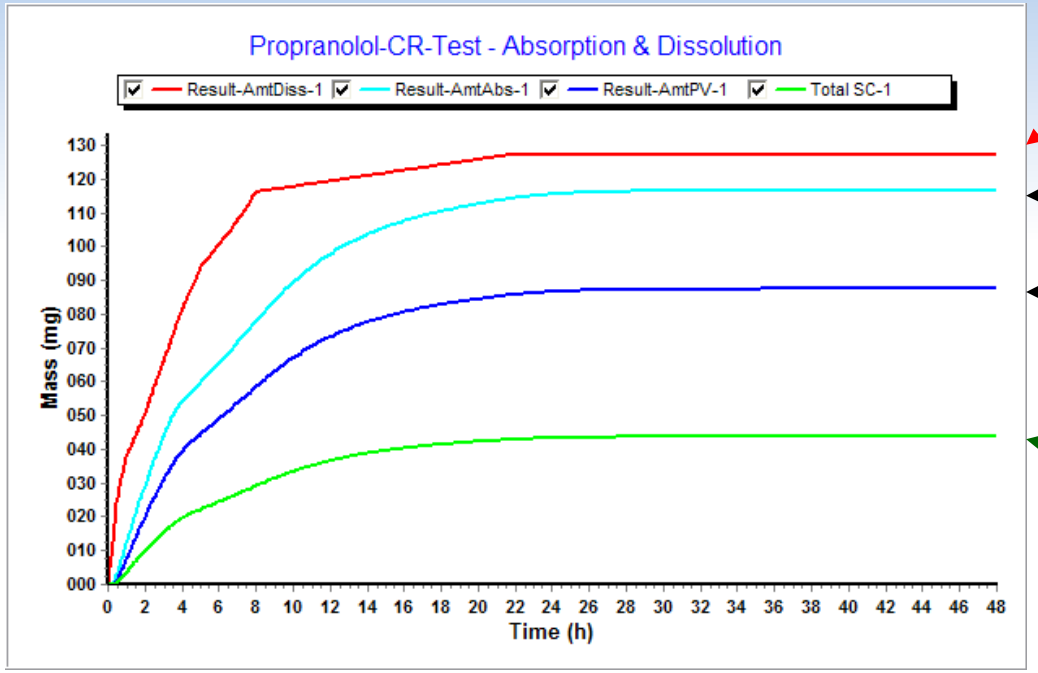
  A model that combines all available *in silico*, *in vitro* and *in vivo* information and provides:
  - *in vivo* dissolution, absorption and bioavailability vs. time profiles
  - Description of site dependent absorption
  - Description of tissue contributions to first pass extraction

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

Formulation vs. Bioavailability



Total amount dissolved

- Deconvolved profile from mechanistic approach

Total amount absorbed

Total amount into portal vein

Total amount into systemic circulation (bioavailability)

- Deconvolved profile from traditional methods

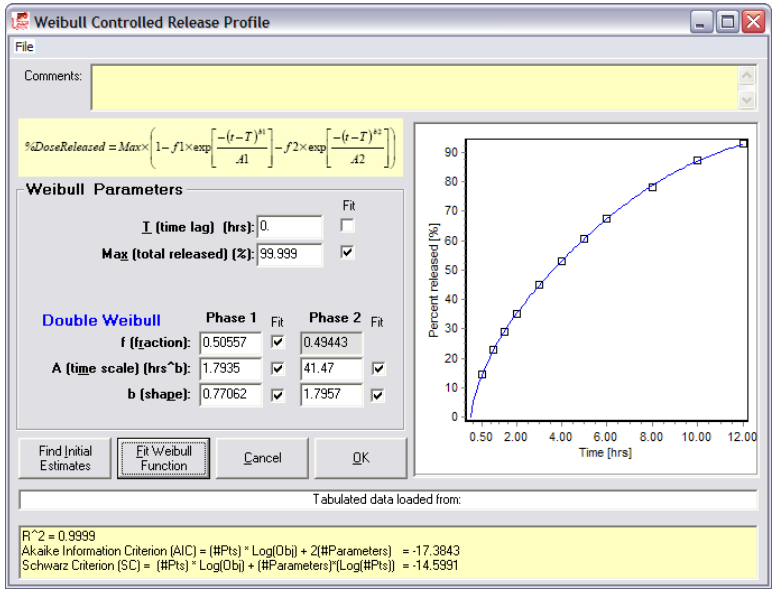
Mechanistic Absorption Deconvolution: Deconvolute Then Correlate

Fit the *in vivo* release profile (using the Weibull function) 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

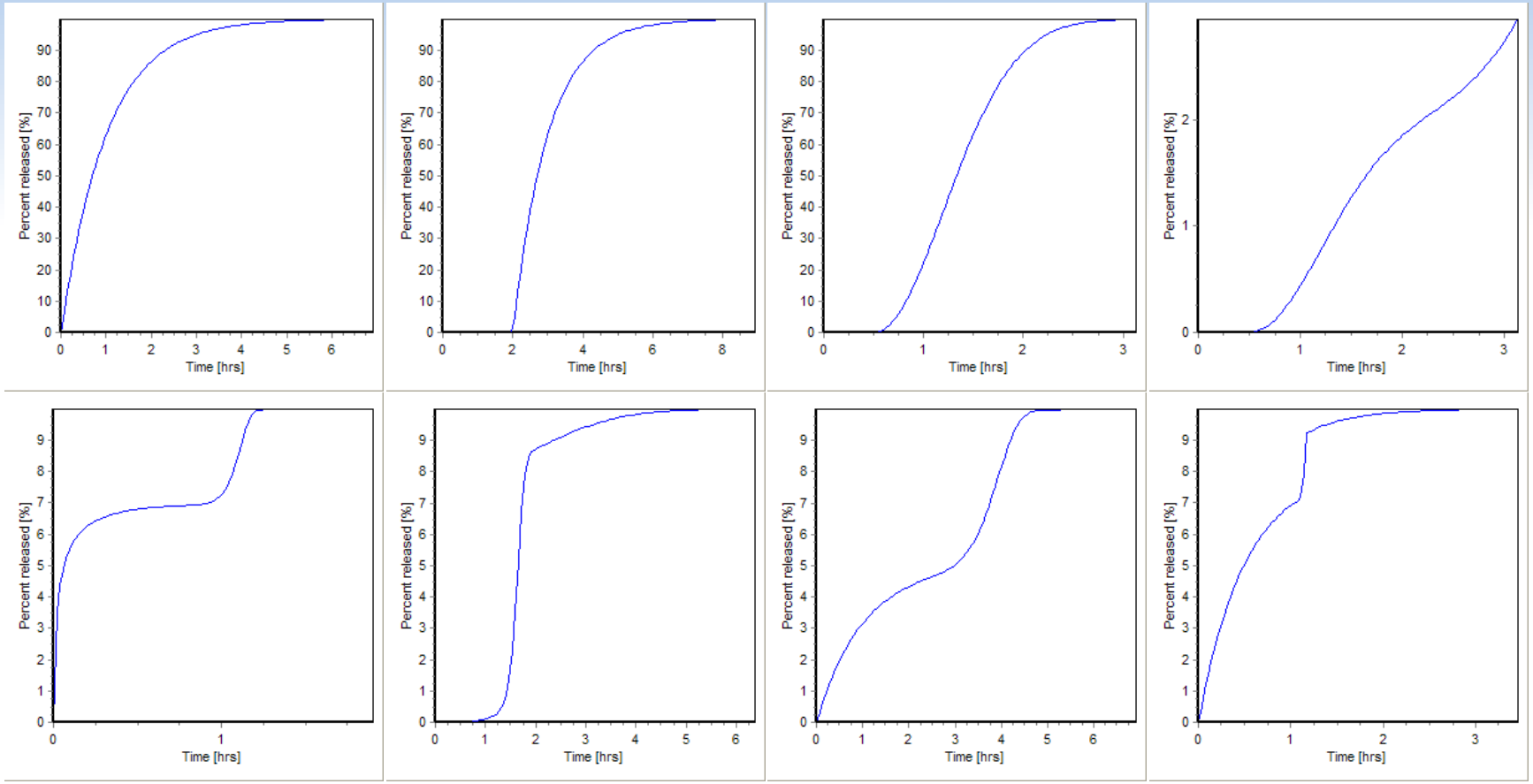
Find the *in vivo* dissolution versus time profile that best fits the plasma concentration-time data

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



Flexibility of the Weibull Function?

- Step 1 is optimization of *in vivo* release profile in a form of a Weibull function
- GastroPlus offers single-, double-, and triple-Weibull functions for optimization of *in vivo* release profile, which cover wide variety of release profile shapes



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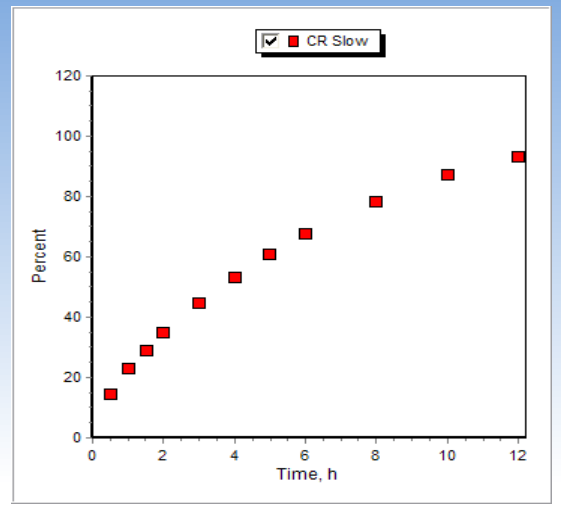
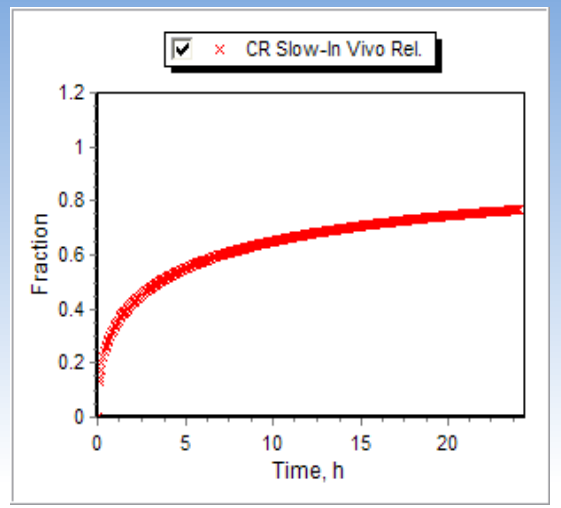
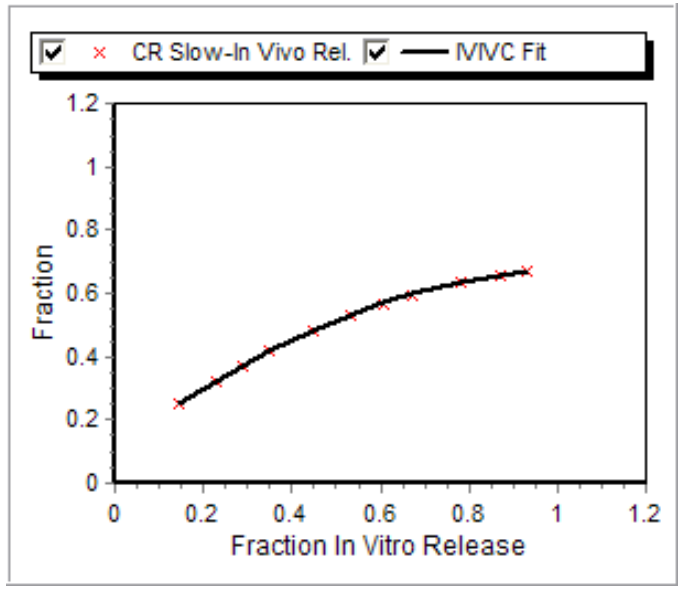
Step 2: Correlation



Correlation



- Find the correlation between the *in vitro* dissolution profiles and the deconvolved *in vivo* release:
  - Linear
  - Power function
  - Quadratic polynomial
  - Cubic polynomial
  - Time shift/scale (currently available only with mechanistic deconvolution)



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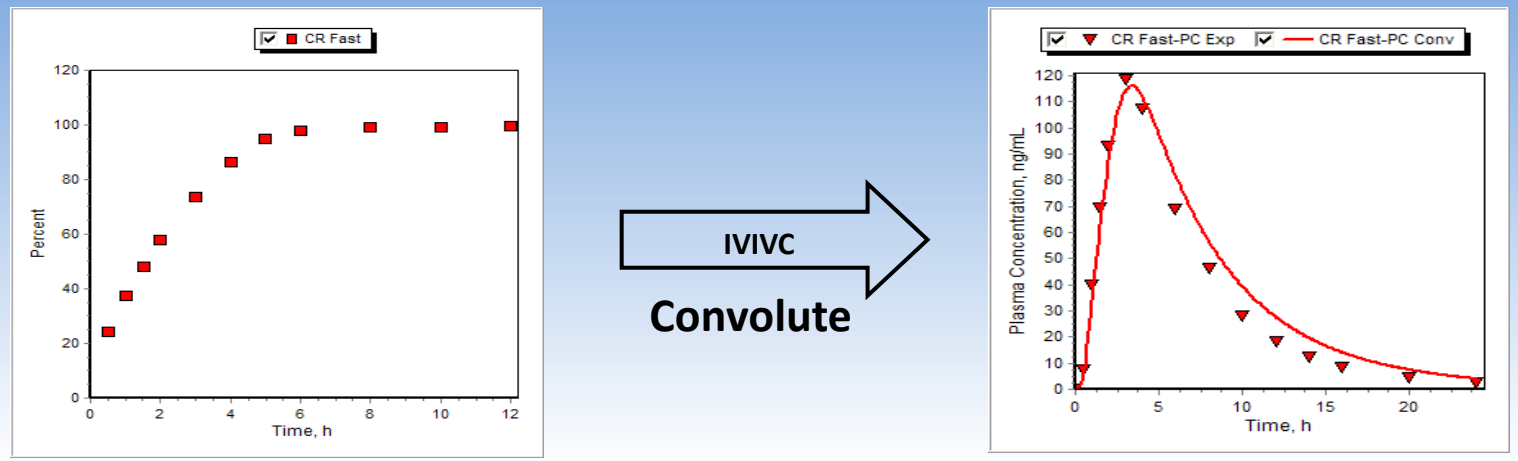
Step 3: Convolution



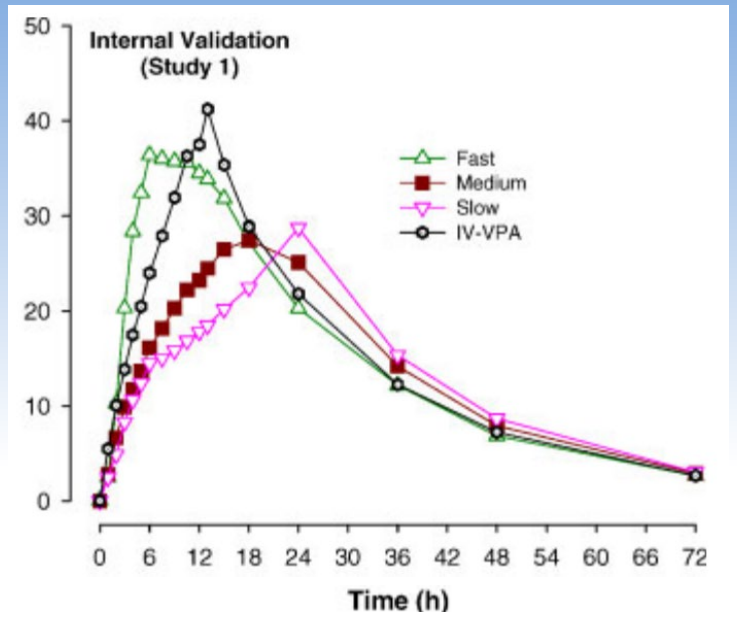
- Predict the plasma concentration-time profile using the IVIVC equation and *in vitro* dissolution curve:
  - Internal validation: use the formulations involved in the development of the IVIVC
  - External validation: use the formulations NOT involved in the development of the IVIVC

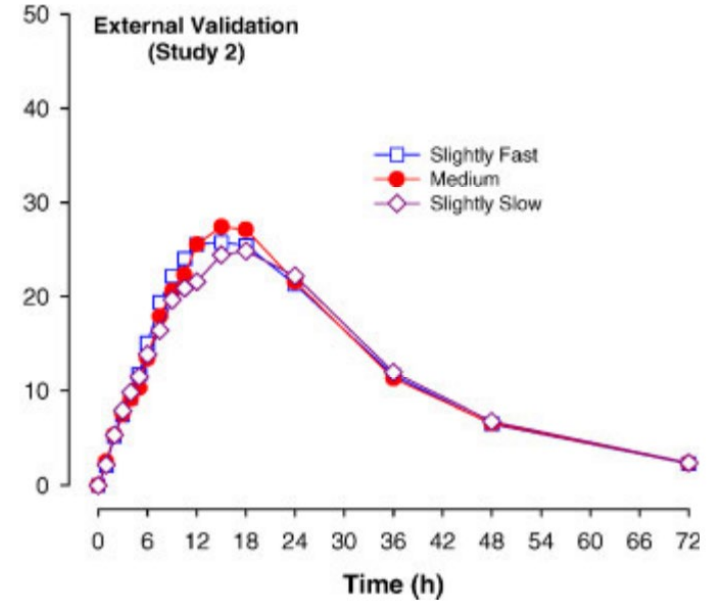
- Acceptance criteria:
  - Internal validation:
    - ≤ 15% absolute prediction error (PE) for C_{max} and AUC of <u>each formulation</u>
    - ≤ 10% <u>mean</u> absolute prediction error (PE) for C_{max} and AUC
  - External validation:
    - ≤ 10% absolute prediction error (PE) for C_{max} and AUC

Example:
Traditional (Loo-Riegelman) vs. Mechanistic Deconvolution:
IVIVC Establishment & Validation

Valproate *In Vivo/In Vitro* Data

In Vivo Data





In Vitro Data

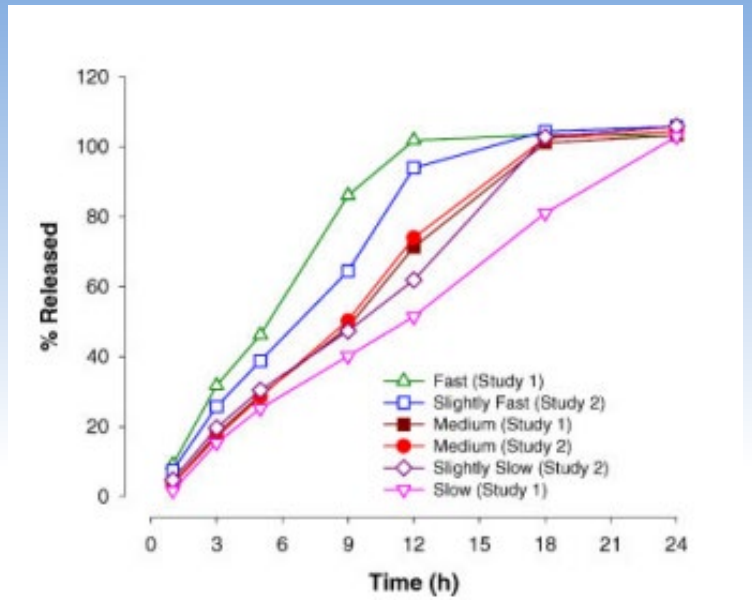


Figure 1. Mean *in vitro* release of five ER formulations of divalproex sodium used in development and validations of IVIVC.

Dutta, et al, J PHARM SCI, 2005, 94(9), 1949-1956

Reference formulation : Medium

Example - IVIVC

1) Open the database **Valproate.mdb** in the **Valproate IVIVC** folder using the **File → Open Drug Database** command
2) Explore the IV and CR records of the database with the instructor.
3) Run the **Human CR Fast - PBPK** record and notice the poor fit at early time points.
4) Use the **Controlled Release Weibull** menu item to fit a Weibull function to the *in vitro* dissolution. Then optimize a single Weibull to get the mechanistic deconvolution of the *in vivo* release that best fits the Cp vs. time profile.
5) Click on **Modules (Optional) → 1 IVIVCPlus**
6) In the **Drug Records** section of the ***In Vitro*** **Data** tab, click on **Slow, Moderate, and Fast**
7) Click on the ***In Vivo*** **Data** tab and you will see that the *in vivo* plasma concentration-time data for the selected drug records with an .opd support file were also loaded
8) Go to the **IVIVC** tab. Only drug records with both .dsd and .opd. support files will be shown in the **Drug Records** list. Click on the **Slow, Moderate,** and **Fast** drug records. Under **Deconvolution Methods** click on **Loo-Riegelman (2-compartment model)**. Under **IVIVC Procedure** select the **Deconvolute Then Correlate** option if is not already selected.

Example-IVIVC

6) Click on the **Deconvolute** button.
7) After deconvolution, you will see a plot of Fraction Absolute Bioavailability vs. Fraction *in Vitro* Release, the **Correlation Function** frame will appear and **Form Correlation** button will be enabled. In the **Correlation Function** frame you can select the correlation functions you want to try to fit to the data.

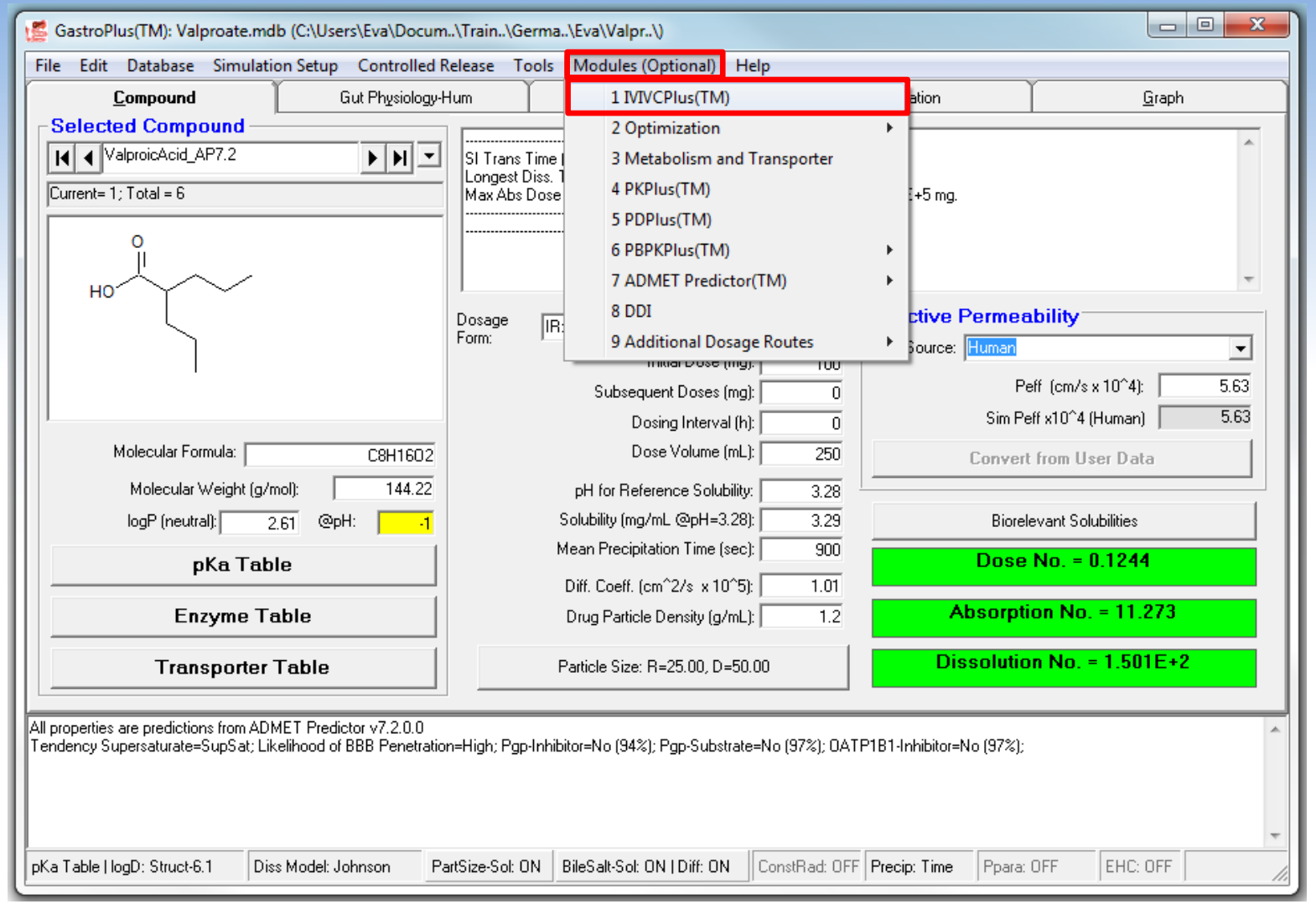
   For this example, we will keep the **Select All** selection, so all the boxes are checked. All checked correlation functions will be fitted to the data and the program will pick the best fit based on lowest Akaike Information Criteria. Click on the **Form Correlation** button.

6) When the program is finished fitting all the correlation functions, the best fit is shown in the **Status window** on the **IVIVC** tab as well as on the Fraction Absolute Bioavailability vs. Fraction *In Vitro* Release plot.
7) The **Status window** gives the following information about the correlation (Rsq=R2, SEP=Standard Error of Prediction, MAE=Mean Absolute Error, and AIC=Akaike Information Criterion).

Example-IVIVC

8) Next click on the **Convolution** tab. The correlation function you generated above is displayed in the **Status Window**. Under Drug Records, select **Slow, Moderate, and Fast**.
9) Click on the **Start** button to run the convolutions. When convolution is finished the observed and predicted plasma concentration-time profiles using the correlation function for all selected drug records will be shown in the plot and the validation statistics will be shown in the **Status Window**.
   Note: Only drug records with an .opd support file are included in the mean absolute percent prediction error calculation.
10) Perform a similar external validation using the **Slightly Slow** and **Slightly Fast** records?
11) Repeat steps (5-9) but choose **Mechanistic Absorption Model** under “Deconvolution Methods”.
12) Save the final IVIVC.
13) Close IVIVCPlus.

The IVIVCPlus Module



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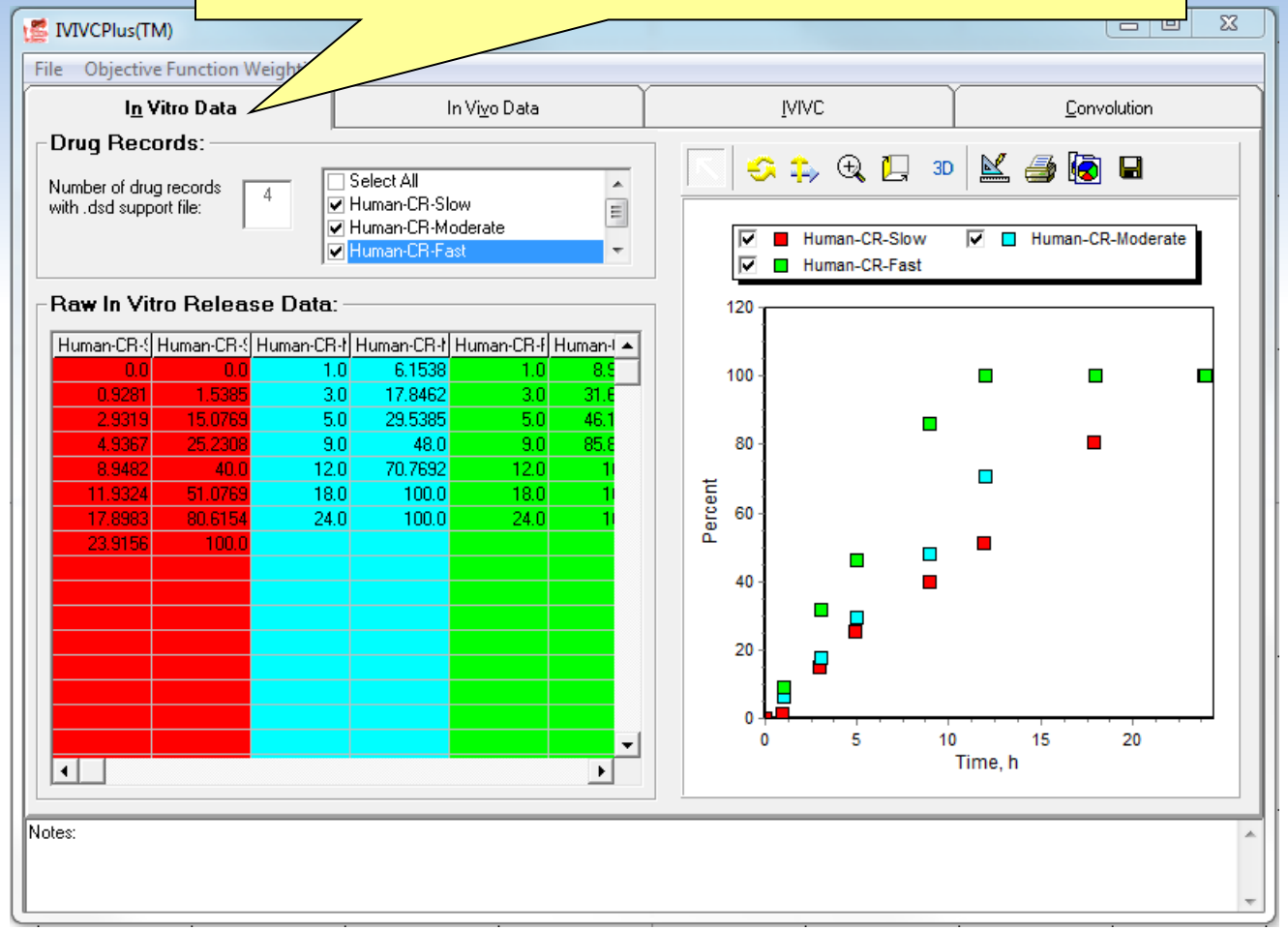
In Vitro Data Tab

Display and plot the *in vitro* dissolution data for the selected drug records



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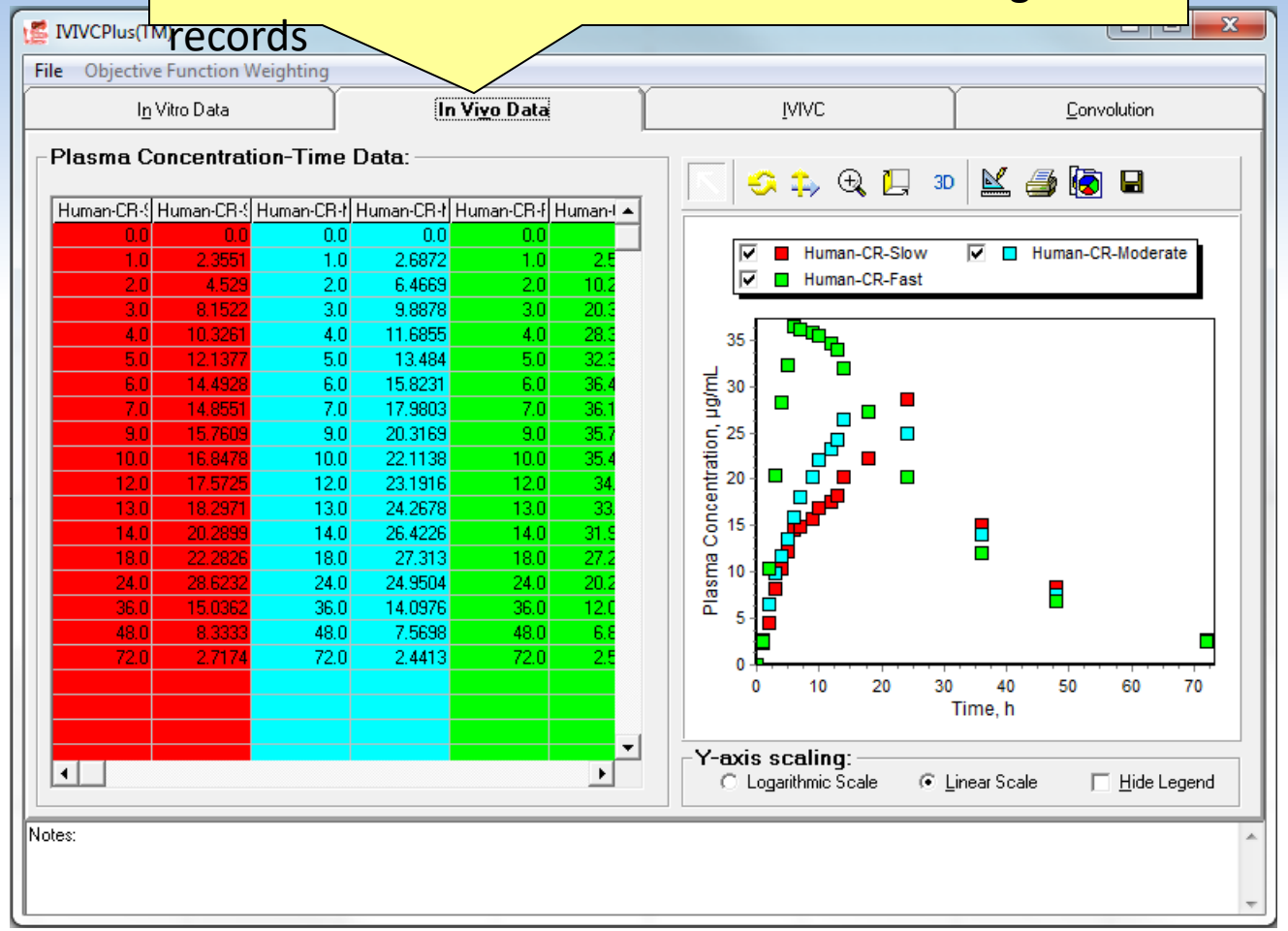
In Vivo Data Tab

Display and plot the *in vivo* oral plasma concentration-time data for the selected drug records



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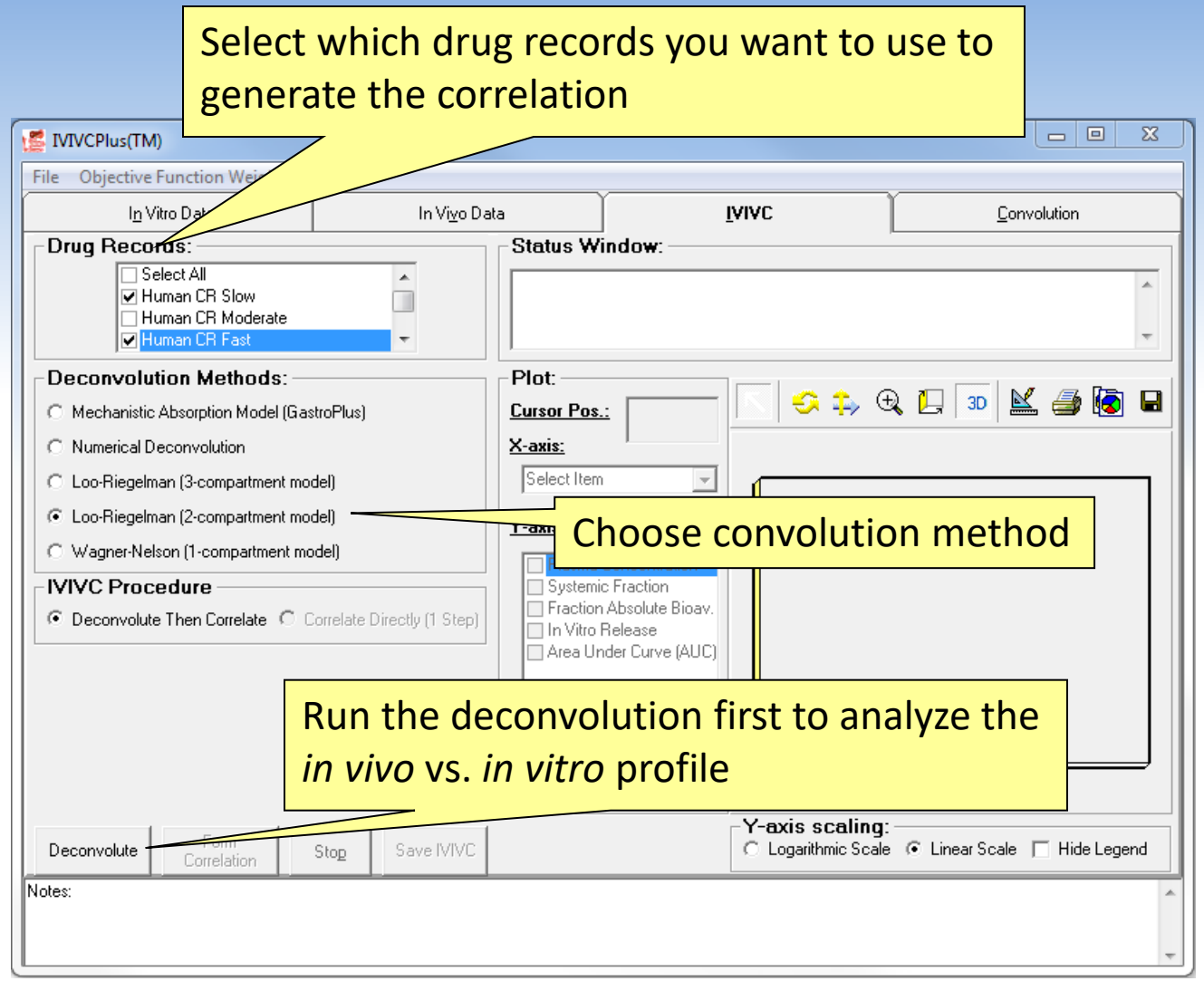
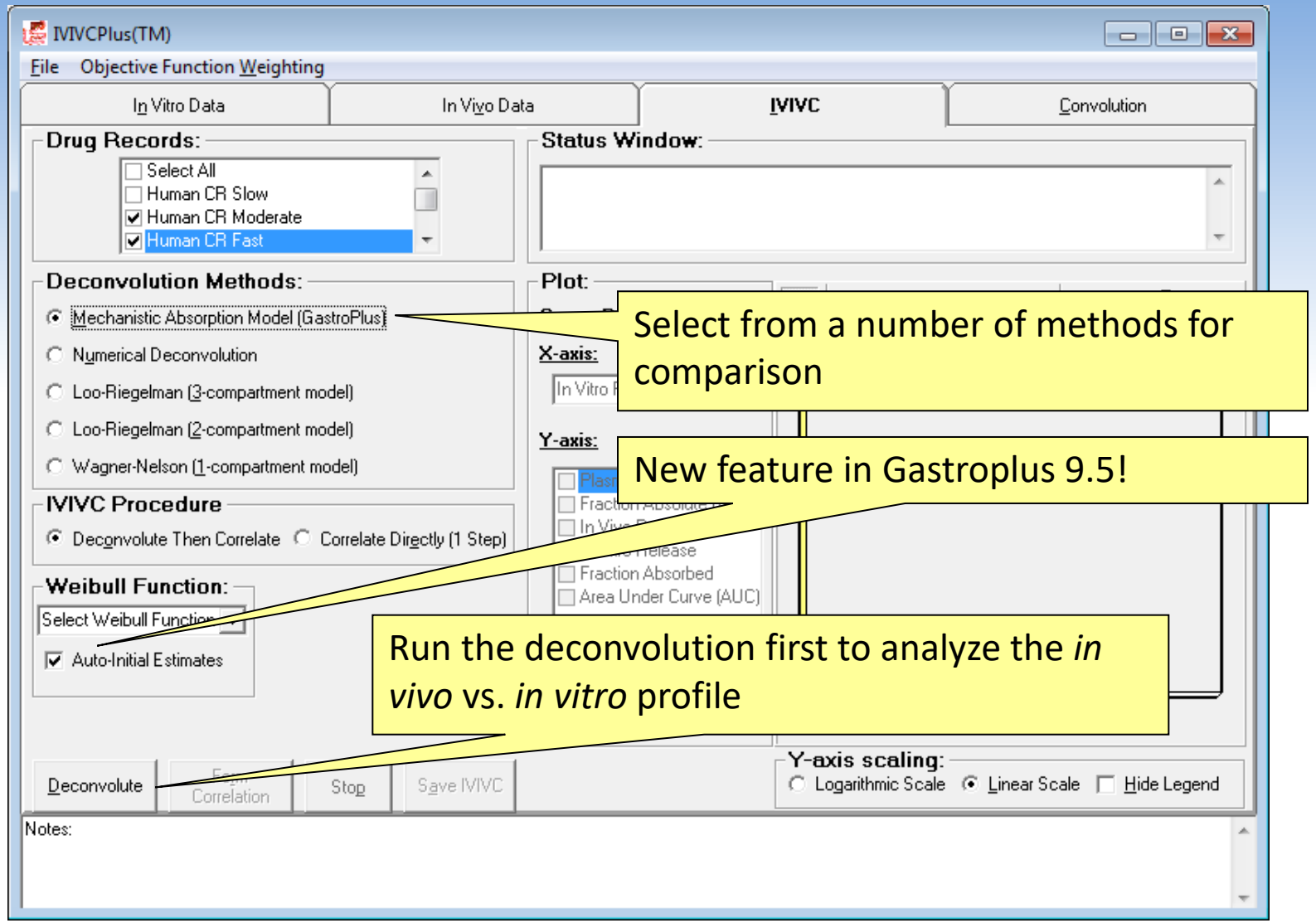
IVIVC Tab



Let's build the IVIVC…

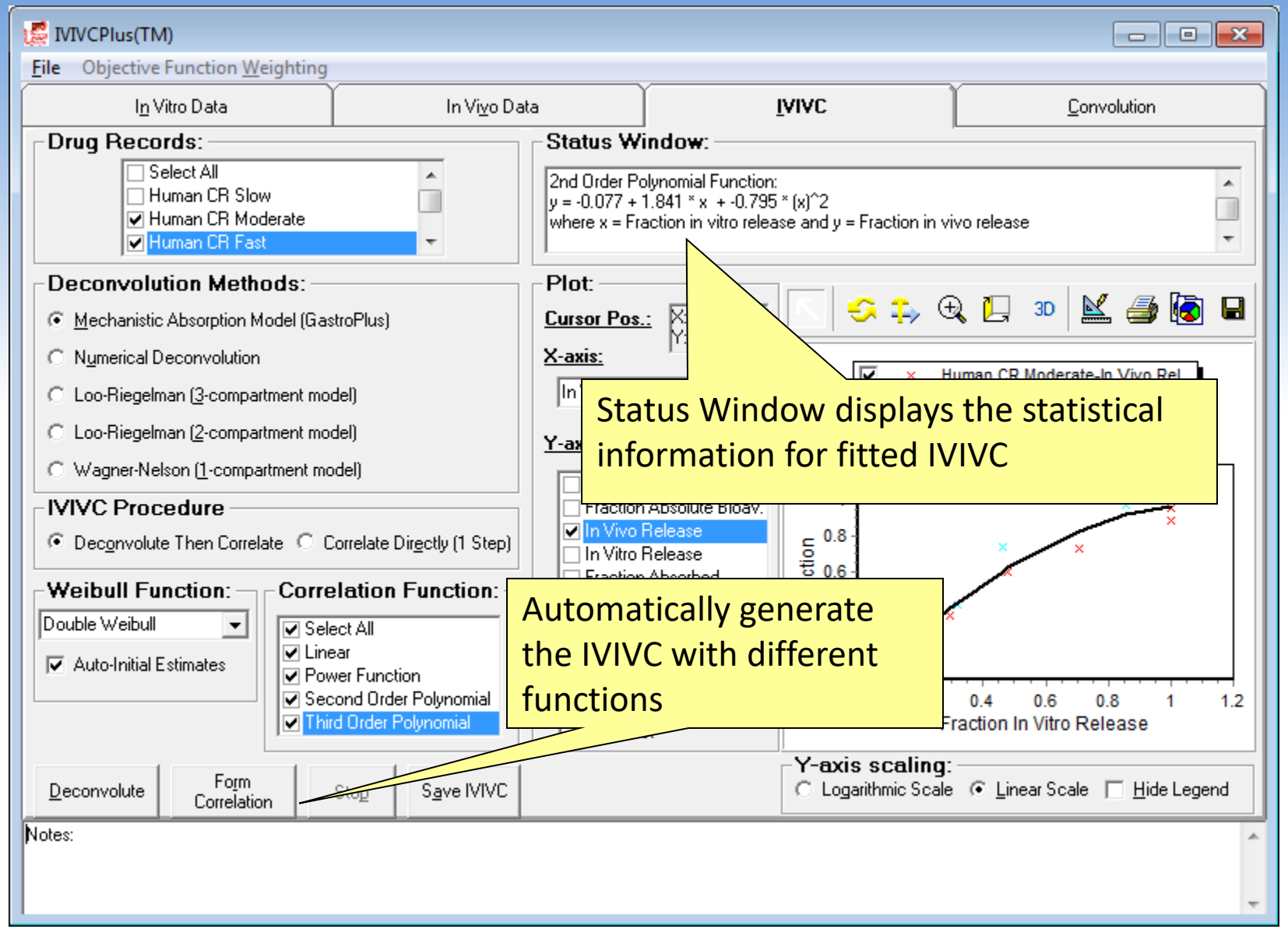


Select from a number of methods for comparison

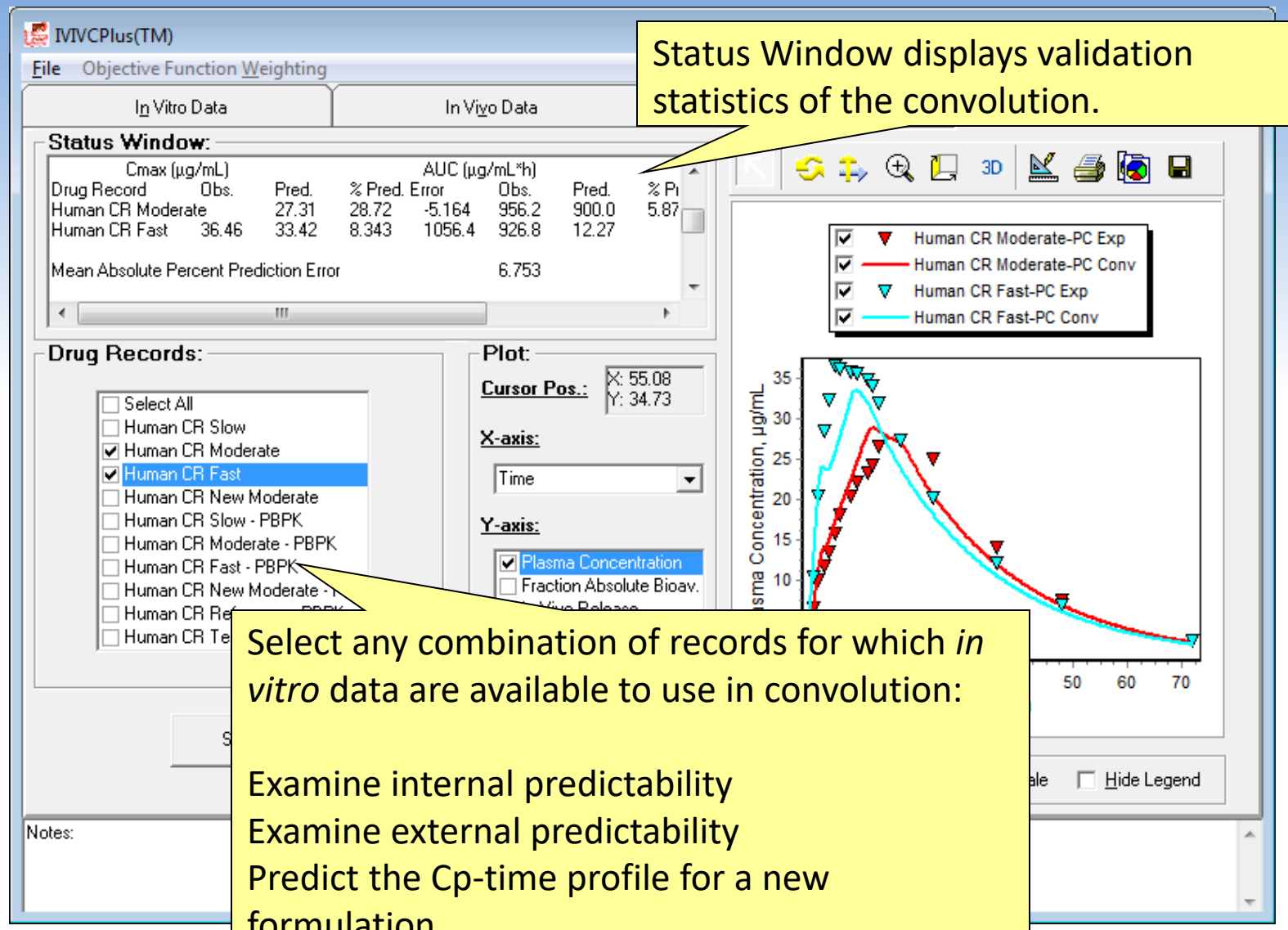
New feature in Gastroplus 9.5!

Run the deconvolution first to analyze the *in vivo* vs. *in vitro* profile

Form the Correlation



Is it valid?



Status Window displays validation statistics of the convolution.

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

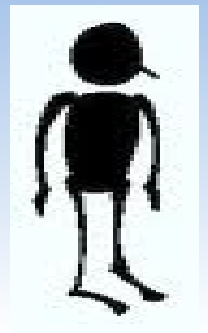
Examine internal predictability
Examine external predictability
Predict the Cp-time profile for a new formulation

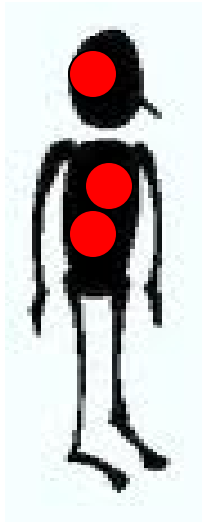
Virtual Bioequivalence Trials: Reference vs. Test Products

GastroPlus Population Simulator

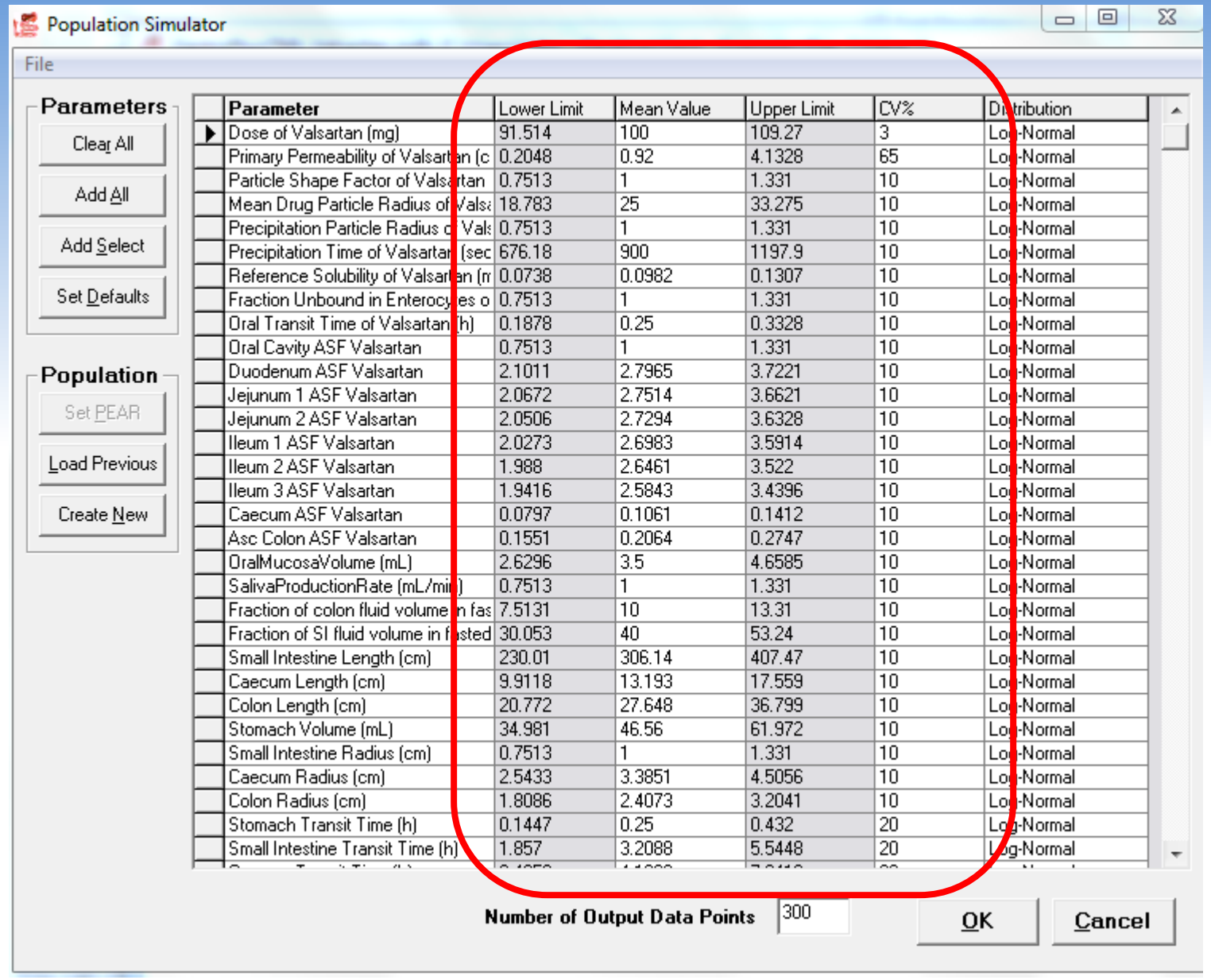
- Enables you to simulate a population of up to 2500 subjects
- Populations are generated, not sampled from a database
  - An infinite number of populations is possible
- Subjects are generated by Monte Carlo sampling of selected parameters within their defined distributions:
  - Gut physiology parameters
  - Pharmacokinetic parameters
  - PBPK parameters
  - Dosage form and compound parameters
- Populations can be saved and reused for **crossover studies**
- Covariation of model parameters is a complex issue:
  - Population simulator algorithms have been updated in version 9.6 to better account for the known physiological covariates

Populations vary as a function of age, gender, weight, height (BMI), & disease state

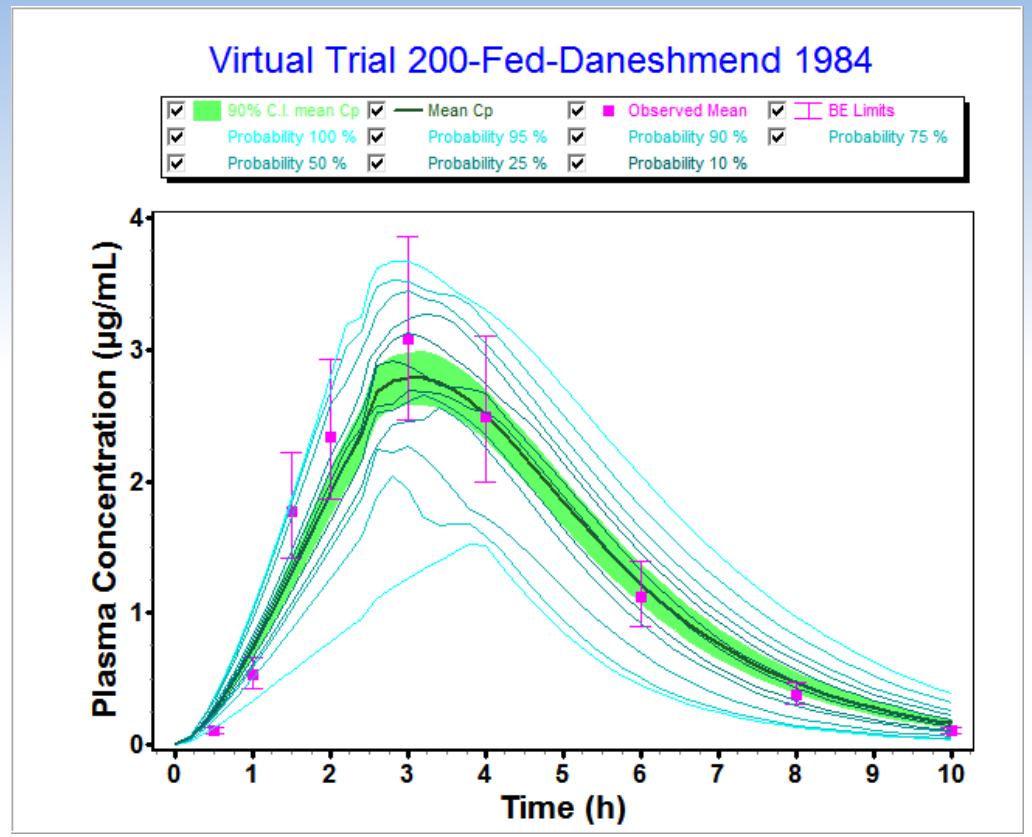




You

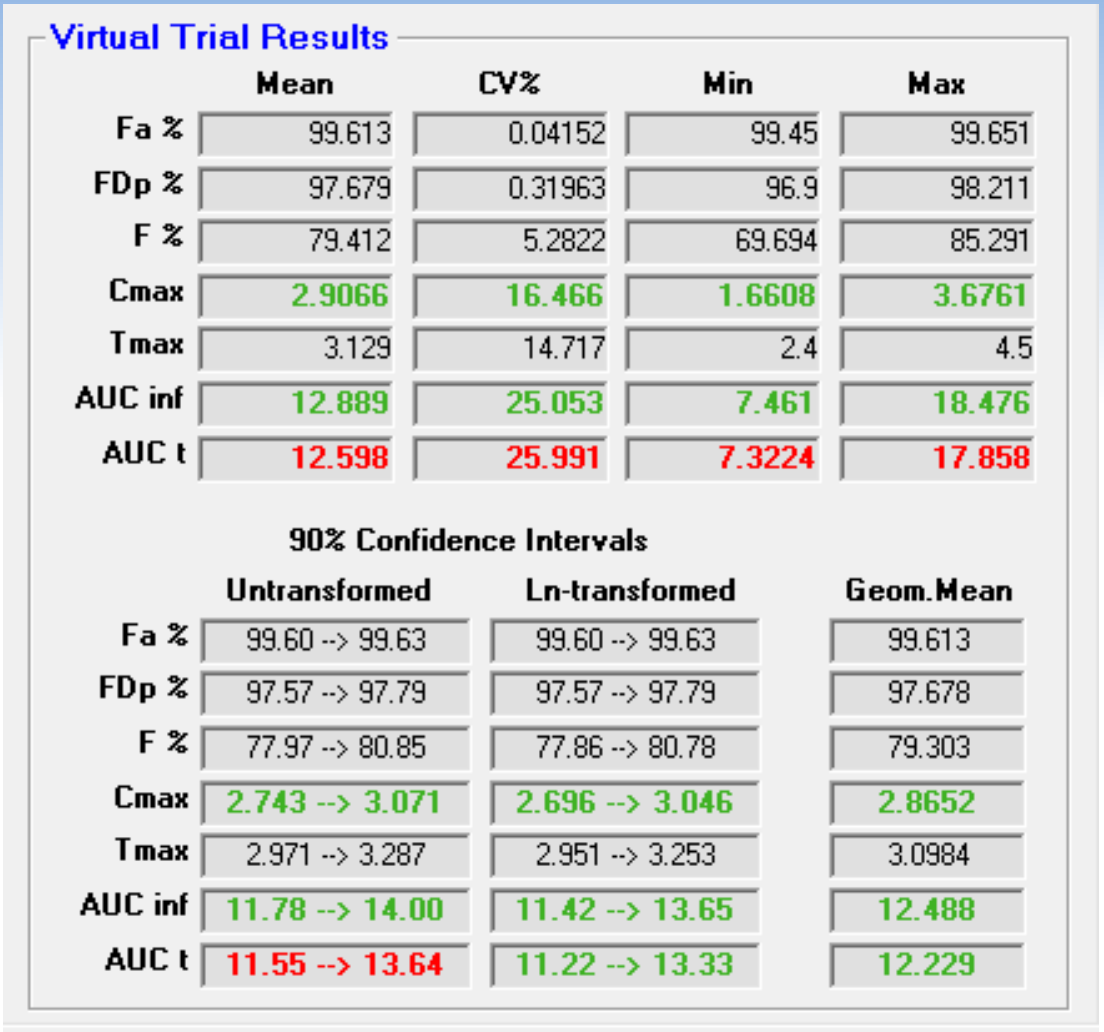


Sensitivities for Population Simulator



- Solid blue line is mean of "n" subjects
- Green band is 90% confidence interval
- Light blue lines are probability contours for the virtual population
- Pink bars are the 80 to 125% BE limits or % CVs

Population Simulator Results and Files



Virtual Trial Results

	Mean	CV%	Min	Max
Fa %	99.613	0.04152	99.45	99.651
FDp %	97.679	0.31963	96.9	98.211
F %	79.412	5.2822	69.694	85.291
Cmax	2.9066	16.466	1.6608	3.6761
Tmax	3.129	14.717	2.4	4.5
AUC inf	12.889	25.053	7.461	18.476
AUC t	12.598	25.991	7.3224	17.858

90% Confidence Intervals

	Untransformed	Ln-transformed	Geom.Mean
Fa %	99.60 --> 99.63	99.60 --> 99.63	99.613
FDp %	97.57 --> 97.79	97.57 --> 97.79	97.678
F %	77.97 --> 80.85	77.86 --> 80.78	79.303
Cmax	2.743 --> 3.071	2.696 --> 3.046	2.8652
Tmax	2.971 --> 3.287	2.951 --> 3.253	3.0984
AUC inf	11.78 --> 14.00	11.42 --> 13.65	12.488
AUC t	11.55 --> 13.64	11.22 --> 13.33	12.229

- Upper Table (mean)
  - Green means that the simulated 90% CI is within the 80 – 125% BE limits.
- Lower Table (Geom. Mean)
  - Green means that the simulated Geom. mean is within the 80 – 125% BE limits.

Virtual Bioequivalence Trials

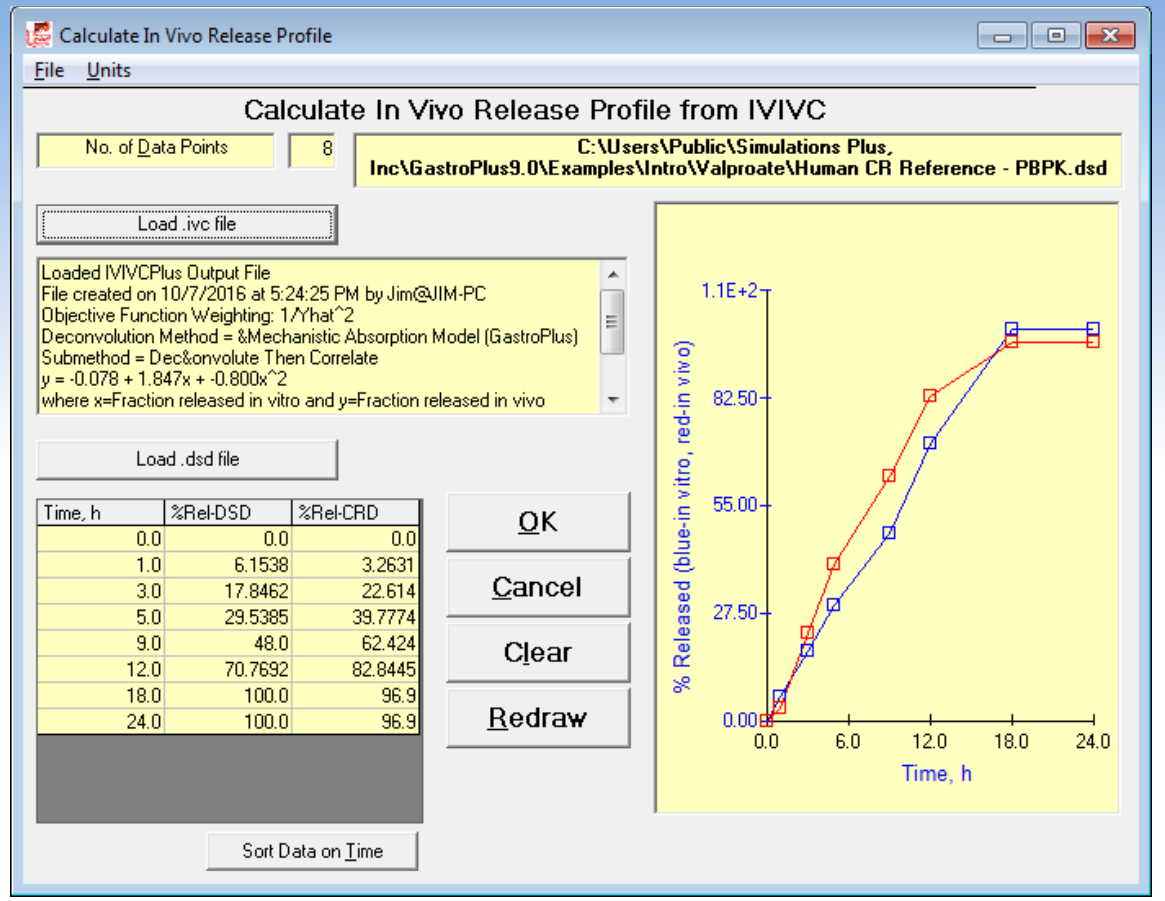
- Bioequivalence trials are run to demonstrate bioequivalence between a test formulation and a reference formulation.
- To demonstrate bioequivalence, the test product must duplicate the Cmax and AUC of the reference product within 80-125% at 90% confidence intervals under both fasted and fed conditions.
- The number of subjects in the trial can affect the outcome. If the number of subjects is too small, the trial might fail when the product is actually bioequivalent. If the number is too large, time and money are wasted.
- Virtual bioequivalence trials can help to predict whether a formulation is *likely* to pass or fail. They are not perfect, but they provide an important decision-making tool to use with all other information.
- What is the best way to run Virtual Bioequivalence Trials?
  - Select the population parameters you want to vary and a number of subjects
  - Run several virtual crossover trials to confirm a consistent trend between the Cmax and AUC ratios

Case Study: Valproate BE Test vs. Reference

- Open the “Valproate” database in your Examples\Valproate folder
- Navigate to the **Human CR Test - PBPK** record and review the model parameters
  - Test product is simulated first, then the reference is simulated, due to the order of operations in the population simulator
- Convert *in vitro* dissolution .dsd → to *in vivo* dissolution .crd
  - see next slide
- Calculate the Weibull function for the *in vivo* dissolution (.crd file) using the Controlled Release→Weibull Function menu

Converting .dsd to .crd

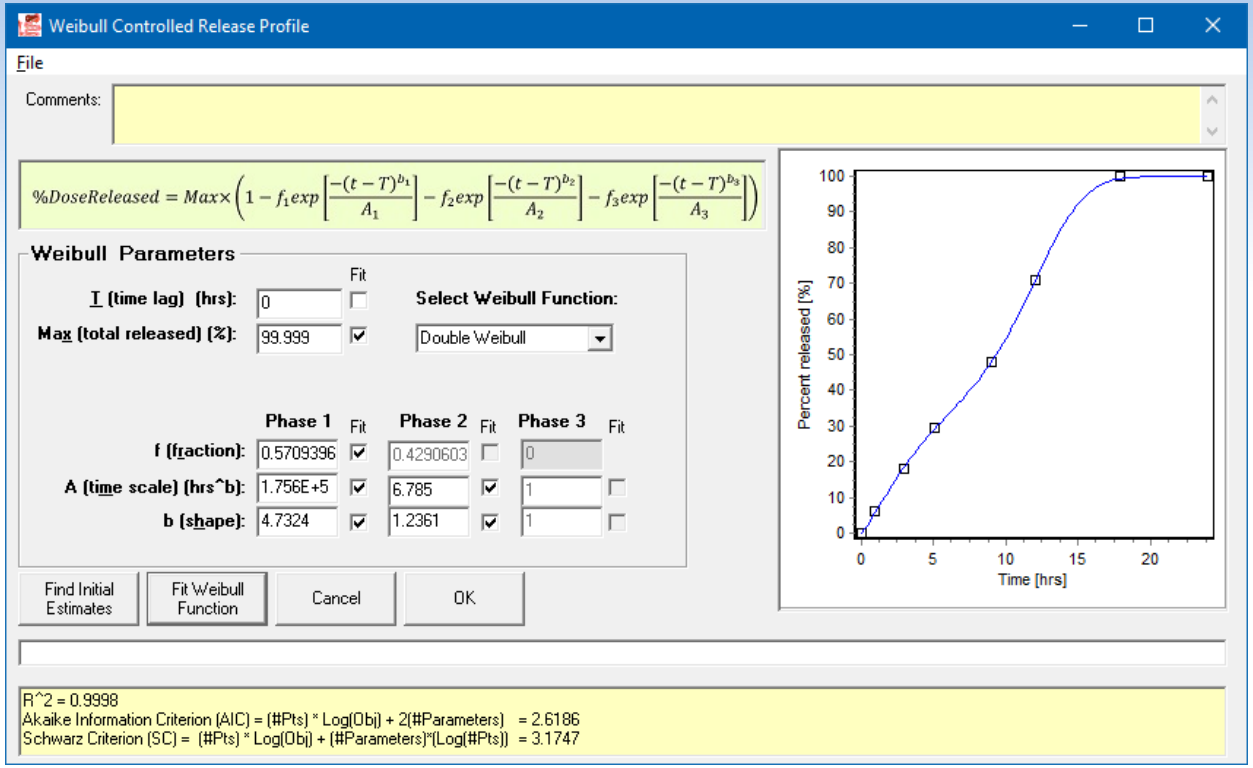
- Click File →Load→3 Load *In Vivo* Controlled Release vs. Time Profile (.crd)
- Click Tools → Calculate CRD from IVIVC
- Click Load .ivc file and load the correlation we previously developed
- Click OK to finish (return to .crd window)
- Your newly converted dissolution profile is now in the table.



Note: This is only sample figure – your profiles and CRD values will be different

Fit Weibull Function to *In Vivo* Dissolution

- In the .crd window click Fit Weibull Function
- In the Weibull window:
  - Click Find Initial Estimates
  - Select Double-Weibull function and Set f (fraction) = 0.5
  - Select parameters to be fitted
  - Click Fit Weibull Function
  - Click OK to close the Weibull window and return to the .crd window
- The fitted Weibull parameters will appear in the Comments section of the .crd window.
- Click File → Save As to write the new .crd file



Note: This is only sample figure – your profile and parameters will be different

Case Study: Valproate BE

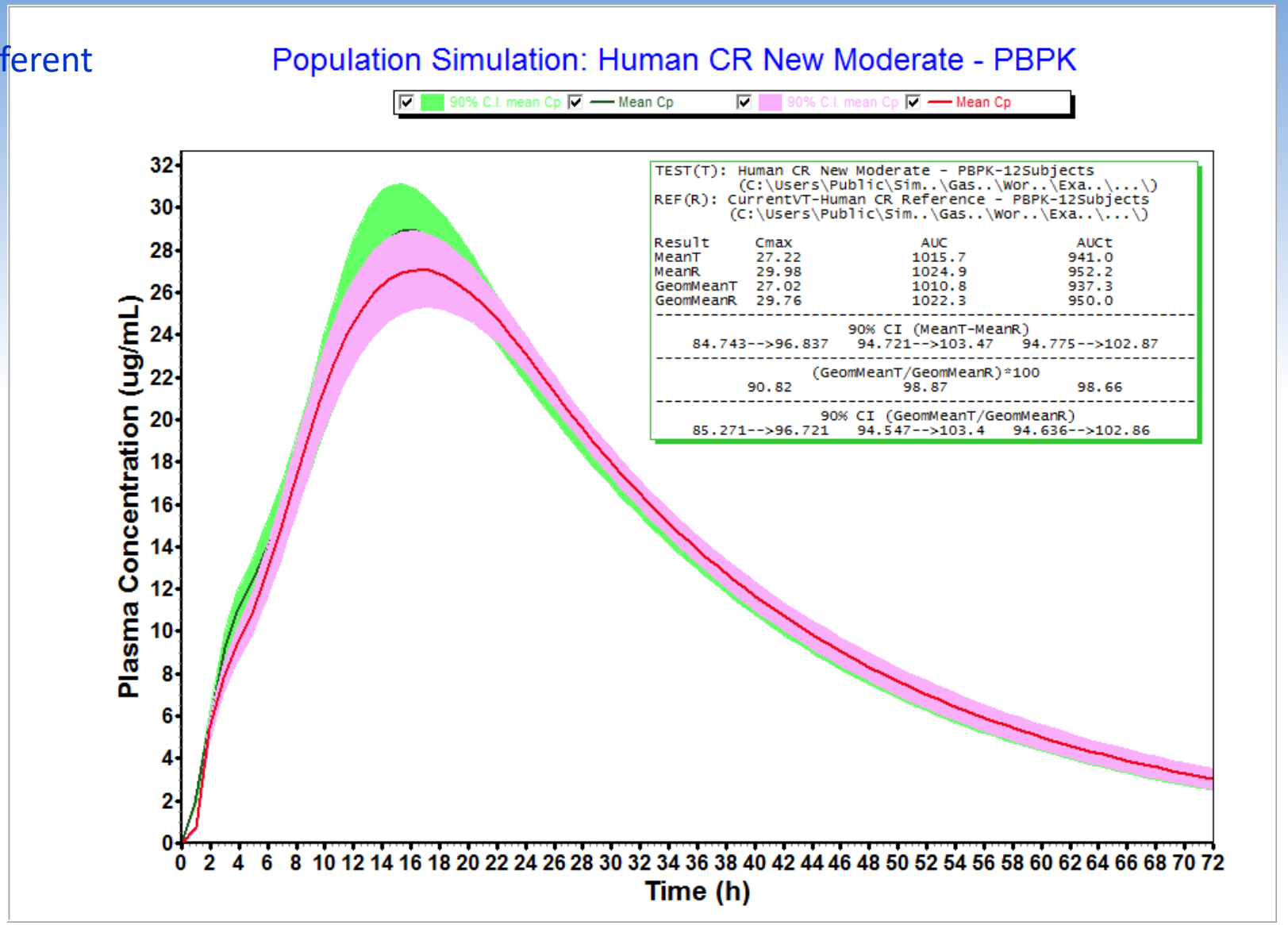
- Run a Single Simulation for record **Human CR Test - PBPK**, make sure to select “Use Weibull CR Profile Already in Memory” option
- Select the Population Simulator option on the Simulation tab to open the Population Simulator window
- Set the CV% for Dose = 3%; keep all other CV% at their default numbers. Change the Number of Output Data Points to 75
- On the PEAR Population Simulator Settings window, define the age range to run from 21 – 40 years old, with a 50/50 split between males & females
- Set the Sample Size = 12 subjects (small pilot study) and click Start
- Review the results

Case Study: Valproate BE

- Navigate to the **Human CR Reference - PBPK** record
- Convert *in vitro* dissolution .dsd → to *in vivo* dissolution .crd
- Calculate the Weibull function for the *in vivo* dissolution (.crd file) using the Controlled Release→Weibull Function menu
- Run a Single Simulation, making sure to select "Use Weibull CR Profile Already in Memory" option
- Select the Population Simulator option on the Simulation tab to open the Population Simulator window
- Click on the **Load Previous** population button on the left and select the 12-subject file generated from the Reference product simulation. Set the CV% for Dose = 3%
- Click on the Start button on the Simulation tab. When finished, navigate to the Graph tab and click on the New Plot button

The Population Simulation – Virtual BE

Illustration only –
your results will be different



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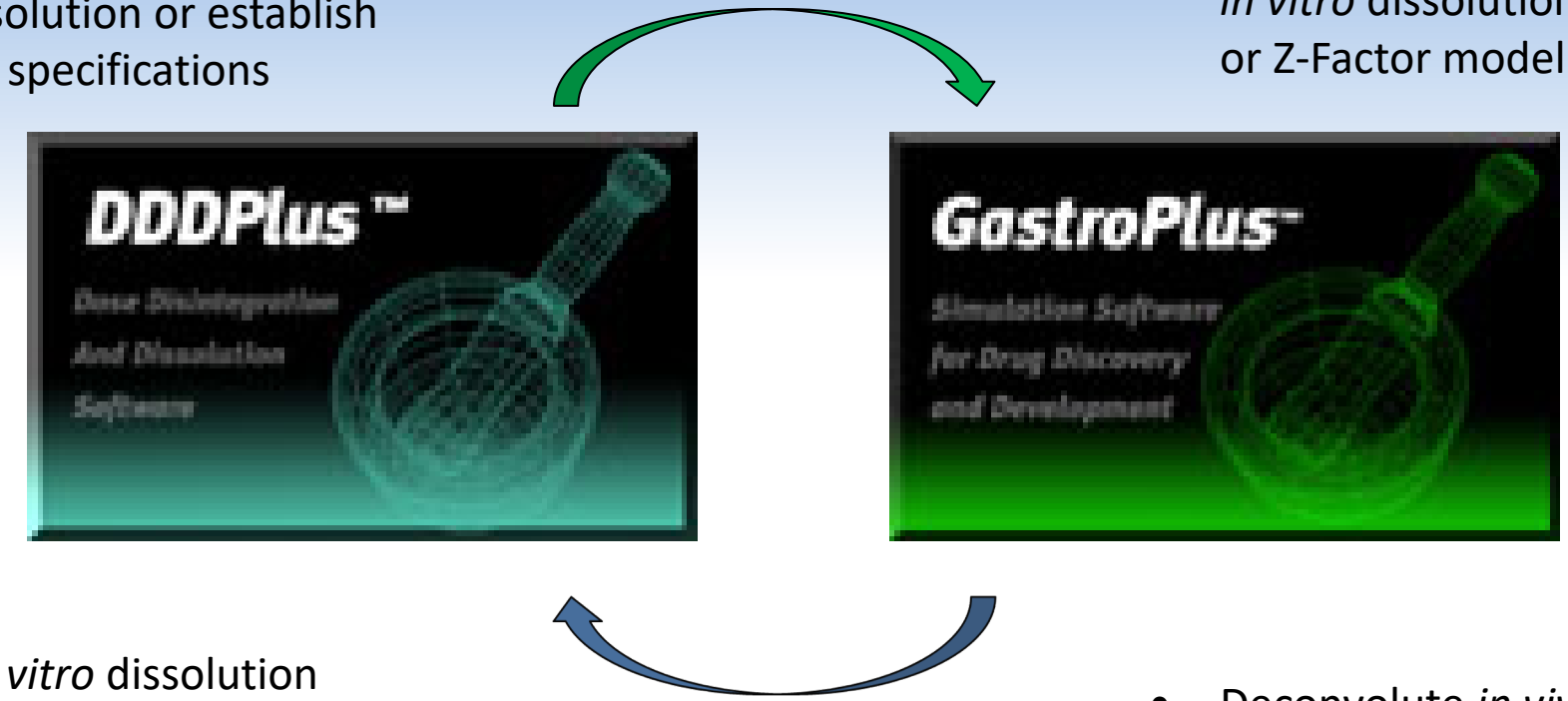
Establishing Dissolution Specifications: Mechanistic dissolution variability – synergy with DDDPlus™

Synergy between DDDPlus™ and GastroPlus®

- Design a formulation to simulate *in vitro* dissolution or establish dissolution specifications

- Simulate PK profiles using predicted *in vitro* dissolution profiles (raw data or Z-Factor model)



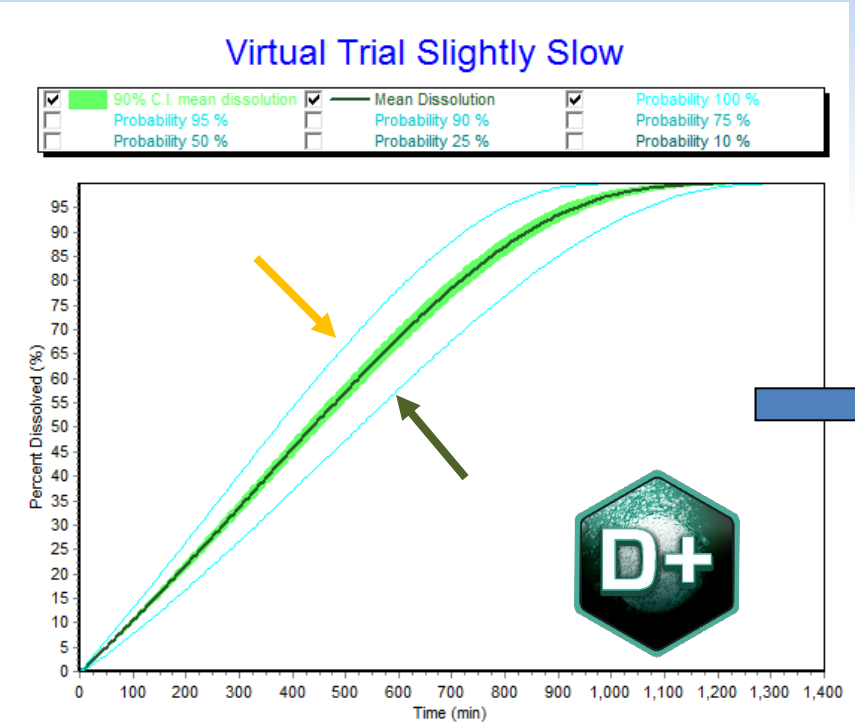
- Design an *in vitro* dissolution method using the deconvoluted *in vivo* release curve as the “target”

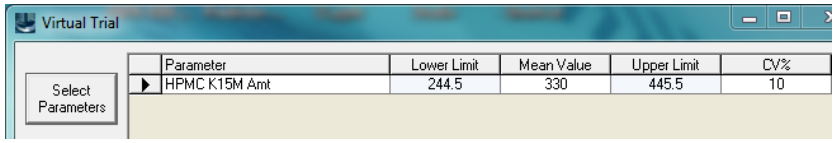
- Deconvolute *in vivo* release using measured PK data

Establish design or safe spaces

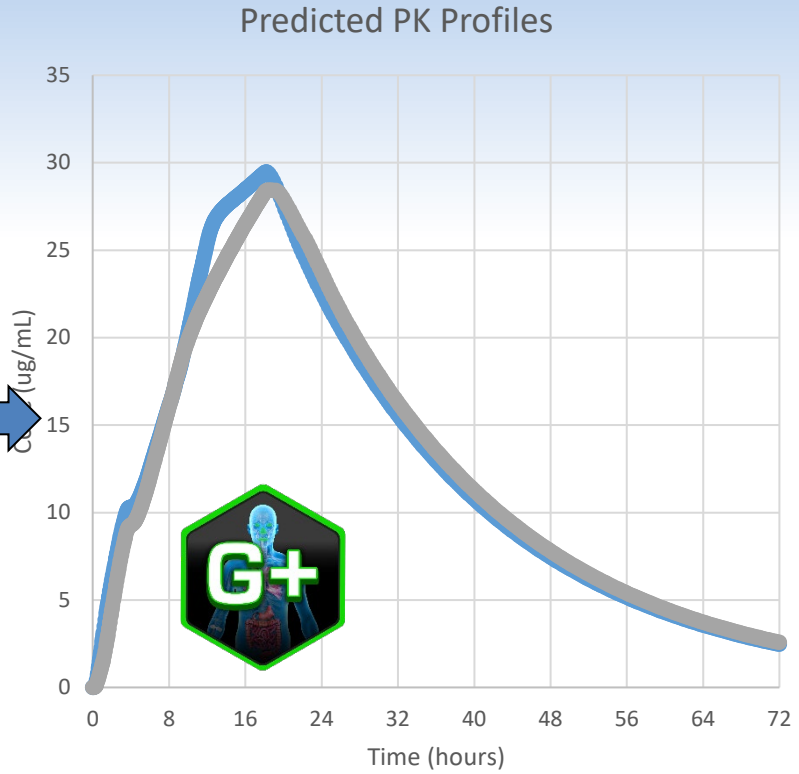
10% variability around HPMC content

25 virtual lots simulated in DDDPlus





100th percentile ('extreme') dissolution profiles loaded into GastroPlus to predict PK



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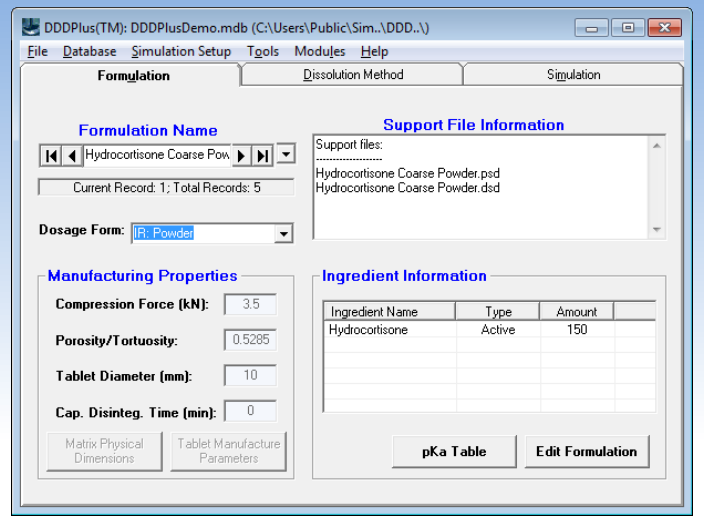
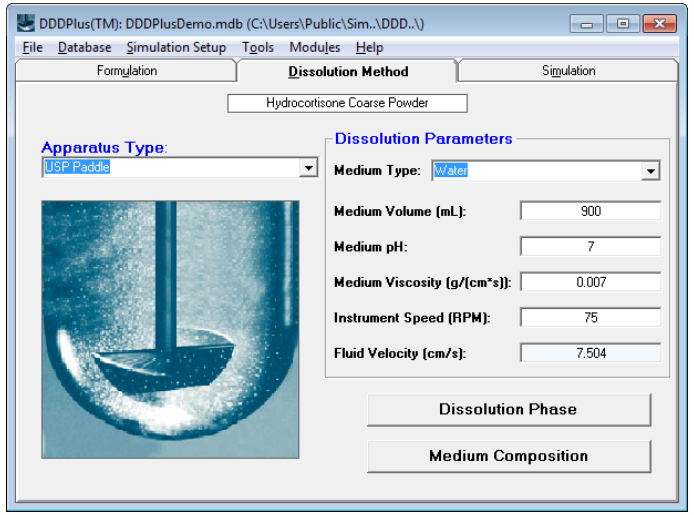
What does DDDPlus consider?

DDDPlus is a state-of-the-art formulation simulation computer program that contains equations to account for the following:

- Dissolution rate for active pharmaceutical ingredient (API) and excipients
- Multiple particle size distribution for API and excipients
- Variety of dosage form models
- Solubility-dynamic microclimate pH calculation for API and excipients
- pH of buffers from composition of acids, bases, and salt equivalents.
- Selection of USP and biorelevant experimental apparatus and conditions





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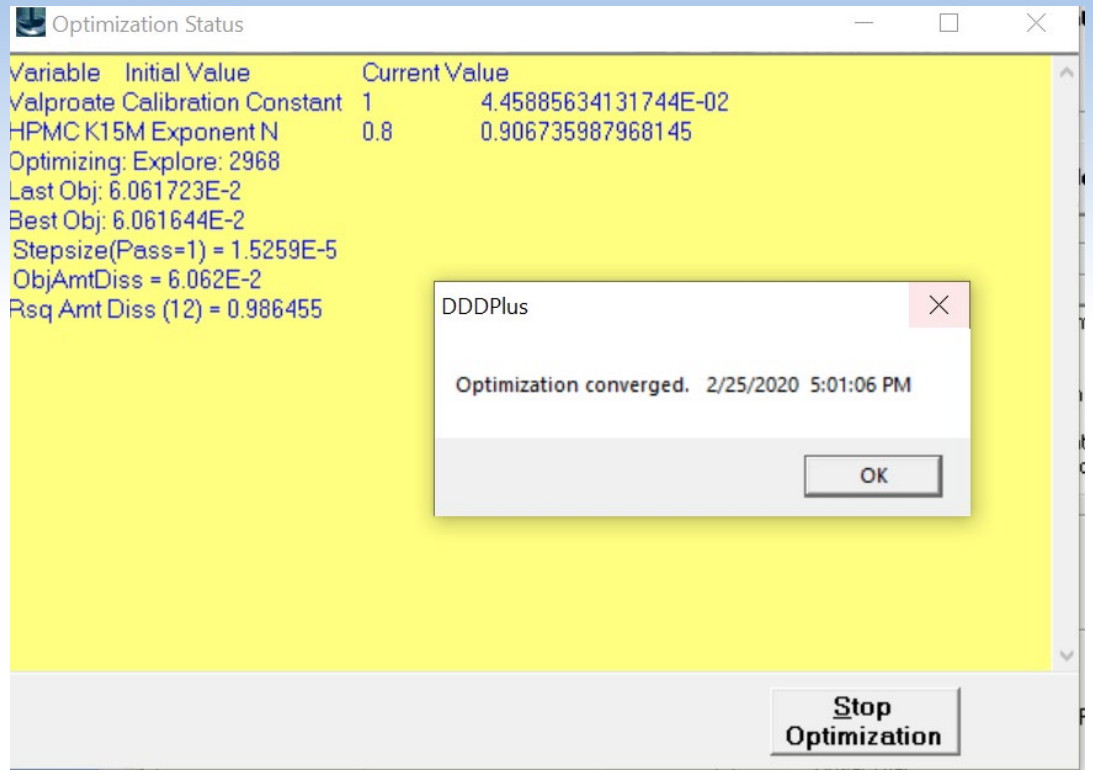
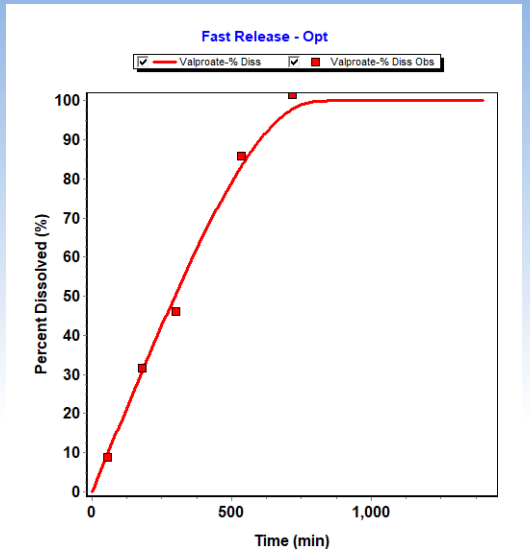
Activity: DDDPlus Modeling

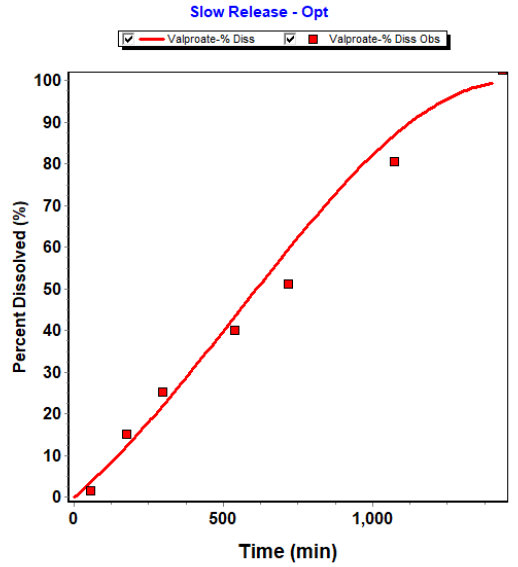
- Open the Valproate DDDPlus database project in DDDPlus (File→Open Formulation Database)
- Let's perform a query and select only those records with the keyword 'Opt' – go to the 'Database→Select Subset by' menu
- We are going to build a DDDPlus model by optimizing parameters across the 2 records
  - Go to the 'Modules→Optimization→1 Select Parameters and Objective Function' menu
  - Let's make sure to 'Match Predicted vs. Observed for All Records'
  - Select the Valproate Calibration Constant (Formulation tab) and the HPMC K15M Exponent N (Release Exponent tab)
- Validate the model by using the same parameters to predict the remaining formulations

DDDPlus Model Training

- Use the Optimization Module to determine release parameters using the fast and slow formulation



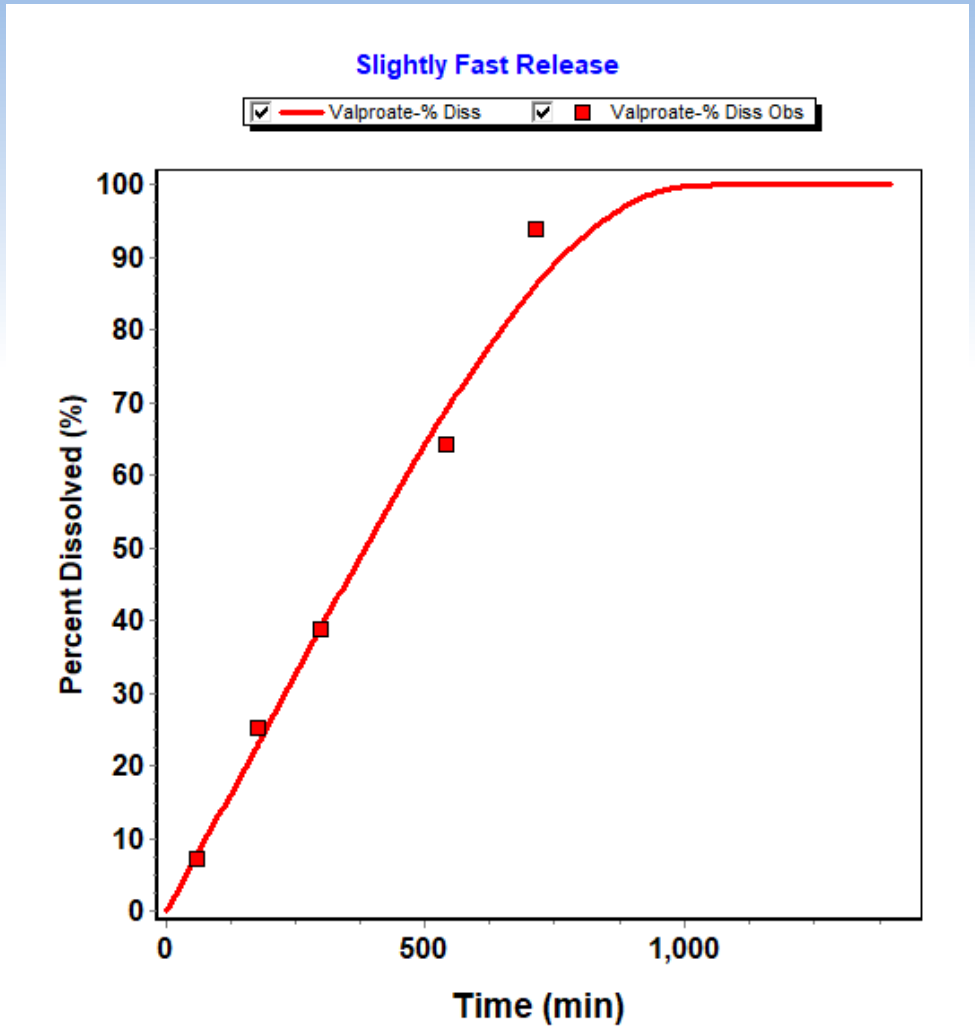




Calibration Constant = 4.4589E-2
Release Exponent = 9.0674E-1

Predict New Formulation

- Use these release parameters to design a new formulation



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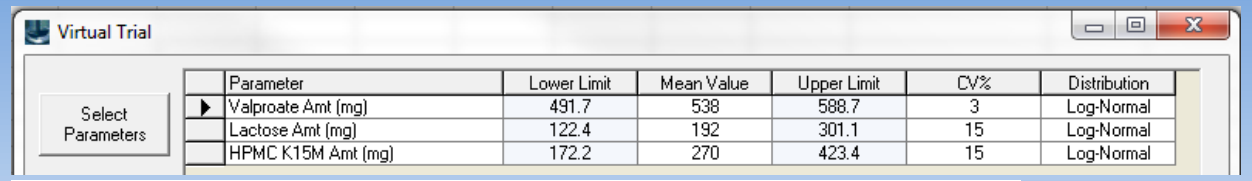
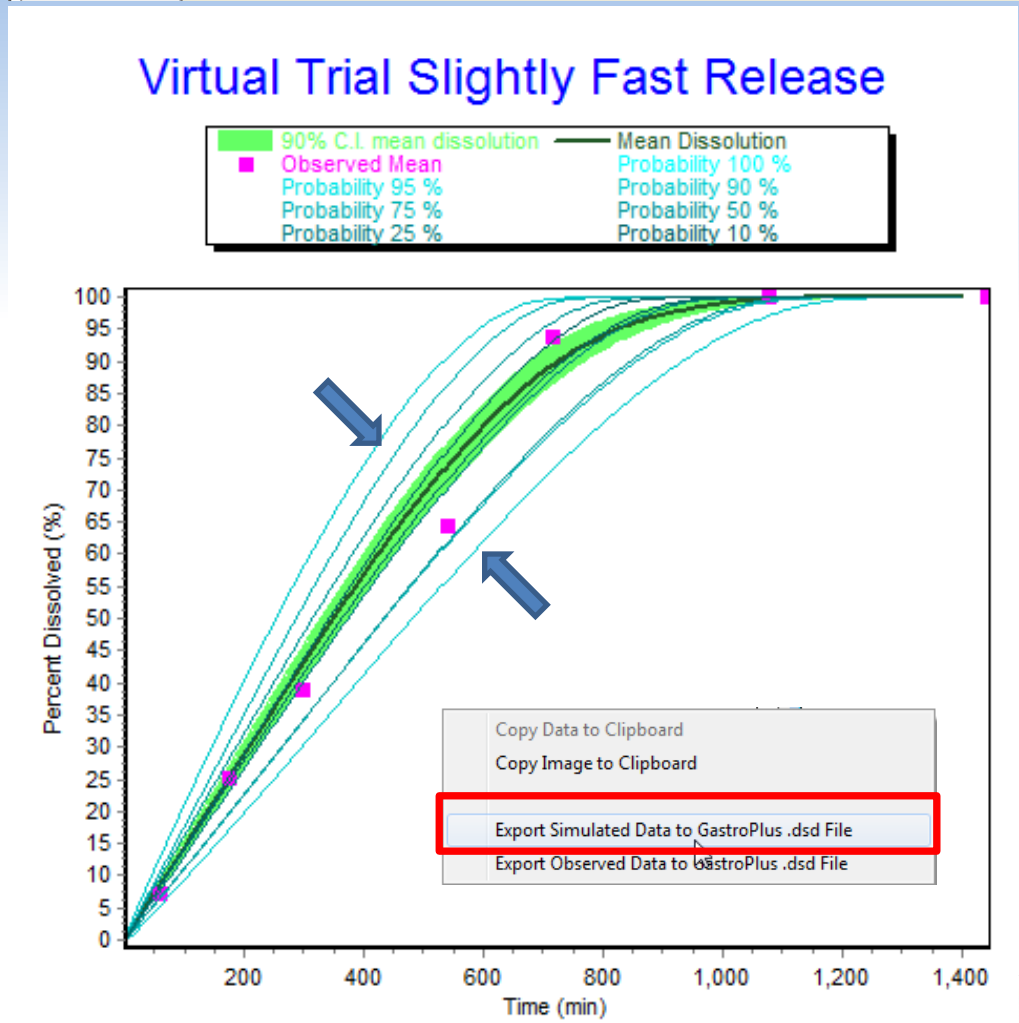
Activity: DDDPlus Modeling (cont.)

- Let's assess the variability around the content of Valproate, Lactose and HPMC
  - Navigate to Slightly Fast Release record; update to optimized values of calibration constant of valproate and release exponent of HPMC K15M
  - Go to the Simulation tab and select 'Virtual Trial'
    - Choose the Valproate amount and set the CV% = 3%
    - Choose the Lactose amount and set the CV% = 15%
    - Choose the HPMC amount and set the CV% = 15%
  - We will generate 25 virtual lots and run the simulation
- Let's review the variability around the dissolution profile. Can we use these results to assess the variability around the PK curves in GastroPlus?

Virtual Trials to Estimate Dissolution Variability

- Define the parameters, mean value, CV% and distribution type
- Export the virtual trial simulated dissolution variability to GastroPlus (new): Right click on the graph and Export Simulated Data to GastroPlus .dsd File
- In the next section, we will run virtual bioequivalence studies to determine if the dissolution method variability is within bioequivalence (Maximum and Minimum Profile vs Mean Profile)





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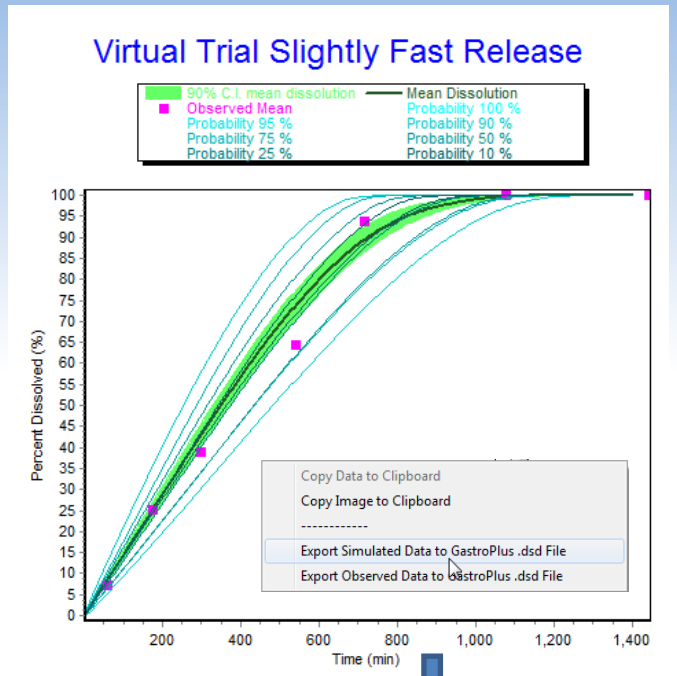
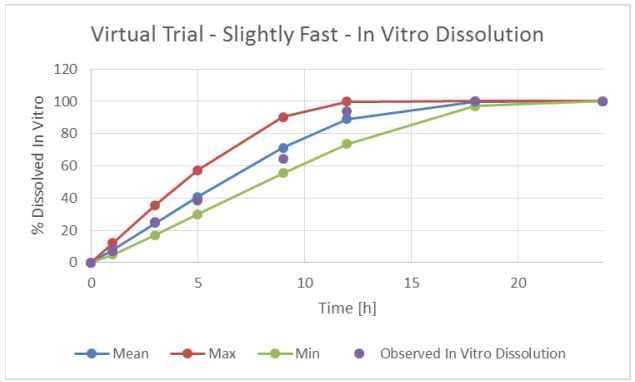
Convert the *In Vitro* Dissolution into an *In Vivo* Dissolution using IVIVC

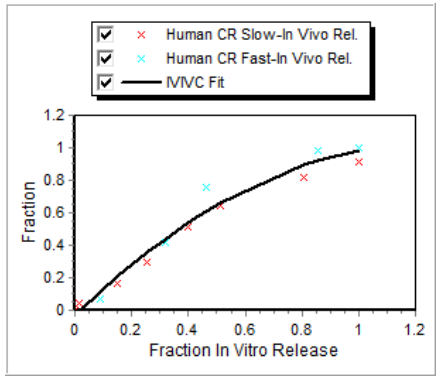
In Vitro Dissolution .dsd File



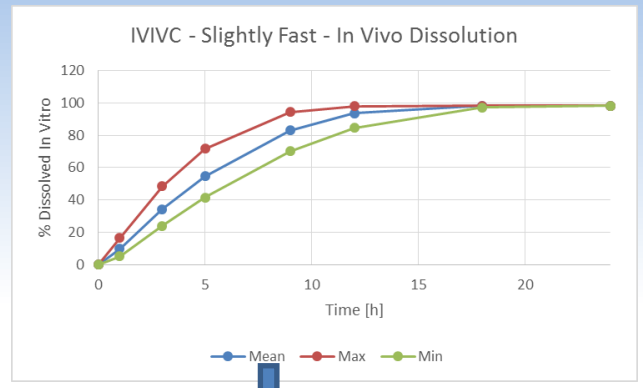


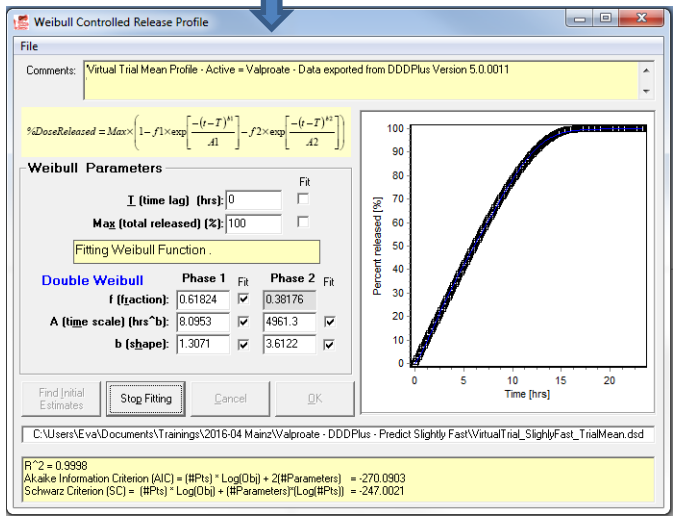
Take the Max, Mean, and Min Profiles and Convert them with the Established IVIVC

$$y = -0.032 + 1.703x - 0.689x^2$$



GastroPlus .crd File
Fit Weibull Function for Each Profile





New automated conversion in 9.5!

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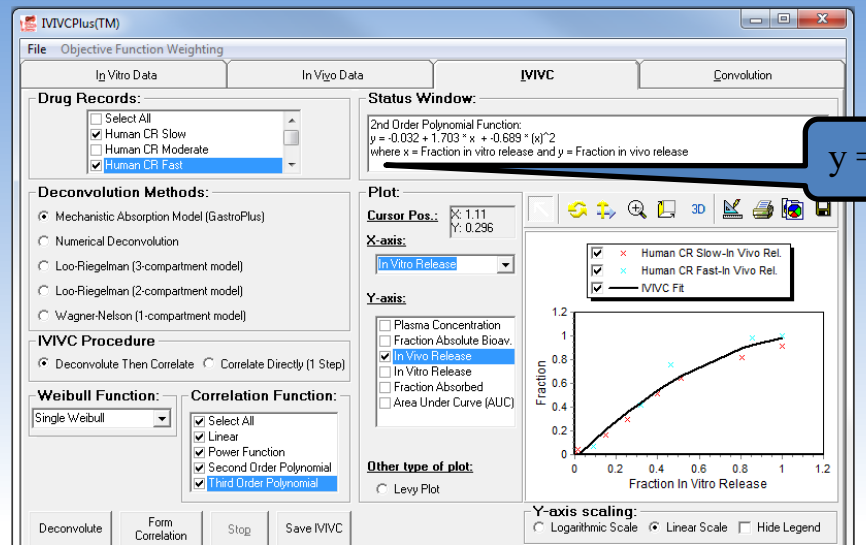
.dsd versus .crd Files

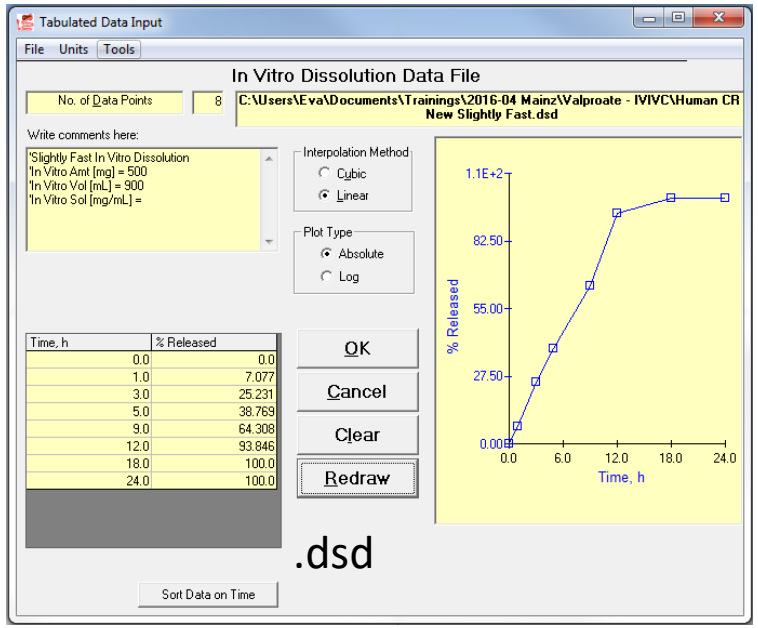


$y = -0.032 + 1.703x - 0.689x^2$

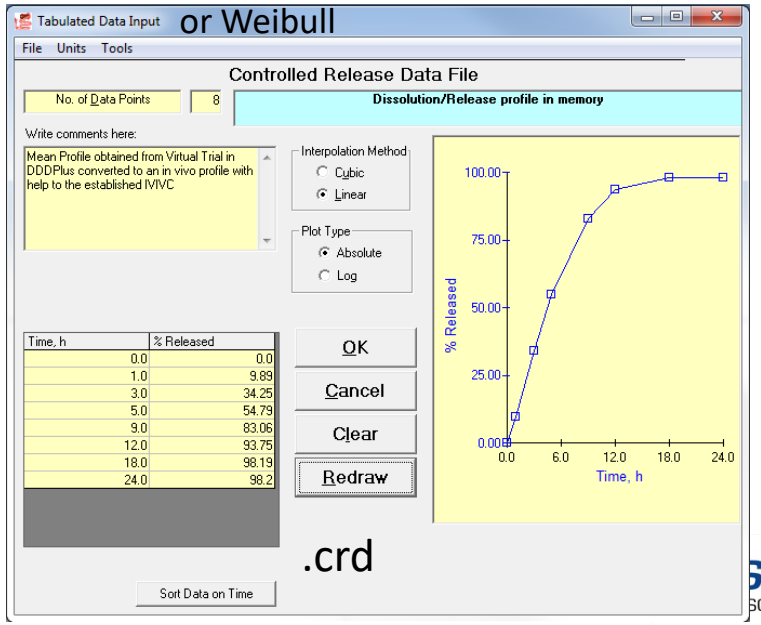
Measured *in vitro* release

Correlation function from IVIVC

Expected *in vivo* release or Weibull



.dsd



.crd

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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
- DDDPlus was utilized to mechanistically predict the variability in dissolution through *in silico* modeling – Able to appreciate the impact of changes to content uniformity on the dissolution without guessing
- Using the IVIVC established in GastroPlus, the 'low limit' and 'high limit' dissolution profiles were converted into *in vivo* release curves and used in virtual BE simulations – Establish dissolution specifications by identifying the impact on predicted PK endpoints (Cmax and AUC)

Q&A

Questions & Answers

GastroPlus®

SimulationsPlus

Learn More! simulations-plus.com/gastroplus

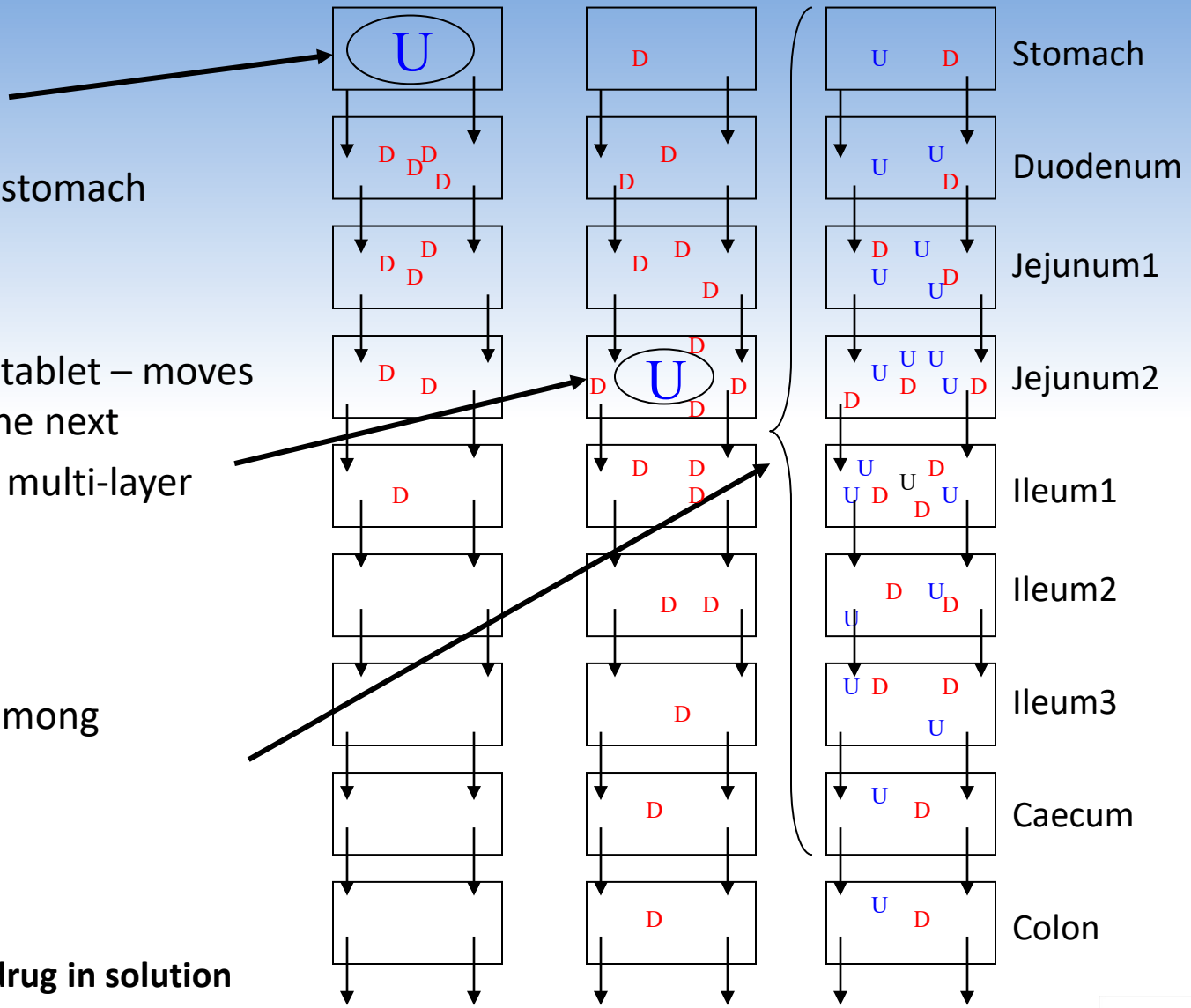
Modeling Controlled Release Formulations in GastroPlus

3 Models Based on Where Drug is Released

- 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

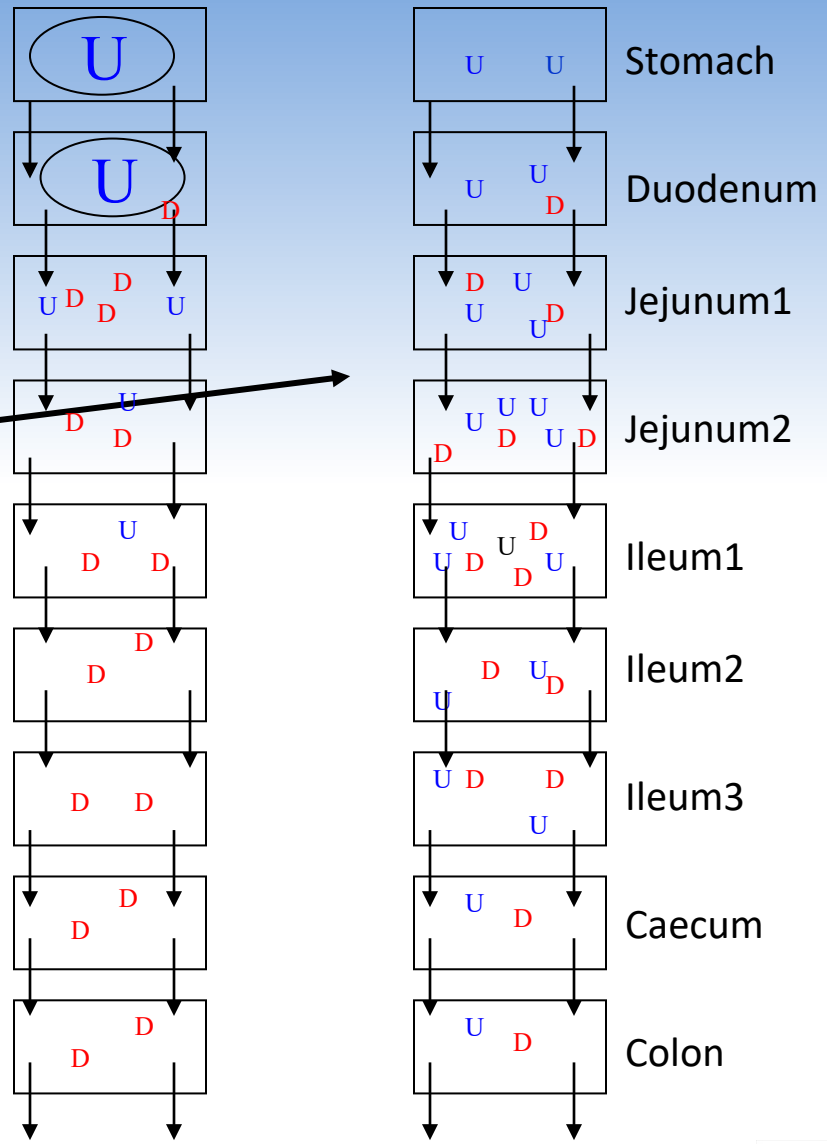
    (e.g., beads)



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

Delayed 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 – <u>not</u> user specified pH range

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