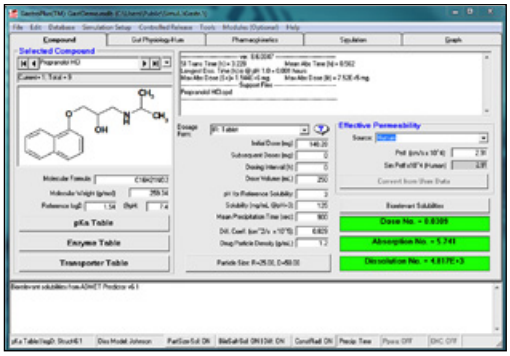
GastroPlus® Leading the modeling and simulation revolution...

GastroPlus is a mechanistically based simulation software package that simulates intravenous, oral, oral cavity, ocular, inhalation, dermal/subcutaneous, and intramuscular absorption, pharmacokinetics, and pharmacodynamics in humans and animals. This smoothly integrated platform combines a user-friendly interface with powerful science to help you make faster and more informed project decisions!



GastroPlus is by far the most commonly used software of its kind. It has been identified as the #1-ranked program for *in vitro - in vivo* extrapolation (IVIVE) and has been the focus of several publications from the FDA!

The GastroPlus simulations include:

FOR DISSOLUTION & ABSORPTION -

- The Advanced Compartmental Absorption and Transit (ACAT™) model – only in GastroPlus!
- Physiological gut models for human, dog, rat, mouse, rhesus monkey, cynomolgus monkey, minipig, rabbit and cat – fasted or fed conditions defined
- Vast selection of dosage forms: immediate release, delayed release, controlled release (including dispersed systems, gastric-retention, and more)
- pH-dependent solubility and logD models – ionization effects on dissolution & absorption considered
- Paracellular absorption – estimate paracellular permeability
- Mechanistic effect of bile salts on drug solubility and dissolution
- Enhanced treatment of nanoparticle effects on solubility and dissolution
- Mechanistic models to predict *in vivo* precipitation
- Options for defining pH-dependent dissolution (Z-factor) and precipitation rates
- Saturable metabolism and/or influx/efflux transport along the GI tract
- Mechanistic deconvolutions and *in vitro - in vivo* correlations (IVIVCs) for various formulations

FOR PHARMACOKINETICS -

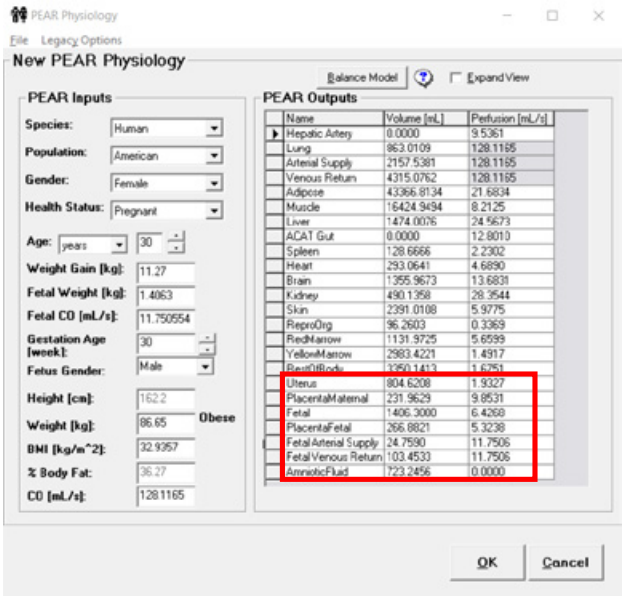
- Whole body, physiologically-based pharmacokinetic (PBPK) models defined – including **pediatrics**
- One-, two-, or three-compartment conventional pharmacokinetic model options available
- Transporter-based IVIVE: automated scaling of permeability across all tissues with PBPK
- Saturable metabolism and transport in liver or any PBPK tissues
- Metabolite tracking – easily link the formation of metabolites with the metabolism of the parent(s) in a single simulation
- Mechanistic treatment of biliary secretion and enterohepatic circulation
- Mechanistic static and dynamic DDI predictions
- Automated PBPK/PD model selection with industry standard pharmacodynamic models

Simulation Modes Available -

- Population Simulator™ – predict likely distributions of PBPK/PD results over different populations
- Parameter Sensitivity Analysis – quickly test sensitivity of results to changes in model parameters
- Batch Simulations – screen compound libraries for bioavailability & PK exposure in different species

What's new in Version 9.7?

- **NEW** ability to add lysosomal trapping effect to PBPK tissues
- **NEW** mechanistic pregnancy PBPK model (with fetus compartment)
- **ADDITIONAL** solubility inputs for different drug forms (crystalline, amorphous)
- **NEW** models of standard compounds (substrates/inhibitors/inducers) in DDI Module
- **EXPANDED** fed state conditions based on meal type
- **NEW** ability to allow different tissue model types (perfusion- or permeability-limited) between parent and metabolites or victim perpetrator in metabolite tracking/DDI simulations
- PK-PD model **ADDITIONS** to PDPlus™ Module
- **UPDATES** to the dermal absorption (TCAT™) model through Cosmetics Europe project
- **NEW** effect of immune response with intramuscular injection models
- **UPDATED** default populations for extensive, intermediate, and poor metabolizers based on specific genotypes



ADMET Predictor™ Module

CYP metabolism predictions from chemical structure – quickly create full PBPK models in seconds.

The ADMET Predictor® Module extends the capability of GastroPlus by enabling you to obtain predictions from structure of all physico-chemical, pharmacokinetic, and CYP metabolism kinetic parameters required for GastroPlus PBPK simulations. The module uses the same models as our best-in-class ADMET Predictor software.

Enhanced pKa model developed in collaboration with **Bayer HealthCare** - ALL models retrained with greater accuracy!

This module automatically generates predictions for the following properties:

- CYP metabolism kinetics – Vmax, Km, and CLint
- P-gp and OATP transporter inhibition models (classification)
- Aqueous solubility vs. pH profile
- Biorelevant solubility (FaSSIF, FeSSIF, and FaSSGF)
- logD vs. pH profile
- Rabbit corneal permeability
- Human volume of distribution
- Blood:brain barrier permeation (classification)
- pKa(s)
- Tendency to supersaturate in water
- Diffusion coefficient in water
- Human effective permeability
- Human plasma protein binding
- Human blood:plasma concentration ratio

The ADMET Predictor Module has several critical benefits:

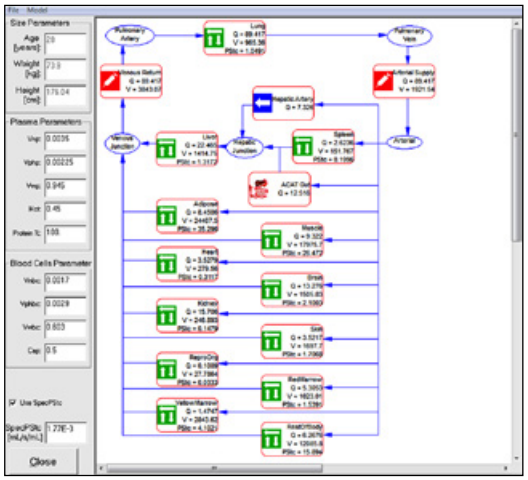
(1) by loading a library of chemical structures, you can quickly set up a database for screening fraction absorbed & bioavailability – decide which compounds to carry forward into *in vivo* studies

(2) use the *in silico* predictions and Parameter Sensitivity Analysis to guide your *in vitro* studies

(3) begin evaluating different formulation strategies to assess the importance of factors like particle size, solubility and dose on absorption

PBPKPlus™ Module

Ranked #1 in *in vitro-in vivo* Extrapolation (IVIVE) by Pfizer!
(Cole et al., 2nd Asian Pacific Regional ISSX Meeting, May 2008, Shanghai, China)



Only in GastroPlus! Transporter-based IVIVE: automated scaling of permeability across tissues in the PBPK model

The PBPKPlus Module extends GastroPlus to define a "whole body" PK model, consisting of various tissues. You can easily simulate the distribution & elimination of compound throughout the body and track concentrations in any tissue. Tissues can be defined as needed, or default models can be used with a standard set of compartments:

- Adipose
- Gut
- Liver
- Spleen
- Arterial blood
- Heart
- Muscle
- Reproductive organs
- Brain
- Lungs
- Skin
- Venous blood
- Yellow marrow
- Kidney
- Red marrow

NEW ability to add lysosomal trapping effect to PBPK tissues

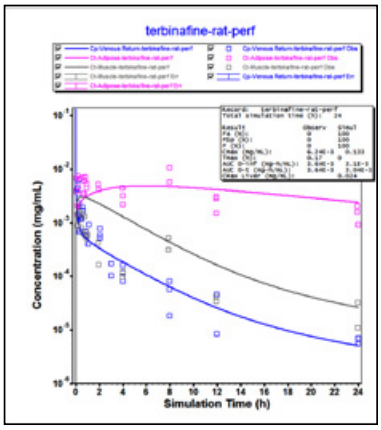
Customize your PBPK model by treating any tissue as either a perfusion-limited or permeability-limited model, and quickly add/delete tissues as needed – all without writing any equations!

The PBPKPlus Module also provides:

- Generation of physiological model parameters (tissue weights and volumes, composition, perfusion rates, etc...) with our built-in PEAR Physiology™ (Population Estimates for Age-Related Physiology).

Current physiologies are:

- **NEW** mechanistic pregnancy PBPK model (with fetus compartment)
- Human (American, Japanese, and Chinese, Male or Female, based on age)
- Infant/pediatric groups
- Hepatic impairment
- Renal impairment
- Obesity
- Rat
- Dog
- Mouse
- Monkey
- Rabbit
- Minipig



- Population simulations based on parameter variances in a sample population – define your own age range, % male vs. female, and the number of "virtual" subjects you wish to create
- Novel methods for estimating tissue partition coefficients from logD, pKa, plasma protein binding and Rbp – only in GastroPlus!
- Physiological model for kidney including glomerular filtration and reabsorption
- Fitting models to *in vivo* data (plasma/tissue concentrations, amount excreted in urine, etc...)
- Linking of pharmacodynamic effect directly to concentrations in specific tissues
- Mechanistic transport of drug from hepatocytes to bile in liver, modeled either as a linear process or through carrier-mediated transport
- Report-quality plotted output of all time-dependent results in all tissues
- ... and more!

Drug-Drug Interaction (DDI) Module

The DDI Module in GastroPlus allows you to predict drug-drug interactions (DDIs) among drugs and metabolites.

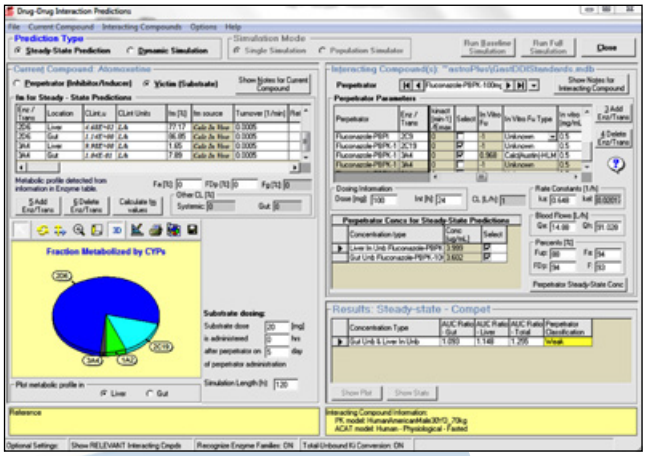
The ability to accurately estimate potential DDIs *in silico* has several benefits for companies:

- Explore possible effects on the pharmacology and toxicology of drugs
- Identify species-specific changes to estimate how a drug behaves in animals vs. humans
- Investigate the safety profile of drugs that are co-administered prior to filing regulatory submissions with agencies around the world

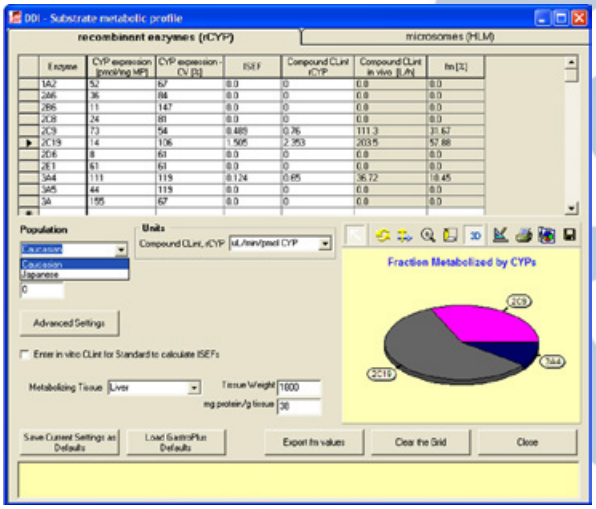
With the DDI Module, calculating either steady-state and/or dynamic DDIs is managed through our easy-to-use interface. We provide a database of standard compounds for which all relevant parameters (including reported inhibition/induction constants and full compartmental PK/PBPK models) are defined. Of course, you may predict DDIs among any compounds by simply entering the required inputs. As with other GastroPlus modules, there is no equation or code writing required.

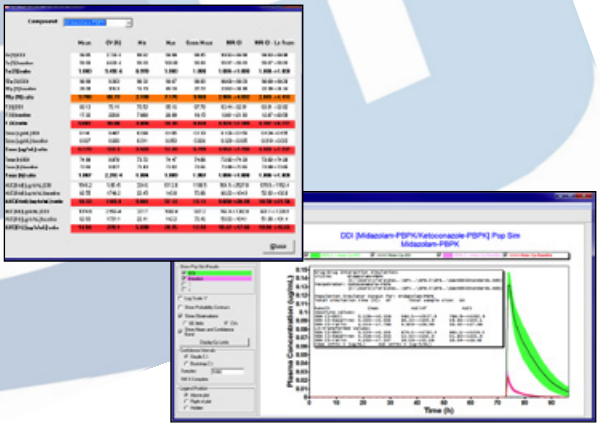
What are some of the advantages to using the DDI Module?

- **NEW** models of standard compounds (substrates/inhibitors inducers)
- PBPK models for DDI standard compounds
- Population Simulator™ linked with DDI predictions
- Transporter-based drug-drug interactions
- Metabolic and/or transporter induction
- Linked with the industry's #1-ranked dissolution/absorption (ACAT™) model
- Use with either compartmental PK or PBPK models
- Apply competitive and/or time-dependent inhibition kinetics by parent and/or metabolite(s)
- Simulate DDIs for any species
- Account for enzyme expression level differences in various human populations
- Built-in tool to easily calculate the fraction metabolized (fm) from *in vitro* assays (rCYPs and microsomes are accommodated)



- Incorporate nonlinear gut contributions to DDIs
- Predict the inhibitor effect using simulated concentrations at the site of metabolism (gut, liver, or any PBPK tissue) for dynamic DDI simulations
- Include the effects of multiple substrates on clearance of other substrates metabolized by the same enzyme





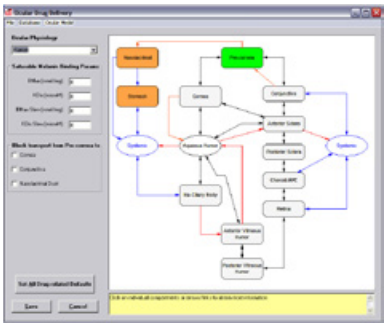
Additional Dosage Routes Module

The Additional Dosage Routes Module in GastroPlus extends the program beyond the traditional oral and intravenous administration routes. With this module, you can simulate drug disposition through additional dosing sites – dermal, intraoral (oral cavity), ocular, pulmonary (intranasal and respiratory), and intramuscular. These models were all developed in collaboration with top 5 pharmaceutical companies. The ability to predict concentration profiles in different regions of the skin, mouth, eye, lungs, nose, and muscle can help you:

- Explore various formulation/drug delivery options to achieve desired therapeutic effects
- Identify species-specific changes to estimate how a drug is handled in animals vs. humans

With the Additional Dosage Routes Module, simulating concentrations through these sites is managed through our easy-to-use interface. Mechanistic, physiologically-based models are provided for each tissue, for different species. You can also customize your own physiology by entering available information into the program. These models are linked with either compartmental or physiologically-based pharmacokinetics (PBPK) in GastroPlus, so you may predict your drug's distribution and elimination once it enters into the systemic circulation. As with other GastroPlus modules, there is no equation or code writing required.

Ocular Model (Ocular Compartmental Absorption & Transit (OCAT™) Model



- Nonlinear metabolism or transport in any eye tissue!
- Two-site melanin binding options!
- Convective flow incorporated into the ocular disposition model
- Physiology models (human, rabbit, and monkey)

The ocular model of the Additional Dosage Routes Module provides dosing as:

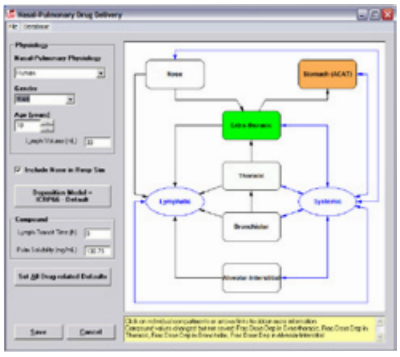
- Eye drop (topical solution or suspension)
- Intravitreal or subconjunctival implants
- IVT (intravitreal injection)

Some of the processes which can be modeled include:

- Nonlinear metabolism or transport in any eye tissue
- Convective flow incorporated into the ocular disposition model
- Two-site melanin binding options
- Predefined physiology models (human, rabbit, and monkey)

Pulmonary (Intranasal/Respiratory) Model (Pulmonary Compartmental Absorption & Transit (PCAT™) Model

- Nonlinear metabolism or transport in any lung tissue!
- Age-dependent scaling of the pulmonary physiology!
- Physiology models (human, rat, mouse, and dog)



The pulmonary model provides dosing via the intranasal or respiratory route as an:

- Immediate release solution
- Immediate release powder

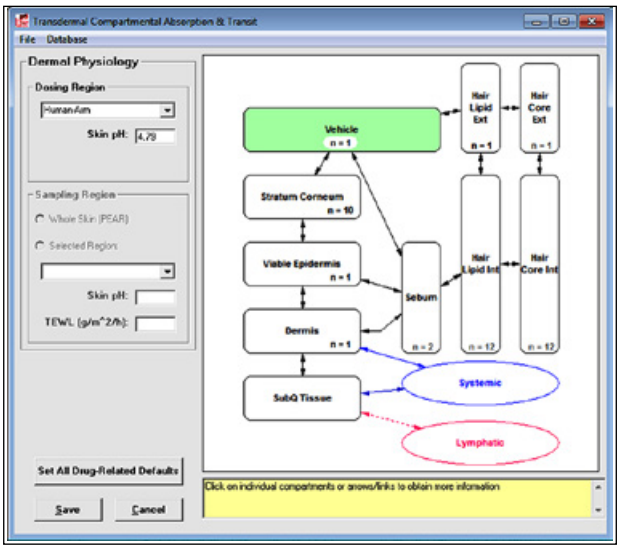
The pulmonary model includes the advanced ICRP 66 deposition model (Smith et al., 1999, LUDEP) for calculating deposition fractions in each compartment of both API and carrier particles. Additionally, you may account for the following processes in your simulations:

- Mucociliary transit
- Nonlinear metabolism or transport in any lung tissue
- Lymphatic transport & systemic absorption
- Age-dependent scaling of the human physiology

Dermal/Subcutaneous Model

The Transdermal Compartmental Absorption & Transit (TCAT™) model represents the skin as a collection of the following compartments: stratum corneum, viable epidermis, dermis, subcutaneous tissue, sebum, hair lipid, and hair core. The subcutaneous tissue is also considered. The diagram is shown in the figure below.

UPDATES to the dermal absorption (TCAT™) model through Cosmetics Europe project



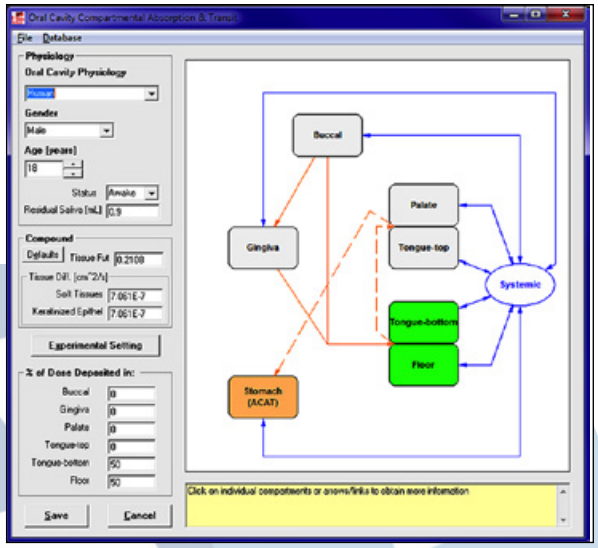
The model can simulate a variety of transdermal & subcutaneous dosage forms, specified at different places on the body, including:

- liquid formulations (solutions, lotions, suspensions)
- semi-solid formations (gels, creams, lotions, pastes)
- subcutaneous injections (bolus or controlled release)

Some of the processes modeled include:

- vehicle evaporation
- absorption from the vehicle into the various tissue regions
- nonlinear metabolism in any tissue region
- systemic circulation and lymphatic absorption

Measured *in vivo* data for any dermal tissue can be used to compare with simulation results. All standard GastroPlus features, including the Population Simulator and Parameter Sensitivity Analysis, can be used with the dermal model.



Oral Cavity Delivery Model

The Oral Cavity Compartmental Absorption & Transit (OCCAT™) model represents the oral cavity (mouth) as a collection of the following compartments: buccal, gingival, palate, top of the tongue, bottom of the tongue, and mouth floor. The diagram is shown in the figure at right.

The model can simulate a variety of dosage forms including:

- sublingual solutions & tablets
- lingual sprays & supralingual tablets
- controlled release buccal patches

Some of the processes modeled include:

- dissolution & precipitation in the saliva
- diffusion through the oral mucosa
- uptake into systemic circulation
- swallowing of unabsorbed drug

Measured *in vivo* data for any oral cavity tissue can be used to compare with simulation results. All standard GastroPlus features, including the Population Simulator and Parameter Sensitivity Analysis, can be used with the oral cavity model.

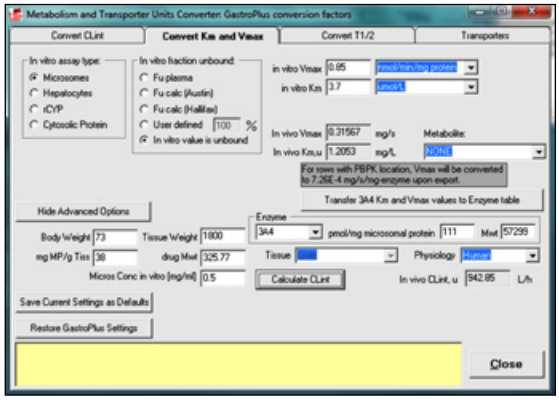
Metabolism and Transporter Module

When linked with the upgraded ADMET Predictor Module, predict CYP metabolism pathways & kinetics, and have the Enzyme Table automatically populated with the correct locations and units!

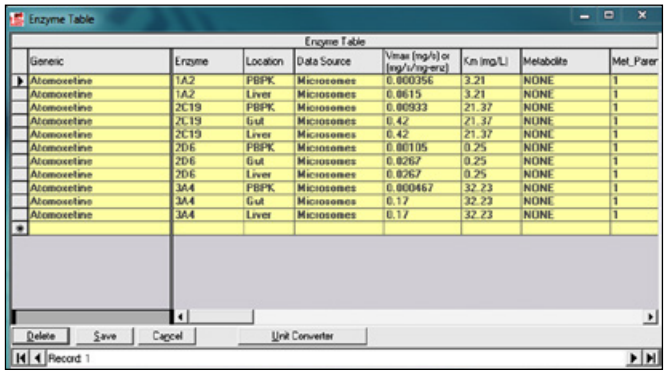
- Enzyme and transporter expression levels across species – including UGTs and SULTs!
- Metabolite tracking options!

The Metabolism and Transporter Module is an optional module that extends the capabilities of GastroPlus to include saturable metabolism and carrier-mediated transport into any compartment (gut, liver, and/or any PBPK tissue), along with metabolite tracking. This module calculates Michaelis-Menten rates for gut and liver (or any PBPK tissue) metabolism and for carrier-mediated transport (influx or efflux) based on input values for Vmax and Km. You can provide Vmax and Km values for each enzyme/transporter independently, or you can lump them into a single effective Vmax and Km, depending on your data. The distribution factors on the Physiology tab are automatically loaded for recognized gut enzymes and transporters, and provide the relative amounts of enzymes or transporters in the various ACAT™ gut model compartments. The Vmax and Km scale factors on the Pharmacokinetics tab are provided to allow fitting nonlinear kinetic models to your data.

The Metabolism and Transporter Module includes a Units Converter for easy transformation of a variety of your *in vitro* metabolism or transporter kinetic parameters into parameters and units that can be utilized by the GastroPlus model.

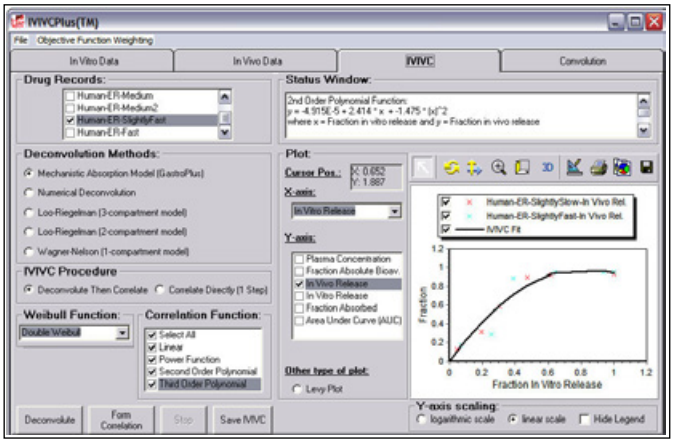


The Units Converter window provides a convenient way of converting *in vitro* measurements to *in vivo* inputs for the GastroPlus model.



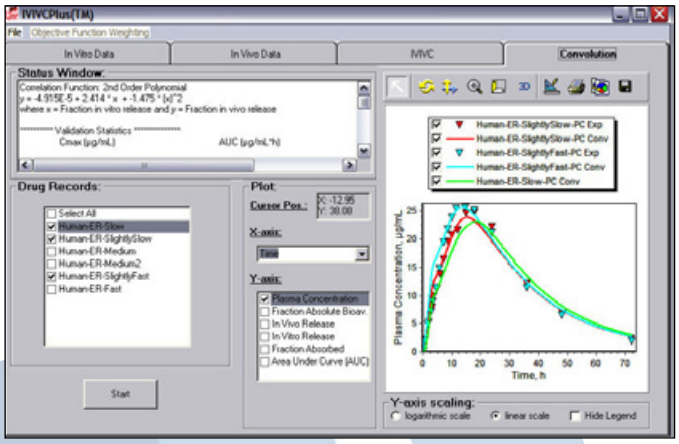
Define multiple metabolic / transport pathways, with enzymes and transporters placed into the tissues or organs of your choice! Also link formation of different metabolics in a single simulation!

New article from FDA scientists compares the Mechanistic Absorption deconvolution in GastroPlus vs. traditional methods – conclusion is that GastroPlus provides "greater predictive accuracy" - Mirza et al., Pharm. Res. 2012



IVIVCPlus is an optional add-on module that provides a convenient way to develop a correlation between either *in vitro* release and *in vivo* release or *in vitro* release and absolute bioavailability. The formed correlation can then be used to predict PK profiles for formulations with different *in vitro* release rates.

GastroPlus was the first software program to offer "mechanistic deconvolutions", which deconvolute, or fit, the *in vivo* dissolution vs. time along the gut lumen. An advantage to using the mechanistic deconvolution method is that it can be linked to a PBPK model. We are pleased to validate the mechanistic deconvolution method through a 5-year **Research Collaboration Agreement with the U.S. FDA**.



IVIVCPlus offers five methods for deconvolution:

1) Mechanistic Absorption Model (GastroPlus)
2) Numerical Deconvolution
3) Loo-Riegelman (2-compartment model)
4) Loo-Riegelman (3-compartment model)
5) Wagner-Nelson (1-compartment model)

The Mechanistic Absorption Model (GastroPlus) deconvolution method directly deconvolutes the *in vivo* release rate. The other four methods are traditional deconvolution methods that calculate the rate of appearance of compound into the systemic circulation. For formulation scientists, the correlation between *in vitro* release and *in vivo* release is much more intuitive and valuable.

Depending on the deconvolution method selected, a correlation can be made between *in vitro* release and *in vivo* release or *in vitro* release and absolute bioavailability. Currently, linear, power, and polynomial (second or third order) functions may be selected for the functional form of the correlation.

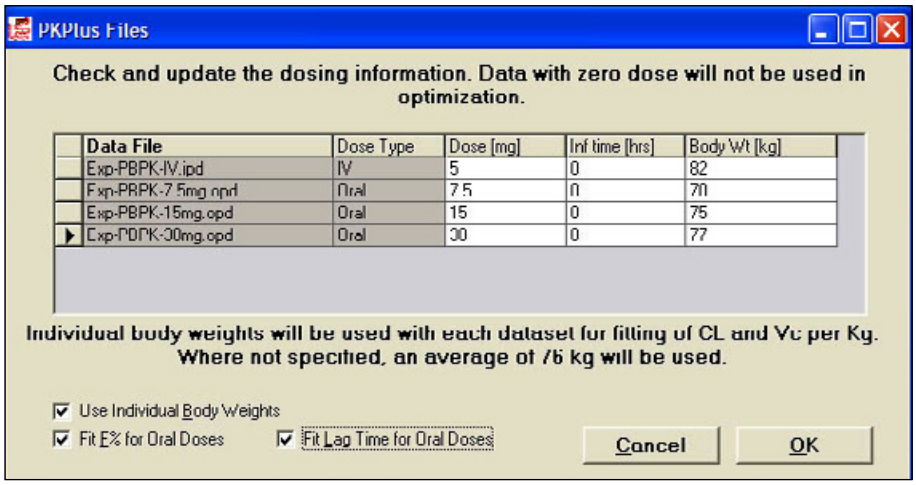
Run Convolutions: The correlation function can be used to calculate an *in vivo* release-time profile or absolute bioavailability-time profile for a new formulation of the compound exhibiting a different *in vitro* release-time profile. A plasma concentration-time profile for the new formulation can be constructed with the calculated *in vivo* release-time or absolute bioavailability-time profile.

Evaluate Validation Statistics: After running a convolution, IVIVCPlus outputs the observed values, predicted values, prediction errors, and mean absolute percent prediction error for both Cmax and AUC. These statistics can be used to evaluate the internal or external predictability of the correlation as described in the FDA's "Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro*/*In Vivo* Correlations".

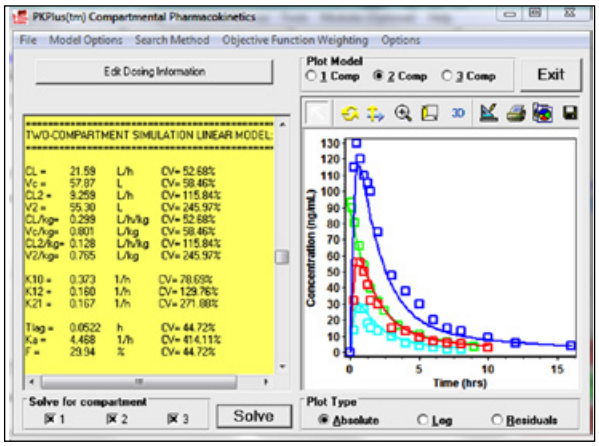
PKPlus™ Module

PKPlus extends GastroPlus to rapidly estimate pharmacokinetic (PK) parameters for non-compartmental analysis (NCA), along with 1-, 2-, & 3-compartment models from IV and oral plasma concentration-time (Cp-time) data, without the need to run full simulations. The fitted parameters include PK parameters, first order absorption rate, bioavailability and absorption lag time (if both IV and oral data are included in fitting). Required inputs are Cp-time profiles, dose, body weight and infusion time (if applicable). Compartmental PK can be fitted to single IV or oral data as well as across multiple Cp-time profiles - IV, oral, or combination of IV and oral as well as different dose levels. Linear or saturable clearance models can be selected easily.

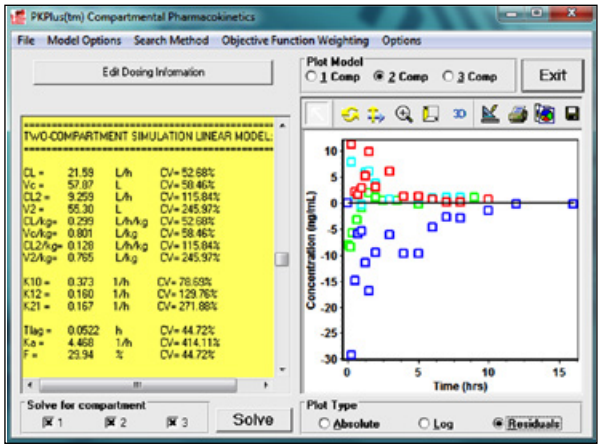
Full statistics, including Akaike Information Criterion and R^2, are provided for all models. Residual information is also captured and can be plotted. Once finished in PKPlus, the parameter values of the selected model can be easily transferred back to the main GastroPlus model, and all model results can be saved into report-quality outputs.



Plotting of absolute, log, and residuals for each model is selected with a mouse click, allowing rapid comparison of models.



2-compartment model for midazolam fitted across IV and three oral doses



Residuals plot for 2-compartment model for midazolam fitted across IV and three oral doses

Automated model selection – fit across all direct and indirect models, along with phase-nonspecific cell killing options, with a single mouse click!

PDPlus allows you to fit standard pharmacodynamic (PD) models to observed data and use the fitted models to predict PD effect changes due to changes in dose, dosage form, and dosing regimens. The PDPlus module adds the Pharmacodynamics Table, which contains the PD model, the site of PD action, and the parameters that determine
the kinetics of the action. Multiple PD models (therapeutic and adverse) can be accommodated for each drug record.

- PK-PD model **ADDITIONS** to PDPlus™ Module
- Easily fit PD models across multiple data sets (e.g, doses)

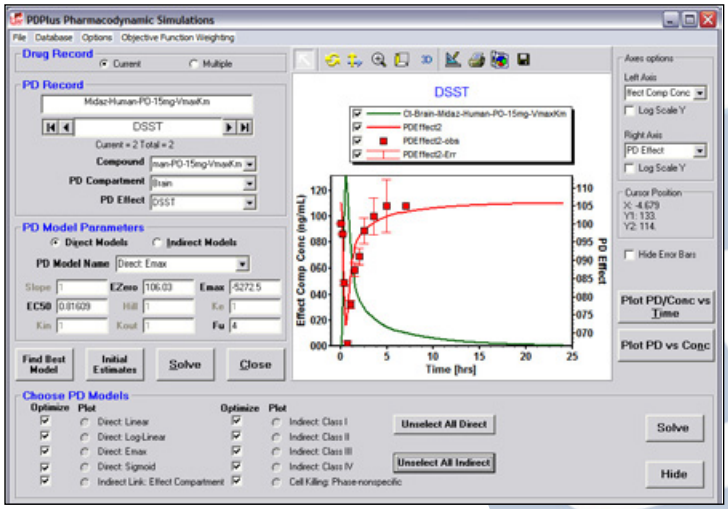
With PDPlus, fitting pharmacodynamic models to observed effect data is quick and easy. You may fit any of the standard PD models:

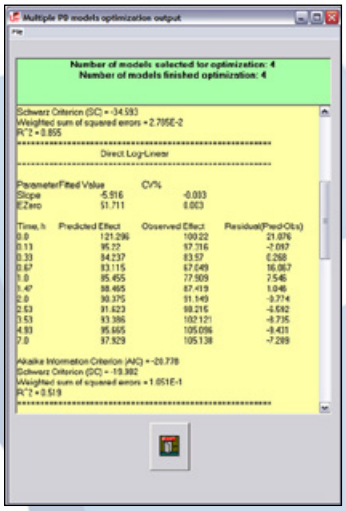
Direct Link: Linear, Log Linear, Emax and Sigmoid Emax

Indirect Link: Class 1, Class 2, Class 3, Class 4

Other: Phase-nonspecific cell killing (for tumor PBPK/PD modeling)

Convenient plotting of both plasma concentration-time and effect vs. time or concentration is provided with absolute and log plots available for each. Plus, all model results can be saved into report-quality outputs.





The effect can be linked directly to drug concentration in a specific tissue to easily perform PBPK/PD modeling.

The Optimization Module for GastroPlus extends and enhances the program's basic capabilities in several important ways:

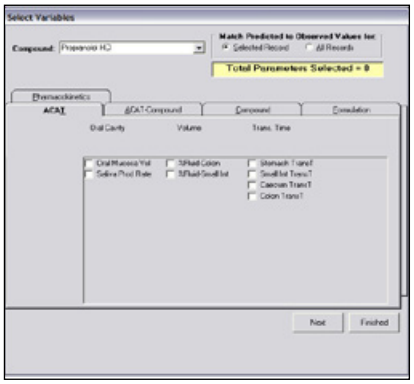
- To automatically fit model parameters to data
- To optimize study designs (e.g., dosing regimens) and dose

Fitting models to data

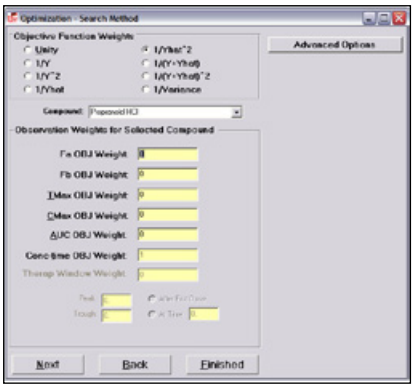
One of the most important uses of GastroPlus is to fit absorption, pharmacokinetic, and pharmacodynamic models to observations. In doing so, researchers gain tremendous insight into how their compound is behaving *in vivo*. When a single set of model parameters can be found that properly describes the observed plasma concentration-time for all dose levels, a useful model has been obtained. In general, if the model parameters must be changed for each dose level, then something is not being accounted for correctly. The Optimization Module performs the multidimensional search needed to fit model parameters to one or more data sets automatically.

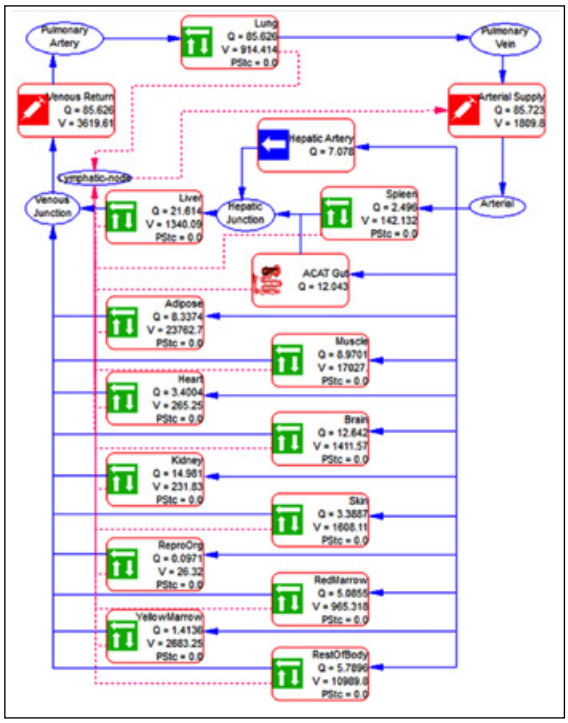
Model fitting can include (but is not limited to):

- PBPK model parameters to plasma and/or tissue concentration vs. time data
- Peff and absorption scale factors to determine regional dependencies
- A wide variety of physiological parameters (when necessary)
- Parameters to match profiles of parent drugs or any of their metabolites



Model parameters can be fitted to data for a single record, or across multiple records simultaneously. The program will run one simulation for each record each time it changes the value(s) of one or more model parameters. Typically, hundreds of iterations will be performed, each with N simulations, where N is the number of records whose observations are being used to compare predicted and observed values. Objective function weighting is user-defined, and includes the most common weighting schemes.



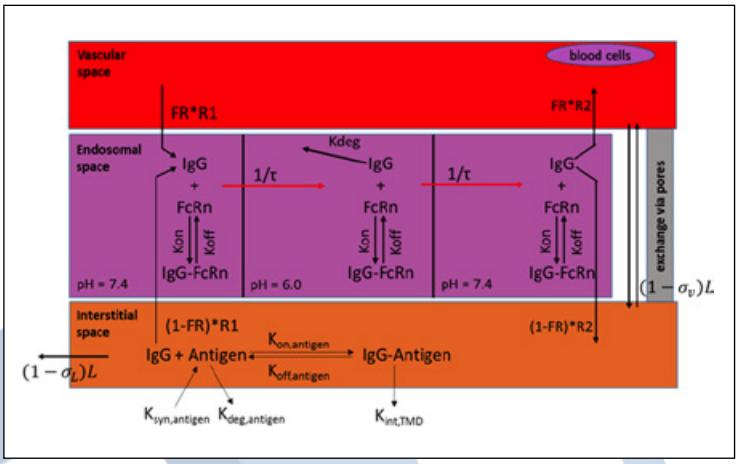


Each organ in the PBPK model is divided into three major compartments representing the vascular, endosomal, and interstitial spaces, as shown in the image at right.

PBPK models for antibody-drug conjugates (ADCs)

Starting in GastroPlus 9.0, we are pleased to offer PBPK models for large molecules (biologics). The Biologics Module simulates the absorption, distribution, and clearance of biological drugs. In the current implementation, both monoclonal antibodies (mAb) and antibody-drug conjugates (ADCs) administered as an intravenous bolus dose, intravenous infusion, or subcutaneous (SQ) injection can be modeled. As with other GastroPlus modules, there is no equation or code writing required. A schematic diagram of how the different organs are connected to one another is shown at left.

All major organs are connected in an anatomical fashion with plasma flow represented by blue solid arrows and lymph flow by red dashed arrows. The lymph node collects the lymphatic drainage from organs and lymph fluid is returned to the systemic circulation. Each organ in the PBPK model is divided into three major compartments representing the vascular, endosomal, and interstitial spaces, as shown below.



Some of the key processes accounted for in the GastroPlus models include:

- Convective transport and fluid phase endocytosis describing uptake of antibody into the tissue
- mAb-FcRn (neonatal FC receptor) binding & recycling
- Target mediated elimination in the interstitial space to include the influence of specific antigen-mAb interactions on mAb disposition
- Within the endosomal space, the competition for binding to FcRn between endogenous IgG and the therapeutic mAb
- mAb administration by either intravenous (IV) or subcutaneous (SQ) injection
- Complete default physiology parameters for humans – flexibility to create custom species models
- With ADCs, distribution and elimination processes of multiple ADC species with different DAR (drug-to-antibody ratio):
  - o Distribute to peripheral compartments
  - o Cleared by nonspecific clearance
  - o Bind to target receptor, internalize, and be cleared in the cell lysosome

T1130-13-104

A PBPK model of the negative effect of chitosan on acyclovir absorption: The mucus-chitosan interaction

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PURPOSE

A recent bioavailability study raises questions about the universality of the permeability enhancing effect of chitosan on poorly permeable drugs1. Unexpectedly, chitosan reduced the bioavailability of acyclovir. The purpose of this study was to establish a hypothesis that could be tested using a mechanistic oral absorption model to help establish a possible mechanism for this result. .

METHOD(S)

Experiments were conducted *in vitro* to measure permeability through rat intestinal tissue and changes in pig mucus viscosity and rheology in the presence of chitosan. Effective permeability (Peff) values were incorporated into a PBPK model, and the aqueous diffusion coefficient (D) of acyclovir was varied according to viscosity observations. A mechanistic PBPK model for acyclovir was developed using GastroPlus™ 9.6 (Simulations Plus, Inc.) Advanced Compartmental Absorption and Transit™ (ACAT™) model and PBPKPlus™ module to mechanistically explain absorption, distribution, and clearance mechanisms. The kinetic parameters (K_m and V_{max}) for alcohol dehydrogenase (ADH1) mediated metabolism were obtained from literature (K_m) or fitted (V_{max}) to intravenous (IV) and oral (PO) formulations. The model utilized an all tissue permeability-limited model with active renal secretion mediated by two transporters: 1) organic anion transporter 2 (OAT2) on the basolateral membrane and 2) multidrug and toxin 1 (MATE1) on the apical membrane. The model was developed using IV and PO data from oral administration in the absence of chitosan. The model was further validated by comparing simulated and observed plasma concentration-time profiles for acyclovir obtained from clinical studies in the presence of two concentrations of chitosan.

METHOD(S) CONT.

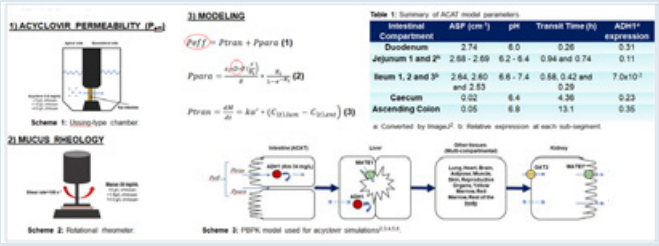

Table 1: Summary of ACAT model parameters

Intestinal Compartment	ASF (cm⁻¹)	pH	Transit Time (h)	ADH1[a] expression
Duodenum	2.74	6.0	0.26	0.31
Jejunum 1 and 2[b]	2.68 - 2.69	6.2 - 6.4	0.94 and 0.74	0.11
Ileum 1, 2 and 3[b]	2.64, 2.60 and 2.53	6.6 - 7.4	0.58, 0.42 and 0.29	7.0×10^{-3}
Caecum	0.02	6.4	4.36	0.23
Ascending Colon	0.05	6.8	13.1	0.35

a: Converted by $Image J^2$. b: Relative expression at each sub-segment

RESULT(S)

The control acyclovir Peff was 3.07×10^{-5} cm/s ; chitosan decreased acyclovir permeability to 1.95×10^{-5} and 2.38×10^{-5} cm/s at 1.6 and 4.0 g/L, respectively. Mucus viscosity increased in the presence of those chitosan concentrations by approximately 4 and 64 times, respectively (Fig.1). Rat jejunum Peff was incorporated in the absorption model to predict the chitosan effect previously observed in clinical studies in healthy subjects[1] (Fig. 2). The results from a mechanistic oral absorption modeling support a hypothesis that a chitosan-mucus interaction might be responsible for a reduction in acyclovir paracellular permeability by decreasing the effective diffusion coefficient of acyclovir *in vivo*. The model accurately predicted acyclovir's bioavailability and the chitosan effect by considering both Peff and D (see Figure 2).

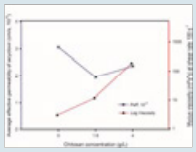

Figure 1. Chitosan effect on acyclovir permeability and mucus viscosity. The viscosity experiments in this graph were conducted using a mucus concentration of 30 mg/mL and a shear rate of 100 s^{-1}. Permeability is shown as a black line with (x) symbols according to the left axis. Viscosity is shown as an orange line with (triangles) symbols according to the right axis.

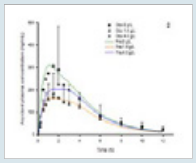

Figure 2. Observed and predicted plasma concentration vs time profile after PO administration of acyclovir 200 mg. Observed plasma concentration profiles were extracted from Kubbinga et al. at 0 (triangles), 1.6 g/L (circles) and 4.0 (squares) g/L of chitosan[1]. Predicted profiles are shown as simulation outputs at 0 (green line), 1.6 g/L (orange line) and 4.0 g/L (blue line) of chitosan.

RESULT(S) CONT.

Table 2. Mechanistic absorption at different Peff and D conc.

Peff (cm/s, 10^{-5})	3.07		1.95	
D (cm^2/s, 10^{-5})	0.97	0.45	0.97	0.45
Enterocyte Uptake (%)	31.5	45.5	9.31	28.1
Fraction metabolized (%)	23.4	30.7	8.40	21.6
Transcellular absorption (%) = Enterocyte uptake - Fraction metabolized	8.1	14.8	0.91	6.5
Paracellular absorption (%)	10.5	4.7	11.6	5.2

Acyclovir enterocyte uptake followed the ranking: jejunum > duodenum > ileum. However, both the regional ADH1 expression and enterocyte concentrations of acyclovir lead to the transcellular absorption ranking: ileum > jejunum > duodenum. In presence of chitosan, both the enterocyte uptake and metabolism remained roughly the same. Peff and D reductions lead to a decrease in paracellular absorption.

CONCLUSION(S)

The absorption and pharmacokinetics of acyclovir in healthy subjects were modeled using *in vitro* and *in silico* data. The model was successfully applied to capture the gut and liver metabolism of acyclovir by ADH1, and renal elimination mediated by secretory influx and efflux transporters. The application of a mechanistic oral absorption/PBPK model helped to identify the critical parameters that can explain the anomalous decrease in AUC induced by chitosan which is normally considered to be an excipient that enhances the absorption of poorly permeable drugs.

FUNDING/REFERENCE

MAG is granted by the CONICYT's program: Becas de doctorado en el extranjero, Becas Chile, no 72180466. This work is contributed as sideground to the ORBiTo Initiative Joint Undertaking (HTTP://WWW.IMI.EUROPA.EU).

Reference:
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M1330-05-036

HTPK: Conducting PK modeling and simulations at high speed

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PURPOSE

In silico pharmacokinetic (PK) simulations are now routinely incorporated into drug development workflows, especially in the later stages. Such simulations can provide insight into the results of Phase I/II clinical trials, which is crucial to deciding when or if to progress a drug candidate. For example, the best way to identify reasons for the lack of in vivo drug efficacy is through full-scale physiologically-based PK (PBPK) studies. There is no fundamental reason, however, not to use PK simulations in drug discovery. Practical arguments against doing so were computational cost and availability of appropriate input parameters. We present and test a new method that addresses these problems.

OBJECTIVE

This study is a comparison of predicted percent absorbed and percent bioavailable between the high throughput PK (HTPK) simulation module of ADMET Predictor™ and the ACAT™ / compartmental PK predictions from GastroPlus™ and tests its performance.

METHODS

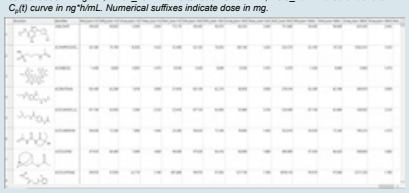
We have implemented a PK simulation capability (termed the HTPK Simulation Module) within ADMET Predictor [1] that runs compartmental PK simulations based on the Advanced Compartmental Absorption and Transit (ACAT™) model [2] while omitting some advanced capabilities (e.g., accounting for active transport). Special attention was paid to high computational performance. Inputs to the simulation are automatically generated from predictive ADMET or provided as experimental values, should those be available. In principle, only molecular structures are needed to run simulations.

RESULTS

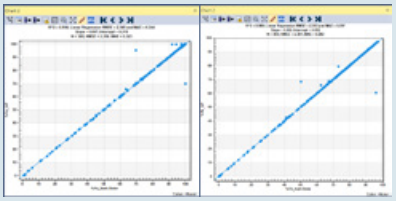
HTPK calculation of fraction absorbed and fraction bioavailable in human after 24 h, at three different IR doses (1 mg, 10 mg, 100 mg) for each of the 2284 drugs extracted from the World Drug Index.

Platform	Processing time for 2284 drugs
Laptop A [3]	3.9 min (~0.1 s/drug)
Laptop B [4]	2.5 min (~0.06 s/drug)

*Table of results for the first 8 drugs of the 2284 set mentioned above. %Fa_hum = fraction absorbed in human, %Fb_hum = fraction bioavailable, Cmax_hum = maximal attained plasma concentration in ng/mL, Tmax_hum = time to reach Cmax in h, AUC_hum = area under the $C_p(t)$ curve in ng*h/mL. Numerical suffixes indicate dose in mg.*

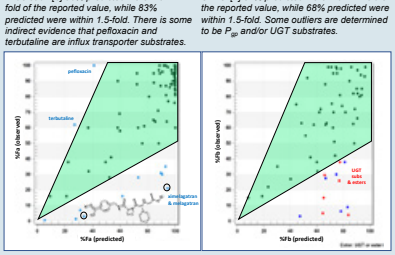


Comparison of HTPK simulation results (%Fa, left chart, and %Fb, right chart, all at 10 mg dose) vs. compartmental ACAT results obtained in GastroPlus [5] for a subset of 300 representative drugs extracted from the World Drug Index.



HTPK vs. experiment: predicted and observed human fraction absorbed for 115 passively-absorbed compounds published by Zhao et al. [6] 90% predicted were within 2-fold of the reported value, while 83% predicted were within 1.5-fold. There is some indirect evidence that pefloxacin and terbutaline are influx transporter substrates.

HTPK vs. experiment: predicted and observed human fraction bioavailable for 62 compounds metabolized primarily by hepatic CYPs. [7] 81% predicted were within 2-fold of the reported value, while 68% predicted were within 1.5-fold. Some outliers are determined to be P_{gp} and/or UGT substrates.



Required inputs and corresponding ADMET Predictor models

Input required for %Fa and %Fb	Model
Diffusivity in water	DiffCoef
Solubility in water	S+Sw
Salt solubility factor	SolFactor
Solubility in fasted intestinal fluid	S+FaSSIF
Solubility in fed intestinal fluid	S+FeSSIF
pKa	S+pKa
Human jejunal permeability	S+Peff
log P	S+logP
Volume of distribution	Vd
Percent unbound in plasma	hum_fup%
Microsomal fraction unbound	S+fumic
Metabolic clearance	CYP_HLM_CLint
Blood to plasma ratio	RBP
Precipitation time	<user input>
Dose	<user input>
Dose volume	<user input>
Particle radius	<user input>
Body weight	<user input>

Outputs generated by fraction absorbed / bioavailable and optimal dose models

Outputs generated by the %Fa/%Fb model
Fraction absorbed
Fraction bioavailable
Cp(t) = plasma concentration vs. time profile
C_max = maximum plasma concentration
t_max = time of peak plasma concentration
AUC = area under the Cp(t) curve
Sensitivity to permeability and solubility
Mechanistic estimation of the volume of distribution

Outputs generated by the OptDose model
Optimal dose to reach desired plasma concentration at steady state

CONCLUSION

HTPK Simulation Module simulations can be expected to match experimental results as well as ACAT plus central compartmental analysis in GastroPlus does. The new HTPK Simulation Module in ADMET Predictor provides a high-throughput pharmacokinetic tool for addressing likely absorption and bioavailability problems early in drug discovery. It can quickly estimate bioavailability potential of thousands of analogs generated in silico, e.g., via combinatorial explosion, thereby saving both time and effort.
In summary, it is simple enough to be fast, yet complicated enough to get the job done.

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[3] DELL XPS with Intel® Core™ i7-3537U CPU 2.5 GHz, 8 GB RAM, 64-bit, running Windows 7.
[4] ASUS R.O.G. with Intel® Core™ i7-7700HQ CPU 2.8 GHz, 16 GB RAM, 64-bit, running Windows 10.
[5] GastroPlus™ v9.6 is distributed by Simulations Plus, Inc. (http://www.simulations-plus.com).
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[7] Toshimoto et al. Drug Metab. Dispos. **2014**, 42:1811.

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W11230-05-037

In Vitro to *In Vivo* Extrapolation (IVIVE) of Itraconazole Precipitation using a Biphasic Dissolution Test and Mechanistic Absorption Model

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PURPOSE

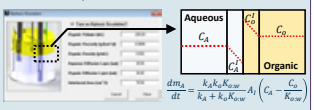
Regulatory agencies have encouraged the use of mechanistic absorption (MAM) and physiologically-based pharmacokinetic (PBPK) modeling to reduce cost and time to market for new and generic drug products. Models require parameterization, and many physicochemical parameters must be determined as a part of the development process. For low solubility weak bases with high solubility in gastric and low solubility in intestinal fluids, precipitation requires evaluation. Simple *in vitro* transfer experiments have been shown to overestimate precipitation *in vivo*. The biphasic test incorporates an absorptive phase to lower supersaturation similar to *in vivo* and to provide more accurate precipitation estimates. In this work, we present an *in silico* model to extract precipitation parameters from a biphasic *in vitro* dissolution test coupled with a MAM/PBPK model to predict precipitation *in vivo*. The goal was to test whether the biphasic *in vitro* assay provides more relevant parameters for *in vivo* extrapolation.

OBJECTIVES

- Utilize *in vitro* dissolution data to predict precipitation kinetics
- Identify the importance of mechanistic absorption modeling in drug development
- Understand mass transfer in the biphasic dissolution test

METHODS

The mechanistic nucleation and growth model parameters were determined by fit to *in vitro* data using a new biphasic dissolution model in DDDPlus™ v6.0 (Simulations Plus, Inc.) and were compared to parameters fit to PK data in Gastroplus™ (Simulations Plus, Inc.). The biphasic model is shown in Figure 1. The experimental data for ITZ *in vitro* precipitation was obtained from the literature[2]. The drug was introduced as a solution to the aqueous phase of 40 mL phosphate buffer @ pH 6.5. The drug transport into 30 mL of decanol was modeled simultaneously to precipitation using the mechanistic nucleation and growth model (Figure 2). A boundary layer thickness of 17.78 mm was the average of the boundary layer determined from 12 other compounds in the dataset[2].

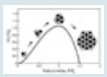


m_A Mass drug in aqueous — $K_{o:w}$ Organic/water partition coefficient
k_A, k_o Mass transfer coefficient — C_A, C_A^I Conc. drug in aqueous and interface
A_I Interfacial area — C_o, C_o^I Conc. drug in organic and interface

Figure 1: DDDPlus™ Biphasic Dissolution Model

METHODS CONT.

The PBPKPlus™ module in GastroPlus (Simulations Plus, Inc.) was used to model the PK of ITZ and its three metabolites[1]. The Advanced Compartmental Absorption and Transit (ACAT™) model was used to describe the intestinal dissolution, precipitation, and absorption of ITZ after p.o. administration. Human physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR™) Physiology™ module. The biopharmaceutical parameters for both ITZ and its metabolites were either obtained from literature or predicted by ADMET Predictor™ 6.5 (Simulations Plus, Inc.). Tissue/plasma partition coefficients for all the compounds were calculated using the Lukacova method from *in vitro* and *in silico* property estimates. The metabolism series from ITZ to hydroxy-ITZ to keto-ITZ to N-desalkyl-ITZ (CYP3A4 enzyme) was modelled by Michaelis-Menten kinetics with *in vitro* kinetic parameters and built-in expression levels of CYP3A4 in gut and liver. N-desalkyl-ITZ (CYP3A4 enzyme) was modelled by Michaelis-Menten kinetics with *in vitro* kinetic parameters and built-in expression levels of CYP3A4 in gut and liver. The Johnson dissolution model was used for both solution and capsule dosage forms. Particle size for the capsule dosage form was adjusted to 3 µm to account for the formulation effect. The permeability of ITZ was predicted in MembranePlus™ 1.0 (Simulations Plus, Inc). The mechanistic nucleation and growth (MNG) model in GastroPlus was used to account for possible precipitation as ITZ solubility changes in different intestinal regions.



Schmelzer, J. Non-Crystalline Solids (2010) 356

D_{mono} = Diffusion monomer (cm²/min)
N_A = Avogadro's number
c = Concentration monomer (mol/cm^3)
k_B = Boltzman's constant
T = 310° K
γ = Interfacial tension (Newtons/cm)

S = Solubility at the current pH
R^* = Critical radius (cm)
l = Effective radius from Lindfors (cm)
$ExpCorr$ = exponential correction factor
n_m = Molecular volume
ρ = density

Nucleation Rate:

$$\frac{dN}{dt} = D_{mono} N_A c^2 \left(\frac{k_B T}{\gamma}\right)^{\frac{1}{2}} ln\left(\frac{C}{S}\right) \frac{R^*}{R^* + \lambda} exp\left(-ExpCorr \frac{16\pi}{3}\left(\frac{\gamma}{k_B T}\right)^3 \frac{v_m^2}{ln\left(\frac{C}{S}\right)^2}\right)$$

Growth Rate:

$$\frac{dX_{xc}}{dt} = 4\pi R_D^2 \frac{D_{eff}}{h}(C_b - S_b) \quad where \quad R_D = \left(\frac{4X_{xc}}{3\pi\rho}\right)^{\frac{1}{3}}$$

X_{xc} = rate of particle growth
R_D = radius of particle
D_{eff} = effective diffusion coefficient
h = diffusion layer thickness
S_b = solubility in the bile micelle media
C_b = bile and free drug concentrations

Figure 2: Mechanistic Nucleation and Growth Precipitation Model

RESULTS

The exponential correction factor of 0.1707 (unitless) and Lindfor's parameter of 0.1984 µm were fit to the *in vitro* data utilizing the DDDPlus biphasic dissolution model. The simulation is shown in Figure 3. The red curve represents the % released of total ITZ 5mg solution dose precipitating down to its estimated crystalline solubility of 0.000189 mg/mL[4]. The green curve represents the % dissolved of ITZ in the organic layer. Initially, the appearance rate is very fast, but reduces dramatically as precipitation occurs. The grey curve represents the precipitate radius in micron. The parameters in Figure 3 were then utilized to predict the *in vivo* PK of ITZ using the GastroPlus PBPK model built by Szeto[1] (See graphs labeled "DDDPlus ppt." The *in vivo* formulations were 200 mg capsule and 100/200 mg solution administered in fasted and fed state[4]. The predictions were compared to the simulation results where the mechanistic nucleation and growth model parameters (0.23 and 0.5 µm for the exponential correction factor and Lindfor's parameter, respectively) were fitted to match the observed PK data in GastroPlus (Figure 4, graphs labeled "G+ Fit ppt.").

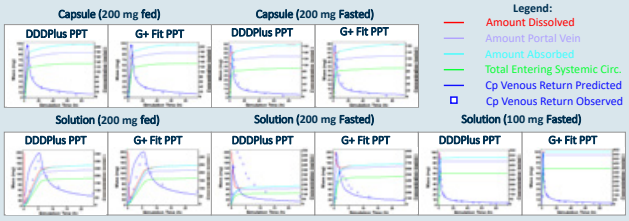


Figure 4: Itraconazole IVIVE Extrapolation of precipitation and pharmacokinetics vs. *in vivo* fitted precipitation parameters.

RESULTS CONT.

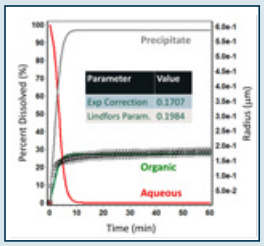


Figure 3: Biphasic Dissolution of ITZ appearance in organic phase (green) and precipitation in the aqueous phase (red). The grey curve is the radius of precipitate in microns.

CONCLUSION(S)

Utilizing *in vitro* precipitation parameters gave reasonable prediction of ITZ PK across all datasets except the 200 mg solution dose in fasted state. For all other doses, the precipitation IVIVE gave results similar to fitting *in vivo* parameters against observed PK profiles. This shows the utility of more advanced absorptive dissolution tests in extraction of precipitation parameters.

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W1230-05-039

A Physiologically Based Pharmacokinetic Model of Rivaroxaban: Role of OAT3 and P-gp Transporters in Renal Clearance

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PURPOSE Rivaroxaban is an oral anticoagulant which acts by inhibiting factor Xa of the coagulation network. It is used in the prevention and treatment of thromboembolism in patients undergoing knee or hip replacement surgery and in stroke prevention in patients with atrial fibrillation. Rivaroxaban undergoes CYP-mediated oxidative metabolism mainly via CYP3A4 with a minor contribution of CYP2J2. It is also a substrate for efflux transporter P-gp and uptake transporter OAT3 in kidney. These enzymes and transporters were incorporated in the model presented.

OBJECTIVES The aim of this work was to develop a physiologically based pharmacokinetic (PBPK) model of rivaroxaban and explore the role of OAT3 and P-gp transporters in its renal excretion and CYP mediated metabolism. The model was applied to different populations to account for genetic changes for these populations

METHODS A mechanistic PBPK model for rivaroxaban was developed using GastroPlus™ 9.6 (Simulations Plus, Inc.) Advanced Compartmental Absorption and Transit™ (ACAT™) model and PBPKPlus™ module were used to mechanistically explain absorption, distribution, and clearance mechanisms. The kinetic parameters (Km and Vmax) for CYP3A4-mediated metabolism were obtained from literature: CYP2J2, being a minor pathway, was not included in this model. For transporters, the values were obtained either from literature (OAT3) [1] or fitted. The model was calibrated against plasma concentration-time (Cp-time) profile after intravenous administration and with oral doses with in fasted condition, as well as with Cp-time and urinary excretion profiles after oral administration of 10 mg doses reported in literature. The model was further validated by comparing simulated and observed Cp-time profiles of rivaroxaban obtained from clinical studies reported in literature for 1.25, through 80 mg oral doses administered to Caucasian subjects. The model for the Chinese population was developed by reducing OAT3 expression in kidney 2-fold [2]. The expression level for P-gp remained the same as in Caucasian population [3]. The remaining physiological parameters, including CYP3A4 expression levels, were used as generated for Chinese subjects by built-in algorithms in GastroPlus. Physiochemical properties used for model are listed in Table 1

Table 1: Physiochemical properties of rivaroxaban

Parameter	Value	Units
Log P	1.5	
pKa (acid)	10.87	
pKa (acid)	13.6	
Solubility		
Water	7	mg/mL
FaSSIF	0.02	mg/mL
FeSSIF	0.08	mg/mL
Caco-2 Papp	7.45 E-6	cm/s
Plasma Fup	5.1	%
Blood to plasma conc ratio	1.08	

RESULTS The in vitro Km of CYP3A4 (5.78 µM) and OAT3 (1.1 µM) were used as reported in literature [1], Km for Pgp was fixed as 10 mg/L, and all Vmax values were fitted: CYP3A4 (2.96 E-5 mg/s for gut, 4.13 E-6 mg/s/mg enz for Liver); OAT3 (1.8E-6 mg/s/mg trans), P-gp (5E-4 mg/s for gut and 1.52E-4 mg/s/mg trans for Kidney). Simulated plasma concentration-time profiles of rivaroxaban with fitted Vmax values were in close agreement with observed data across different dose levels as summarized in Table 2. Similarly the model captured rivaroxaban PK after administration of 10 mg and 20 mg doses in fasted and fed state (Figure 1 and Table 2). The validated final model was able to match the fraction of compound cleared via urinary excretion (light blue lines), ~30% of dose cleared for a 10 mg dose up to 24 hours reported in literature [4] and confirm the role of OAT3 and P-gp in urinary excretion of rivaroxaban. Our model simulated renal excretion of 24 % in fasted and 33 % in fed conditions after 24h of 10 mg PO dose of rivaroxaban.

Figure 2: : Simulated vs observed concentration profiles of Rivaroxaban in Chinese subjects after administration of 10 mg (A) and 20 mg (B) dose in fasted state. The colors of lines and symbols are the same as described in Figure 1.

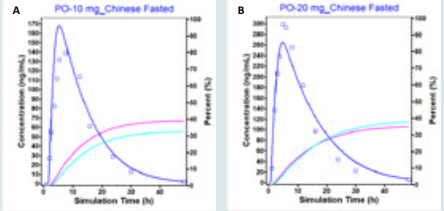

Figure 1: Simulated vs observed concentration profiles of Rivaroxaban in Caucasian subjects in fasted (A) and fed (B) state; dark blue line -simulated plasma profile, blue squares - observed data, light blue line-percent of dose secreted in urine, pink line – percent of dose metabolized.

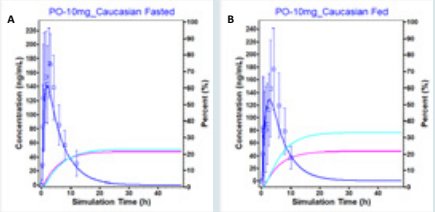

Table 2: PK parameters of Rivaroxaban in different Chinese and Caucasian population

		Observed		Predicted		Ratio (Obs/Pred)	
Population	Dose (mg)	Cmax (ng/mL)	AUC 0-inf (ng-h/mL)	Cmax (ng/mL)	AUC 0-inf (ng-h/mL)	Cmax	AUC
Chinese	5	79	1120	88	1183	0.90	0.95
	10	139	2140	168	2355	0.83	0.91
	20	298	4138	264	4344	1.13	0.95
	30	426	6147	426	6587	1.00	0.93
Caucasian Fasted	1.25	20	79	16	107	1.25	0.74
	10	174	1285	141	1032	1.23	1.25
	10	133	940	120	874	1.11	1.08
	10	158	893	118	858	1.34	1.04
	10	120	904	121	898	0.99	1.01
	10	161	841	126	912	1.28	0.92
	20	165	1508	200	1605	0.83	0.94
	20	186	1610	202	1606	0.92	1.00
	40	191	2357	299	2631	0.64	0.90
	80	287	3138	401	4256	0.72	0.74
Caucasian Fed	10	176	1123	129	1035	1.36	1.09
	20	180	1367	200	1653	0.90	0.83

CONCLUSIONS The model was successfully applied to capture the gut and liver metabolism of rivaroxaban by CYP3A4, and renal elimination mediated by P-gp and OAT3 transporters. Chinese population showed slightly lower total clearance of rivaroxaban compared to the Caucasian population. The differences in PK between these two populations are explained by 1) lower expression levels of CYP3A4 and 2) lower expression levels of OAT3 in Chinese populations.

Rivaroxaban is significantly cleared renally, current model captures the renal CL adequately and could be potentially applied to predict rivaroxaban PK in subjects with renal impairment. Validation of the model for this application is ongoing.

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Development of *In Vitro-In Vivo* Correlation for Long Acting Injectable Microsphere Formulations

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PURPOSE

The concept of *in vitro-in vivo* correlations (IVIVCs) for long-acting injectable (LAI) microsphere formulations has gained more significance in the past decade. However, this problem is challenging due to the multiphase release characteristics of compositionally equivalent formulations, the lack of a mechanistic deconvolution method, and the lack of compendial *in vitro* release testing methods. This study aims to (1) determine whether an IVIVC can be established for long-acting injectable microsphere formulations with different release profiles; (2) assess the role of mechanistic deconvolutions in determining the *in vivo* release profiles; and (3) explore the potential for using a triphasic Weibull function on improving results of the deconvolution process.

OBJECTIVE(S)

The Objectives of this study are to investigate the feasibility of establishing IVIVC for long acting injectable microsphere formulations and to discover important aspects of this process.

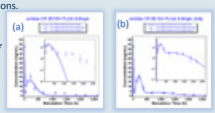
METHOD(S)

We attempted to establish validated Level A IVIVCs using GastroPlus™ 9.6 (Simulations Plus, Inc.) for several drugs formulated as long-acting injectable microspheres. Literature data for several poly (d,l- lactide-co-glycolide) (PLGA) or poly(d,l-lactide) (PLA) formulations administered subcutaneously in Sprague-Dawley rats for olanzapine [1], intramuscularly in beagle dogs for huperzine A [2], and subcutaneously in rats for orntide [3] were used in this study. For each case study, the PK was established based on plasma concentration-time (Cp-time) profiles after intravenous (IV) (huperzine A), intraperitoneal (IP) (olanzapine), or subcutaneous (SC) (orntide) injection. The PK model was subsequently linked to the intramuscular or subcutaneous controlled release model in the Additional Dosage Routes Module (ADRM) in GastroPlus, and the complete model was used to deconvolute the *in vivo* release profile for each formulation. Finally, level A IVIVCs between the deconvoluted *in vivo* release and *in vitro* dissolution profiles were established and evaluated across different formulations for each test compound.

RESULT(S)

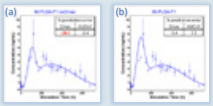
A level A IVIVC was established for each of the test compounds and formulations and several important aspects were discovered in the process.

(1) Complex *in vivo* Profile: The *in vivo* release profiles for these long-acting injectable microspheres may be complex and cannot be always accurately described by a single- or double-Weibull function. A triple-Weibull function was required to accurately describe the *in vivo* release profiles for orntide formulations.



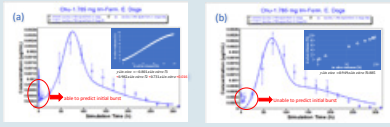
*Simulated Cp-time profiles after SC injection of one orntide LAI formulation in rat. The in vivo release profile was fitted as **(a)** double-Weibull and **(b)** triple-Weibull function.*

(2) Optimization Target Criteria: When fitting the *in vivo* release profile against the entire observed Cp-time profile, the error on Cmax is often higher than allowed by the IVIVC criteria due to the number of other concentration points outweighing the contribution of the single Cmax value. This issue can be addressed by including additional weight on Cmax during the deconvolution/optimization process.



*Simulated Cp-time profiles for a naltrexone LAI microsphere formulation considering **(a)** target observed Cp-time profile and **(b)** additional weight added to Cmax in the optimization function.*

(3) Insufficient *in vitro* Sampling: The density of *in vitro* sampling points is also important for prediction of the correct shape of the Cp-time profile. In the case of huperzine A, the IVIVC was able to predict the Cmax and AUC for new formulations, but a smaller initial peak was not captured due to the lack of *in vitro* data points representing the initial release of the drug. This limitation was addressed by using interpolated data points in the *in vitro* dissolution profile.



*Predicted Cp-time profiles for a huperzine A LAI microsphere formulation based on IVIVC built **(a)** with and **(b)** without using the interpolated in vitro data*

CONCLUSION(S)

The possibility of establishing IVIVCs for long-acting injectable microsphere formulations was investigated. The results show promise, but the desired success is yet to be achieved. Several important aspects have been discovered, including:

- The significance of using a triple-Weibull function in the mechanistic deconvolution and describing the more complex *in vivo* release of some long-acting injectable microspheres
- The role of the selected optimization objective function in the mechanistic deconvolution, specifically in the case of lacking sufficient *in vivo* sampling points
- The effect of using interpolated *in vitro* data in establishing an IVIVC and predicting the correct shape of the Cp-time profile

We aim to continue our study on the pharmacokinetics of LAI microspheres with the goal of better characterizing the *in vivo* environmental parameters that affect polymer degradation, microsphere dispersion, and API pharmacokinetics after *in vivo* injection of these formulations.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

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Application of Physiologically Based Pharmacokinetic (PBPK) Models in Predicting Drug Pharmacokinetics for Different Ethnic Groups

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PURPOSE

The purpose of this study was to evaluate the ability of PBPK models to predict the pharmacokinetics (PK) of different compounds in two ethnic groups, Caucasian and Chinese. The test set included compounds that have different clearance mechanisms. The population difference was captured by the built-in physiologies provided in GastroPlus™ (Simulations Plus, Inc.), which accounted for the differences in tissue sizes, blood flow rates, enzyme expression levels, glomerular filtration rates, plasma protein binding, and other factors in the two population groups.

METHOD(S)

The PBPKPlus™ module in GastroPlus was used to model the PK for multiple drug compounds, which have different enzymatic clearance (Table 1) and varying fractions of renal secretion. The Advanced Compartmental Absorption and Transit (ACAT™) model was used to describe the intestinal dissolution, precipitation, absorption, and intestinal metabolism (where applicable) after oral (p.o.) administration. The default dissolution model was used for most of the compounds. Human physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR™) Physiology™ module. The Chinese physiology model is based on multiple publications and the weight and height data is based on the China Health and Nutrition survey data (CHNS). The organ sizes are calculated as functions of age, weight and height (and/or other parameters such as bioimpedance, BSA).

Tissue/plasma partition coefficients for most compounds were calculated by the default Lukacova algorithm (some used measured Kp values for a few tissues) based on tissue composition and *in vitro* and *in silico* physicochemical properties. Physicochemical and biopharmaceutical properties for all compounds (and metabolites, where applicable) were either obtained from literature or predicted by ADMET Predictor™ (Simulations Plus, Inc.). Metabolic reactions were modelled by Michaelis-Menten kinetics with built-in expression levels of each particular enzyme in gut and liver for the corresponding populations. Enzyme kinetic parameters (Km and Vmax) were used as reported in literature from *in vitro* experiments or fitted against *in vivo* plasma concentration-time (Cp-time) profiles in Caucasian populations only.

Table 1. Modeling details for the list of compounds

Compound	Theophylline	Ketoconazole	Atomoxetine	Fluconazole
BCS Class	I	II	I	I
Main Clearance Pathway	CYP 1A2	CYP 3A4	CYP 2D6 CYP 2C19	Renal
Num of Data Sets	8	7	7	10
Dosage Forms	IV, Tab	Tab	Cap	IV, Cap, Tab

Compound	Gemfibrozil	Midazolam	Rifampicin	Tolbutamide
BCS Class	II	I	II	II
Main Clearance Pathway	CYP 3A4 UGT 2B7	CYP 3A4	Esterase, CYP 3A4, Renal	CYP 2C9
Num of Data Sets	9	10	5	7
Dosage Forms	Tab, Cap	IV, Tab, Sol	Cap, Tab	IV, Tab

RESULT(S)

The model accurately described the mean Cp-time profiles for the listed compounds and their metabolites (where applicable) for different doses and formulations in both populations and explained inter-ethnic differences in the PK of specific compounds. The detailed information of each compound is given in Table 1. The overall prediction errors for Cmax and AUC averaged across all compounds/studies are both less than 20%: 15.9% for Cmax and 17.1% for AUC. Some compounds exhibit more pronounced population differences, such as midazolam (AUC difference > 70%), and some compounds have only minimal effects, such as rifampicin (AUC difference < 20%). Predictions of representative studies for 5 of the 8 test compounds are shown in Figures 1-5, where we presented those with most distinct clearance pathways. Studies with similar dose amounts and formulations in Chinese and Caucasian subjects were selected to show for an easy comparison of inter-ethnic differences.

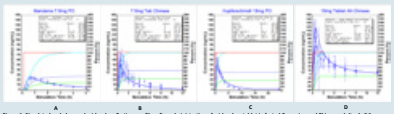

Figure 1: Simulated and observed midazolam Cp-time profiles after administration of midazolam tablet in fasted Caucasian and Chinese adults. **A.** 7.5 mg midazolam in a 22-year-old, 69 kg Caucasian male. **B.** 7.5 mg midazolam in a 23-year-old, 63.6 kg Chinese male. **C.** 15 mg midazolam in a 25-year-old, 70 kg Caucasian male **D.** 15 mg midazolam in a 40-year-old, 67.3 kg Chinese male. Km and Vmax values for 3A4 were from [Paine 1997].

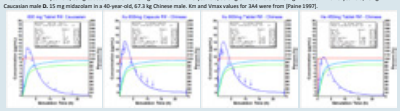

Figure 2: Simulated and observed rifampicin Cp-time profiles after rifampicin administration in fasted Caucasian and Chinese adults. **A.** 600 mg rifampicin tablet in a 30-year-old, 70kg Caucasian male. **B.** 600 mg rifampicin capsule in a 21-year-old, 62.8 kg Chinese male. **C.** 600 mg rifampicin tablet in a 21-year-old, 62.8 kg Chinese male. **D.** 450 mg rifampicin tablet in a 22-year-old, 65.5 kg Chinese male. Esterase and renal clearance were derived from [Lau 2007]. Km for 3A4 was from [Kajosaari 2005] and Vmax value was estimated from [Lau 2007].

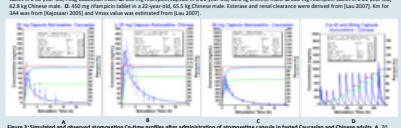

Figure 3: Simulated and observed atomoxetine Cp-time profiles after administration of atomoxetine capsule in fasted Caucasian and Chinese adults. **A.** 20 mg atomoxetine in a 52-year-old, 81 kg Caucasian male. **B.** 20 mg atomoxetine in a 24-year-old, 59 kg Chinese male. **C.** 90 mg atomoxetine in a 30-year-old, 74 kg Caucasian male. **D.** 40 and 80 mg atomoxetine (40 mg once daily (qd) for 3 days (days 1, 2 and 3), followed by atomoxetine 80 mg qd for 7 days (days 4–10)) in a 30-year-old, 62 kg Chinese male of 62 kg. Km values were from [Ring 2002] and Vmax values were fitted.

NOTE: In all plots, the dark blue colored lines and data points represent plasma concentrations (shown on the left Y-axis). The red, cyan, light blue and green colored lines are cumulative percents of the dose dissolved, absorbed, entering portal vein and entering systemic circulation, respectively (shown on the right Y-axis). The observed data are from multiple publications listed in the references and the subject weight and age are averages of the subjects in these studies.

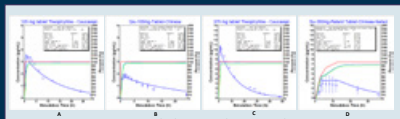

Figure 4: Simulated and observed theophylline Cp-time profiles after administration of theophylline tablet in fasted Caucasian and Chinese adults. **A.** 125 mg theophylline in a 30-year-old, 62 kg Caucasian male **B.** 100 mg theophylline in a 30-year-old, 60 kg Chinese male. **C.** 375 mg theophylline in a 30-year-old, 62 kg Caucasian male. **D.** 350 mg theophylline (as modified release tablet) in a 25-year-old, 63 kg Chinese male. The controlled released profile used in the GastroPlus simulation was from published in vitro dissolution data. Km for 1A2 was from [Tjia, 1996] and Vmax value was fitted.

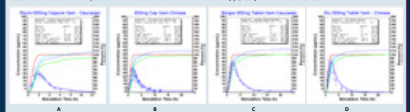

Figure 6: Simulated and observed gemfibrozil Cp-time profiles after gemfibrozil administration in Caucasian and Chinese adults. **A.** 600 mg gemfibrozil in a 30-year-old, 70 kg Caucasian male. **B.** 600 mg gemfibrozil in a 21-year old, 59.8 kg Chinese male. **C.** 900 mg gem fibrozil in a 30-year-old, 65 kg Caucasian male. **D.** 900mg gemfibrozil in a 25-year-old, 65.5 kg Chinese male. The percent entered portal vein is over 100%, which is caused by the conversion of the glucuronide metabolite back to the parent compound in the intestine. Km for UGT2B7 was from [Mano 2007] and Vmax value was fitted.

CONCLUSION(S)

The work described the use the mechanistic absorption model/ physiologically based pharmacokinetic MAM/PBPK approach for drug development and demonstrates the ability to predict inter-ethnic differences in PK over a range of compounds. The current approach helps to quantify dose regimens for different ethnic groups; hence, it will be very useful in a number of areas including drug safety, pharmacodynamics, and drug-drug interactions. The MAM/PBPK approach incorporates all of the relevant processes in drug absorption, distribution, metabolism, and elimination, and facilitates prediction of PK for different dosage forms and study designs.

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*note, this is only a selected list

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