GastroPlus™

PBPK modeling software...
from discovery through development

www.simulations-plus.com +1-661-723-7723
GastroPlus is a mechanistically based simulation software package that simulates intravenous, oral, oral cavity, ocular, inhalation, dermal/subcutaneous, and NEW! 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 9.5?

- **NEW!** PBPK models for antibody-drug conjugates (ADCs)
- **NEW!** PBPK physiology models for Chinese (pediatric and adults) and hepatic impairment populations
- **NEW!** Bolus & controlled release models for subcutaneous and intramuscular injections
- **Updated!** Animal physiology models for non-oral delivery pathways
- **Improved!** Reporting functions – easy export into Excel spreadsheets
- **Upgraded!** Automated mechanistic deconvolutions and easier virtual BE simulation setup
- **Enhanced!** More covariate relationships in the Population Simulator
- ... and more!

**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.

**Updated!** 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, 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:

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tissue</th>
<th>Tissue</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>Arterial blood</td>
<td>Brain</td>
<td>Yellow marrow</td>
</tr>
<tr>
<td>Gut</td>
<td>Heart</td>
<td>Lungs</td>
<td>Kidney</td>
</tr>
<tr>
<td>Liver</td>
<td>Muscle</td>
<td>Skin</td>
<td>Red marrow</td>
</tr>
<tr>
<td>Spleen</td>
<td>Reproductive organs</td>
<td>Venous blood</td>
<td></td>
</tr>
</tbody>
</table>

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:
- Human [American, Japanese, and NEW! Chinese, Male or Female, based on age]
- Infant/pediatric groups
- NEW! Hepatic impairment
- 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!
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!** PBPK models for DDI standard compounds: warfarin and simplified itraconazole
- 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 NEW! 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 NEW! 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 NEW! 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, NEW! mouse, and NEW! 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.

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!

**Updated!** Enzyme and transporter expression levels across species – including UGTs and SULTs!

**Enhanced!** 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 that 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 metabolites in a single simulation!
IVIVCPlus™ Module

New article from FDA scientists compare 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 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 R², 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.
**Enhanced!** 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.

**Updated!** 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 datasets 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.
NEW! 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.

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.

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]:
  - Distribute to peripheral compartments
  - Cleared by nonspecific clearance
  - Bind to target receptor, internalize, and be cleared in the cell lysosome
Mechanistic Absorption and Physiologically Based Pharmacokinetic Modeling of Itraconazole and Its Application for Drug-Drug Interaction with Midazolam in Adult Populations

Ke X. Sztco, Viera Lukacova, John DiBella, Walter S. Woltoz, and Michael B. Bolger
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INTRODUCTION

Itraconazole (ITZ) is a triazole antifungal (suspected to be a non-inert metabolite of ketoconazole) that inhibits the cytochrome P450 3A4 (CYP3A4) enzyme, which clears many drugs. It has been used in the treatment of fungal infections and as an antiretroviral agent. When given with certain drugs, it may result in drug-drug interactions (DDIs) due to the inhibition of CYP3A4 by ITZ.

METHODS

The PBPK models used to simulate ITZ and its metabolites were generated from rat data using the ADMET Predictor™ v7.2 program. Simulations were performed using default physiology and GFR in GastroPlus 9.0 for premature infant matching GA, PNA, and weight using rat data (Figure 1). The model was validated by simulation of adult human PK (Figure 2).

RESULTS

Simulation results for the PBPK model were compared with the observed Cp-time profile after 5 mg/kg i.v. administration of ITZ in rats (Figure 2). The model was able to predict the Cp-time profile after 5 mg/kg dose in adult humans (Figure 2). The model was successfully scaled to predict VCN PK in adult humans (Figure 2). Finally, the model was successfully scaled to predict VCN PK in children (Figure 2).

CONCLUSIONS

The PBPK approach incorporates all relevant processes in drug absorption, distribution, metabolism, and excretion with a high degree of accuracy. This approach is particularly valuable for the prediction of drug interactions and the design of clinical trials.


table 1

**Table 1. Ki and Km values**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ki (µM)</th>
<th>Km (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITZ</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>MID</td>
<td>14.4</td>
<td>27.0</td>
</tr>
</tbody>
</table>

**References**


Physiologically based pharmacokinetic (PBPK) model for prediction of vancomycin pharmacokinetics in children

Lukacova, V., W.S. Woltoz, M.B. Bolger
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**Aim**

Clinical considerations prevented extensive clinical trials in pediatric populations; however, the use of the PBPK modeling in vivo data from the literature and PBPK models for vancomycin (VCN) is supported. This approach is valuable for the prediction of VCN PK in children and adults.

**Methods**

VCN pharmacokinetics was simulated using the PBPK models. VCN was administered to children using oral solution and intramuscular (i.m.) injection. Dosing regimens were based on weight and age. PBPK predicted (red dots) and PopPK concentrations for VCN were compared with observed concentrations.

**Results**

VCN concentrations predicted by the PBPK model were in excellent agreement with the observed concentrations. The PBPK model predicted the Cp-time profile after 5 mg/kg i.v. administration of ITZ in rats (Figure 2). The model was able to predict the Cp-time profile after 5 mg/kg dose in adult humans (Figure 2). The model was successfully scaled to predict VCN PK in adult humans (Figure 2).

**Conclusions**

The PBPK approach is a valuable tool for the prediction of drug interactions and DDI effects. It can be used to design clinical trials and to optimize drug dosing regimens.

**References**

Physiologically Based Pharmacokinetic Modeling of Rosuvastatin and Prediction of Transporter-Mediated Drug-Drug Interactions Involving Gemfibrozil

Joyce S. Macwan, Viera Lukacova, Gratyna Fraczkiewicz, Michael B. Bolger, Fatemeh Ahklaghi, Walter S. Woltosz

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**PURPOSE**
Roscuvastatin (C4702), a prodrug of rosuvastatin (C4701), is a novel HMG-CoA reductase inhibitor that is approved for the treatment of primary hyperlipidemia and hypertriglyceridemia. Rosuvastatin (C4701), the active moiety of C4702, is metabolized to active metabolites in gut and liver.

**METHODS**
The GastroPlus™ 9.0 (Simulations Plus, Inc.) Advanced Compartamental Absorption and Transport (ACAT™) model was used in conjunction with the PBPKPlus™ and GastroPlus™ PBPK models to produce a PBPK model of rosuvastatin following oral administration, and to apply this model to predict the transporter-mediated drug-drug interactions with gemfibrozil.

**RESULTS**
The model adequately described the nonlinear disposition and dose proportional pharmacokinetics of rosuvastatin as the dose range of 10 to 80 mg in different populations of subjects following oral administration (Figure 2A, B, C, and D).

**CONCLUSIONS**
The absorption and pharmacokinetics of rosuvastatin were accurately modeled using PBPK models derived from the PBPKPlus™ and PBPKPlus™ and GastroPlus™ PBPK models. The model can help to identify populations at increased risk for side effects and to optimize their dosing regimens for the safe and effective use of rosuvastatin.

**REFERENCES**

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Physiologically Based Pharmacokinetic Modeling of Buspironone and the Effect of Liver Cirrhosis on its Disposition

Joyce S. Macwan, Gratyna Fraczkiewicz, Viera Lukacova, Michael. B. Bolger, Walter S. Woltosz

Simulations Plus, Inc., 42505 10th Street West, Lancaster, California 93534, USA

**PURPOSE**
The aim of this work was to develop a physiologically based pharmacokinetic (PBPK) model for buspironone following oral administrations in healthy and cirrhosis populations to predict the effects of pharmacological changes associated with liver cirrhosis in compensated and decompensated hepatic impairment patients.

**METHODS**
- The GastroPlus™ 9.0 (Simulations Plus, Inc.) Advanced Compartamental Absorption and Transport (ACAT™) model was used in conjunction with the PBPKPlus™ and GastroPlus™ PBPK models to produce a PBPK model of buspironone following oral administration, and to apply this model to predict the transporter-mediated drug-drug interactions with buspironone in compensated and decompensated hepatic impairment patients.

**RESULTS**
- The model adequately described the nonlinear disposition and dose proportional pharmacokinetics of buspironone at the dose range of 10 to 80 mg in different populations of subjects following oral administration (Figure 2A, B, C, and D).

**CONCLUSIONS**
The absorption and pharmacokinetics of buspironone were accurately modeled using PBPK models derived from the PBPKPlus™ and PBPKPlus™ and GastroPlus™ PBPK models. The model can help to identify populations at increased risk for side effects and to optimize their dosing regimens for the safe and effective use of buspironone.

**REFERENCES**
Level IV Using a Comprehensive Absorption/ PBPK Model for Metoprolol

John I. Chung, Viera Lukacova, John R. Crison, Michael B. Bolger, & Walter S. Woltosz
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Introduction

Subcutaneous administration of certain drugs may be the preferred route of administration for patients who cannot swallow tablets or capsules and who have difficulty delivering medication via the oral route. In order to improve the bioavailability of subcutaneously administered drugs, it is critical to develop a comprehensive PBPK model for subcutaneous administration in rats and humans.

Purpose

This PBPK model was developed for subcutaneous administration of metoprolol in rats and humans. The model was calibrated using pharmacokinetic data from different studies and was used to simulate the subcutaneous absorption of metoprolol in rats and humans.

Methods

The PBPK model is based on the GastroPlus™ software developed by Simulations Plus, Inc. The model was developed using the PBPK modeling approach and was calibrated using the pharmacokinetic data from different studies.

Results

The model accurately predicts the subcutaneous absorption of metoprolol in rats and humans.

Conclusions

The PBPK model for subcutaneous administration of metoprolol in rats and humans is a useful tool for predicting the subcutaneous absorption of metoprolol in rats and humans.

References


Conclusively, the PBPK model for subcutaneous administration of metoprolol accurately predicts the subcutaneous absorption of metoprolol in rats and humans. The model can be used to predict the subcutaneous absorption of metoprolol in different species and can be used to optimize the subcutaneous administration of metoprolol.