2026 Volume 1 Issue 2:11-24

The International Journal of Multidisciplinary and Medical Research (IJMMR)

https://ijmmr.org/index.php/ijmmr/about

GastroPlus in Model-informed Drug Development: PBPK Modelling, ACAT Modelling, and Regulatory Relevance

Mutiba Kamal[1]

Jinnah University for Women, Karachi Pakistan

Abstract

GastroPlus is a popular mid-21st century modeling software used in the drug development world to simulate in vivo drug behaviours based on in vitro and physicochemical data. It combines the most important parameters of solubility, permeability, dissolution, particle size, pKa and gastrointestinal physiology to mimic drug absorption, distribution, metabolism and excretion (ADME). To make it easier to anticipate plasma concentration–time profiles in various physiological and dosage settings, the platform integrates sophisticated compartmental modeling of the gastrointestinal tract and systemic pharmacokinetic processes.Additionally, GastroPlus is a crucial tool in drug development for dose selection, bioavailability increase, formulation design optimization, and reducing the need for extensive animal and human research. It turns out to be a useful technique for preclinical and clinical assessments to determine how food, disease states, and population variability affect drug efficacy. Furthermore, it can be integrated with pharmacokinetic and pharmacodynamic (PK/PD) modeling, which helps in lead optimization and regulatory submissions.GastroPlus is a complete in silico tool that can improve oral medication absorption and systemic exposure prediction accuracy, reduce development costs, shorten time to market for new therapies, and increase efficiency.

Keywords: Compartmental Pharmacokinetics, Cheminformatic Predictors, GastroPlus, PBPK Modeling, ACAT Modeling

Corresponding Author mutibakamal@gmail.com ,ORCID ID: https://orcid.org/0009-0002-8976-5343

Submitted on 02-04-2026– Revised on 26-04-2026– Accepted on 20-05-2026 Published on 31-5-2026

INTRODUCTION:

A fundamental aspect of contemporary drug development and clinical pharmacology is the absorption, distribution, metabolism, and excretion (ADME) of pharmacological molecules. These pharmacokinetic processes are caused by the drug's physicochemical characteristics, formulation elements, and the physiological milieu of the human body. The prediction of the ADME behaviour is important to optimise the efficacy of the drug, to reduce the toxicity, and

to enhance the pharmaceutical success rate. During recent years, computational modelling and simulation techniques have gained importance for forecasting in vivo drug performance, decreasing experimental costs and aiding in the regulatory decision-making process in the drug development process (Morningstar-Kywi et al., 2023).

Of these tools, physiologically based pharmacokinetic (PBPK) modelling has proven to be a very powerful tool that can combine information about the drug with information about the human physiology to simulate the drug's behaviour in the body, specifically. By taking into account gastrointestinal transit, organ blood flow, enzyme activity, tissue distribution, and other factors, the PBPK models provide a mechanistic explanation of drug absorption and systemic disposition. Pharmaceutical research frequently uses these models to optimise dosages, create formulations, look into drug-drug interactions, evaluate bioequivalency, and forecast pharmacokinetics in certain populations (Tubic-Grozdanis et al., 2008).

PBPK modeling can be supported by a few software platforms, including PK-Sim, Simcyp Simulator, and GastroPlus. Because of its advanced mechanistic modelling capabilities, user-friendly interface, and superior predictive capacity, GastroPlus has proven effective in both academia and the pharmaceutical business. GastroPlus, developed by Simulations Plus, allows for modelling the whole body using compartmental absorption and transit models and whole body PBPK models, allowing for a comprehensive simulation of all oral and non-oral drug delivery systems (Hamdi & Mohamed, 2022).

One unique aspect of GastroPlus is the Advanced Compartmental Absorption and Transit (ACAT) model, which mechanistically models gastrointestinal drug absorption by breaking up the gastrointestinal tract into multiple physiological compartments. Because of the inclusion of many important variables like pH variation, intestinal permeability, gastric emptying time, dissolution, precipitation, metabolism and regional absorption, the ACAT model can be used to predict the oral drug absorption and bioavailability with high precision. This functionality has proven to be useful in formulation optimisation, biowaiver applications, and predicting in vivo performance based on in vitro data (Arafat et al., 2021).

GastroPlus can also perform advanced PBPK simulations to predict tissue distribution, plasma concentration–time profiles, food effects, and pharmacokinetic variability between patient populations, in addition to oral absorption modelling. The software is being used in more and more aspects of drug development, ranging from discovery, selection of drug candidates, to clinical trial design and submission to the regulators. The use of its has increased considerably due to the increasing regulatory attention on model-informed drug development (MIDD) approaches (Almajidi et al., 2025).

This review will give a general overview of the evolution of GastroPlus in drug development, the mechanistic basis of the ACAT model, and the use of GastroPlus in PBPK modelling. Moreover, the review emphasises the importance of GastroPlus in improving prediction accuracy, formulation development, and decision-making in the field of pharmaceutical research and development.

GastroPlus Software:

GastroPlus is among the most popular physiologically based pharmacokinetic (PBPK) modelling software platforms available today in drug development. Simulations Plus developed the software, and it combines in one package the drug-specific physicochemical properties along with human physiological parameters to allow for prediction of the absorption, distribution, metabolism and excretion (ADME) processes. GastroPlus is widely used in pre-

clinical and clinical development to support the formulation optimisation, selection, bioequivalence studies and prediction of food and drug–drug interactions (Wang et al., 2023).

The Advanced Compartmental Absorption and Transit (ACAT) model is a major advantage of GastroPlus, as it is a mechanistic model of oral drug absorption across multiple GI compartments. The ACAT model includes the effects of pH changes, dissolution, precipitation, permeability in the intestine, transit time and first-pass metabolism to predict oral bioavailability of the drug. This feature is particularly beneficial to poorly soluble drugs and modified-release dosage forms. Additionally, GastroPlus can incorporate tissue distribution, enzyme activity, and transporter activity, enabling whole-body PBPK modelling. The software enables researchers to simulate plasma concentration–time profiles and evaluate pharmacokinetic behaviour in healthy and special populations. PBPK modelling is gaining wider acceptance as a component of model-informed drug development by regulatory agencies (Hui et al., 2024). Regulatory agencies now consider PBPK modelling as a part of model-informed drug development. The predictive capability and mechanistic approach make GastroPlus an invaluable tool to cut down on experimental workload, speed up formulation development and aid decision making throughout the pharmaceutical development process.

Principles of Pharmacokinetics and Modelling

The foundation of the GastroPlus model is the principles of pharmacokinetics that include absorption, distribution, metabolism and excretion (ADME). The software is used to simulate the behaviour of a drug within the human body after it has been administered, using mechanistic mathematical models. GastroPlus simulates systemic medication exposure and plasma concentration-time curves by combining physicochemical and physiological factors. Physiologically based pharmacokinetic (PBPK) modeling and compartmental pharmacokinetic techniques are integrated in the program. In PBPK models, the actual organs and tissues are connected by blood flow, whereas in standard compartmental models, the body is separated into fictitious compartments. To provide a more accurate forecast of tissue distribution, oral absorption, and elimination, GastroPlus uses PBPK models (Silva et al., 2022).

One of the fundamental and most important parts of developing accurate models in GastroPlus is obtaining the proper and reliable literature and experimental data. Simulations include parameters like solubility, pKa, permeability, LogP, plasma protein binding and intrinsic clearance. Software then predicts oral bioavailability, absorption rate, half-life and systemic exposure (Arora & Khurana, 2022). GastroPlus is designed to help support model-informed drug development, enabling rapid assessment of changes to formulations, food effects and population variability. It is designed in a mechanism that helps to understand the behaviour of the drug and helps to minimise in vivo research (Kuentz et al., 2006).

Cheminformatics Predictions

GastroPlus uses cheminformatics predictions to assist early-stage drug development and PBPK. The software is often used in conjunction with another software developed by Simulations Plus called ADMET Predictor to get the properties of the physicochemical and pharmacokinetic properties directly from the structure. When there is limited experimental data, these predicted parameters can be used as inputs for GastroPlus simulations. Predictive properties are important, such as pKa, solubility, logP, logD, permeability, diffusion coefficient, plasma protein binding and metabolic stability. They have a significant effect on

drug absorption and systemic exposure (Kadiri et al., 2024). These values enable GastroPlus to create initial PBPK models early in development.

One of the most important benefits of the integration of cheminformatics is the rapid screening of drug candidates. Multiple compounds can be assessed and their oral absorption, dissolution properties and pharmacokinetic performance predicted before laboratory testing. This saves development costs and assists in rationalising the selection of formulation. But prediction accuracy hinges on the quality of the algorithms used for computation and the datasets available (Pernaa, 2022). Thus, GastroPlus models are usually adjusted based on in vitro and clinical information. Despite the constraints, the use of cheminformatics tools in conjunction with GastroPlus in a model-informed drug development process can be very efficient and help optimise candidates significantly faster (Batchelor, 2026).

Dissolution and Absorption

The specific concepts of dissolution and absorption play a key role in GastroPlus modelling, especially in the Advanced Compartmental Absorption and Transit (ACAT) model. The software is based on a mechanistic approach that takes into account the many physiological compartments of the gastrointestinal tract to mechanistically predict the oral drug absorption (Hamdi & Mohamed, 2022). Factors that are accounted for in each compartment include pH, fluid volume, transit time, and absorption surface area. GastroPlus predicts dissolution and membrane transport by examining the relationship between pKa, ionisation, solubility, permeability and lipophilicity. Weak acids and weak bases will have different ionisation profiles at different pH levels in the gastrointestinal tract and will directly affect absorption profiles. The software also takes into account precipitation, supersaturation, and dissolution rate limits (Krstevska et al., 2025).

ACAT is especially applicable for drugs with poor solubility and modified-release. GastroPlus can be used to simulate the regional absorption, food effects, and formulation-dependent dissolution behaviour in order to predict the oral bioavailability. These simulations are used in order to optimise particle size, salt forms, excipients and release characteristics. GastroPlus can be used for in vitro–in vivo correlation (IVIVC) and bioequivalence assessment by combining in vitro dissolution data with physiological parameters (Hens et al., 2022). This mechanistic approach is a replacement for extensive clinical studies and enhances the prediction of the oral drug performance under various physiological conditions (Silva et al., 2022).

Compartmental Pharmacokinetics

GastroPlus's built-in compartmental pharmacokinetic modelling capabilities enable analysis and prediction of systemic drug exposure. Compartmental models assume the body is divided into one or more hypothetical "compartments" in which the drug is uniformly distributed. It is well known that these models are employed to estimate the pharmacokinetic parameters like clearance, volume of distribution, elimination rate constant and half-life (Jadhav et al., 2023).

The software can be used to model observed plasma concentration-time data with one, two, or multi-compartment models. This can be helpful to describe the absorption and elimination of the product before building more complicated PBPK models. GastroPlus can compare the compartmental predictions with mechanistic PBPK simulations to assess model performance. While the model is simple and can be used to fit data, it is not physiologically detailed. GastroPlus is able to address this limitation by incorporating compartmental analysis with mechanistic absorption and distribution models. Researchers can thus be able to bring together

the empirical pharmacokinetic analysis with physiologically meaningful simulations(De Sutter et al., 2024).

Compartmental pharmacokinetic functions are particularly applicable when optimising doses, conducting bioequivalence studies, and performing clinical pharmacokinetic evaluation in GastroPlus. Incorporating actual clinical information with the ability to simulate behaviour at the system level enhances knowledge of systemic drug behaviour and aids rational decision-making during pharmaceutical development (Liu et al., 2025).

Midpoint Presentation

Molecular property, parameter implementation and preliminary model performance are the focus of the midpoint step in the GastroPlus modelling. This is the point when the researchers analyse the relationship between physicochemical and pharmacokinetic parameters and the predicted drug behaviour in the simulated system and pinpoint parameters that need to be improved. Important factors like pKa, solubility, permeability, particle size, logP, plasma protein binding, and intrinsic clearance are all included in GastroPlus. The PBPK model uses these characteristics to compute oral absorption, tissue distribution, metabolism, and systemic exposure (Yasin et al., 2025). The dependability of the simulation results depends heavily on the parameter selection.

Researchers can use GastroPlus to compare their observed experimental or clinical results with projected plasma concentration–time patterns. Sensitivity analysis is frequently used to identify factors that significantly affect the model's performance. Predictions of bioavailability are often influenced by features like as intestinal permeability, dissolution rate, and metabolic clearance. Model structure and input data constraints can also be found using the midpoint assessment. Researchers can alter tissue partition coefficients, optimize dissolution profiles, or include additional metabolic pathways to improve prediction accuracy. As the iterative evaluation continues, GastroPlus will further develop knowledge of how molecular characteristics correlate with pharmacokinetic properties (Khadka et al., 2023).

Metabolism and Transport

GastroPlus has the ability to include enzyme metabolism and transporter activity within its PBPK models to more accurately predict systemic drug exposure. The main enzymes that metabolise drugs are the cytochrome P450 enzymes (CYP3A4, CYP2D6 and CYP2C9), and the transport proteins that affect absorption and distribution to tissues are P-glycoprotein. The software allows for the integration of enzyme kinetics, transporter expression and first pass metabolism in mechanistic models. GastroPlus can model non-linear pharmacokinetics due to saturation of enzymes or transporters at higher drug concentrations (Yin et al., 2024). The functions are especially useful for predicting drug–drug interactions and oral bioavailability variability.

Transporters have a major influence on absorption and elimination by regulating the transport of drugs across biological membranes. GastroPlus includes transporter-mediated uptake and efflux processes in the gastrointestinal and hepatic compartments. This enhances the prediction of systemic exposure and tissue distribution. The software is also used extensively with respect to the evaluation of the metabolic interactions between co-administered drugs. Researchers can simulate enzyme inhibition or induce and determine the consequences on plasma concentration profiles. GastroPlus can be used to facilitate safer dose selection, assessment of drug

interactions, and regulatory decision-making in drug development by including metabolism and transport processes (Perrier et al., 2023).

PBPK Models

Physiologically based pharmacokinetic (PBPK) modelling is a key component of the capabilities of GastroPlus and is the basis for its predictions. PBPK models view the body as a set of interconnected compartments (organs and tissues). These models include anatomical, biochemical and molecular parameters and simulate drug disposition mechanistically. GastroPlus combines drug-specific parameters (including solubility, permeability, lipophilicity and intrinsic clearance) with physiological parameters (organ blood flow, tissue composition and enzyme expression) (Yang et al., 2025). This allows prediction of absorption, tissue distribution, metabolism and excretion by various populations. One of the primary benefits of GastroPlus PBPK models is the ability to simulate pharmacokinetics in special populations, such as pediatric, geriatric, hepatically impaired and renally impaired patients. The software can also predict food effects, drug-drug interactions and first-in-human dosing (Gomes & Vale, 2025).GastroPlus integrates PBPK frameworks and the ACAT absorption model and enables the simultaneous evaluation of gastrointestinal dissolution and systemic distribution. This approach is integrated and enhances the accuracy of prediction for oral formulations while enabling model-informed drug development. The mechanistic structure and regulatory relevance make GastroPlus an important tool for pharmaceutical research and regulatory submission (Godinho, 2025).

Model Refinement

In order to properly simulate observed pharmacokinetic data, initial PBPK models must be optimised to improve the model, which is a necessary step in model refinement. The Refinement aims to fine-tune the model parameters, test the sensitivity, and compare the model's output to experimental or clinical results. The sensitivity analysis tools in GastroPlus help determine parameters that are significant to the PK outcome. Plasma concentration–time profiles can be significantly affected by variables like permeability, dissolution rate, tissue partition coefficients, gastric emptying time, and metabolic clearance. Models are enhanced with observed dissolution data, permeability studies, metabolic stability data, and clinical pharmacokinetic data. This is a recursive procedure that will increase the prediction accuracy as well as the certainty of the procedure (Shijith et al., 2025). GastroPlus also allows for the modification of enzyme kinetics, transporter activity and regional absorption parameters. Drugs with poor solubility, modified-release systems and those that exhibit nonlinear pharmacokinetics are examples of compounds that require special attention for model refinement. GastroPlus combines observed data and mechanistic simulations to aid in building accurate PBPK models for formulation optimisation and regulatory purposes (Zagaja et al., 2026).

Table 1: Functional Capabilities of GastroPlus and Types of Output in PBPK Modelling.

GastroPlus Function/Module	Purpose/Application	Type of Output Generated	Examples of Output
ACAT Model (Advanced Compartmental Absorption and Transit)	It is used to simulate oral drug absorption throughout the GIT.	The results can be in form of graphs, regional absorption tables, and numeric data.	Fraction absorbed, Plasma concentration-time curves, GI absorption profiles.
PBPK Modeling	It uses physiological compartments to predicts systemic pharmacokinetics.	Tissue distribution tables, graphs, numerical pharmacokinetic parameters.	AUC, Tmax, Cmax, organ exposure data, tissue concentration plots.
Compartmental PK Modelling	Observe clinical data by fitting PK models.	PK parameters, graphs, numeric data.	Half-life clearance, volume of distribution, one or two compartment fitting curves.
IVIVC (In Vitro–In Vivo Correlation)	It used to correlates dissolution data with the help of in vivo absorption.	Prediction error tables, correlation plots.	IVIVC validation statistics, Absorption vs Dissolution graphs.
Dissolution Modeling	It helps to predict the dissolution pattern of different formulations.	Numerical dissolution profiles, dissolution curves.	Drug dissolution over tie, dissolution rate constant.
Food Effect Simulation	Examine the impact of fasted vs fed conditions.	Pharmacokinetic tables and comparative graphs.	Bioavailability comparison, Fed vs Fasted plasma concentration profiles.
Drug–Drug Interaction (DDI) Modelling	It helps to predict the enzyme or transported mediation interaction.	Inhibition of induction data tables, concentration plots.	Altered Cmax and AUC values, Cytochrome P450 (CYP) enzymes inhibition effects.
Population Simulation	It helps to simulate pharmacokinetic variability among large population.	Population Distribution tables and Statistical plots.	Percentile Pharmacokinetic distribution, virtual patient variability graphs.
Parameter Sensitivity Analysis (PSA)	Highlight parameters that affects PK behaviour of drug or formulation.	Ranking tables and sensitivity graphs.	Parameter impact ranking and Tornado plots.
PKPlus Module	It helps to perform non-compartmental PK analysis.	Numerical pharmacokinetic data and graphs.	Concentration-time plots, MRT, half-life, and AUC.
ADMET Predictor Integration	It helps to predict ADMET and physiochemical properties.	Prediction tables and numeric datasets.	Solubility prediction, LogP, pKa, and permeability.
Pulmonary Simulation Module	Lung absorption and Models inhalation.	Concentration tables and lung deposition graphs.	Systemic exposure data and pulmonary absorption curves.
Controlled Release Simulation	It helps to predict sustained-release and modified-release formulations.	PK profiles and release kinetic graphs.	Prolonged plasma concentration profiles and Drug release curves.
Biowaiver Assessment	It supports Bio-waiver and BCS-based studies.	Absorption outputs and comparative dissolution outputs.	F2 (Similarity factor) and predicted BE outcomes.
Transporter Modelling	It simulates transported-mediated efflux or uptake.	Pharmacokinetic graphs and Numeric transporter kinetics.	Intestinal transport data and P-gp efflux profiles
Metabolism Modelling	It helps to predict enzyme-mediated metabolism	Pharmacokinetic curves and metabolic rate tables.	Metabolite formation profile and CYP-mediated clearance.
Virtual Trial Simulation	It simulates PK in a virtual population.	Variability graphs and statistical summaries.	CI plots and mean PK profiles.
Formulation Optimization	It compares excipient and formulations effects.	Prediction tables and comparative graphs.	Optimised dissolution profiles and BA comparison.
Regional Absorption Prediction	It helps to identify site-specific drug absorption in the gastrointestinal tract.	Gastrointestinal compartment graphs and absorption percentages.	GI (Jejunum/ileum) absorption distribution charts.
Nonlinear PK Simulation	It models saturation kinetics as well as dose-dependent pharmacokinetics.	Non-linear pharmacokinetic tables and dose-response curve.	Concentration-dependent clearance and saturable metabolism graphs.

Well-refined models can more closely predict bioavailability, food effects and drug–drug interactions. This leads to improved scientific validity and utility of GastroPlus simulations for model-informed drug development.

The table below shows the key functional components and simulation capabilities of GastroPlus in pharmaceutical research and drug development. It emphasises the major uses of each GastroPlus module, such as oral absorption modelling, physiologically based pharmacokinetic (PBPK) modelling, compartmental pharmacokinetic (CPK) modelling, dissolution modelling, metabolism and transporter modelling, food effect modelling, and formulation modelling. The table also illustrates the different output formats that can be produced by the software, including numerical pharmacokinetic parameters, statistical data, graphical concentration–time profiles, dissolution curves, sensitivity plots, and tissue distribution charts. The results of these outputs allow a mechanistic and quantitative investigation of the behaviour of the drug under various physiological and formulation conditions. Additionally, the figure highlights the use of GastroPlus for computational modelling of experimental data for bioequivalence assessment, virtual clinical trials, dose optimisation, and model-informed drug development. In summary, the summarised functions highlight the versatility of GastroPlus as a predictive simulation platform suitable for use to advance formulation strategies, minimise experimental trial effort, and maximize decision making throughout the drug development process, both in preclinical and clinical phases.

Steps in the GastroPlus Simulation workflow

GastroPlus contains a simulation workflow that is step-wise and incorporates the physicochemical, biopharmaceutic, and physiological data into a predictive pharmacokinetic outcome. The workflow starts with the entry of the drug-specific physicochemical properties, including molecular weight, pKa, logP/logD, solubility, permeability, particle size and plasma protein binding. These parameters are the intrinsic absorption and disposition parameters of the compound (Krstevska et al., 2025).In the second step, in vitro dissolution data are included to account for the drug release behaviour, which is dependent on formulation. This is especially critical for modified release and poorly soluble drugs, for which dissolution rate is a key factor affecting oral bioavailability. This information is used in the Advanced Compartmental Absorption and Transit (ACAT) model to simulate gastrointestinal dissolution and regional absorption.Then the physiological parameters are set for the model, such as the pH of the gastrointestinal tract, transit times, blood flow of organs, expression of enzymes, and activity of transporters. The system parameters can be used to simulate under various conditions (fasted, fed, healthy, diseased).

Then, parameter optimisation is carried out based on experimental or literature data on the pharmacokinetics. Adjusting key parameters like clearance, permeability, and dissolution rate to enhance predictions with the model fitting process.The PBPK simulation is then run, and outputs are obtained representing plasma concentration–time and tissue distribution. Validation is carried out by comparing the simulated results to the clinical or preclinical data. Lastly, GastroPlus can offer predictive outputs such as Cmax, Tmax, AUC, bioavailability and regional absorption profiles that aid in decision-making for formulation development and drug optimisation (Batchelor, 2026).

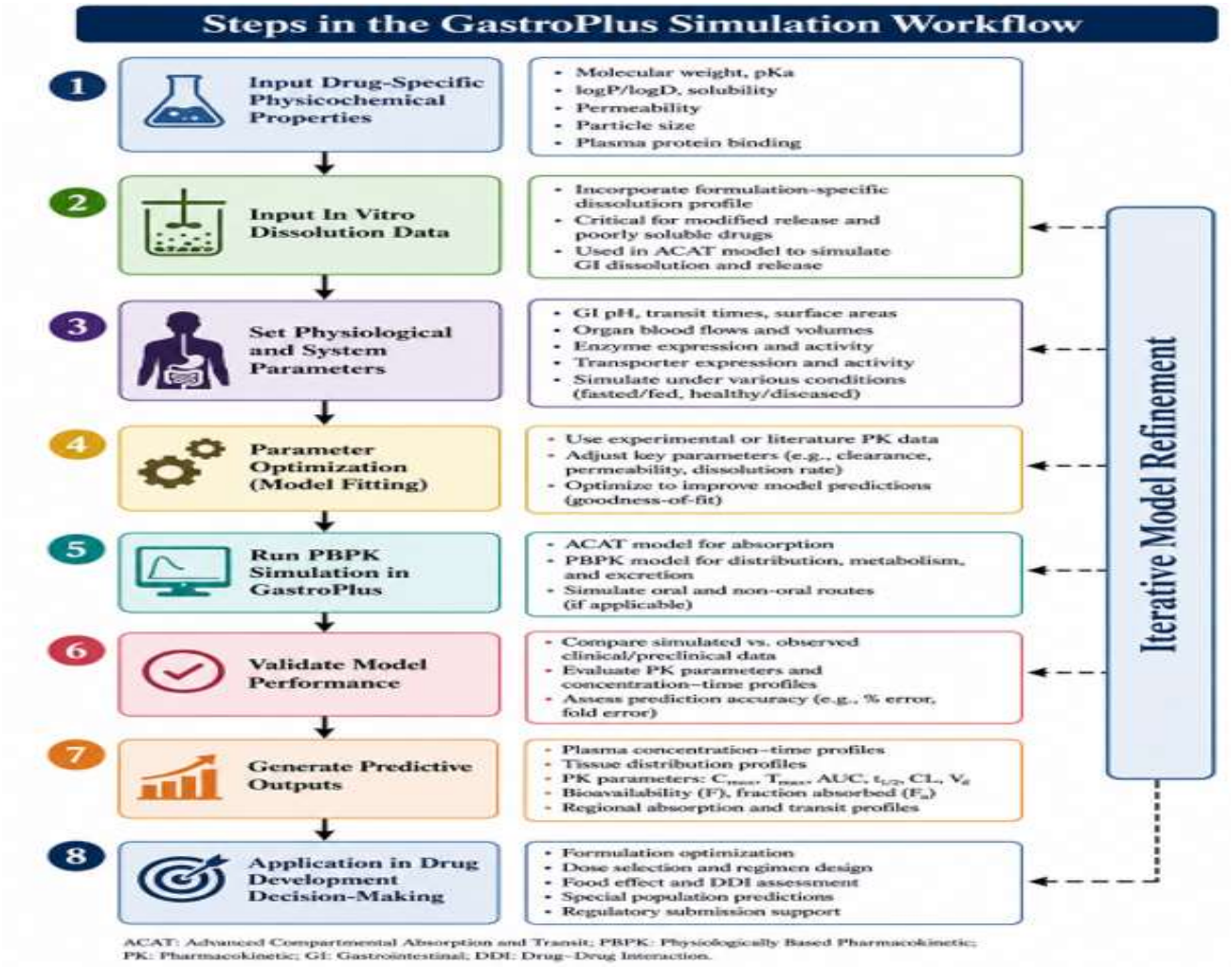

Figure 1: Steps in the GastroPlus Simulation Workflow

Connecting with regulators to discuss the importance of GastroPlus.

GastroPlus is increasingly being used in regulatory science and model-informed drug development (MIDD). Physiologically Based Pharmacokinetic (PBPK) modelling has been acknowledged by regulatory agencies like the FDA and EMA as a scientifically sound method for providing scientific information to aid in drug development decisions and minimise the need for large clinical trials (Kollipara et al., 2024).PBPK simulations have been accepted by the FDA for applications such as drug–drug interaction (DDI) prediction, dose selection, pediatric extrapolation, and first-in-human studies. Likewise, EMA guidelines favour the use of mechanistic PBPK modelling in the assessment of pharmacokinetics in various physiological states and special populations. Due to its mechanistic absorption model (ACAT) and whole-body PBPK framework, GastroPlus is often employed in regulatory submissions (Yang et al., 2024).An important regulatory use is the justification of waiving bioavailability/bioequivalence studies, where GastroPlus is used to predict in vivo bioavailability/bioequivalence from in vitro dissolution data. This is especially useful for Biopharmaceutics Classification System (BCS) based waivers. Furthermore, GastroPlus is extensively used for virtual bioequivalence (VBE) studies, which compare a generic an

eference formulation using simulated PK profiles. Also, GastroPlus can be used to simulate various clinical scenarios before clinical trials, enabling model-informed drug development (Cvijić et al., 2023). This involves optimising dosing regimens, investigating food effects and assessing inter-individual variability. Given the regulatory guidance that computational modelling is gaining in popularity, GastroPlus is becoming a valuable tool to connect preclinical information with clinical decision-making.

A comparison to other PBPK software

Physiologically based pharmacokinetic (PBPK) modelling platforms are broadly applied in drug research, and there are several drug disposition simulation and prediction software packages available. Of these, the most widely used systems are GastroPlus, Simcyp Simulator and PK-Sim, which have unique advantages and disadvantages (Dallmann et al., 2024).

Software	Strengths	Limitations
GastroPlus	Strong ACAT-based oral absorption modelling, robust integration of dissolution, and PBPK frameworks are widely used in formulation development and regulatory submissions.	It is a commercial software that requires a license. It is relatively high-cost.
Simcyp Simulator	Good population-based pharmacokinetics modelling, strong capabilities for drug-drug interaction and variability analysis.	It has a complex interface that requires extensive training and user expertise.
PK-Sim (Open Systems Pharmacology)	It is an open-source platform, transparent modelling structure, and strong mechanistic PBPK framework.	It has limited advanced GI absorption modelling compared to the GastroPlus ACAT system.

Figure 2 Comparison of GastroPlus to Other PBPK Softwares

One of GastroPlus's most unique features is its Advanced Compartmental Absorption and Transit (ACAT) model, which simulates the behaviour of gastrointestinal formulations in a detailed manner. Simcyp, on the other hand, is more widely used for the variability of the population and for clinical trial simulation, while PK-Sim provides a flexible open-source environment for academic research and model transparency (Pawestri, 2023).

In general, the choice of PBPK software application will be dependent on the research question; GastroPlus is best suited for oral absorption and formulation studies, while Simcyp and PK-Sim will be applied to population-based pharmacokinetic and academic studies (De Sutter et al., 2024).

Future Direction:

Advancements in computational capacity, data science, and regulatory acceptance of model-informed drug development will greatly influence the future of GastroPlus and physiologically based pharmacokinetic (PBPK) modelling. A notable trend is the application of artificial intelligence (AI) and machine learning (ML) to enhance PBPK models. Another promising area of development is the use of artificial intelligence (AI) and machine learning (ML) in conjunction with PBPK modelling (Garg et al., 2026). Parameter prediction can be improved using AI-based models to predict key parameters like: solubility, permeability, metabolic

clearance, and transporter kinetics. These methods, in conjunction with the use of GastroPlus simulations, enhance the accuracy of predictions at early stage of the drug development process and minimize the need for large amounts of experimental data. AI also facilitates automatic sensitivity analysis and quicker optimization of the formulation and dosing strategy, improving the efficiency and cost-effectiveness of drug development (Kreutz et al., 2026).

Real-time clinical modelling is another direction of future research. As more clinical pharmacokinetic data become available and digital health technologies become more prevalent, PBPK models are projected to become dynamic, continually updating predictions in real-time. One or more gastroPlus-based frameworks can incorporate patient specific information (e.g. renal function, liver biomarkers, therapeutic drug monitoring) to continually update the PK predictions during clinical treatment. In critical care and precision medicine settings, this will result in much better individualisation of treatment, therapeutic drug monitoring, and adaptive trial design (Ali et al., 2026).Digital twin pharmacology is a truly groundbreaking development in PBPK. A digital twin is a virtual copy of a patient that can be used to model the real-time physiologic and pharmacologic responses of that patient. Digital twins can incorporate genomic, proteomic, metabolic, and clinical data to enable prediction of individual drug response with high accuracy using GastroPlus as a mechanistic core. This allows for simulation of various therapeutic scenarios before drug administration, enhancing safety and efficacy results. Another way digital twin systems can help is by enabling virtual clinical trials, which help limit the number of patients required and speed up regulatory approval (Samajdar et al., 2025).

In conclusion, the integration of AI, real-time data, and digital twin technology is poised to transform the landscape of PBPK modeling. GastroPlus will also be a key component in this transformation, moving beyond being just a predictive simulation tool to an intelligent and adaptive platform for precision pharmacology and next-generation drug development.

CONCLUSION

GastroPlus has proven to be a critical computational resource for the modern pharmaceutical research and drug development environment. It integrates physiochemical drug properties with gastro-intestinal physiological parameters and offers a solid predictive tool for the understanding of the oral drug absorption and of systemic pharmacokinetics. It is able to mimic real-life clinical settings, such as fed/fasted states, disease states and population variability, which is extremely useful to formulation scientists and clinical pharmacologists (Dhivya et al., 2025).

By using GastroPlus, experimental workload is significantly reduced, late drug failure is minimized, and rational dose optimization and formulation strategies are supported for drug decision making. The benefits of this research are offset by the accuracy and precision of predictions, which relies on the data quality and correct modelling validation. Thus, experimental validation is still required in order to validate the results from in silico studies.

To conclude, GastroPlus is one of the most fundamental tools in today's model-informed drug development (MIDD) workflow and is gaining increasing importance as a key enabler between in vitro and in vivo results, and will ultimately play a role in safer, faster and cost-efficient drug development (Chou et al., 2026).

REFERENCE:

Ali, A., Muhammad, I. N., Iffat, W., Tasneem, S., Ali, S. A., Khan, S. J., & Siddique, S. (2026). Al-driven ANN and RSM-CCD integrated optimization of cinnarizine-domperidone

bilayer tablet: In-vitro evaluation and in-silico PBPK modeling using GastroPlus®. *Pakistan Journal of Pharmaceutical Sciences*, *39*(2).

Almajidi, Y. Q., Faisal, R. R., & Yaseen, A. (2025). GastroPlus® as simulating/conducting software for modeling physiologically-based pharmacokinetics & physiologically based biopharmaceutics. *Maaen Journal for Medical Sciences*, *4*(2), 10.

Arafat, M., Sarfraz, M., & AbuRuz, S. (2021). Development and in vitro evaluation of controlled release Viagra® containing Poloxamer-188 using Gastroplus™ PBPK modeling software for in vivo predictions and pharmacokinetic assessments. *Pharmaceuticals*, *14*(5), 479.

Arora, D., & Khurana, B. (2022). Computer-aided biopharmaceutical characterization: gastrointestinal absorption simulation and in silico computational modeling. In *Computer aided pharmaceutics and drug delivery: an Application Guide for Students and Researchers of Pharmaceutical Sciences* (pp. 189-215). Springer.

Batchelor, H. (2026). Modeling and Simulation for Pediatric Formulation Development. In *Pediatric Formulations: A Roadmap* (pp. 413-422). Springer.

Chou, W.-C., Li, M., & Lin, Z. (2026). Application of machine learning and artificial intelligence methods in physiologically based pharmacokinetic modeling. In *Machine Learning and Artificial Intelligence in Toxicology and Environmental Health* (pp. 99-138). Elsevier.

Cvijić, S., Ignjatović, J., Parojčić, J., & Đurić, Z. (2023). Gastrointestinal absorption. *Computer-Aided Applications in Pharmaceutical Technology: Delivery Systems, Dosage Forms, and Pharmaceutical Unit Operations*, 199.

Dallmann, A., Teutonico, D., Schaller, S., Burghaus, R., & Frechen, S. (2024). In-Depth Analysis of the Selection of PBPK Modeling Tools: Bibliometric and Social Network Analysis of the Open Systems Pharmacology Community. *The Journal of Clinical Pharmacology*, *64*(9), 1055-1067.

De Sutter, P.-J., Gasthuys, E., & Vermeulen, A. (2024). Comparison of monoclonal antibody disposition predictions using different physiologically based pharmacokinetic modelling platforms. *Journal of Pharmacokinetics and Pharmacodynamics*, *51*(6), 639-651.

Dhivya, G., Gowrishallini, P., Devi Sowndarya, N., & Suprraja, S. (2025). Virtual Humans in Drug Development: Integrating Digital Models with Pharmacological Science. *Asian Journal of Pharmaceutical Research and Development*, *13*(3), 145-152.

Garg, R., Kotak, B. P., Pebbili, K. K., Yadav, S. K., Kollipara, S., Saha, P., Chander Kanuru, V. P., & Bhureddy, S. (2026). PHYSIOLOGICALLY BASED BIOPHARMACEUTICS MODELLING FOR MESALAMINE SACHET FORMULATIONS: PREDICTION OF IN VIVO PERFORMANCE AND COMPARISON AMONG FORMULATIONS AVAILABLE IN INDIA. *International Journal of Medicine & Public Health*, *16*(1), 1202.

Godinho, M. M. (2025). PBPK Modeling to Predict Pharmacokinetics of Indomethacin and Phenytoin: A Focus on Pregnancy and Enzyme-Mediated Drug-Drug Interactions.

Gomes, B., & Vale, N. (2025). Simulated Pharmacokinetic Compatibility of Tamoxifen and Estradiol: Insights from a PBPK Model in Hormone-Responsive Breast Cancer. *Targets*, *3*(4), 33.

Hamdi, D. S., & Mohamed, M. B. M. (2022). Formulation of metoclopramide HCl gastroretentive film and in vitro-in silico prediction using Gastroplus® PBPK software. *Saudi Pharmaceutical Journal*, *30*(12), 1816-1824.

Hens, B., Seegobin, N., Bermejo, M., Tsume, Y., Clear, N., McAllister, M., Amidon, G. E., & Amidon, G. L. (2022). Dissolution Challenges Associated with the Surface pH of Drug

Particles: Integration into Mechanistic Oral Absorption Modeling: Hens et al. *The AAPS journal*, *24*(1), 17.

Hui, Z., Lai-Fa, W., Xue-Qin, W., Ling, D., Bin-Sheng, H., & Li, J.-M. (2024). Mechanisms and therapeutic potential of chinonin in nervous system diseases. *Journal of Asian Natural Products Research*, *26*(12), 1405-1420.

Jadhav, H., Augustijns, P., & Tannergren, C. (2023). Approaches to account for colon absorption in physiologically based biopharmaceutics modeling of extended-release drug products. *Molecular Pharmaceutics*, *20*(12), 6272-6288.

Kadiri, S. K., Sathavalli, D., & Tiwari, P. (2024). delivery system. *Computational Drug Delivery: Molecular Simulation for Pharmaceutical Formulation*, 71.

Khadka, P., Tucker, I. G., & Das, S. C. (2023). In vitro dissolution testing of rifampicin powder formulations for prediction of plasma concentration–time profiles after inhaled delivery. *Pharmaceutical research*, *40*(5), 1153-1163.

Kollipara, S., Martins, F. S., Sanghavi, M., Santos, G. M. L., Saini, A., & Ahmed, T. (2024). Role of physiologically based biopharmaceutics modeling (PBBM) in fed bioequivalence study waivers: regulatory outlook, case studies and future perspectives. *Journal of Pharmaceutical Sciences*, *113*(2), 345-358.

Kreutz, A., Chang, X., Lawless, M., Proença, S., Schaller, S., Kleinstreuer, N., & Hogberg, H. T. (2026). Comparison of physiologically based pharmacokinetic modeling platforms for developmental neurotoxicity in vitro to in vivo extrapolation. *Toxicological Sciences*, *209*(2), kfaf147.

Krstevska, A., Nedelkov, I., Petrović, M., Ivković, B., Dobričić, V., & Cvijić, S. (2025). Simulation-guided dissolution testing: Coupling DDDPlus™ and GastroPlus® to predict aripiprazole oral bioperformance. *Journal of Drug Delivery Science and Technology*, 107621.

Kuentz, M., Nick, S., Parrott, N., & Röthlisberger, D. (2006). A strategy for preclinical formulation development using GastroPlus™ as pharmacokinetic simulation tool and a statistical screening design applied to a dog study. *European journal of pharmaceutical sciences*, *27*(1), 91-99.

Liu, J., Dolton, M. J., Nagapudi, K., & Chiang, P.-C. (2025). Exploring a new approach in biopharmaceutics to improve the estimation of stomach solubilization from the mathematical model with a single stomach compartment setting: The impact of stomach solubilization on the food effect of quazepam. *Journal of Pharmaceutical Sciences*, *114*(11), 103981.

Morningstar-Kywi, N., Morris, D. N., Romero, R. M., & Haworth, I. S. (2023). Teaching of drug disposition using physiologically based pharmacokinetic modeling software: GastroPlus as an educational tool. *Advances in Physiology Education*.

Pawestri, S. A. (2023). Application in silico modeling simulation in bioequivalence studies: A review. *Journal of Food and Pharmaceutical Sciences*, 763-769.

Pernaa, J. (2022). Possibilities and challenges of using educational cheminformatics for STEM education: A SWOT analysis of a molecular visualization engineering project. *Journal of Chemical Education*, *99*(3), 1190-1200.

Perrier, J., Gualano, V., Helmer, E., Namour, F., Lukacova, V., & Taneja, A. (2023). Drug–drug interaction prediction of ziritaxestat using a physiologically based enzyme and transporter pharmacokinetic network interaction model. *Clinical and Translational Science*, *16*(11), 2222-2235.

Samajdar, S. S., Biswas, N., Modi, A., Saboo, B., Hirani, H., & Joshi, S. R. (2025). Artificial Intelligence, Pharmacokinetic/Pharmacodynamic Modeling, and Digital Twins in Clinical Pharmacology: A Convergence toward Model-informed Precision Dosing. *SBV Journal of Basic, Clinical and Applied Health Science*, *8*(4), 229-235.

Shijith, K., Charyulu, N. R., Chandran, S. C., Patil, P., & Jose, J. (2025). Predicting the Pharmacokinetic behavior of Mangiferin using Gastro Plus and ADMET Predictor: Insights for Optimized Formulation Development. *Research Journal of Pharmacy and Technology*, *18*(6), 2796-2802.

Silva, D. A., Cor, M. K., Lavasanifar, A., Davies, N. M., & Löbenberg, R. (2022). Using GastroPlus to teach complex biopharmaceutical concepts. *Pharmacy Education*, *22*(1), 336-347.

Tubic-Grozdanis, M., Bolger, M. B., & Langguth, P. (2008). Application of gastrointestinal simulation for extensions for biowaivers of highly permeable compounds. *The AAPS journal*, *10*(1), 213-226.

Wang, L., Chen, J., Chen, W., Ruan, Z., Lou, H., Yang, D., & Jiang, B. (2023). In silico prediction of bioequivalence of atorvastatin tablets based on GastroPlus™ software. *BMC Pharmacology and Toxicology*, *24*(1), 69. https://doi.org/10.1186/s40360-023-00689-4

Yang, C.-G., Chen, T., Si, W.-T., Wang, A.-H., Ren, H.-C., & Wang, L. (2025). High-performance PBPK model for predicting CYP3A4 induction-mediated drug interactions: a refined and validated approach. *Frontiers in Pharmacology*, *16*, 1521068.

Yang, R., Lin, Y., Chen, K., Huang, J., Yang, S., Yao, A., Yang, X., Lei, D., Xiao, J., & Yang, G. (2024). Establishing virtual bioequivalence and clinically relevant specifications for omeprazole enteric-coated capsules by incorporating dissolution data in PBPK modeling. *The AAPS journal*, *26*(4), 82.

Yasin, H. K. A., Al-Tabakha, M. M., & Chan, S. Y. (2025). Advancing Personalized Medicine Through FDM 3D Printing: Ketoprofen Tablets with Customizable Drug Release Profiles and In Silico Simulation. *Pharmaceutics*, *17*(11), 1495.

Yin, X., Cicali, B., Rodriguez-Vera, L., Lukacova, V., Cristofoletti, R., & Schmidt, S. (2024). Applying physiologically based pharmacokinetic modeling to interpret carbamazepine's nonlinear pharmacokinetics and its induction potential on cytochrome P450 3A4 and cytochrome P450 2C9 enzymes. *Pharmaceutics*, *16*(6), 737.

Zagaja, K. M. P., Kopec, A. K., Harney, J., Hardink, M. A., Middleton, J., & Hens, B. (2026). Establishing the Human Duodenum Chip as a Surrogate for Effective Human Permeability: In Vitro and In Silico Assessment. *The AAPS journal*, *28*(1), 1-13.