

IN SILICO GASTROINTESTINAL SIMULATION MODELS FOR ORAL DRUG ABSORPTION

Anjali Joshi*, Shailendra Chauhan, Hemant Khambete, Sanjay Jain

Faculty of Pharmacy, Medicaps University, Indore, Madhya Pradesh, 453331, India.

Article Received: 08 September 2026 | Article Revised: 15 September 2026 | Article Accepted: 16 September 2026

*Corresponding Author: Anjali Joshi

Faculty of Pharmacy, Medicaps University, Indore, Madhya Pradesh, 453331, India.

DOI: <https://doi.org/10.5281/zenodo.23052985>

How to cite this Article: Anjali Joshi, Shailendra Chauhan, Hemant Khambete, Sanjay Jain (2026) *IN SILICO GASTROINTESTINAL SIMULATION MODELS FOR ORAL DRUG ABSORPTION*. World Journal of Pharmaceutical Science and Research, 5(10), 31-45.



Copyright © 2026 Anjali Joshi | World Journal of Pharmaceutical Science and Research.

This work is licensed under creative Commons Attribution-NonCommercial 4.0 International license (CC BY-NC 4.0).

ABSTRACT

This review outlines the concept of *in silico* GI simulation models for oral drug absorption. It highlights the gap between standard laboratory testing and actual clinical reality by providing the mechanistic prediction that shows physiological alterations in specific population by using simulation models. As the oral route is the most common route but still prediction of gastrointestinal absorption is a major challenge in drug development because the *pH* of GIT is different in both gastric environment and in small intestine. Highly acidic gastric environment to alkaline small intestine which can degrade acid labile drug, also there is lack of data on volume and composition of GI fluid in different population. *In silico* GI simulation models, such as physiologically based pharmacokinetics (PBPK), Advanced compartmental absorption and transit (ACAT), Compartmental Absorption and Transits (CAT), and various software platforms such as Simcyp, GastroPlus, and PK-Sim they provide mechanistic predictions for the oral absorption. These models combine anatomical, physiological, and drug-specific parameter that simulate absorption, distribution, metabolism and elimination processes. They also optimize dosing strategies, guide formulation development, and predict pharmacokinetic variability in different populations. *In silico* approaches reduce reliance on animal studies, accelerate development, and enhance regulatory decision-making in a oral drug therapy. These types of model can enable Virtual Clinical Trial in future which can replace human testing.

KEYWORDS: GastroPlus; SimCYP; PK-sim; ACAT; PBPK Model; Mechanistic.

INTRODUCTION

The oral route is the common, convenient and easiest route for delivery of various drugs, and many advanced approaches have been developed and studied to achieve specific objectives.^[1] Oral route is very common route for administration of drug, even also among the newly introduced drugs it will probably consider to be the most common in the coming years. There are many advantages for the widespread use of the oral route in drug delivery when

compared with other routes of administration such as pulmonary, intravenous and rectal delivery. Oral drug delivery system are safe and convenient for most of the patients as the patients can administer the dosage form to themselves so that discomfort is minimal.^[2,3] Early detection of these issues allows for better decision-making, whether that means adjusting the treatment or discontinuing the drug altogether in more severe cases. Drug absorption is affected by various factors such as interaction in the gastrointestinal tract, physicochemical properties, etc.^[4] The objective of this review is to provide comprehensive evaluating *in silico* gastrointestinal simulation models to predict oral drug absorption. It focuses on their mechanism, applications in drug development and prediction of ADME properties. There are some limitations of experimental oral absorption studies such as the *pH* of GIT ranges from acidic stomach to alkaline intestine which can degrade acid labile drug and also there is lack of detailed data on volume and composition of GI fluid across different populations.^[5,6] Mainly animals are used in preclinical studies for studying the effect of drug but animals have different gut *pH* levels, transit time and metabolic enzymes as compare to humans thus a drug showing optimum response in animals may not show same effect on humans. Since *in vivo* and human data are limited, therefore computational and/or mathematical tools are used for identification of absorption problems from discovery stage or early development stage,^[2] also designing oral formulations for large biomolecules like peptides and proteins is very challenging because of low stability and poor absorption in the gut thus molecular dynamics simulations are utilized.^[7] Models like Physiologically-Based Pharmacokinetic Modelling (PBPK) allow researchers to simulate entire body in which different variables like patients age, disease state and meal are applied to predict how absorption will change without the need of a clinical trials,^[6] also for understanding pharmacological and toxicological effect at the target site pharmacokinetic profile plays an important role.^[8] Modelling tools help in dose finding, formulation selection and design of clinical studies.

Importance of In Silico Approach in Oral Drug Absorption

This review examines *in silico* models designed to simulate a gastrointestinal process for evaluating drug pharmacokinetics after oral administration. To better characterize and understand these models, the Absorption, Distribution, Metabolism, and Excretion (ADME) processes are analyzed by *in silico* prediction models.^[9,10] *In silico* approaches serve as a predictive tool for digestive behavior, enabling the estimation of parameters such as drug digestibility and gastric emptying through extrapolation of existing data within defined model constraints. Overall, this review highlights the current advancements and applications of *in silico* modelling in representing the human digestive system.^[11] In addition to modeling gastrointestinal processes, *in silico* GI simulation models have become an essential tools for overcoming these challenges as they serves as mechanistic models.^[12] of drug absorption and distribution, allowing the prediction of pharmacokinetics in diverse populations, reducing the reliance on animal studies, accelerating progression from discovery to clinical trials, improving cost-efficiency, and providing supporting data for regulatory submissions.^[11]

GASTROINTESTINAL ABSORPTION SIMULATION

Computer-aided biopharmaceutical characterization involves application of validated mathematical model and simulation techniques to predict, analyze, and optimize the ADME properties of drug, which give emphasis on gastrointestinal absorption. *In silico* absorption model must integrate mathematical representations of processes such as membrane permeation, solubility, dissolution, partitioning, particle size and growth, physiological descriptions of different gastrointestinal regions, including fluid volumes, transit times, and luminal *pH*.^[13] As they are the basic

processes of human gastrointestinal tract. Simulation of motility of gastrointestinal tract is very challenging due to complex human physiology, it plays a major role in mixing, absorption and elimination of drug.^[14]

History of Simulation Models

The evolution of simulation models in biopharmaceutics has progressed significantly over the decades. In the 1980s, the first mathematical approach that is compartmental pharmacokinetic was used to describe drug absorption using a linear compartmental framework. During the 1990s, the Advanced Compartmental and Transit model (ACAT model) was introduced by YU and Amidon having nine gastrointestinal compartments. In the 2000s, physiologically based pharmacokinetic models integrated with gastrointestinal simulations were introduced with various commercial software platforms such as GastroPlus and Simcyp. They are used to enhance predictive capabilities, also it was estimated that high-throughput method gives a reliable, robust and animal-free evaluation.^[15] By the 2010s, Regulatory acceptance was provided to PBPK simulation data for drug submission and labelling purposes. In 2020s, the simulation techniques were incorporated with artificial intelligence (AI) and has enhanced the accuracy and efficacy of predictive modelling. The computational tools are also paired with machine learning to screen thousands of molecules. For example QSAR models were built using deep neural network to test permeability.^[16] Software modelling is also used to study large and complex molecules. A comprehensive analysis evaluates how computer-based QSAR models, cell assays and animal studies predict intestinal absorption across a dataset of 1000 diverse population.^[17] QSAR tools are paired with docking pipelines to design central nervous system agents, tracking how elective structural adjustment alter compound binding affinity with virtual distribution metrics.^[18]

GASTROINTESTINAL TRACT: ANATOMY AND PHYSIOLOGY

The gastrointestinal tract is a tubular system which is hollow and it begins with the oral cavity, from where food is ingested which extends through the pharynx, oesophagus, stomach, small intestine (duodenum, jejunum, and ileum), and a large intestine (*Caecum*, transverse colon, ascending colon, sigmoid colon, descending colon), at last terminates at the rectum and anal canal.^[19,20] In human length of the gastrointestinal tract is approximately 9 meters.

The stomach has a *pH* ranging from 1.2-3 which exhibits a highly acidic,^[5] its volume is around 900 mL with a transit time of 20-120 minutes. It is mainly responsible for the absorption of weakly acidic drugs. As we know that small intestine is divided in three parts then the duodenum has 4-5.6 *pH* with a volume of 25-50 mL which has a short transit time of around 5-10 minutes making it a region of high permeability. Another part of small intestine is jejunum which is subdivided into four other segments mainly the jejunum has a *pH* range of 6-7 and has volume of about 100 mL with transit time of 60-90 minutes. It is a major site for drug absorption. Last part of small intestine is ileum it has a *pH* range of 7-7.5 with a volume of 129 mL and transit time is 90-180 minutes, through this site moderate drug absorption occurs.

The large intestine also has various parts first we will discuss about the caecum, which has a *pH* of around 7. Another one is the colon which exhibits a *pH* range of 6–7.5 which has low fluid volume and has a prolonged transit time of around 12–48 hours, results in limited drug absorption in that region. Around 40% of oral medications are approved over the last decade shows a significant food effect that changes in the body.^[21,3]

As the ACAT model divides the gastrointestinal tract into 9 compartments. Each of 9 compartments has its own fixed fluid volume. At fasted state models use smaller volumes but at fed state volume increases to 900-1000 mL.^[22] The *pH*

of gastric fluid affect degree of ionization of molecules of drug, influencing their permeation and dissolution behavior, along with the drug delivery systems performance. The gastric emptying time was measured by magnetic resonance imaging. Time required to get back to fasted gastric volumes, is approximately 45 min after a glass of water approx. 240 mL and more than 6 h after a high-caloric breakfast.^[23,24]

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

In 1995, Amidon *et al.* introduced the concept of Biopharmaceutics Classification System (BCS) which is based on solubility and permeability.^[25] It is Categorized into four classes^[26,27] that are as follows:

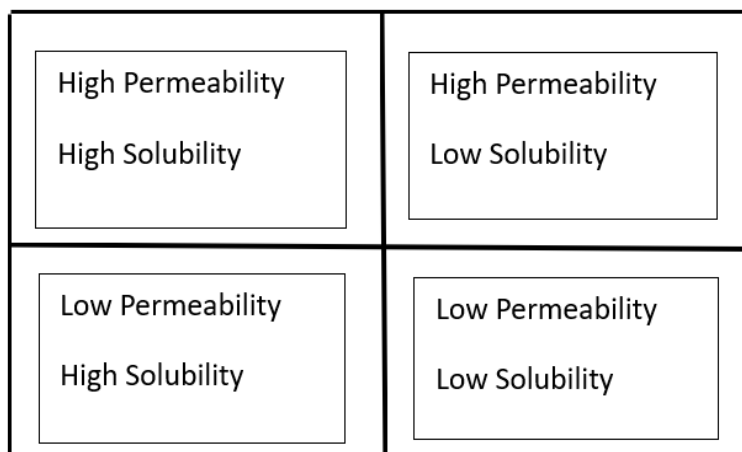


Figure 1: BCS Classification.

The goal of biopharmaceutical classification system is to demonstrate how in-silico predictions of physical and chemical properties can be used to estimate solubility and permeability. The in-silico calculation of the physical and chemical properties are useful for the early classification of drugs according to the BCS classification that are useful in the research and development process of oral drug products.^[26] The rate-limiting step for oral drug absorption was determined according to this classification. The rate limiting step for class II is dissolution.^[28] *In silico* models are heavily utilized to address the dissolution limitations of BCS Class II ‘brick dust’ drugs.^[29] There are various applications for BSC Class drugs one of which is to improve the evaluation of Class I, an artificial gut simulator was developed that tracks dissolution and membrane transport simultaneously,^[30] Second is that class II compounds include coupling miniaturized biorelevant dissolution systems with computer modelling. A study used an advanced tiny-TIM artificial gut model with simulation to map an investigational drug.^[31] Another study shows that virtual trials are used to check isosorbide mononitrate which is a BCS Class I drug and researchers simulated how different batches dissolve and move through the body.^[32]

Table 1: Characteristics of BCS Classification Groups.

Features	BCS Class I	BCS Class II	BCS Class III	BCS Class IV
Rate limiting step	Gastric Emptying	Dissolution	Permeability	Both Dissolution and Permeability
Biowaiver	Possible	Conditional (acid-soluble)	Possible with excipient control	Not eligible
Example	Metoprolol, Propranolol, Diltiazem, Verapamil.	Ibuprofen, Carbamazepine, Ketoconazole and Phenytoin.	Cimetidine, Ranitidine, Atenolol, Cefadroxil, and Neomycin	Hydrochlorothiazide, Furosemide and Cyclosporin A.

GASTROINTESTINAL SIMULATION MODELS

Physiologically Based Pharmacokinetic (PBPK) Models

Teorell introduced the fundamental framework for Physiologically based pharmacokinetic modelling (PBPK) was proposed in 1937.^[33] Also known as physiologically based biopharmaceutics modeling when PBPK analysis is applied for the applications of biopharmaceutics.^[34,35] These models are considered as the advances in *in silico* tools, that integrate both clinical and non-clinical data.^[36] PBPK based software programs, Gastroplus and SIMCYP were used for building PBPK models.^[37] The primary objective of PBPK models is to predict pharmacokinetic behaviour of a substance by utilizing its preliminary ADME properties.^[38] These models enable assessment of accumulation of a compound or drug in specific designated organs by accounting for the rates of absorption, distribution, and metabolism within individual tissues.^[39,12,13] Additionally, PBPK models are valuable for predicting pharmacokinetic variability across different populations, including variations in ethnicity, age groups, and disease conditions. Surveys and polls showed that approximately 70% of pharmaceutical developers actively employ early-stage PBPK/PD modelling in therapeutic areas.^[40] Structurally, a PBPK platforms are divided into two primary elements: a biological framework containing host-specific, drug-independent physiological variables, with a substance-specific module that are used characterizes different ADME properties in various tissue compartments.^[33] For example, Jain et al. (1981) used full body PBPK model to look at how zinc sulfate moves through rates. They did this by considering the rats body as a network of 21 connected organ parts.^[9] The PBPK model has some advantages some of them are as follows: 1)PBPK models provide a real representation of the human body because they are based on actual physiological parameters such as size of organs, perfusion rates, and tissue characteristics of different body parts. 2)They can predict human pharmacokinetics from *in vitro* and animal data, which reduces the need for extensive clinical trials. 3) These models are used throughout drug development in both early and late stages, to get a clear look at ADME processes. They make it easier to guess how a drug will work in different species and to change in specific populations, such as children or people with certain health conditions.^[42] This study is clearly stated in recent work by Robins et.al.(2024) who integrated PBPK framework within PK-Sim to show age related gastrointestinal updates^[43] 4)PBPK modeling helps in predicting drug–drug interactions by incorporating enzyme and transporter mechanisms. 5)It also assists dose optimization by simulation of different dosing conditions and routes of administration. 6) PBPK models save time and cost during drug development in comparison to *in vivo* studies.^[44] Major regulatory bodies including are EMA and FDA approving their use much more often now. It also has some of the disadvantages such as 1) PBPK models require a large amount of detailed physiological and drug-specific data, which may not always be available. 2) This type of model developed is complex and requires expertise in pharmacokinetics and modelling software. 3) They are based on some assumptions, which causes uncertainty and affect prediction accuracy. 4) PBPK model validation is challenging process and also it depends on the availability of the reliable experimental data. This difficulty was seen during trials with seven different CYP3A4 substrate drugs, for calculating clearance gut enzyme data alone failed.^[45] 5) These models depend on specialized software like PK-Sim or Simcyp, which are not always be accessible. 6) For new drugs those having limited data, the predictions may be less reliable, and the models can be computationally intensive, and they requiring proper technical resource.7) On combining *in silico* molecular descriptors with *in vitro* clearance data by random forest regression, reduces pharmacokinetics prediction errors in a dataset of around 600 compounds.^[46]

Variables included in this model

- 1) Gastric Emptying: It is a physiological process influenced by the fed and fasted state. It is used for determining T_{max} and Peak plasma concentration.
- 2) pH - dependent Solubility: It integrates systemic GI pH with systemic blood and tissue pH to predict how the drug will distribute into different organ after it has been absorbed. This are useful for weakly basic drugs such as ketoconazole, posaconazole and dipyridamole. These drugs easily dissolves in acidic environment but precipitates in intestine for this reverse translation modeling is used to adjust these precipitation.^[47] Simulations were used to evaluate how acid-reducing drug alter the absorption of weaky basic drugs.^[48]
- 3) Dissolution Rate: It is based on the capacity of solvent of the GI fluid and the blood flow.
- 4) Intestinal Permeability: It represents the highest level of complexity as it includes active transporters (p-glycoprotein efflux transporter) and gut-wall metabolising enzyme (CYP3A4) in the enterocytes.

Compartmental Absorption and Transit Models

The Compartmental Absorption and Transit model (CAT model) was introduced by Amidon and Co-workers^[41] in 1996. It represents a significant advancement in PBPK modelling. This model formulates the gastrointestinal tract into a series of compartments, including one compartment for stomach, one for the colon, one representing the plasma and seven for small intestine.

The mathematical framework of CAT model relies on a system of ten ordinary differential equations (ODEs) and these equations are solved numerically by eighteen parameters.

The CAT model has been appropriately applied to various case studies involving oral drug administration, encompassing both immediate-release and controlled-release formulations, including drugs classified under Biopharmaceutics Classification System (BCS) Class IV.^[9] The CAT model usually assumes that poorly water-soluble weak base such as cinnarizine dissolves quickly but they supersaturates when simulation was conducted for intestinal fluid.^[49] A multi-bolus continuous approach has been developed for tracking the movement of drug against local blood flow while reducing the need for complex parameter inputs.^[50]

Variables included in this model

1. Gastric Emptying: In the basic CAT model, this variable is not included. The drug dose is typically assumed to enter the first segment of the small intestine directly.
2. pH -dependent Solubility: This model generally assumes a uniform pH throughout the intestinal segments. There is no complexity of regional pH change.
3. Dissolution Rate: The CAT model typically assumes the drug is already in solution (liquid phase). It does not provide a mechanistic calculation for the dissolution of solid dosage forms.
4. Intestinal Permeability: It assumes a constant permeability (P_{eff}) value across all segments of the small intestine.

Advanced Compartmental Absorption and Transit (ACAT)

Success of the CAT framework influenced researchers to introduced the ACAT Model (Advanced Compartmental Absorption and Transit), and software for ACAT is GastroPlus.^[51,53] Because the ACAT model is a commercial in nature but its specific operational details are unavailable, yet it has been proven to be highly successful in simulation of diverse drug delivery pathways. ACAT model divides the GI Tract into distinct 9 compartments, each have specific

physiological parameters mass balance equations govern drug between compartments^[9] and divides each compartment into six states drug component including undissolved, degraded, dissolved, metabolized, unreleased and absorbed.^[53,54]

The mechanistic ACAT models are highly effective for evaluating virtual bioequivalence and establishes *in vitro-in vivo* extrapolation (IVIVE) for immediate-release formulations.^[53]

Table 2: Compartments of ACAT model.

Organs	pH	Volume of Media	Transit Time	Absorption
Stomach	1.2-3	900ml	20-120 min	Weakly acidic drugs
Duodenum	4 – 5.6	25-50	5-10 min	High Permeability
Jejunum I	6 – 6.5	100ml	60-90	Primary Absorption Site
Jejunum II	6.5-7	100ml	60-90	
Ileum	7 – 7.5	120ml	90-180	Moderate drug Absorption
Colon	6 – 7.5	Low fluid Volume	12-48 hours	Limited Drug Absorption
Caecum	7			

Variables included in this model

1. Gastric Emptying: This model includes the stomach and uses a first-order rate constant which is applied to regulate that how a therapeutic compound migrates toward duodenum.
2. pH-dependent Solubility: This model assigns pH values based on regions for 9 distinct segments (stomach to colon). It uses the Henderson-Hasselbalch equation to calculate ionization.^[56]
3. Dissolution Rate: It applies the Noyes-Whitney equation. It uses the drug's particle size and calculates dissolution based on the fluid volume of each segment. Studies shows that using exact particle distribution data in computer simulations is a reliable way to check the quality of different batches before testing them on real patients.
4. Intestinal Permeability: It estimates that absorption is often higher in the proximal small intestine than in the distal segments.

Table 3: Comparison of major gastrointestinal simulation models used for oral drug absorption.

Model	Concept	Parameters	Applications	Strengths	Limitations	Software
PBPK	Combines drug specific features with physiological/biochemical data	Physiology, absorption, distribution, metabolism and excretion	Drug development, exposure prediction, evaluation of drug-drug interactions, and regulatory applications	The use of a mechanistic approach and the capability of accounting for physiological variation	Need for good physiological and drug-specific input data	Simcyp®, PK-Sim®
CAT	Compartmental modelling of gastrointestinal absorption and transit	Gastrointestinal transit, dissolution, absorption and permeability	Oral drug absorption and exposure prediction	Relatively structured model of GI processes	Potential oversimplification of some physiological processes	GastroPlus®
ACAT	Describes the gastrointestinal tract using interlinked compartments	Gastric emptying, intestinal transit, dissolution, solubility and permeability	Regional absorption and oral drug exposure prediction	Good for mechanistic representation of gastrointestinal absorption and transit	Needs several physiological and drug parameters	GastroPlus®

APPLICATIONS OF IN SILICO MODELS

1. In research and development: PBPK models are highly valuable across all drug research stages. They do three things: supporting regulatory communication, making choices during clinical trials, and better understanding that why certain type of clinical results occur.^[33]
2. Safety evaluation of botanical products: Computational models are responsible for screening complex plant and herbal chemicals by combining QSAR and PBPK data. This approach predicts absorption which is responsible to test natural products safely.^[57]
3. Dosing and Interaction studies: There are various tools that are used for managing drug-drug interactions. For example researchers used PK-Sim to build simulation profile for the epilepsy medication such as valproic acid and estimated how its level is altered after coadministration of antibiotic meropenem.^[58]
4. Clinical Trial Designing: Computer-aided simulations are very important clinical trial protocol to investigate drug candidate. This simulation evaluates how other conditions such as aging, liver impairment, fasted and fed condition, and coadministration affects drug level in blood.^[59]
5. Industrial applications: Drug manufacturer uses these computational frameworks to conduct virtual bioequivalence trials.^[60] For example, modelling enteric-coated omeprazole capsules to identify dissolution specifications^[61], also open-source PK-Sim software was utilized to simulate the oral absorption of pravastatin in populations suffering from inflammatory bowel disease and irritable bowel syndrome.^[62,63]
6. PBPK models are utilized to predict human pharmacokinetic (PK) profiles at anticipated clinical doses and dosing regimens, during the lead optimization phase.
7. When the candidate were selected at selection stage, PBPK modelling is particularly valuable when a drug is metabolized by some enzyme such as polymorphic enzymes (CYP2D6 or CYP2C19). In such cases, simulations can estimate drug exposure in different subpopulations, including poor metabolizers, thereby aiding decisions on their inclusion or exclusion in first-in-human (FIH) trials.
8. In the drug development phase, one of the most widely applied uses of PBPK modelling is the prediction and assessment of drug-drug interaction (DDI) risks.
9. PBPK models are also employed to simulate drug exposure in patients with hepatic or renal impairment, which is critical for dose adjustment and safety evaluation.^[33]

SOFTWARE PLATFORMS

GastroPlus

GastroPlus is a mechanistically based simulation software that simulates various route of administration, including intravenous, oral, buccal, ocular, inhalation, and dermal or subcutaneous delivery in both humans and animals.^[64] The platform have a user-friendly interface with powerful science to help you make faster and informed project decisions. It is designed to model drug absorption, pharmacokinetics (PK), and pharmacodynamics (PD). It facilitates efficient analysis and supports informed decision-making during drug development.^[65]

The GastroPlus simulation framework includes physiologically based gut models for various species such as human, dogs, rats, mice, rhesus monkeys, cynomolgus monkeys, minipigs, rabbits, and cats. It also enables the prediction of drug dissolution and absorption. In addition, it combines a full body PBPK models to simulate systemic drug disposition and pharmacokinetic behavior. It is used to test various drug for example atorvastatin to check that generic tablets would behave same as branded tablet or not by comparing simulated curves. It shows that software is a great

tool for predicting bioequivalence.^[66] One more study uses GastroPlus to investigate how food intake and acid reducing proton-pump inhibitors affect the encorafenib which is a cancer medication. This software successfully identified that this complex properties, showing that taking antacid will not lower the overall drug exposure in patients.^[67]

Sim-CYP

A Simcyp which is a Population-Based ADME Simulator it is a mechanistic modelling and simulation platform, coupled with an extensive database, designed to predict the ADME processes of drugs and drug candidates across diverse populations. It splits these populations group according to their age, disease state, and ethnicity, which makes it easier to predict drug–drug interactions. Simulators integrates several key components, including drug-specific data, population demographics, pharmacokinetic (PK) parameters, and PK profiles.^[68,41] The ADAM (Advanced Dissolution Absorption and Metabolism) model in the Simcyp® software uses a compound's properties along with population and study design information to determine how drug is absorbed and distributed in human body.^[69]

The functional capabilities of Simcyp include: (1) The ADAM model which has several compartment one for stomach, seven for small intestine and one for colon it includes factors that affects the rate and extent of oral drug absorption, like.^[70,71] and how much time it take to pass through the intestinal and colon.^[70] (2) It has Extensive database for virtual trials which include healthy people, Caucasians, and Japanese subjects. It also include special population such as morbidly obese individuals with moderate or severe liver and kidney failure. (3) Prediction of metabolically mediated drug–drug interactions, includes the simultaneous assessment of competitive enzyme inhibition which enable more accurate simulation of potential clinical outcomes.^[68]

PK-sim

PK-Sim® is physiologically based pharmacokinetic modelling (PBPK) platform which is open-source that simulates ADME processes of various drugs using physiological parameters. It employs a whole-body approach, integrating dissolution, absorption, metabolism, and excretion within a single, unified model. PK-Sim® is widely applied in drug development to predict oral absorption, optimize dosing regimens, and evaluate potential drug–drug interactions.

For model construction the basic PBPK framework was used which is PK-Sim® and for protein-related MoBi is used. A 'plug-flow-with-dispersion' approach is used to represent oral absorption in PK-Sim which treats the small intestine like a single long continuous compartment that has varying physiological properties.^[42,72]

A key feature of PK-Sim® is that its ability to describe particularly drugs, in mammals using equations that simulate relevant physical and physiological processes. Uniquely, PK-Sim® fully integrates oral absorption, systemic dispersion, metabolism, and excretion inside a single simulation, allow for comprehensive whole-body PBPK analysis.^[24] There are some other tools used, one of which is the PhysPK software suite which features with Phys-DAT modelling framework. This software separates the gut into nine compartments. This software accurately predicts peak concentration and drug exposure.^[73]

DISCUSSION

The in silico GI simulation models represent a valuable mechanistic technique for predicting oral absorption of drugs under various physiological scenarios. The PBPK, ACAT, and CAT models that are based on platforms like GastroPlus, Simcyp, and PK-Sim can take into consideration individual differences in GI pH, transit times, GI fluid composition,

and drug characteristics. Such modeling approaches may be applied to formulation development and dosing design as well as for prediction of pharmacokinetic differences between certain groups of patients. However, the reliability of these models is highly dependent on the quality of physiological and drug-related information available. Thus, the *in silico* models should be considered as supplements to, but not replacements for, experimental and clinical studies.

CONCLUSION

In silico gastrointestinal simulation models become an essential tool in a modern drug development, providing mechanistic predictions for oral drug absorption and systemic pharmacokinetics. PBPK, CAT, and ACAT models, supported by advanced software platforms such as GastroPlus®, Simcyp, and PK-Sim®, allow accurate representation of complex physiological processes which enable simulation in different populations, including special patient groups. The CAT model acts as a useful tool for screening at early stage, ACAT model provides detailed analysis of absorption and performance of the formulation. The PBPK of absorption and performance of the formulation. The PBPK model serves as a real whole-body representation, which makes it a gold standard for predicting clinical outcomes and drug interactions. Current limitations can be overcome by integrating these models, improve regulatory decision-making and also early identification of absorption limitations is facilitated by these models. They also guide BCS classification of drug, dosing strategies are optimized as well as predict drug interactions. When *in silico* models are integrated with experimental and clinical data it significantly reduces time and costs, enhances regulatory decision-making, and improves successful oral drug delivery despite challenges such as data requirements and computational complexity. Some future advances are AI-augmented simulations that refine predictive accuracy and also expand the scope of these tools in personalized medicine and in virtual patient population for creating Digital-twins, *etc.*

ACKNOWLEDGEMENTS

The authors gratefully acknowledge their teachers, mentors, and colleagues for their valued assistance, encouragement, and support in developing this review paper. The authors are also thankful to researchers who have contributed through their published research in understanding *in silico* gastrointestinal simulation, physiologically based pharmacokinetics, and mechanistic prediction of oral drug absorption. The authors are thankful to their affiliated organization for providing them with an academic atmosphere for completing this assignment.

REFERENCES

1. Safaa HD, Basim Mohsin Mohamed M. Formulation of metoclopramide HCl gastroretentive film and *in vitro-in silico* prediction using Gastroplus® PBPK software. Saudi Pharmaceutical Journal, 2022; 30(12): 1816–24.
2. Dokoumetzidis A, Kalantzi L, Fotaki N. Predictive models for oral drug absorption: from *in silico* methods to integrated dynamical models. Expert Opinion on Drug Metabolism & Toxicology, 2007; 3(4): 491–505.
3. Gaohua L, Miao X, Dou L. Crosstalk of physiological pH and chemical pKa under the umbrella of physiologically based pharmacokinetic modeling of drug absorption, distribution, metabolism, excretion, and toxicity. Expert Opinion on Drug Metabolism & Toxicology, 2021; 17(9): 1103–24.
4. Liang X, Fraczekiewicz G, Harish Jain KM, Wan B, Ishida K, Lai Y. Physiologically Based Pharmacokinetic (PBPK) Modeling of Oral Drug Absorption for Integrating Nonclinical Data into Human Pharmacokinetic Predictions. AAPS Journal, 2026; 28(3): 78.
5. Lou J, Duan H, Qin Q, Teng Z, Gan F, Zhou X, et al. Advances in Oral Drug Delivery Systems: Challenges and Opportunities. Pharmaceutics, 2023; 15(2): 484.

6. Stillhart C, Vučićević K, Augustijns P, Basit AW, Batchelor H, Flanagan TR, et al. Impact of gastrointestinal physiology on drug absorption in special populations—An UNGAP review. *European Journal of Pharmaceutical Sciences*, 2020; 147: 105280.
7. Kneiszl R, Hossain S, Larsson P. In Silico-Based Experiments on Mechanistic Interactions between Several Intestinal Permeation Enhancers with a Lipid Bilayer Model. *Molecular Pharmaceutics*, 2022; 19(1): 124–37.
8. Liu Y, Sprando RL. Physiologically based pharmacokinetic modeling and simulation of cannabinoids in human plasma and tissues. *Journal of Applied Toxicology*, 2023; 43(4): 589–98.
9. Lamberti G, Cascone S, Marra F, Titomanlio G, d'Amore M, Barba AA. Gastrointestinal behavior and ADME phenomena: II. In silico simulation. *Journal of Drug Delivery Science and Technology*, 2016; 35: 165–71.
10. Johansson F, Paterson R. Physiologically Based in Silico Models for the Prediction of Oral Drug Absorption. In: Ehrhardt C, Kim KJ, editors. *Drug Absorption Studies* [Internet]. Boston, MA: Springer US, 2008; 486–509.
11. Muttakin S, Moxon TE, Gouseti O. In vivo, In vitro, and In silico Studies of the GI Tract. In: Gouseti O, Bornhorst GM, Bakalis S, Mackie A, editors. *Interdisciplinary Approaches to Food Digestion* [Internet]. Cham: Springer International Publishing, 2019; 29–67.
12. Patel N, Polak S, Jamei M, Rostami-Hodjegan A, Turner DB. Quantitative prediction of formulation-specific food effects and their population variability from in vitro data with the physiologically-based ADAM model: A case study using the BCS/BDDCS Class II drug nifedipine. *European Journal of Pharmaceutical Sciences*, 2014; 57: 240–9.
13. Sjögren E, Westergren J, Grant I, Hanisch G, Lindfors L, Lennernäs H, et al. In silico predictions of gastrointestinal drug absorption in pharmaceutical product development: Application of the mechanistic absorption model GI-Sim. *European Journal of Pharmaceutical Sciences*, 2013; 49(4): 679–98.
14. Li Y, Kong F. Simulating human gastrointestinal motility in dynamic in vitro models. *Comprehensive Reviews in Food Science and Food Safety*, 2022; 21(5): 3804–33.
15. Geci R, Gadaleta D, De Lomana MG, Ortega-Vallbona R, Colombo E, Serrano-Candelas E, et al. Systematic evaluation of high-throughput PBK modelling strategies for the prediction of intravenous and oral pharmacokinetics in humans. *Archives of Toxicology*, 2024; 98(8): 2659–76.
16. Williams J, Siramshetty V, Nguyễn ĐT, Padilha EC, Kabir Md, Yu KR, et al. Using in vitro ADME data for lead compound selection: An emphasis on PAMPA pH 5 permeability and oral bioavailability. *Bioorganic & Medicinal Chemistry*, 2022; 56: 116588.
17. Price E, Kalvass JC, DeGoey D, Hosmane B, Doktor S, Desino K. Global Analysis of Models for Predicting Human Absorption: QSAR, In Vitro, and Preclinical Models. *Journal of Medicinal Chemistry*, 2021; 64(13): 9389–403.
18. Olasupo SB, Uzairu A, Shallangwa GA, Uba S. Computer-aided drug design and in silico pharmacokinetics predictions of some potential antipsychotic agents. *Scientific African*, 2021; 12: e00734.
19. Yang Y, Zhao Y, Yu A, Sun D, Yu LX. Oral Drug Absorption. In: *Developing Solid Oral Dosage Forms* [Internet]. Elsevier, 2017; 331–54.
20. Bruneau E. Basic Anatomy and Physiology of the Gastrointestinal Tract. In: Loveitt A, Martin MM, Neff MA, editors. *Passing the Certified Bariatric Nurses Exam* [Internet]. Cham: Springer International Publishing, 2017; 19–25.

21. Pepin X, Arora S, Borges L, Cano-Vega M, Carducci T, Chatterjee P, et al. Parameterization of Physiologically Based Biopharmaceutics Models: Workshop Summary Report. *Molecular Pharmaceutics*, 2024; 21(8): 3697–731.
22. Hens B, Bolger MB. Application of a Dynamic Fluid and pH Model to Simulate Intraluminal and Systemic Concentrations of a Weak Base in GastroPlus™. *Journal of Pharmaceutical Sciences*, 2019; 108(1): 305–15.
23. Mudie DM, Murray K, Hoad CL, Pritchard SE, Garnett MC, Amidon GL, et al. Quantification of Gastrointestinal Liquid Volumes and Distribution Following a 240 mL Dose of Water in the Fasted State. *Molecular Pharmaceutics*, 2014; 11(9): 3039–47.
24. Koziolok M, Grimm M, Garbacz G, Kühn JP, Weitschies W. Intra-gastric Volume Changes after Intake of a High-Caloric, High-Fat Standard Breakfast in Healthy Human Subjects Investigated by MRI. *Molecular Pharmaceutics*, 2014; 11(5): 1632–9.
25. Dahan A, Wolk O, Agbaria R. Provisional in-silico biopharmaceutics classification (BCS) to guide oral drug product development. *Drug Design, Development and Therapy*, 2014; 1563.
26. Wang K, Amidon GL, Smith DE. Physiological Dynamics in the Upper Gastrointestinal Tract and the Development of Gastrointestinal Absorption Models for the Immediate-Release Oral Dosage Forms in Healthy Adult Human. *Pharmaceutical Research*, 2023; 40(11): 2607–26.
27. Soliman ME, Adewumi AT, Akawa OB, Subair TI, Okunlola FO, Akinsiku OE, et al. Simulation Models for Prediction of Bioavailability of Medicinal Drugs—the Interface Between Experiment and Computation. *AAPS PharmSciTech*, 2022; 23(3): 86.
28. Berthelsen R, Sjögren E, Jacobsen J, Kristensen J, Holm R, Abrahamsson B, et al. Combining in vitro and in silico methods for better prediction of surfactant effects on the absorption of poorly water soluble drugs—a fenofibrate case example. *International Journal of Pharmaceutics*, 2014; 473(1–2): 356–65.
29. Da Silva TM, Sarcinelli MA, Cunha Chaves MH, Dias ADA, Patricio BFDC, Prado LD, et al. Physiologically Based Pharmacokinetic Modeling of Efavirenz Nanoparticles: from Animal Model to Human Extrapolation. *ACS Omega*, 2025; 10(39): 45382–99.
30. Meena Harish Jain K, Hou HH, Siegel RA. An Artificial Gut/Absorption Simulator: Description, Modeling, and Validation Using Caffeine. *AAPS Journal*, 2022; 24(5): 87.
31. Luo L, Thakral NK, Schwabe R, Li L, Chen S. Using Tiny-TIM Dissolution and In Silico Simulation to Accelerate Oral Product Development of a BCS Class II Compound. *AAPS PharmSciTech*, 2022; 23(6): 185.
32. Zhang F, Zhou Y, Wu N, Jia R, Liu A, Liu B, et al. In silico prediction of bioequivalence of Isosorbide Mononitrate tablets with different dissolution profiles using PBPK modeling and simulation. *European Journal of Pharmaceutical Sciences*, 2021; 157: 105618.
33. Zhuang X, Lu C. PBPK modeling and simulation in drug research and development. *Acta Pharmaceutica Sinica B.*, 2016; 6(5): 430–40.
34. Wu F, Shah H, Li M, Duan P, Zhao P, Suarez S, et al. Biopharmaceutics Applications of Physiologically Based Pharmacokinetic Absorption Modeling and Simulation in Regulatory Submissions to the U.S. Food and Drug Administration for New Drugs. *AAPS Journal*, 2021; 23(2): 31.
35. Lin W, Chen Y, Unadkat JD, Zhang X, Wu D, Heimbach T. Applications, Challenges, and Outlook for PBPK Modeling and Simulation: A Regulatory, Industrial and Academic Perspective. *Pharmaceutical Research*, 2022; 39(8): 1701–31.

36. Kato T, Nakagawa H, Mikkaichi T, Miyano T, Matsumoto Y, Ando S. Establishment of a clinically relevant specification for dissolution testing using physiologically based pharmacokinetic (PBPK) modeling approaches. *European Journal of Pharmaceutics and Biopharmaceutics*, 2020; 151: 45–52.
37. Sinha VK, Snoeys J, Osselaer NV, Peer AV, Mackie C, Heald D. From preclinical to human – prediction of oral absorption and drug–drug interaction potential using physiologically based pharmacokinetic (PBPK) modeling approach in an industrial setting: a workflow by using case example. *Biopharmaceutics & Drug Disposition*, 2012; 33(2): 111–21.
38. Zhang F, Jia R, Gao H, Wu X, Liu B, Wang H. In Silico Modeling and Simulation to Guide Bioequivalence Testing for Oral Drugs in a Virtual Population. *Clinical Pharmacokinetics*, 2021; 60(11): 1373–85.
39. Jones H, Rowland-Yeo K. Basic Concepts in Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development. *CPT: Pharmacometrics & Systems Pharmacology*, 2013; 2(8): 1–12.
40. Piñero J, Furlong LI, Sanz F. In silico models in drug development: where we are. *Current Opinion in Pharmacology*, 2018; 42: 111–21.
41. Hansmann S, Darwich A, Margolskee A, Aarons L, Dressman J. Forecasting oral absorption across biopharmaceutics classification system classes with physiologically based pharmacokinetic models. *Journal of Pharmacy and Pharmacology*, 2016; 68(12): 1501–15.
42. Niederalt C, Kuepfer L, Solodenko J, Eissing T, Siegmund HU, Block M, et al. A generic whole body physiologically based pharmacokinetic model for therapeutic proteins in PK-Sim. *Journal of Pharmacokinetics and Pharmacodynamics*, 2018; 45(2): 235–57.
43. Robins D, Lehmann A, Krollik K, Vertzoni M. Analyzing parametric influences driving age-associated changes in absorption using a PBPK-GSA approach. *European Journal of Pharmaceutical Sciences*, 2024; 202: 106881.
44. Cvijic S, Ibric S, Parojcic J, Djuris J. An in vitro - in silico approach for the formulation and characterization of ranitidine gastroretentive delivery systems. *Journal of Drug Delivery Science and Technology*, 2018; 45: 1–10.
45. Henriot J, Dallmann A, Dupuis F, Perrier J, Frechen S. PBPK modeling: What is the role of CYP3A4 expression in the gastrointestinal tract to accurately predict first-pass metabolism? *CPT: Pharmacometrics & Systems Pharmacology*, 2025; 14(1): 130–41.
46. Kosugi Y, Hosea N. Prediction of Oral Pharmacokinetics Using a Combination of In Silico Descriptors and In Vitro ADME Properties. *Molecular Pharmaceutics*, 2021; 18(3): 1071–9.
47. Franco YL, Da Silva L, Charbe N, Kinvig H, Kim S, Cristofolletti R. Integrating Forward and Reverse Translation in PBPK Modeling to Predict Food Effect on Oral Absorption of Weakly Basic Drugs. *Pharmaceutical Research*, 2023; 40(2): 405–18.
48. Segregur D, Barker R, Mann J, Moir A, Karlsson EM, Turner DB, et al. Evaluating the impact of acid-reducing agents on drug absorption using biorelevant in vitro tools and PBPK modeling - case example dipyridamole. *European Journal of Pharmaceutical Sciences*, 2021; 160: 105750.
49. Kesharwani SS, Ibrahim F. A Combined In-Vitro and GastroPlus® Modeling to Study the Effect of Intestinal Precipitation on Cinnarizine Plasma Profile in a Fasted State. *AAPS PharmSciTech*, 2023; 24(5): 121.
50. Cacace F, Menci M, Papi M, Piemonte V. In-Silico Prediction of Oral Drug Bioavailability: A multi-boluses approach. *Medical Engineering & Physics*. 2021; 98(1): 140–50.
51. Sjögren E, Thörn H, Tannergren C. In Silico Modeling of Gastrointestinal Drug Absorption: Predictive Performance of Three Physiologically Based Absorption Models. *Molecular Pharmaceutics*, 2016; 13(6): 1763–78.

52. Subhani S, Kim C, Muniz P, Rodriguez M, Van Os S, Suarez E, et al. Application of physiologically based absorption and pharmacokinetic modeling in the development process of oral modified release generic products. *European Journal of Pharmaceutics and Biopharmaceutics*, 2022; 176: 87–94.
53. Alqahtani S, Mohamed LA, Kaddoumi A. Experimental models for predicting drug absorption and metabolism. *Expert Opinion on Drug Metabolism & Toxicology*, 2013; 9(10): 1241–54.
54. Ilić M, Đuriš J, Kovačević I, Ibrić S, Parojčić J. In vitro – in silico – in vivo drug absorption model development based on mechanistic gastrointestinal simulation and artificial neural networks: Nifedipine osmotic release tablets case study. *European Journal of Pharmaceutical Sciences*, 2014; 62: 212–8.
55. Rahim N, Naqvi SBS. In Vitro In Vivo Extrapolation and Bioequivalence Prediction for Immediate-Release Capsules of Cefadroxil Based on a Physiologically-Based Pharmacokinetic ACAT Model. *AAPS PharmSciTech*, 2024; 25(5): 100.
56. Zhou D, Chen B, Sharma S, Tang W, Pepin X. Physiologically Based Absorption Modelling to Explore the Formulation and Gastric pH Changes on the Pharmacokinetics of Acalabrutinib. *Pharmaceutical Research*, 2023; 40(2): 375–86.
57. Liu Y, Lawless M, Li M, Fairman K, Embry MR, Mitchell CA. Prediction of physicochemical and pharmacokinetic properties of botanical constituents by computational models. *Journal of Applied Toxicology*, 2024; 44(8): 1236–45.
58. Gandevia L, Thotakura S, Mallayasamy S. Physiologically based pharmacokinetic model of valproic acid using PK-sim. *The Thai Journal of Pharmaceutical Sciences*, 2023; 47(2).
59. Zhang M, Lei Z, Yu Z, Yao X, Li H, Xu M, et al. Development of a PBPK model to quantitatively understand absorption and disposition mechanism and support future clinical trials for PB-201. *CPT: Pharmacometrics & Systems Pharmacology*, 2023; 12(7): 941–52.
60. Pawestri SA. Application in silico Modeling Simulation in Bioequivalence Studies: A Review. *Journal of Food and Pharmaceutical Sciences*, 2023; 763–9.
61. Yang R, Lin Y, Chen K, Huang J, Yang S, Yao A, et al. Establishing Virtual Bioequivalence and Clinically Relevant Specifications for Omeprazole Enteric-Coated Capsules by Incorporating Dissolution Data in PBPK Modeling. *AAPS Journal*, 2024; 26(4): 82.
62. Alsmadi MM, Abudaqqa AA, Idkaidek N, Qinna NA, Al-Ghazawi A. The Effect of Inflammatory Bowel Disease and Irritable Bowel Syndrome on Pravastatin Oral Bioavailability: In vivo and in silico evaluation using bottom-up wbPBPK modeling. *AAPS PharmSciTech*, 2024; 25(4): 86.
63. Pathak SM, Ruff A, Kostewicz ES, Patel N, Turner DB, Jamei M. Model-Based Analysis of Biopharmaceutic Experiments To Improve Mechanistic Oral Absorption Modeling: An Integrated in Vitro in Vivo Extrapolation Perspective Using Ketoconazole as a Model Drug. *Molecular Pharmaceutics*, 2017; 14(12): 4305–20.
64. Deb S, Hopefl R. Simulation of drug-drug interactions between breast cancer chemotherapeutic agents and antiemetic drugs. *DARU Journal of Pharmaceutical Sciences*, 2023; 31(2): 95–105.
65. Almajidi YQ, Faisal RR, Yaseen A, Al-Hakeem MAL. GastroPlus® as simulating/ conducting software for modeling physiologically-based pharmacokinetics & physiologically based biopharmaceutics. *Maaen Journal for Medical Sciences*, 2025; 4(3).
66. Wang L, Chen J, Chen W, Ruan Z, Lou H, Yang D, et al. In silico prediction of bioequivalence of atorvastatin tablets based on GastroPlus™ software. *BMC Pharmacology and Toxicology*, 2023; 24(1): 69.

67. Piscitelli J, Hens B, Tomaszewska I, Wollenberg L, Litwiler K, McAllister M, et al. Effect of Food and a Proton-Pump Inhibitor on the Absorption of Encorafenib: An In Vivo – In Vitro – In Silico Approach. *Molecular Pharmaceutics*, 2023; 20(5): 2589–99.
68. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp® Population-based ADME Simulator. *Expert Opinion on Drug Metabolism & Toxicology*, 2009; 5(2): 211–23.
69. Hens B, Pathak SM, Mitra A, Patel N, Liu B, Patel S, et al. In Silico Modeling Approach for the Evaluation of Gastrointestinal Dissolution, Supersaturation, and Precipitation of Posaconazole. *Molecular Pharmaceutics*, 2017; 14(12): 4321–33.
70. Kostewicz ES, Aarons L, Bergstrand M, Bolger MB, Galetin A, Hatley O, et al. PBPK models for the prediction of in vivo performance of oral dosage forms. *European Journal of Pharmaceutical Sciences*, 2014; 57: 300–21.
71. Karkossa F, Klein S. Individualized in vitro and in silico methods for predicting in vivo performance of enteric-coated tablets containing a narrow therapeutic index drug. *European Journal of Pharmaceutics and Biopharmaceutics*, 2019; 135: 13–24.
72. Willmann S, Lippert J, Sevestre M, Solodenko J, Fois F, Schmitt W. PK-Sim®: a physiologically based pharmacokinetic ‘whole-body’ model. *BIOSILICO*, 2003; 1(4): 121–4.
73. Cuquerella-Gilabert M, Reig-López J, Serna J, Rueda-Ferreiro A, Merino-Sanjuan M, Mangas-Sanjuan V, et al. processes using PhysPK®. *Computer Methods and Programs in Biomedicine*, 2024; 243: 10792.