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Physiologically Based Pharmacokinetic (PBPK) Modelling for In Vitro-In Vivo Extrapolation: Emphasis on the Use of Dissolution Data

Vivek M. Ghate, Pinal Chaudhari, and Shaila A. Lewis*
Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, India.

e-mail: s.lewis@manipal.edu

ABSTRACT

Recently the pharmaceutical sector has witnessed a drastic rise in the advancement and incorporation of computer-based technology into several unit operations. Drug dissolution profiling is an important consideration for the successful development of immediate and extended orally delivered formulations. Physiologically based pharmacokinetic (PBPK) modelling has gained a lot of attention when compared to the one- and two-compartmental modelling in establishing a relationship between the in vitro and in vivo parameters. Moreover, the influence of various factors like food, disease, population variations, transporters, and gastric emptying play a significant part in the in vivo outcome of the dosage form. In silico techniques are capable of addressing these limitations by incorporation of near-to-life replica of the in vivo conditions and are able to provide newer interpretations of conventional dissolution data that cannot be concluded by the generation of pharmacokinetic descriptors alone. This review focuses on the various in silico tools including the theory and studies conducted with dissolution data in recent years.

KEYWORDS: Dissolution, in vitro, in silico, kinetics, release profiles, PBPK

INTRODUCTION

During the development of a new molecule or the reformulation of an existing drug candidate, the formulators usually look for an appropriate technology to deliver the drug by the oral route (*1, 2*). Oral route (inclusive of tablets and capsules) is majorly preferred due to the convenience, formulation stability, ease of manufacture, owing to the well-established methods being available, and the highly controllable aspect of release, dissolution, and pharmacokinetic (PK) parameters of the drug candidate (*2*). For immediate-release formulations, the solubility and dissolution of the drug in the gastrointestinal (GI) fluid along with its permeation from the GI membranes play an important role in determining the bioavailability in vivo. In the case of sustained-release formulations, release of the drug from the dosage form (via diffusion, coating and/or osmosis) in addition to the intrinsic solubility and permeation plays a significant role in presenting the overall PK profile in vivo. With a high significance provided by the drug regulatory and approval bodies to the Quality by Design (QbD) aspect during the filing of new drug application (NDA) and in the post-approval scenario including formulation changes and production of generic products, dissolution has a critical contribution in the development of a dosage form for orally administered drug candidates (*3, 4*). Dissolution of drugs also impacts the stamp of bioequivalence, effective quality control, and a check for any batch-to-batch variations during manufacturing and processing (*5*). However, optimization of a tablet or capsule is inherent with several drawbacks and limitations exhibited by the physicochemical properties of the drug, excipient interactions, in vitro release characteristics, and the in vivo dissolution (*6*). With regards to the optimization of the aforesaid parameters, various modifications of the in vitro and in vivo studies and the use of in silico approaches has gained traction in addition to the classical theories of in vitro-in vivo correlation (IVIVC). During the last few decades, researchers and formulators had to rely on extensive in vivo animal based studies followed by the human trials to effectively judge the effect of the various parameters on the overall outcome of the pharmacological action.

Nowadays, almost all the processes in a pharmaceutical industry have been partially or completely taken over by computer- or in silico-based technologies (*7*). Artificial intelligence and machine learning have been in the

* Corresponding author.

forefront of research in modelling the in vivo behavior of drug candidates from simple in vitro and ex vivo studies. These models can be extended to meet the requirements of the human population, and with the same ease, be translated into profiles matching the diseased states, fasted and fed conditions, and special populations (pediatric and geriatric individuals) (*8*). In the purview, the case with drug dissolution studies has been no different. Several in vivo predictions and models can be made using simple computer-based applications and resources (*9*). Major advantages of these systems include comparison over large datasets, less time consuming, reproducibility, and automatic documentation, thereby eliminating potential for error. Moreover, the predictions based on the in vitro data coupled with in silico techniques can attract a waiver from the in vivo bioequivalence studies for generic products and me-too formulations (*10*).

EMPIRICAL DISSOLUTION MODELS AND RELEASE KINETICS

Beginning from the Noyes-Whitney's equation, the modelling of dissolution data is well-documented using the empirical calculations (*11*). To date, a large number of equations and theories have been put forth by mathematicians and researchers alike, including the gamma and power laws along with the conventional profiling based on time-dependent modelling of dissolution data (*12–15*). Monte Carlo simulations have been used extensively in modelling drug dissolution profiles (*16, 17*). Though these models have profound influence on the current methodology of drug development, they are limited within themselves in terms of incomplete mimicking of in vivo behavior of the drug dissolution kinetics. Thus, the empirical calculations are largely concentrated in the in vitro domain of dissolution modelling (*18*). On the other hand, the kinetics of drug dissolution have also seen vigorous and energetic alterations incorporating the rate processes in terms of surface area, distance, solvent layers, and partition coefficient data (*19*). Some of the widely accepted and acknowledged kinetic models include the Higuchi model, which considers the drug to be homogeneously dispersed in a matrix; the Korsmeyer-Peppas model, which explains drug release from a polymeric matrix; the Weibull parameter for sustained-release formulations; and the first- and zero-order rate profiles, which are also used to explain the dependency of the release mechanism on drug concentration. Though these classical kinetic models are not categorized as empirical modelling tools for dissolution data, they are used to fit the coefficients of the models to the experimental data and provide proof for the release mechanism and time-dependent observations. Advantages of these empirical methods for calculation of drug release kinetics can be extrapolated to the in vivo profiles (*18, 20–22*).

The GI transit time is a main foothold for formulators of an oral immediate- or extended-release drug product. The absorption of a well-formulated and well-absorbed drug relies on the gastric emptying time (GET) (*19*). In line with GET, the intrinsic solubility of the drug and the content of the GI tract largely influence the dissolution and release of the drug candidate, resulting in over or below the desired absorption and ultimately the success of a drug formulation. The profiling of GET can be achieved through various experimental procedures such as radioactive tracing, gamma scintigraphy, nuclear magnetic resonance (NMR) spectroscopy, and nowadays, in silico techniques (*23–25*).

CLASSICAL APPROACHES

Classical PK modelling is carried out using mathematical models describing a large central compartment (plasma), which is usually linked to a limited number of peripheral compartments with appropriate rate constants (*26*). Majorly representing the clearance and the volume of distribution, the classical type of compartmental modelling provides a more meaningful interpretation than the calculations made from purely empirical methods due to the generation of half-life data for the drug in question. Having a wide utility in preclinical and clinical studies, the PK descriptors aid in the selection of lead drug compounds, dose selection, and establish a dose-concentration relationship. Classical PK models, however, have limited applications when predicting the descriptors for similar classes of drugs or when considering the effect of various physiological conditions of the body. To establish the IVIVC and to extrapolate the models to various physiological conditions and drug categories, physiologically based PK modelling (PBPK) modelling is more appropriate. PBPK models are also built upon a similar mathematical framework as the classical PK models, but PBPK models incorporate a diverse range of parameters including the drug concentration in the tissues, with an ability to incorporate the variations of diseased conditions and healthy individuals (*27*).

According to the US Food and Drug Administration's (FDA) guidelines, a high level of IVIVC should establish a point-to-point overlap between the in vitro dissolution and the in vivo drug concentration profiles (*28*). The generation of IVIVC can be carried out using either one-stage convolution or a two-stage deconvolution approach. The former uses

the dissolution time profiles along with the PK descriptors to establish the in vivo behavior of the drug, whereas the latter uses the in vitro dissolution profiles of multiple drug formulations along with the input of the in vivo plasma drug concentration profiles. The process of deconvolution can be carried out using model-dependent methods including the one-compartmental Wagner-Nelson model or the two-compartmental Loo-Riegelman model (*29, 30*). As explained in the case of classical PK modelling, the model-dependent two-stage procedure to establish the IVIVC is limited to the number of compartments and the determination of limited descriptors. On the other hand, the model-independent approaches are the widely used and reported techniques for deconvolution to establish the IVIVC.

IN SILICO APPROACHES FOR PBPK MODELING

For an oral dosage form, disintegration and dissolution play a significant role in absorption and predicting the systemic availability of drug molecule. Again, the disintegration and dissolution are influenced by various physiological and physicochemical parameters of a drug molecule and dosage form including wettability, solvation, and diffusion of solids into dissolution along with transit time, GET, pH-variation, and availability of electrolytes and surfactants in the GI tract. These are prominent contributing parameters that have an influence on drug dissolution and are useful in determining the in vivo precipitation, dissolution, solubilization, and eventual absorption of the drug (*31–33*). The PK profile of a drug candidate, which comprises absorption, distribution, metabolism, excretion, and toxicity (ADMET), determines the in vivo fate of the drug within the human body, and ADMET, in turn, is controlled by various physicochemical factors that govern the rate and extent of ADMET phenomena, not to ignore the influence of age, sex, and body weight of individuals in regulating the drug's fate inside the body (*34–36*).

The approaches to physiological modelling can be different based on the details used to portray ADMET phenomena. The in silico models can be built based on different approaches; i.e., compartment modelling and its extension into the PBPK modelling, both being set within similar mathematical frameworks (*37*). The PK and GI behavior models are detailed based on two different approaches; i.e., empirical and mechanistic (*38*). The empirical approach considers concentration-time data with the use of very limited and distinguishable body compartments. The approach is simple and anticipates the data with limited variables, without assessing physical and physiological variables. On the other side, a mechanistic approach is based on the physiologic and anatomic relevance of the body. It is detailed by using coordinated physiologically realistic body compartments with specific mass transfer flow. This approach is further categorized into three different models based on their dependency on spatial and temporal variables (*39*). The quasi-equilibrium model is independent of spatial and temporal variables, the steady-state model is dependent on spatial variables only, and the dynamic model is dependent on both spatial and temporal models. The PK models can be simple like the Nestorov model, which reduces the whole body PBPK models dimensionality and complexity by lumping together the identical tissues into one, or complex like the Jain model, which was developed by dividing the body into 21 compartments, 38 ordinary differential equations, and 99 model parameters (*40, 41*).

The development of all in silico models germinated with the introduction of the "compartmental absorption transit" (CAT) model by Yu et al (*41*). The model includes the amount of drug in various compartments effective permeability, and the radius of the intestinal lumen. It incorporated a total of nine compartments: stomach, duodenum, two and four for jejunum and ileum, respectively, and colon. The model was further developed by GastroPlus (Simulations Plus Inc., Lancaster, CA, USA) to incorporate the release, dissolution, metabolism, and the transporter systems to make the model a more realistic representation of the actual in vivo conditions (*43*). This new model is termed as the "advanced compartmental absorption transit" (ACAT) model. To date, several forms of CAT models have surfaced in the software market and are aiding drug development to a considerable extent. The modified CAT model is also a part of the platform termed "Stella" (isee systems, Lebanon, NH, USA) and the PBPK simulator called "PK-Sim" (Bayer Technology Services GmbH, Leverkusen, Germany) (*37, 44*). The latter assumes the compartments to be a large tube described by the Gaussian function, and a continuous drug concentration profile dominates the descriptions. A comprehensive list of the various in silico platforms used for the modelling of drug dissolution are provided in Figure 1, and the corresponding versions and developer details are provided in Table 1.

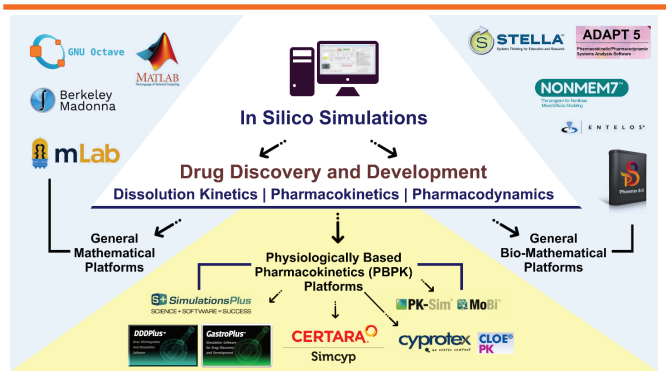

Figure 1. Various software's available currently and as a freeware for simulations and prediction based on in vitro drug dissolution data. Logos of the software's represented here have been taken from the respective websites to provide a graphical indication.

Table 1. In Silico Software for Physiologically Based Pharmacokinetic (PBPK) Modeling of Dissolution Data

Name of Software	Latest Version	Developer/Provider
GNU Octave	5.1.0	Octave
MATLAB	R2019a	The MathWorks Inc., USA
R Statistical Environment (R Project)	3.6.0	The R Foundation for Statistical Computing
Berkeley Madonna	9.1.3	University of California at Berkeley, CA, USA
mLab (Now MongoDB Atlas)	4.0	MongoDB Company, USA
DDDPlus GastroPlus	6.0 9.7	Simulations Plus Inc., Lancaster, CA, USA
Simcyp Phoenix	18 8.1	Certara, USA
CLOE PK		Cyprotex, UK
PK-Sim and MoBi	Systems Biology Suites 6.3	Bayer Technology Services GmbH, Leverkusen, Germany
Stella		isee systems, Lebanon, NH, USA
Adapt	5	Biomedical Simulations Resource, CA, USA
Nonmem	7	ICON, Dublin, Ireland

THE MOVE FORWARD

In silico approaches developed 10 to 20 years ago were limited by inadequacy of simulating geometry, gastric pH change, gastric motility, GET, and GI transit time. Today in silico approaches are in a state of continuous improvement and have overcome the drawbacks associated with early approaches by trying to prevail the gap between IVIVCs. PBPK models combine the existing knowledge related to physiology, anatomy, and biochemistry factors of humans and animals, physicochemical properties of drug molecules and formulation development aspects to predict the in vivo performance of a drug (*45*). In silico modelling is a valuable technique to evaluate and predict the PK profile of poorly soluble drugs during drug development, dosing, and formulation development. In silico models are a vital tool for determining the drug absorption pattern, food-related effects, first-pass metabolism, and intestinal transporter effects (*46*). These techniques have a potential role in assuring the safety and efficacy of the developed pharmaceutical oral dosage forms by precisely predicting the in vivo plasma profile of the drug. Along with dissolution, absorption, and plasma profiles, PBPK modelling provides great insights into the distribution of the drug molecule, which has a significant influence on the kinetics and pharmacodynamics of the drug molecule (*47*). PBPK models offer potential advantages to determine the effect of a specific disease condition or related demographic factor on altered plasma profiles. The acidic environment of the stomach has a favourable effect on solubility of weakly basic drugs, but a change in gastric pH from acidic to basic towards the small intestine with gastric emptying or coadministration of gastric acidity reducer (i.e., proton pump inhibitor [PPIs] and antacids) can alter the oral drug absorption and hence, the bioavailability (*48*). The pH-based saturation and precipitation of drug in the GI tract can adversely affect drug solubility and the prediction of drug reaching the systemic circulation.

APPLICATIONS OF IN SILICO TECHNIQUES

Numerous publications and research data have surfaced since the advent of the in silico approaches to model the in vitro drug dissolution data. A general outline of in silico process is presented in Figure 2. Berlin et al. reported comparative studies of a dissolution PBPK model and a saturation and precipitation PBPK model to examine the effect of saturation and precipitation on the plasma profile of cinnarizine in fasting and fed states using Stella simulation software (*49*). In vitro dissolution experiments were coupled with in silico PBPK model to accurately predict the in vivo dissolution and absorption behavior. They observed that fasting resulted in significant variability of in vivo absorption, and supersaturation and precipitation plays a significant role in precisely predicting the systemic bioavailability. Hansmann et al. carried out in silico PBPK distribution modelling to generate more insight on the in vivo plasma profile of ciprofloxacin on different patient populations and varying gastric environments by simulating a hypochlorhydric and achlorhydric environment (*50*). The volume of distribution

at steady state (Vss) was predicted relative to the varying patient population, and they observed that Cmax was dependent on Vss. The data obtained from this in silico PBPK model suggests that ciprofloxacin behaves like a biopharmaceutics classification system (BCS) class I molecule in vivo, which is contradictory to literature reports suggesting ciprofloxacin as borderline class II/IV molecule.

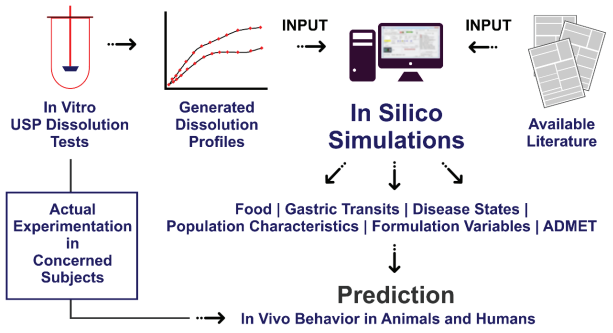

Figure 2. General outline of the flow of processes for predicting the in vivo behavior of a drug product using in silico techniques. USP: United States Pharmacopeia; ADMET: absorption, distribution, metabolism, excretion and toxicity.

Kambayashi et al. also studied the precipitation kinetics of two weakly basic drugs (i.e., dipyridamole and ketoconazole) in the intestinal lumen by using a simplified transfer model approach to obtain in vitro dissolution data, which is further integrated into Stella simulation software to predict the in vivo drug behavior (*51*). The reported in silico technique will be useful for predicting the probability of precipitation of weakly basic drugs and hence plasma profiles of the drug, which can be further utilized for deciding the dose and dosage form of the oral formulations. Berlin et al also utilized Stella to study the dissolution, precipitation, and saturation of atazanavir before and after gastric emptying (*52*). In silico modelling can help to study the relative impact of different factors that have a significant impact on in vivo drug performance and influence the in vivo absorbance. In silico modelling revealed that pre- and post-absorption events are a crucial, so a better understanding of these events can help to evaluate and predict the in vivo drug behavior and bioavailability.

For oral medications, different drugs behave differently in vivo in terms of solubility and permeability based on the surrounding GI tract environment. Numerous drugs exhibit pH-dependent solubility, and weakly basic drugs have high solubility in an acidic environment and precipitate out in the basic environment (*53*). Reduced gastric fluid secretion observed with aging, in patients with cancer, or with coadministration of antacids leads to the altered gastric acidity. This altered gastric acidity significantly influences the in vivo dissolution profile of the drug and hence, raises safety, efficacy, and toxicity concerns. Research towards the development of accurate technologies to simulate the in vivo physiological conditions is continuously growing, and the mini GI simulator (mGIS), which is similar to an artificial stomach duodenum has been developed to predict in vivo dissolution profiles. Tsume et al. assessed the in vitro dissolution profile of dasatinib, a weakly basic anticancer drug, using mGIS (*54*). The obtained data were combined with the in silico model, GastroPlus, and compared with clinical data to validate the model. The predicted plasma profile of dasatinib at varying gastric pH levels (i.e., acidic pH 0.5–1.8 and basic pH 4.0–6.0) with mGIS exhibited significant differences with 90%–98% Cmax reduction and 41%–89% AUC reduction at the elevated gastric pH range compared to acidic gastric. The in vitro dissolution techniques were unable to capture the influence of pH on drug dissolution and absorption, which can be overcome at a great extent with existing simulation methodology. These methodologies still exhibit a significant difference when compared with clinical data, which underscores the complexity of the human GI tract and suggests that better comparable methodologies are needed. The in silico techniques are valuable and have the potential to reduce the gap between the in vitro profiles and the in vivo plasma profiles.

The observed in vitro precipitation rate and dissolution rate tend to differ from the in vivo rates because most in vitro dissolution studies are devoid of the simulation to incorporate the absorption of the drug through the biological membranes. The introduction of an absorptive compartment would be a crucial step towards predicting bioperformance of the BCS class IIB drug. The influence of absorptive phase on prediction of in vivo drug profile was studied by introducing the absorptive compartment in a GI simulator (GIS). The jejunum chamber of the GIS was filled with the organic solvent, 1-decanol, which acts as -absorptive phase and aqueous phase. Ketoconazole and raloxifene as used as model BCS class IIb drugs, and Tsume et al. reported that inclusion of the absorptive phase into the GIS lead to improvement in prediction of in vivo profiles compared with compendial dissolution methodologies (*55*). Cvijic et al. used an in vitro-in silico approach to study sustained-release gastroretentive floating tablets of ranitidine hydrochloric acid (HCl) (*56*). In silico data explained the peculiar behavior of ranitidine in vivo based on the rate and extent of the ranitidine absorption upon

oral administration. The in silico approach predicted drug plasma profiles that matched with the reported clinical data of ranitidine HCl. As mentioned earlier, inter-individual variability can have a potential effect on in vivo PK profiles of drug molecules due to the diverse GI tract physiology. This slight deviation in plasma profiles will be of prime importance in case of drugs with a narrow therapeutic index (NTI), which can have a serious risk of adverse effects, toxicity, or therapeutic failure. Among the list of currently marketed NTI class drugs, one third are antiepileptic or anticonvulsant medications. Karkossa et al. carried out simulation studies by using a PBPK model and in silico modeling to predict the in vivo PK profile of enteric-coated valproate and the sensitivity of the formulation for inter-individual variability (*57*). It was observed that GET is a crucial parameter for variability observed in individual plasma profiles. It was also concluded that other GI parameters can also affect the in vivo drug release and absorption profiles, and assessment of the same is crucial for risk management of NTI drugs.

PLETHORA OF SIMULATIONS

Apart from modelling the in vivo behavior of the drug in normal physiological conditions, in silico tools have advanced ahead of time in bringing together the possibility of exploring the effect of food, diseases, and other conditions that are considered to be extremely hard or nearly impossible to establish in conventional in vitro studies, as well as reducing the working hours and costs during the development of drug dosage forms.

Duque et al. prepared and optimized the extended-release formulations of doxazosin using DDDPlus (Simulations Plus Inc.) along with the design of experiments (*58*). Initially, drug dissolution profiles were predicted in the software using the system-generated constituents of the extended-release formulations and compared with the experimental values obtained in the United States Pharmacopeia (USP) apparatus 2. The correlation (R^2 = 0.99) was obtained for both the profiles, in turn reducing the cost and duration of equipment usage during the manufacturing of extended-release formulations. Model low and high solubility drugs, namely pyrimethamine and metronidazole, respectively, were used by Durque et al. to simulate the intrinsic dissolution profiles using DDDPlus (*59*). Using the literature-reported values as an input factor for physicochemical parameters, the software was able to predict the dissolution profiles with correlation (R^2 > 0.94) within an acidic to neutral pH.

Hens et al. evaluated the GI dissolution in addition to the supersaturation and possible precipitation of a model drug, posaconazole (*60*). The studies were carried out in the acidified and neutral suspension formulation. The authors used a PBPK modelling approach, using the Simcyp modules (Certara, USA). The dissolution in the gastric compartment was higher from the acidified suspension, whereas incomplete dissolution was seen in the neutral formulation. A supersaturated phase was seen in the duodenal compartment and in the intestinal region from the neutral and acidified suspension.

Ibarra et al. attempted to predict the bioequivalence of the oral drug products containing carvedilol, a largely prescribed pharmaceutical candidate (*61*). The study involved a detailed in vitro-in silico-in vivo methodology, wherein the in silico techniques were modelled using the PBPK technique using PK-Sim software. Virtually, single-dose PK profiles were simulated for carvedilol, and the population ratios of bioequivalence were estimated. The study concluded that the in vivo bioequivalence study was indeed necessary, as the prediction was unable to meet the objectives for a possible waiver. Chandra et al. studied the dissolution behavior of telmisartan-inclusion complexes in vitro and used the GastroPlus platform to model and predict the human plasma concentration profiles and the extent of drug absorption in various compartments of the GI tract (*62*). A theoretical workflow pattern is presented in Figure 3. The results demonstrated the ability of the in silico technique to show a maximum drug absorption (39.4%) in the jejunum compared to the other regions.

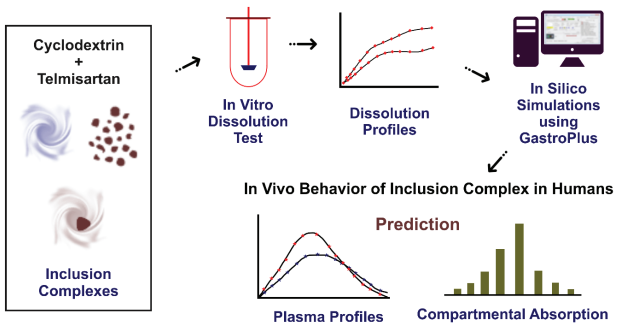

Figure 3. Representation of in silico predictions using dissolution data obtained in vitro for the enhancement of solubility and absorption of telmisartan by inclusion complex with cyclodextrin. The simulations were conducted by Chandra et al. using GastroPlus (Simulation Plus, Lancaster, CA, USA) modeling platform (62).

The presence or absence of food in the GI tract is a major indicator of drug dissolution and absorption in vivo. The unseen interaction between food and the dosage form, especially in the case of extended-release products, can turn harmful and lead to dose dumping. Such an

incident is a threat during the administration of potent medications, which may have severe consequences in the patient. Such an effect is not observed in routine methods of drug dissolution testing and can only be evaluated based on in silico approaches outside the body. A notable study was conducted by Andreas et al wherein the authors reported a negative food effect on the modified-release dosage form of zolpidem (*63*). First, the dissolution profile was generated using normal USP apparatus II, III, and IV. The mean plasma concentration profiles were simulated using GastroPlus and Simcyp. Deconvolution of the profiles was carried out using Qgut models in the Simcyp software, which allowed the addition of first-pass metabolism and liver extraction effects. The drug dissolution profiles clearly followed variable patterns with different reasons in fed and fasted states. In the fed state, dissolution was influenced by GET, and in the fasted state, dissolution was influenced by the formulation properties itself. Another aspect noted in the study was incomplete drug release due to the negative effect of food in the GI tract. Zhang et al investigated the applications of PBPK modelling to explain the positive effect of food on the in vivo dissolution of compound X (a weak base with low solubility and permeability) (*64*). The methodology utilized the GastroPlus platform with the Opt logD module to simulate the profiles in both fasted and fed conditions. The PBPK model satisfactorily provided justification for the positive effect of food on the dissolution of compound X, with solutions to improve the oral absorption. The simulations predicted that the food effect can be overcome by reducing the particle size to a nanometer range and administering under fasted conditions.

CONSIDERATIONS FOR QUALITY PREDICTIONS

Though in silico approaches may appear to be lucrative and beneficial to drug development scientists, it is not a stand-alone solution for modelling the in vivo behavior of the drug formulation. The mere experimental values of drug dissolution in buffers do not effectively translate to a significant model using PBPK simulations. To draw meaningful conclusions, it is of the utmost importance for high-quality data to be provided as input during the simulations. The drug dissolution should preferably be conducted in biorelevant dissolution media or physiologically simulated media (*65*). Moreover, a careful determination of the drug's physicochemical properties needs to be carried out along with permeation in cell culture models.

CONCLUSIONS

The oral route of drug delivery is an attractive mode of therapeutic intervention. Deviating from the conventional and routine analysis of dissolution data has opened exciting avenues for generating many physiologically relevant implications with limited resources and lesser cost. PBPK modelling approaches have largely overcome the effort-based analysis by converting them to a smarter analysis, thereby providing solutions and implications that are rarely found with in vitro research settings. The models developed by using in vitro dissolution data can be used to determine the in vivo behavior of a drug formulation along with the effects of various physicochemical conditions, the presence or absence of the food, the gastric and intestinal transit times, and population-specific parameters. Careful selection of media and methodology to obtain the in vitro data is a prerequisite for the generation of valuable in silico models. Largely PBPK techniques are on their way to revolutionize pharmaceutical research and development, paving a way to faster and efficient regulatory filings and approvals to effectively provide judgemental treatments to life-threatening conditions.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this article.

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