ORIGINAL ARTICLE

Identification of biorelevant dissolution media to assess biopharmaceutical performance of erlotinib formulation with enhanced bioavailability using physiology-based pharmacokinetic modeling

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Abstract

Aim: The aim of the present work was to predict the bioavailability (BA) of poorly soluble drug. *In vitro* dissolution of selected BCS Class II drug was conducted in different dissolution media to identify the discriminatory behaviors of the dissolution media. Further, the development of physiology-based pharmacokinetic modeling performed using GastroPlus® for BA predictions of formulation showing enhanced dissolution. **Study Design:** Using GastroPlus® software (Simulations Plus, Lancaster, CA), a physiology-based pharmacokinetic model for erlotinib was developed. Erlotinib absorption was described using the advanced compartmental absorption and transit model. The input parameters for the simulation were either determined experimentally or gathered from the literature. **Place and Duration of Study:** Amity Institute of Pharmacy, Noida. **Methodology:** *In vitro* dissolution studies were conducted and data were analyze to find the biorelevent dissolution media. GastroPlus® model was built to predict the C_{max} and AUC and also was validated for the prediction error <10%. Validated model was used to predict the BA parameters of optimized formulation using the dissolution profile. **Results:** Based on predicted T/R ratio, it is observed that optimized formulation shows approximately ~ 25% higher rate of absorption and bioavailability. **Conclusion:** Erlotinib tablet formulation was prepared using micronized drug substance, optimized formulation was subjected to various dissolution tests and biorelevent media was identified based on best fit/correlation with the deconvulated profile, which was further used for simulation modeling and BA prediction. Micronization can be used as a technique to enhance the drug dissolution of BCS Class II drugs and corresponding BA. IVIVR GastroPlus modeling and simulations can be useful tool to assess the biopharmaceutical performance for initial screening and further taking up the optimized formulation for clinical studies.

Key words: Biorelevant media, deconvolution, erlotinib, GastroPlus, IVIVR

INTRODUCTION

Oral drug delivery is one of the highly preferred routes of drug administration due to ease of administration/self-medication as well as cost-effectiveness. However, there are key challenges in the research and development of orally administered drugs related to the poor solubility of newly developed drug substance. Oral formulation developed using drugs with poor aqueous solubility usually shows a low and variable bioavailability (BA) due to rate-limited absorption.[1]

Cancer is most prevalent disease in the recent time and due to patient dependence on the anticancer drug for long time, orally administered drugs are very much required. Recently, developed kinase inhibitors for the treatment of cancer have

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poor solubility, high dosing for a long-term administration possess the side effect to the patients.[2]

Erlotinib, an anticancer drug, inhibits the epidermal growth factor receptor (EGFR)'s tyrosine kinase that has a regular intake dose of 150 mg.[3] Erlotinib is a Class II drug with a pH-dependent solubility, indicating it has a low solubility at pH 7 and a higher solubility below 5. It is absorbed in the GIT and reaches its maximum blood concⁿ after about 1 ½ h. In healthy people, absolute BA was shown to be about 59%.[4] Erlotinib inhibits cell proliferation, metastasis, and angiogenesis through inhibiting signaling pathways. Diarrhea, folliculitis, dry skin, and tiredness are all side effects associated with EGFR TKIs. However, after months or years of treatment, some side effects may worsen, and new symptoms may arise. This could result in dose decreases or the early termination of a beneficial treatment. The early and persistent side effects such as folliculitis and diarrhea were rated manageable as a result. In all cases, skin toxicity was present. Due to these adverse effects, many people may be prescribed a lower dose.[5-7]

Biorelevant dissolution media(s) are utilized as an *in vitro* technique for evaluating oral formulations' *in vivo* performance. Biorelevant dissolving media aids in accurately mimicking physiological *in vivo* and *in vitro* conditions.[8]

Compendial dissolving media are typically used for quality control testing and are not ideal for IVIVC of weakly soluble medicines, but they do not reflect for the physiological circumstances of the GI tract.[9,10] As a result, biorelevant media are used to estimate oral formulation efficacy *in vivo*.

Physiologically-based pharmacokinetic (PBPK) modeling is a statistical technique for forecasting absorption, distribution, metabolism, and excretion of drugs in humans and other animals. Pharmaceutical research and medication development, as well as risk assessment for general chemicals, use PBPK modeling.

The various efforts to improve the dissolution rates of drug can help in improving BA, which can further help to reduce the dosage and ultimately the side effect associated with the long-term usage of such drugs. The dissolution rate is one of the limiting criteria for ensuring high BA which can be enhanced by micronization.[11-13] Micronization techniques can be utilized to reduce particle size and speed up the dissolving of erlotinib from tablet dosage forms. The drug dissolution of a tablet formulation made by co-sifting functional excipients and micronized erlotinib hydrochloride in biorelevant media was compared to that of a reference medication.[14]

In the current scenario, various research are being done to resolve and understand and predict the BA and factor affecting the BA. Various regulatory agencies are accepting the *in vitro* based approaches using solubility and dissolution tests and *in silico* approaches with PBPK modeling. However, due to limited predictive power, it is not yet possible to replace clinical studies. The aim of work is to predict the BA of poorly soluble drug. *In vitro* dissolution of selected BCS Class II drug was conducted in different dissolution media to identify the discriminatory behaviors of the dissolution media. Further, the development of PBPK model done using the GastroPlus® for BA predictions of formulation showing enhanced dissolution.[15-17]

METHODOLOGY

Chemicals

The following chemicals were obtained from various sources for preparation of formulations, Erlotinib Hydrochloride, Microcrystalline Cellulose (FMC International, Ireland), Sodium Starch Glycollate (Roquette, France), Magnesium stearate (Avantor, USA) and Opadry White (Colorcon Asia Pvt. Ltd., India), Lactose monohydrate (DFE Pharma, Netherlands), and Sodium Lauryl Sulfate (BASF, Germany).

Formulation

Tablets containing micronized erlotinib hydrochloride were made with lactose monohydrate, microcrystalline cellulose as a diluent, magnesium stearate as a lubricant, SLS as a surfactant, and SSG as a disintegrant. Table 1 lists the quantities of all of the excipients. To guarantee optimal mixing of functional excipients with drug ingredient, all the excipients and drug were sieved through the sieve no. 40. After that, dried excipients were co-sifted and mixed twice with drug. Slugs/flakes were made from dry mix powder, which was then broken down into granules with a 1.5 mm screen and milled granules mixed with extragranular disintegrant, and then lubricated with magnesium stearate. The mixture was compressed using 10 mm round punches on a 12-station single rotational compression machine. Uncoated tablets were coated with aqueous-based Opadry white ready mix in GansCoater to a weight build-up of roughly 5.0%.[14]

Table 1: Formulation of erlotinb tablets[14]

Ingredients	Function	% Of total tablet weight
Erlotinib (equivalent toerlotinib hydrochloride)	Active substance	36
Lactose monohydrate	Bulking agent	24
Microcrystalline cellulose	Bulking agent	28
Sodium lauryl sulfate (SLS)	Surfactant	1
Magnesium stearate	Lubricant	1
Opadry white	Coating agent	5
Sodium starch glycolate	Disintegrant	10

In vitro dissolution study

The *in vitro* dissolution was performed using USP apparatus II (paddle) at 37 ± 0.5°C and 50 rpm. 0.5% SLS solution with pH 1.2, 4.5, and 6.8 media was used for the study. In addition to this, dissolution was also conducted in Fasted State Simulated Gastric Fluid, Fasted State Simulated Intestinal Fluid, and Fed State Simulated Intestinal Fluid dissolution media. Sampling was performed at 10, 15, 30, 45, and 60 min. The withdrawn samples were filtered using 0.2-filters and HPLC was used to evaluate them. The percentage drug dissolved was calculated as follows:

$$\%Drug\ Dissolved = \frac{\frac{A_T}{A_s}\times\frac{W_S}{20}\times\frac{5}{50}\times\frac{1000}{1}}{\frac{P}{LC}\times\frac{393.43}{429.90}}\times$$

Where
A_T is Area counts of erlotinib peak from sample solution
A_s is Average of the sum of the area counts of erlotinib peak from standard solution
W_s is Weight of erlotinib hydrochloride reference/working standard on as is basis
LC is Label claim of erlotinib in erlotinib tablet in mg
P = Potency of erlotinib hydrochloride reference/working standard on as is basis
The 393.4 = Mol. wt of erlotinib and 429.9 = Mol. wt of erlotinib HCl were considered for the calculations.

Pharmacokinetic compartment analysis

pK compartmental analysis was performed using the software, the plasma concⁿ time profile of reference product was taken from literature and used to identify compartmental parameters. Compartmental model fitting was performed using the PKPlus™ module, as shown in Figure 1.[18]

Deconvolution and IVIVR establishment

IVIVC is a crucial approach in the development and testing of oral formulations. Whenever an IVIVC has been developed for a set of formulations, *in vitro* dissolution tests can be used instead of additional bioequivalence studies in the development or modification of new formulations. As a result, IVIVCs serve a critical role in the study and development of various medications, potentially reducing the number of unnecessary clinical studies. Deconvolution, the procedure of producing an *in vivo* "dissolution profile" for point-by-point comparison with *in vitro* dissolution data in what is referred to as a "level A" IVIVC, is at the heart of IVIVC. In the discipline of pharmacokinetics, several deconvolution methods have been utilized over the years. Wagner-Nelson and Loo-Reigelman are two traditional approaches.[19] These techniques have been widely utilized to measure the kinetics of absorption after an oral delivery.

After compartment model fitting, deconvolution of plasma concⁿ time profile of reference product was perform to identify the fraction of drug absorb [Figure 2]. The deconvoluted profile is correlated with different dissolution faction from different dissolution media to identify biorelevant dissolution.

GastroPlus™ (G+) model development

To mechanistically understand the PK and/or pharmacodynamic behaviors of a drug, a PBPK analysis employs models and simulations that incorporate physiology, population, and drug features.

The pharmacokinetic behavior of medications in humans can be predicted using PBPK modeling and simulation.

PBPK modeling has grown in popularity in the recent decade, both in academia and in the pharmaceutical business, and has become an important tool in drug development.

Using GastroPlus™, a physiology-based pharmacokinetic model for erlotinib was constructed (Simulations Plus, Lancaster, CA). Erlotinib absorption was described using the advanced compartmental absorption and transit model (ACAT; with default ASF adjusted Log D, v6.1). The simulation's input parameters were either determined experimentally or taken from the literature. Table 2 contains a list of these variables. The simulation model was built using the plasma concⁿ time profile of the reference product. At a dose of 150 mg, the modeled pharmacokinetics profile demonstrated excellent agreement with the known clinical data.

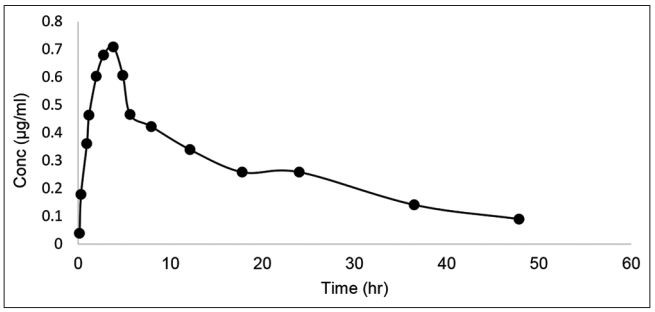

Figure 1: Plasma profile of erlotinib[18]

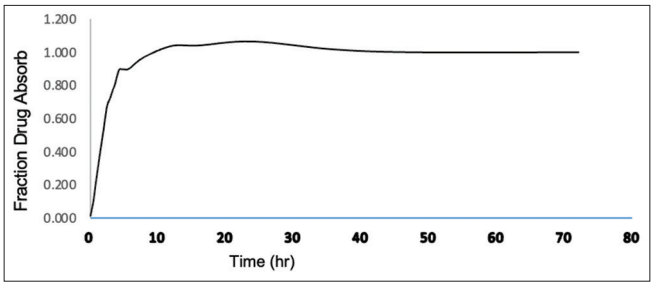

Figure 2: Fraction drug absorbed

GastroPlus model validation and application

The GastroPlus model was validated by simulating plasma profile data taken from literature[16] for erlotinib administered as a single oral dose of 150 mg cotreated with the proton pump inhibitor omeprazole (40 mg) the stomach pH in ACAT model was elevated to 5 to simulate impact of proton pump inhibitors. The built and validated model was further used to simulate the plasma profile for optimized formulation. All input parameters were kept constant except dissolution profile in FaSSGF media. The pharmacokinetic parameters for optimized formulation were compare with pharmacokinetic parameters of reference product.

RESULTS AND DISCUSSION

BCS Class II drug, erlotinib was selected and used for formulation preparation, optimized formulation was used for various dissolutions studies, the dissolution was performed in USP apparatus II over entire physiological ranges including biorelevant media.

The optimized formulation was subjected to various dissolution tests and biorelevant media was identified based on best fit/correlation with the deconvoluted profile, which was, further, used for simulation modeling and BA prediction. The dissolution profiles of erlotinib tablets in different medias are illustrated in Figure 3.

Table 2: Input parameters for simulation of erlotinib absorption using GastroPlus™

Parameter	Value
Molecular formula	$C_{22}H_{23}N_3O_4$
LogP	3.1
pKa	5.47
Jejunal permeability (Peff)	3.58 (10^{-4} cm/s)
Dose	150 mg
pH of reference solubility	0.18 mg/ml (SGF, pH 1.2)
Effective particle density[a]	1.2
Diffusion coefficient	0.64
Fraction unbound in plasma	0.71
Dose volume	250 ml
Clearance	3.12 L/h
Volume of distribution	1.15
Elimination half-life	7.8 h
K12 (min^-)	3.25×10^{-3}
K21 (min^-)	2.17×10^{-3}
Body weight	70 kg
Simulation time	72 h

[a]G+defaults

Formulation development and *in vitro* dissolution study

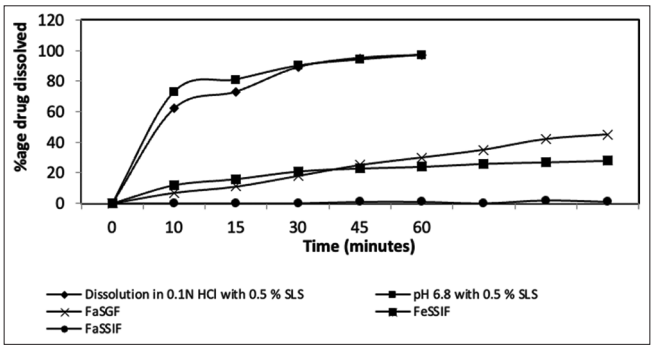

Figure 3: Dissolution profile in different media

Deconvolution and IVIVR establishment to identify biorelevant dissolution media

Deconvolution is the core of IVIVC, and hence, the deconvolution of plasma profile data was done, as shown in Figure 4.

Physiology-based pharmacokinetic simulation

PBPK modeling takes into account a vast amount of drug-specific data, species-physiology characteristics (system data), and a thorough understanding of all active processes affecting a drug's pharmacokinetic properties. System-dependent characteristics (e.g., glomerular filtration rate, tissue volume, blood flow, amount of microsomal protein/hepatocytes per g of liver, plasma protein, enzyme, and transporter abundance) have been compiled in the commercial PBPK for human and preclinical species. All drug-dependent parameters include physicochemical properties (nature of the drug, molecular weight, pKa, and solubility (logD) and permeability, blood cell, and plasma protein binding (e.g. fraction unbound in plasma, blood plasma partitioning [B: P]), transporter contribution to drug disposition, and *in vitro* data on hepatic or ex-hepatic enzyme metabolism (e.g., intrinsic clearance (CLint)). Table 2 shows the data needed to create a basic PBPK model for PBPK simulation. The model was created using GastroPlus simulation software.

The literature-based data were used for model building, the data for normal and elevated stomach pH are represented by triangles and squares, respectively.

The observed and predicted plasma profile of erlotinib are shown in Figure 5, the observed and predicted plasma profile data of erlotinib in presence of proton pump inhibitor are shown in Figure 6.

GastroPlus model was built to predict the Cmax and AUC and was validated, prediction error was found to be <10%. Validated model was used to predict the plasma profile

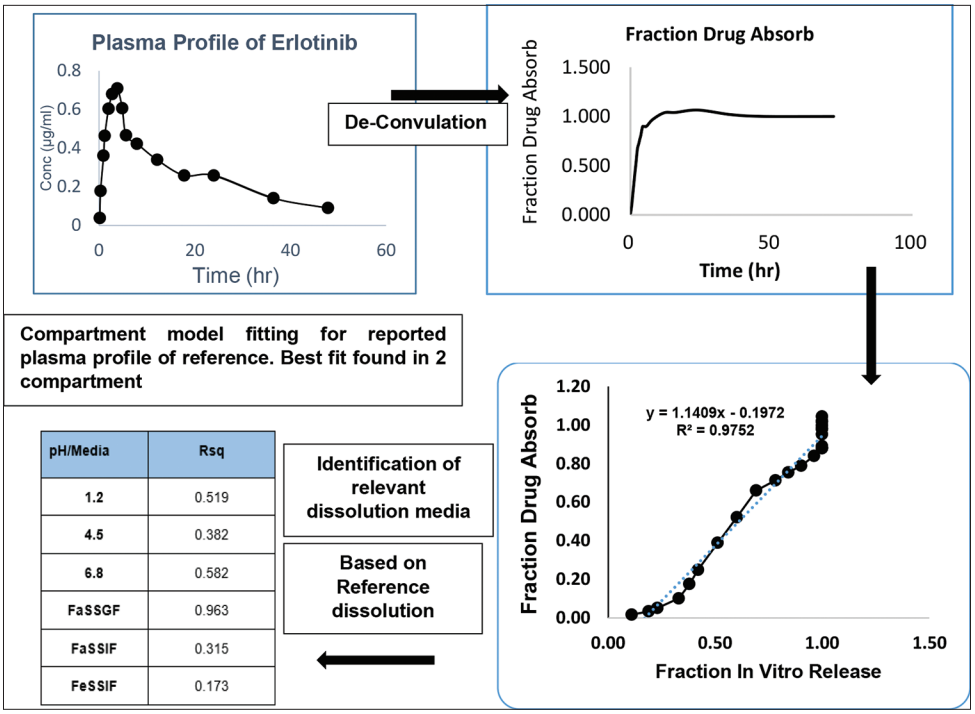

Figure 4: Deconvolution steps – IVIVC module

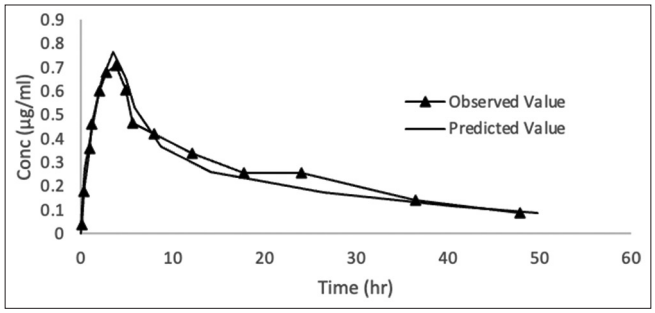

Figure 5: Observed versus predicted plasma profile of erlotinib[16]

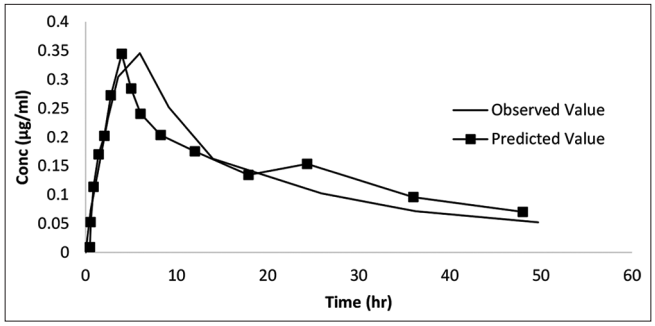

Figure 6: Observed versus predicted plasma Profile-Erlotinib+Proton pump inhibitor[16]

of optimized formulation using the dissolution profile of FaSSGF media keeping all other parameters constant.

The ratio of pK parameter of erlotinib alone is presented in below Table 3 and ration of pK parameter of erlotinib coadminister with proton pump inhibitor is presented in Table 4.

Table 3: Model building using plasma profile erlotinib reference

Model building using plasma profile of erlotinib			
Parameters	**Observed value**	**Predicted value**	**%PE**
Cmax	0.71	0.77	–8.30
AUC	12.76	12.03	5.77

Table 4: Model building using plasma profile of erlotinib reference+proton pump inhibitor

Model building using plasma profile of erlotinib+PPI			
Parameters	**Observed value**	**Predicted value**	**%PE**
Cmax	0.34	0.35	–0.37
AUC	6.86	6.66	2.92

Table 5: Predicted Cmax and AUC of optimized formulation

Parameters	**Predicted value**
Cmax (%T/R)	126.1
AUC (%T/R)	123.4

The predicted plasma profile was compared with the literature reported plasma profile of reference.

Based on predicted T/R ratio, it is observed that optimized formulation shows approximately ~ 25 % higher rate of absorption and BA, as given in Table 5.

CONCLUSION

Optimized formulation was developed using micronized particle size of erlotinib, deconvolution was performed based on the literature reported plasma profile to identify bioindicative dissolution media, FaSSGF, which was further used to build the GastroPlus simulation model. The developed model was validated by simulating the plasma profile of erlotinb in healthy volunteer cotreated with PPI.

The model was built and validated with an prediction error of <10% both C_{max} and AUC parameters.

Further, the validated model showed that optimized formulation may show ~25% higher rate of absorption and BA, which can be further confirmed by conducting the *in vivo* study.

REFERENCES

1. Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in oral drug delivery. Front Pharmacol 2021;12:618411.
2. Bhullar KS, Lagarón NO, McGowan EM, Parmar I, Jha A, Hubbard BP, *et al*. Kinase-targeted cancer therapies: Progress, challenges and future directions. Mol Cancer 2018;17:48.
3. Pandey P, Dureja H, Erlotinib A: Targeted anticancer drug current cancer therapy reviews. Curr Cancer Ther Rev 2017;13:3-16.
4. Yanga KM, Shinc C, Parkd JW, Kimd KS, Kimc DK, Parke K, Kima K. Nanoparticulation improves bioavailability of Erlotinib. Drug Dev Ind Pharm 2017;43:1557-65.
5. Gabr AG, Goto H, Hanibuchi M, Ogawa H, Kuramoto T, Suzuki M, *et al*. Erlotinib prevents experimental metastases of human small cell lung cancer cells with no epidermal growth factor receptor expression. Clin Exp Metastasis 2012;29:207-16.
6. Agero AL, Dusza SW, Benvenuto-Andrade C, Busam KJ, Myskowski P, Halpern AC. Dermatologic side effects associated with the epidermal growth factor receptor inhibitors. J Am Acad Dermatol 2006;55:657-70.
7. Wang Y, Schmid-Bindert G, Zhou C. Erlotinib in the treatment of advanced non-small cell lung cancer: An update for clinicians. Ther Adv Med Oncol 2012;4:19-29.
8. Fotaki N, Vertzoni M. Biorelevant dissolution methods and their applications in *in vitro in vivo* correlations for oral formulations. Open Drug Deliv J 2010;4:2-13.
9. Vertzoni M, Dressman J, Butler J, Hempenstall J, Reppas C. Simulation of fasting gastric conditions and its importance for the *in vivo* dissolution of lipophilic compounds. Eur J Pharm Biopharm 2005;60:413-7.
10. Shono Y, Jantratid E, Janssen N, Kesisoglou F, Mao Y, Vertzoni M, *et al*. Prediction of food effects on the absorption of celecoxib based on biorelevant dissolution testing coupled with physiologically based pharmacokinetic modeling. Eur J Pharm Biopharm 2009;73:107-14.
11. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: Importance and enhancement techniques. Int Sch Res Netw 2012;2012:195727.
12. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, *et al*. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian J Pharm Sci 2014;9:304-16.
13. Kanikkannan N. Technologies to improve the solubility, dissolution and bioavailability of poorly soluble drugs. J Anal Pharm Res 2018;7:00198
14. Kumar N, Dureja H, Chandra A. Enhancement of drug dissolution of erlotinib tablets by micronization technique using pharmaceutical experimental design. J Pharm Res Int 2021;33:70-8.
15. Thakore SD, Thakur PS, Shete G, Gangwal R, Narang AS, Sangamwar AT, *et al*. Assessment of biopharmaceutical performance of supersaturating formulations of carbamazepine in rats using physiologically based pharmacokinetic modeling. AAPS PharmSciTech 2019;20:179.
16. Kesisoglou F, Chung J, van Asperen J, Heimbach T. Physiologically based absorption modeling to impact biopharmaceutics and formulation strategies in drug development industry case studies. J Pharm Sci 2016;105:2723-34.
17. Jones HM, Gardner IB, Watson KJ. Modelling and PBPK simulation in drug discovery. AAPS J 2009;11:155-66.
18. Kletzl H, Giraudon M, Ducray PS, Abt M, Hamilton M, Lum BL. Effect of gastric pH on erlotinib pharmacokinetics in healthy individuals: Omeprazole and ranitidine. Anticancer Drugs 2015;26:565-72.
19. Margolskee A, Darwich AS, Galetin A, Rostami-Hodjegan A, Aarons L. Deconvolution and IVIVC: Exploring the role of rate-limiting conditions. AAPS J 2016;18:321-32.

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