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Role of physiologically based biopharmaceutics modeling in predicting and circumventing the drug-drug interactions of tyrosine kinase inhibitors with acid-reducing agents

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ABSTRACT

Tyrosine kinase inhibitors (TKIs) are molecular targeting agents used to treat various types of cancer. During the treatment with TKIs, acid-reducing agents (ARAs) are prescribed to prevent gastric mucosal damage. However, this co-administration causes increased gastric pH resulting in reduced exposure to TKIs. Thus, avoidance of this interaction through formulation intervention is necessary to have better efficacy. The objective of the present work is to demonstrate the utility of physiologically based biopharmaceutics (PBBM) in predicting and circumventing the interactions of TKIs with ARAs. PBBM was developed for dasatinib, bosutinib, and gefitinib using physicochemical, pharmacokinetic, and physiological inputs. The models were validated against oral and intravenous clinical data. The model successfully predicted ARA interactions (stomach pH is changed to 5 to mimic ARA administration), that are in line with literature-reported data. Solubility generated in the presence of citric acid demonstrated enhanced solubility in the pH range of 4.5–6.8 for all drugs. Integration of enhanced solubility in PBBM demonstrated a nullified ARA effect for all drugs. This result indicated the possibility of dose reduction and reduced intestinal precipitation due to the acidifying effect of citric acid. Overall, PBBM successfully demonstrated potential in predicting and circumventing the ARA effect to enhance the efficacy of TKIs.

INTRODUCTION

As per the reports shared by GLOBOCAN in 2022, the number of new cases and deaths from Cancer was estimated to be 20 and 9.7 million, respectively [1]. The main cause attributed to carcinogenesis is the disrupted gene regulation, which may be potentiated by various risk factors leading to increased prevalence of disease in patients across all age groups [2]. The burden of cancer is expected to be raised to 28.4 million by 2040, which is an estimated increase of 47% when compared against 2022 [3]. The main contributing factors for this significant increase in the prevalence of cancer are attributed to various exogenous (e.g., smoking and lifestyle changes), extrinsic (e.g., immune, microbiota, and hormonal), and intrinsic (e.g., DNA-related alterations) risk factors [4,5]. While these numbers are disturbing, astonishing, and difficult to digest, this also clearly indicates the inability of the currently available medications and the necessity to have more sophisticated, targeted therapies. Availability of novel therapies helps to target the tumor-specific sites thereby potentiating the efficacy of the treatment. These targeted therapies have proven their ability to enhance efficacy in various types of cancers including breast, colon, and small-cell lung cancers [6–8].

Among the targeted therapies, tyrosine kinase inhibitors (TKIs) have gained popularity as major treatment options in drug discovery. TKIs inhibit kinases from phosphorylating tyrosine residues of their substrates and eventually block the activation of downstream signaling pathways and disrupt

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the signaling pathways to prevent abnormal proliferation [9]. These agents have emerged as powerful treatment options for patients suffering from various cancers such as renal, hepatocellular carcinoma, and lung cancer [10–12]. Over the past 20 years, there have been more than 100 TKIs have been approved, targeting more than 58 receptor tyrosine kinases and 32 non-receptor kinases thereby enabling molecular targeting mechanisms [13,14]. In a recent review, Kollipara *et al*. [13] indicated that there are more than 70 TKIs have been approved by the United States Food and Drug Administration from 2021 for targeting EGFR, ALK, ROS1, HER2, and NTRK through molecular mechanisms, thereby portraying the quantum of research ongoing in this direction.

To exert any efficacy, it is essential that the drug formulated as a drug product should exert suitable absorption, distribution, metabolism, and elimination (ADME) to have clinically relevant concentrations at the site of action [15]. Together with the physicochemical properties of the drug, the pharmacokinetic variability also contributes to the drug availability at the target site [16]. In the case of TKIs, the dose as well as dosage regimen is appropriately selected by the oncologists with the aim to have the highest drug concentration at the target site for maximizing efficacy. Additional strategies such as dose reduction, dose escalation, and optimization to balance efficacy and adverse events are routinely followed by medical oncologists [17]. On the other hand, the highest doses of TKIs may be required to have a broad inhibitory profile and enduring clinical benefit [18]. Specific to TKIs, although they are highly efficacious and target specific tumor sites, their administration is associated with significant challenges related to food intake, drug–drug interactions (DDIs) [19]. TKIs exhibit pH-dependent solubility and because of their weakly basic nature, while they get solubilized in the stomach, they may be subjected to precipitation upon entry to the intestine due to increased pH. Because of these aspects, many TKIs including dasatinib, bosutinib, and gefitinib possess challenges for sub-optimal exposures [20]. This aspect becomes prominent as these drugs are used to treat cancers such as chronic myeloid leukemia (dasatinib, bosutinib) and non-small cell lung carcinoma (gefitinib). The situation of sub-optimal exposures gets much more pronounced when TKIs are co-administered with acid reducing agents (ARAs) such as proton pump inhibitors (PPI), H_2 receptor antagonists (H_2RA), or antacids. As the administration of ARA increases the stomach pH, the solubility and dissolution rate of TKIs gets reduced because of precipitation at higher pH thereby leading to DDI. From the treatment perspective, ARAs are prescribed routinely in cancer patients to reduce gastric-related adverse events as well as to prevent gastric mucosal damage caused by cytotoxic chemotherapy [21,22]. However, because of the absorption level DDI between ARA and TKI, the exposure of the TKI gets reduced significantly thereby leading to a decreased survival rate and increased risk of death [23]. A typical practice of reducing the risk of such DDI is through appropriate label recommendation wherein staggering or complete avoidance of ARA may be suggested based on the level of interaction. However, if the recommendation of ARA is inevitable to enhance patient compliance and to reduce gastrointestinal side effects, then the efficacy of the TKI treatment is compromised. Thus, an ideal situation would be a scenario where DDI is mitigated to a greater extent through appropriate formulation innovation. Any formulation approach, that is leading to enhanced solubility of TKIs in the pH range of 4–6.8 may reduce the risk of precipitation thereby providing the possibility to overcome the absorption DDI between TKI and ARA. The literature review indicated the use of novel active pharmaceutical ingredient (API) based or formulation-based interventions that circumvented absorption level DDIs [23,24]. However, such formulation optimizations are time and resource consuming and often require significant efforts to come up with suitable formulation and subsequent clinical studies to demonstrate the absence of DDIs. To reduce the effort towards formulation development, optimization, and clinical evaluations, modeling approaches such as PBBM modeling can be utilized effectively for rational formulation development. Modeling and simulation approaches such as PBBM have gained popularity in recent years due to their plethora of applications at both new drug and generic product development. These models are used to select appropriate formulations for first-in-human studies, evaluating DDIs, establishing dissolution specifications, and enabling biowaivers [25–31]. In the present work, we have successfully utilized PBBM to model and predict, and mitigate the DDIs arising from interactions of TKIs and ARA.

Three drugs were selected for the current study, namely dasatinib, bosutinib, and gefitinib for which ARA restriction has been included in the label due to significant DDIs (Table 1). For all three drugs, using pH versus solubility, permeability, physiology, and pharmacokinetic inputs, PBBM was developed in the fasting condition. The developed models were validated across different oral and intravenous doses and, subsequently, DDI potential was predicted by increasing the stomach pH to 5, mimicking PPI administration. The observed ARA interaction effect was compared against that of clinically reported for determining model credibility. Subsequently, the pH versus solubility data generated in the presence of citric acid was inputted in the model and the DDI potential was estimated. The predicted DDI potential with citric acid-based solubility was compared against that of without citric acid to determine reduced DDI potential due to increased solubility in the pH range of 4–6.8. Subsequently, sensitivity of model towards precipitation potential for all drugs was determined in normal stomach condition (pH 1.3) as well as in altered stomach condition (pH 5) mimicking PPI administration. Further, due to enhanced solubility in the presence of citric acid, possibility of dose reduction has been evaluated for selected drugs. The physical situation being modeled in the present study is to mimic administration of TKIs and ARAs together. Due to significant DDI, such an administration scheme is not possible and thus label has mentioned the restrictions. However, with the help of suitable formulation intervention, such DDIs can be avoided. Thus, our study aimed to mimic a physical situation where TKI and ARA drugs are taken together. Overall, this work portrays the importance of formulation intervention to mitigate ARA impact of TKIs and the utility of PBBM to support the successful formulation development of TKIs to enhance the efficacy of treatment.

Table 1. Literature reported ARAs impact on selected drugs.

Molecule	Dasatinib	Bosutinib	Gefitinib
Antacid	55% and 58% reduction in AUC and C_{max} respectively	Not studied	47% reduction in AUC
	Dose staggering allowed as per label	*No recommendation as per label*	*Dose staggering allowed as per label*
H_2 receptor antagonist	61% and 63% reduction in AUC and C_{max} respectively	Not studied	47% reduction in AUC
	Avoid use as per label	*Dose staggering allowed as per label*	*Dose staggering allowed as per label*
Proton pump inhibitor	43% and 42% reduction in AUC and C_{max} respectively	26% and 46% reduction in AUC and C_{max} respectively	Not studied
	Avoid use as per label	*Avoid use as per label*	*Avoid use or dose staggering as per label*

MATERIALS AND METHODS

Materials

The APIs dasatinib, bosutinib, and gefitinib were obtained as gift samples from Hetero Drugs, Hyderabad. All the reagents used in this study for solubility determination and analytical methodology were of either analytical or HPLC grade. Deionized distilled water was obtained from a Milli-Q water purification system (Millipore, MA). For the solubility study, all the aqueous buffers (pH 2, 3, 4.5, 5, and 6.8) were prepared based on United States Pharmacopoeia [32]. Physicochemical and biopharmaceutical parameters used for the development of PBBM for dasatinib, bosutinib, and gefitinib were primarily collected from available literature, except for the solubility which is generated experimentally. In the absence of literature or in-house data, ADMET-predicted values were utilized for model development. Gastroplus, version 9.9.002 (Simulations Plus Inc., Lancaster, California), was used for the development and validation of PBBM (referred as Gastroplus in later parts of the manuscript). Several Gastroplus modules, i.e., Advanced Compartmental Absorption and Transit (ACAT™), ADMET® Predictor, PKPlus™, and Optimization™ tool were used during model development.

Solubility study

The solubility study was performed using the shake flask method. Aqueous buffers (plain) and aqueous buffers containing 0.2 mg/ml citric acid (5 ml each) were placed in glass vials and kept in a heating orbital shaker at 37°C and 100 rpm for 15–20 minutes to allow the buffers to reach the desired temperature. Considering the average dosage form weight of 500 mg tablet, the amount of acidifier (i.e., citric acid) was considered at 10%, equivalent to 50 mg. Considering the stomach volume of 250 ml, citric acid concentration in the stomach may result in 0.2 mg/ml, and thus, the same concentration was chosen for the solubility experiment. During solubility determination, a weighed amount of the API (dasatinib, bosutinib, and gefitinib) was then added to each vial to create a saturated solution. Samples (150 µl) were withdrawn at different time points (2, 4, and 6 hours), centrifuged for 5 minutes at 12,000 rpm, and the supernatant was analyzed using HPLC after appropriate and immediate dilution to determine the amount of drug solubilized. The solubility data was determined in triplicates and mean, standard deviation were reported for both solubility determinations (with and without citric acid). For the solubility study, a heating orbital shaking incubator (REMI, RIS-24 Plus) and centrifuge (Eppendorf, 5430 R) were used.

HPLC analysis

Chromatographic analysis of the samples obtained from the solubility study was performed using a Shimadzu Prominence HPLC system (Shimadzu Corporation, Kyoto, Japan). The system was equipped with a degasser unit (DGU-20A3R), dual pumps (LC-20AD), an autosampler (SIL-20ACHT), a column oven (CTO-20AC) with temperature control, and a photodiode array-UV detector (SPD-M20A). Data obtained from the HPLC system were analyzed using LC Solutions software (version 1.25, Shimadzu Corporation). All chromatographic separations were carried out on RP18 column (125 × 4 mm, 5 µm) with a flow rate of 1 ml/min. Mobile phase employed was 20 mM Ammonium acetate buffer pH 6.6 and Acetonitrile at 65:35 (%v/v) (dasatinib), 20 mM Ammonium acetate buffer pH 4 and Acetonitrile at 65:35 (%v/v) ratio (bosutinib) and 20 mM Ammonium formate buffer pH 3.5 and Acetonitrile at 75:25 (%v/v) ratio (gefitinib). Separations were carried out at column oven temperatures of 25°C, 45°C, and 40°C were employed for dasatinib, bosutinib, and gefitinib. An injection volume of 10–20 µl was employed during the analysis and wavelengths of 310, 260, and 248 nm were used for dasatinib, bosutinib, and gefitinib, respectively. Using these chromatographic techniques, a retention time between 4 and 6 minutes was obtained for the selected molecules.

In vivo data for PBBM

The *in vivo* data required for PBBM development and validation for all three molecules is gathered from the literature. Dasatinib oral pharmacokinetic profiles for 70 and 100mg doses were gathered from Kovar *et al*. [33]. Bosutinib intravenous infusion (120 mg, 1 hour), and oral pharmacokinetics data for 200, 400, and 500 mg were obtained from the literature [34–37]. Gefitinib intravenous infusion (100 mg, 1 hour), and oral pharmacokinetic data of 250 mg were used from the literature [38]. All the pharmacokinetic profiles (time, mean, and standard deviation) were digitized for the purpose of PBBM development and validation.

PBBM modeling and simulation approach

Gastroplus was used to build the PBBM in fasting conditions for dasatinib, gefitinib, and bosutinib. Human gastrointestinal physiology was incorporated into the model

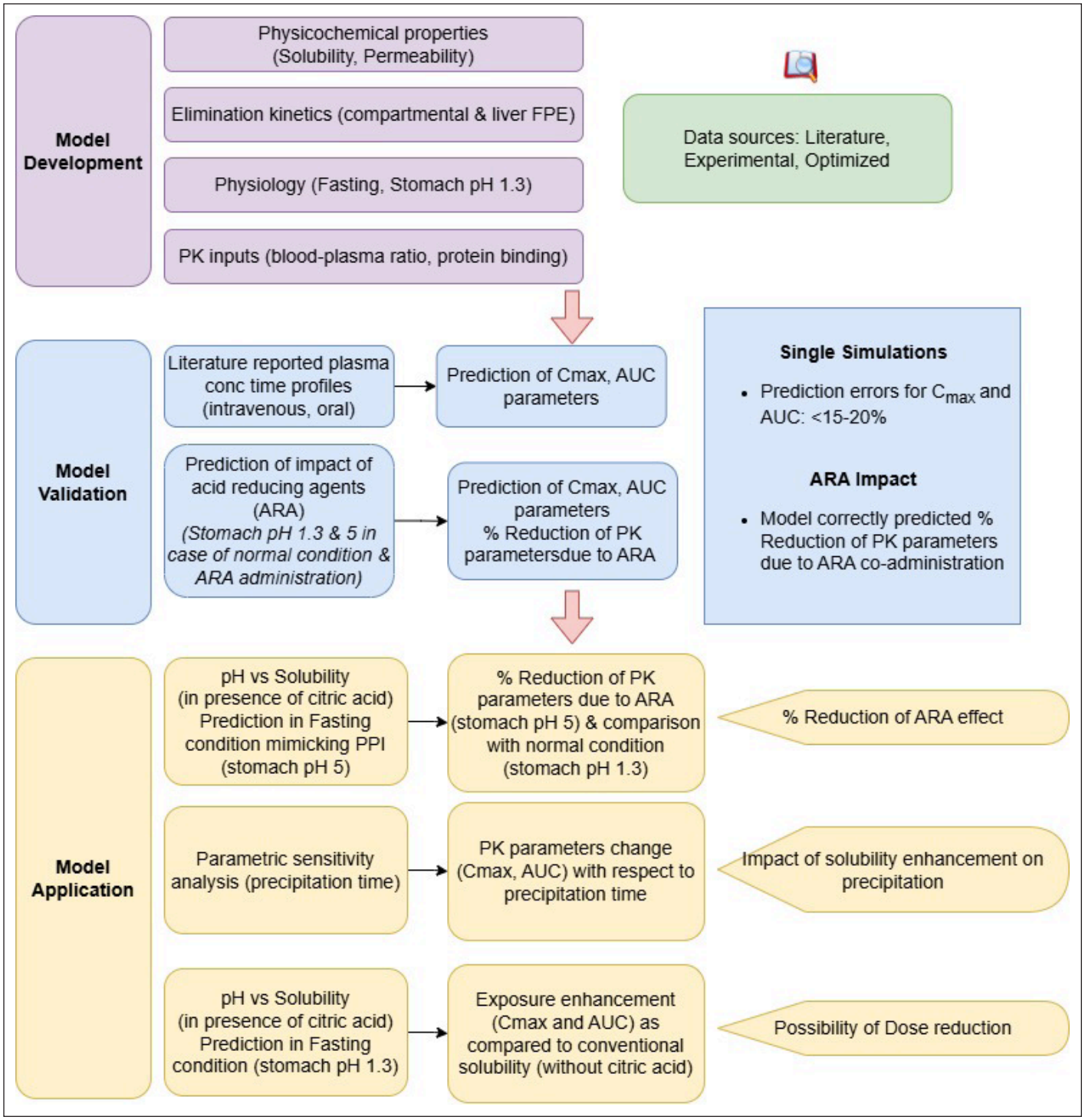

Figure 1. Gastroplus modeling workflow for evaluation of ARA interactions for selected drugs (dasatinib, bosutinib, gefitinib).

through ACAT™. This model accounted for all the processes namely solubilization, dissolution, precipitation, permeation, metabolism, and presence in systemic circulation for all the selected drugs. Additional features such as ADMET Predictor™ and PKPlus™ were used to obtain *in silico* estimates of model parameters and to determine the elimination parameters of the model. The workflow used for the modeling and simulation exercise in the present work is described in Figure 1. The parameters used for model development are described in the following sections.

Physicochemical and biopharmaceutics properties

The physicochemical and biopharmaceutical properties used for the PBBM development for all three

Table 2. Gastroplus model inputs for selected drugs.

Parameter	Dasatinib	Bosutinib	Gefitinib
Molecular weight	488.01	530.46	446.91
Log P	1.8	3.1	4.15
Solubility input (mg/mL, pH)	Refer to Table 3	Refer to Table 3	Refer to Table 3
Human effective permeability ($P_{eff,}$ 10^{-4} cm/s)	1.8	3.1	2.35
Mean precipitation time (sec)	900	2000	900
Blood to plasma ratio (B/P)	1.8	1.2	0.9
Plasma protein binding (%$F_{up,}$ adjusted %F_{up})	4, 3.94	4, 3.89	8.9, 1.36
Dosage form	IR Tablet	IR Tablet	IR Tablet
Physiology	Fasting	Fasting	Fasting
	Normal: stomach pH 1.3	Normal: stomach pH 1.3	Normal: stomach pH 1.3
	ARA: stomach pH 5	ARA: stomach pH 5	ARA: stomach pH 5
Elimination kinetics	CL (L/h/kg)-1.65	CL (L/h/kg)-0.44	CL (L/h/kg)-0.85
	V_c (L/kg)-1.04	V_c (L/kg)-4.03	V_c (L/kg)-4.94
	$T_{1/2}$ (h)-4.11	$T_{1/2}$ (h)-110.04	$T_{1/2}$ (h)-42.24
	K_{12} (1/h)-0.76	K_{12} (1/h)-0.47	K_{12} (1/h)-0.41
	K_{21} (1/h)-2.56	K_{21} (1/h)-0.18	K_{21} (1/h)-0.19
		K_{13} (1/h)-0.12	K_{13} (1/h)-0.03
		K_{31} (1/h)-0.01	K_{31} (1/h)-0.02
%FPE	60%	70%	53%

molecules dasatinib, bosutinib, and gefitinib are provided in Table 2. The solubility input used in the model (i.e., pH *vs.* solubility) with and without citric acid is provided in Table 3. For initial model development, pH versus solubility profile of all the drugs without citric acid is used (termed as conventional solubility). For all the simulations, immediate release tablet was selected as dosage form. For the fasting simulations, 250 ml of water is consumed and same volume as the administration volume is considered during all the simulations. Particle size (i.e., diameter) of 25 µm was considered during all simulations as a default value. During simulations, the *in vivo* dissolution is determined based on particle size, diffusion layer thickness, effective surface area, and diffusion coefficient. Furthermore, a default precipitation time of 900 seconds was used for both dasatinib and gefitinib whereas for bosutinib this value is optimized to 2,000 seconds due to low probability of precipitation at intestinal condition based on solubility data presented in Table 3.

Physiology

For the simulation of *in vivo* pharmacokinetic study in the fasting condition for all three drugs, "Human physiology-fasting" was considered. The absorption scaling factor model used in the present simulations is Opt Log D Model SA/V 6.1. The developed oral mechanistic model accounted for passive absorption and no active transport is included. For all three drugs, ADMET predictor predicted permeability was used during initial simulations and was later optimized to account for *in vivo* T_{max} accurately for oral pharmacokinetic data. The optimized permeability values for all three drugs are presented in Table 2.

Elimination parameters

For physiological models, the best way to describe the elimination parameters is based on intravenous pharmacokinetic data [39,40]. However, in the absence of the intravenous pharmacokinetic data, the elimination parameters can be determined after correcting for bioavailability. In the case of dasatinib, the intravenous pharmacokinetic data is not available, however in preclinical species, the bioavailability ranged from 14% to 34% [41]. Considering the average bioavailability of 20% for humans, the elimination parameters were determined for 100 mg oral profile using 2-compartmental model and the bioavailability was corrected using the liver first pass extraction (%FPE) as indicated in Table 2. In the case of bosutinib and gefitinib, due to the intravenous pharmacokinetic data availability, the oral as well as intravenous pharmacokinetic data fitted together, and elimination parameters, %FPE were determined. In both cases, the elimination parameters followed 3-compartmental model and are presented in Table 2. Other pharmacokinetic inputs such as protein biding and blood-to-plasma ratio are determined from the literature and is indicated in Table 2. Further, a default body weight of 70 kg was used during all simulations for adult healthy human physiology.

Model validation

The model was developed using the above-mentioned model input parameters and was validated using the literature-reported plasma concentration profiles of intravenous infusion as well as oral formulations. For the model validation exercise, prediction error (%PE) as well as folds error (FE) were calculated using the formulas (1) and (2). Both parameters were

Table 3. pH versus solubility data of selected drugs (mean ± SD, n = 3).

pH	Dasatinib		Bosutinib		Gefitinib	
	Without citric acid	With citric acid	Without citric acid	With citric acid	Without citric acid	With citric acid
2	13.311 ± 0.666	13.448 ± 0.807	7.067 ± 0.353	9.812 ± 0.589	4.326 ± 0.216	0.655 ± 0.039
3	2.706 ± 0.216	0.642 ± 0.045	Not performed	Not performed	0.465 ± 0.037	0.397 ± 0.028
4.5	0.288 ± 0.020	0.306 ± 0.028	2.261 ± 0.181	3.702 ± 0.259	0.384 ± 0.027	0.233 ± 0.021
5	0.076 ± 0.005	0.073 ± 0.006	0.773 ± 0.054	1.126 ± 0.101	0.097 ± 0.006	0.486 ± 0.039
6.8	0.013 ± 0.001	0.237 ± 0.014	0.004 ± 0.001	0.978 ± 0.078	0.006 ± 0.001	0.881 ± 0.053

Note: Solubility at pH 5 is used as reference solubility in the simulations.

used to obtain confidence into the developed PBBM for all three drugs [42,43].

$$\%PE = \left(\frac{\text{Observed value} - \text{Predicted value}}{\text{Observed value}} \right) \times 100 \quad (1)$$

$$FE = 10^{\left| \log\left(\frac{\text{predicted}}{\text{observed}} \right) \right|} \quad (2)$$

Further, the model's ability to correctly predict the ARA effect reported in the literature (Table 3) is evaluated [44–46]. In the case of ARA administration, on average, the stomach pH gets increased to 5 and this change was made to simulate ARA administration [47]. Further, the %reduction of AUC parameter in the case of ARA administration is calculated using the formula (3) and this predicted value is compared against observed data in the literature to demonstrate models' credibility for all three drugs. For this purpose, 100, 400, and 250 mg oral doses were used for dasatinib, bosutinib, and gefitinib, respectively [47].

$$\%\ \text{Reduction in AUC} = 100 - \left(\frac{\text{Simulated AUC}_{\text{Stomach pH 5}}}{\text{Simulated AUC}_{\text{Stomach pH 1.3}}} \times 100 \right) \quad (3)$$

Model application

The validated PBBM for all three drugs were subsequently applied with an objective to evaluate the ARA and TKI DDI mitigation strategies as follows.

DDI mitigation due to acidifying agent

The addition of citric acid in the formulation helps to provide acidifying microenvironment in the formulation to enhance the solubility of TKI in the region of pH 4.5–6.8. Further, to evaluate the impact of citric acid on DDI mitigation, the solubility data generated in the presence of citric acid (Table 3) is inputted into the model and the AUC values were simulated at normal stomach pH condition (pH 1.3), and pH condition mimicking ARA administration (pH 5). The % reduction in AUC with this set of solubility data is determined using formula (3).

Solubility enhancement on precipitation behavior

Due to solubility enhancement, especially in the pH range of 4–6.8, there can be the possibility of reduced precipitation of the TKIs upon entering the intestine, thereby, avoiding such potential limitation for absorption. For evaluating this behavior, the *in vivo* dissolution profiles of all three drugs were determined during the simulations. The *in vivo* dissolution profiles were compared with conventional and enhanced solubility (with citric acid) under normal stomach (pH 1.3) and the stomach condition (pH 5) mimicking ARA administration. Further, parametric sensitivity analysis (PSA) analysis was performed under a normal stomach (pH 1.3) with respect to precipitation time for evaluation of the impact of solubility on precipitation.

Table 4. Model validation for selected drugs (observed *vs.* predicted) %PE, FE.

PK parameter	Observed values	Predicted values	%PE	FE
Dasatinib, oral 70 mg				
C_{max} (ng/ml)	62.08	54.85	–11.7	1.13
AUCt (ng.h/ml)	218.51	222.16	1.7	0.98
Dasatinib, oral 100 mg				
C_{max} (ng/ml)	81.36	69.49	–14.6	1.17
AUCt (ng.h/ml)	317.04	318.97	0.6	0.99
Bosutinib, i.v. infusion, 120 mg 1 hour				
C_{max} (ng/ml)	350.73	302.88	–13.6	1.16
AUCt (ng.h/ml)	2543.6	2516.5	–1.1	1.01
Bosutinib, oral 200 mg				
C_{max} (ng/ml)	48.19	46.32	–3.9	1.04
AUCt (ng.h/ml)	960.96	1182.4	23.0	0.81
Bosutinib, oral 400 mg				
C_{max} (ng/ml)	67.499	69.69	3.2	0.97
AUCt (ng.h/ml)	1573	1327.3	–15.6	1.19
Bosutinib, oral 500 mg				
C_{max} (ng/ml)	110.27	78.66	–28.7	1.40
AUCt (ng.h/ml)	2578	2135.5	–17.2	1.21
Gefitinib, i.v. infusion, 100 mg 1 hour				
C_{max} (ng/ml)	308.58	207.49	–32.8	1.49
AUCt (ng.h/ml)	1637.1	1629.2	–0.5	1.00
Gefitinib, oral 250 mg				
C_{max} (ng/ml)	95.65	73.71	–22.9	1.30
AUCt (ng.h/ml)	1935.6	1743.4	–9.9	1.11

Possible reduction in the dose

Due to solubility enhancement in the presence of citric acid, there might be possible dose reduction as the increased solubility can enhance exposures. Thus, the possibility of dose reduction and the folds enhancement in exposures are calculated for all three drugs using the formulas (4) and (5) by performing the simulations in fasting stomach condition (pH 1.3).

$$\text{Folds increase in exposure} = \frac{AUC_{\text{solubility with citric acid}}}{AUC_{\text{conventional solubility}}} \quad (4)$$

$$\%\ \text{Dose reduction} = 100 - \left(\frac{AUC_{\text{solubility with citric acid}}}{AUC_{\text{conventional solubility}}} \times 100 \right) \quad (5)$$

RESULTS

In the present study, PBBM was developed to predict and to demonstrate the mitigation of ARA, and TKIs DDI by using acidifying agent in the formulation (Fig. 1). All PBBMs were developed through the integration of physicochemical, pharmacokinetic, and physiological properties. The developed models enabled multiple applications with respect to the mitigation of DDI, possible dose reductions, and lowered precipitation potential.

Solubility

The solubility study was conducted at 37°C across the pH conditions of 2–6.8 with and without citric acid (at a concentration of 0.2 mg/ml). The generated solubility data is presented in Table 3 and for all the drugs, pH-dependent

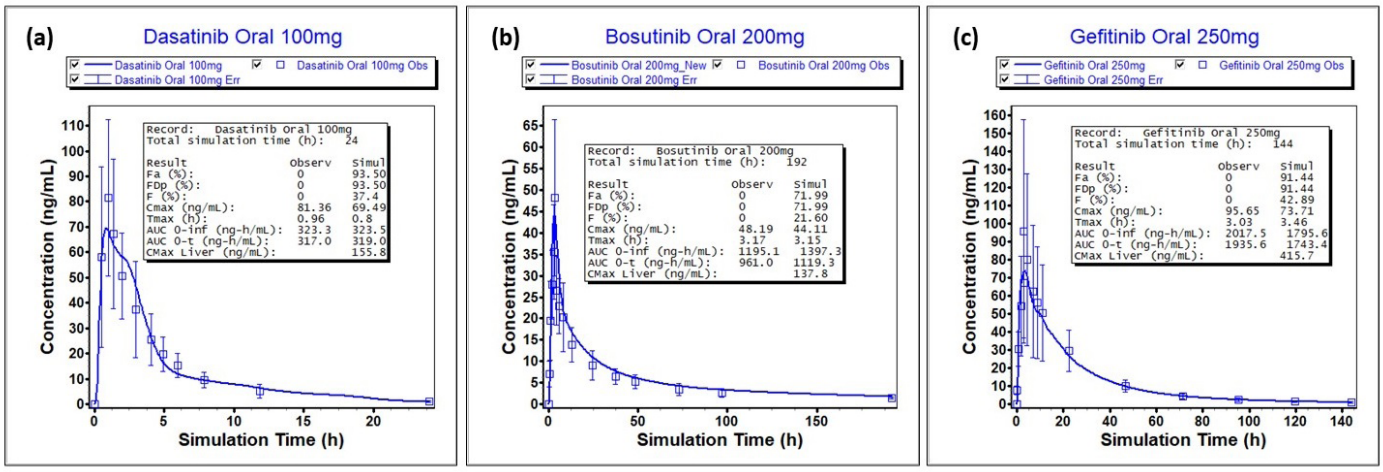

Figure 2. Gastroplus model validation against oral data (a) dasatinib oral 100mg (b) bosutinib oral 200 mg (c) gefitinib oral 250 mg. Horizontal axis: time and vertical axis: plasma concentration.

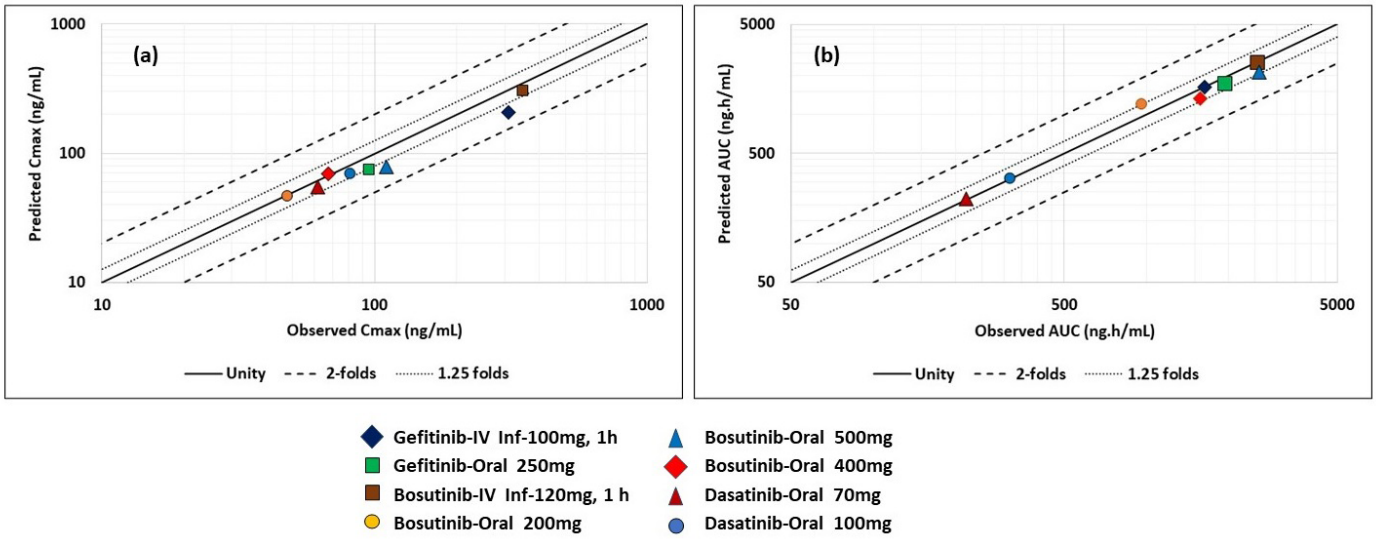

Figure 3. Predictability graphs for C_{max} and AUC parameters across the doses and dosage forms for selected drugs (a) C_{max} (b) AUCt. Horizontal axis: observed parameter and vertical axis: predicted parameter.

solubility has been observed wherein solubility was found to be higher in acidic conditions followed by reduced solubility as the pH increased. The data of three replicates was found to be closer to each other and the variability was found to be lower thereby demonstrating the reliability of the results. When compared with conventional solubility (without citric acid), the presence of citric acid enhanced the solubility especially at the pH conditions of 4.5–6.8 thereby confirming that an acidic environment facilitated more solubilization. This phenomenon was observed for all the studied drugs and specifically, significant improvement in solubility is seen at pH 6.8 due to the presence of citric acid.

PBBM simulations

Model development

Initial PBBM was developed for all the drugs, dasatinib, bosutinib, and gefitinib using the physicochemical properties, pharmacokinetic, and physiological parameters listed in Table 2 and using conventional solubility in Table 3. The elimination kinetics calculated either from the intravenous and oral data (bosutinib, gefitinib) or solely from the oral data (dasatinib) depicted the plasma concentration values appropriately. Further, optimization of precipitation time in the case of bosutinib also ensured matching predictions with that of clinical data thereby enabling model suitability. The incorporation of %FPE to enable accurate bioavailability consideration in the model has yielded acceptable PBBMs for all the molecules. Further, optimized permeability resulted in predictions that are matching with literature-reported data. Human physiology fasting has demonstrated its suitability in the current simulations and thus didn't require any modifications. Overall, together with all model inputs, the models demonstrated acceptability for all the molecules studied.

Model validation

After successful model development, detailed validation has been performed across the dosage forms and doses for all the selected drugs. For dasatinib, model validation has been performed with oral doses whereas for bosutinib and gefitinib, model validation is performed using both intravenous infusion and oral doses. The results of the model validation are depicted in Table 4, Figures 2 and 3. As indicated in Figure 2, for all tree drugs, there is a good agreement between observed versus predicted plasma concentration-time data. The predictions are closer to the observed data and were within the variability observed. As can be seen from Table 4 that the PEs for C_{max} and AUC were acceptable across different dosage forms and different doses thereby confirming the validity of the developed models. Apart from PEs, the FEs were also closer to 1 thereby confirming the validity of the model. Further, it is evident from Figure 3 that both the predicted C_{max} and AUC values within acceptable folds limits as that of the observed data. In most of the cases, the observed versus predicted values are closer to unity and almost all the cases, the results were within 1.25 folds thereby confirming the validity of the developed PBBM. Further, the predictions across dosage forms and doses provided stronger confidence in the models, and subsequently, the models were used to predict the literature reported ARA effect.

To simulate the ARA effect, the predictions for AUC have been performed with a normal stomach (pH 1.3) and an altered stomach (pH 5) due to PPI administration. The AUC values were simulated in both cases and the ratio was determined and subsequently %AUC reduction was calculated. The comparison observed versus simulated ARA DDI is depicted in Figure 4 and represented in Table 5. The simulation results indicated that all the models predicted the ARA effect accurately in comparison with literature-reported data. The data from Figure 4 indicated that the observed versus predicted DDI is within 1.25 folds for two cases (dasatinib, gefitinib) and within 2 folds for one case (bosutinib). The observed DDI effect for bosutinib is significantly lesser (17%) as compared to other drugs and thus the predictions within two folds for this molecule were considered to be acceptable. Overall, the developed PBBM simulated DDI effect well for all the studied drugs.

Model application

The fully validated PBBM was successfully used for various applications as mentioned below.

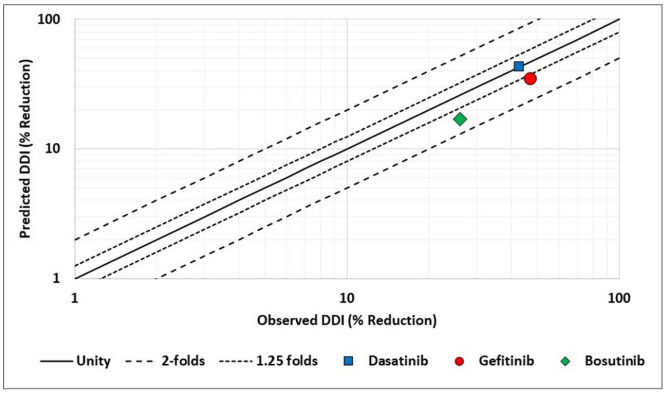

Figure 4. Predictability graphs for observed versus predicted ARA interaction. Horizontal axis: observed interaction and vertical axis: predicted interaction.

Table 5. Observed versus predicted PPI effect and simulated PPI effect with citric acid.

Molecule	Conventional solubility				Solubility (citric acid)		
	Simulated AUCt (ng.h/ml)		% Reduction in AUC		Simulated AUCt (ng.h/ml)		% Reduction in AUC
	Stomach pH (1.3)	Stomach pH (5)	Simulated	Observed	Stomach pH (1.3)	Stomach pH (5)	Simulated
Dasatinib	319	183	43	43	343	342	0.2
Bosutinib	1862	1545	17	26	2981	2974	0.2
Gefitinib	1743	1124	35	47	1909	1909	0.0

DDI mitigation due to acidifying agent

To evaluate the impact of citric acid addition on the DDI mitigation, the model predictions were performed with solubility generated in the presence of citric acid at both normal stomach (pH 1.3) as well as at stomach (pH 5) mimicking ARA administration. The DDI effect in this scenario was calculated and presented in Table 5 and Figure 5 in comparison against that of simulated DDI effect without citric acid addition. In conjunction with the increased solubility in the presence of citric acid (Table 3), the results demonstrated that the DDI effect is almost nullified due to the presence of citric acid. As it can be seen from Table 5 the % reduction in AUC is almost close to zero thereby indicating the possibility of complete DDI mitigation. Overall, from Figure 5, it is evident that the predicted DDI effect is significantly reduced for all the studied molecules.

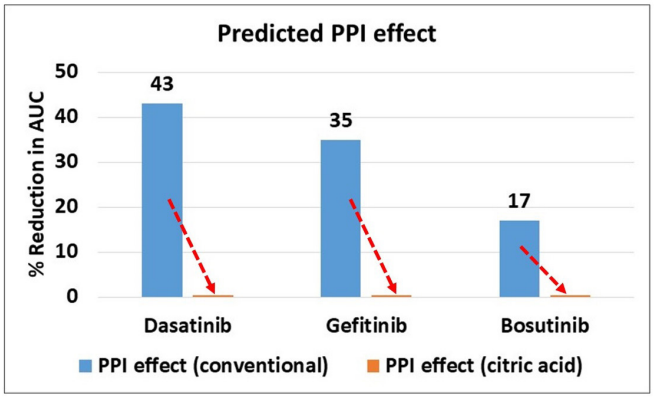

Figure 5. Predicted PPI effect (with citric acid) against conventional (without citric acid) for selected drugs.

Solubility enhancement on precipitation behavior

To understand the impact of solubility enhancement on precipitation behavior, the *in vivo* dissolution curves were simulated at different conditions using conventional solubility and solubility in the presence of citric acid at normal stomach (pH 1.3) and stomach (pH 5) mimicking ARA administration. The result of this exercise is presented in Figure 6 wherein with conventional solubility, solubilization followed by precipitation is observed for all the molecules. With conventional solubility, when stomach pH is increased to 5, the *in vivo* dissolution was slower and incomplete to solubilize the entire dose of the drugs, thereby, demonstrating potential DDI. When solubility with citric acid is incorporated in the model, the models predicted faster *in vivo* dissolution without precipitation thereby indicating a positive impact of solubility. Further, the *in vivo* dissolutions were similar in the normal stomach (pH 1.3) and stomach (pH 5) mimicking ARA administration thereby indicating the absence of interaction. Additionally, no precipitation behavior was seen at both stomach pH of 1.3 and 5 when citric acid-based solubility was used. Further, PSA analysis performed in a normal stomach (pH 1.3) using conventional and citric acid solubility (Fig. 6) indicated that precipitation time has sensitivity towards AUC when conventional solubility is used whereas there is no impact

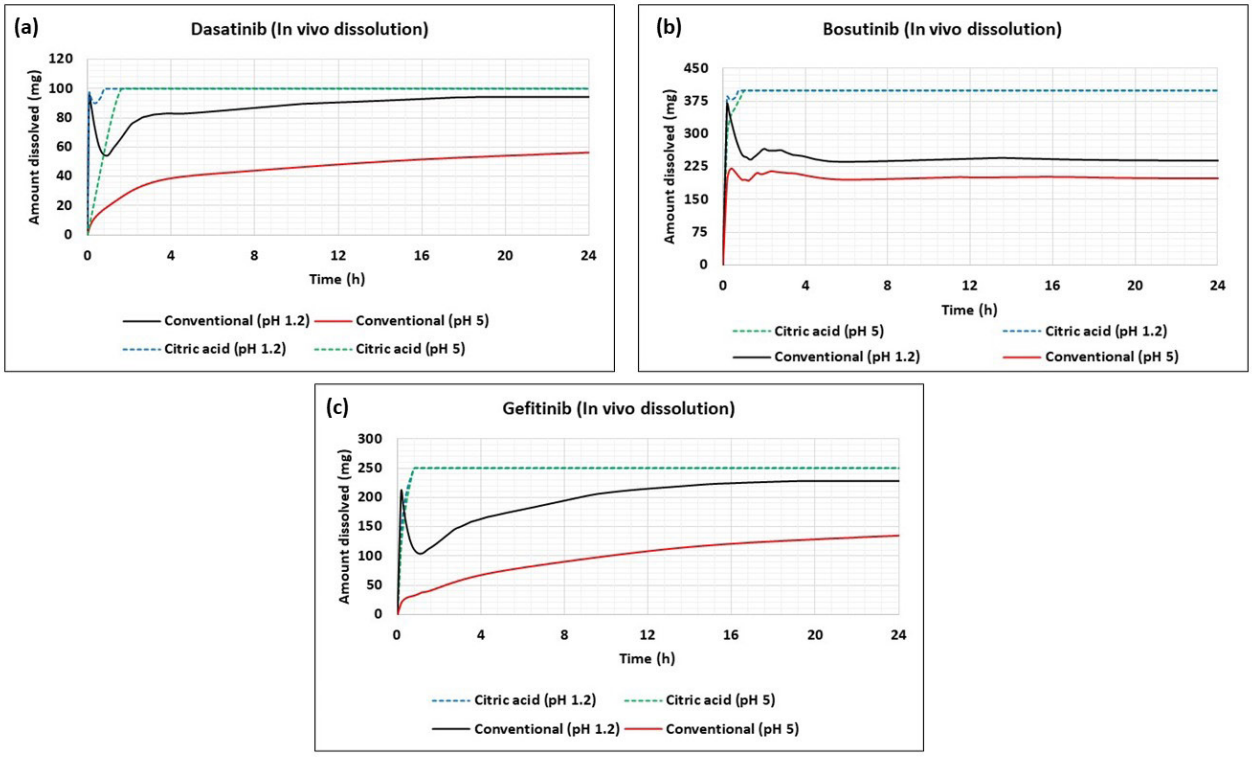

Figure 6. *In vivo* dissolution graphs for selected drugs (a) dasatinib (b) bosutinib (c) gefitinib. Horizontal axis: time and vertical axis: amount dissolved (mg).

Table 6. Dose reduction possibility with increased solubility in presence of citric acid.

Molecule	Dose (mg)	Simulated AUCt (ng.h/ml) in fasting stomach pH 1.3		Folds enhancement	Dose reduction to (mg, %)
		Conventional solubility	Solubility (citric acid)		
Dasatinib	100	319	343	1.08	93, 7%
Bosutinib	400	1862	2981	1.60	250, 37.5%
Gefitinib	250	1743	1909	1.10	228, 8.8%

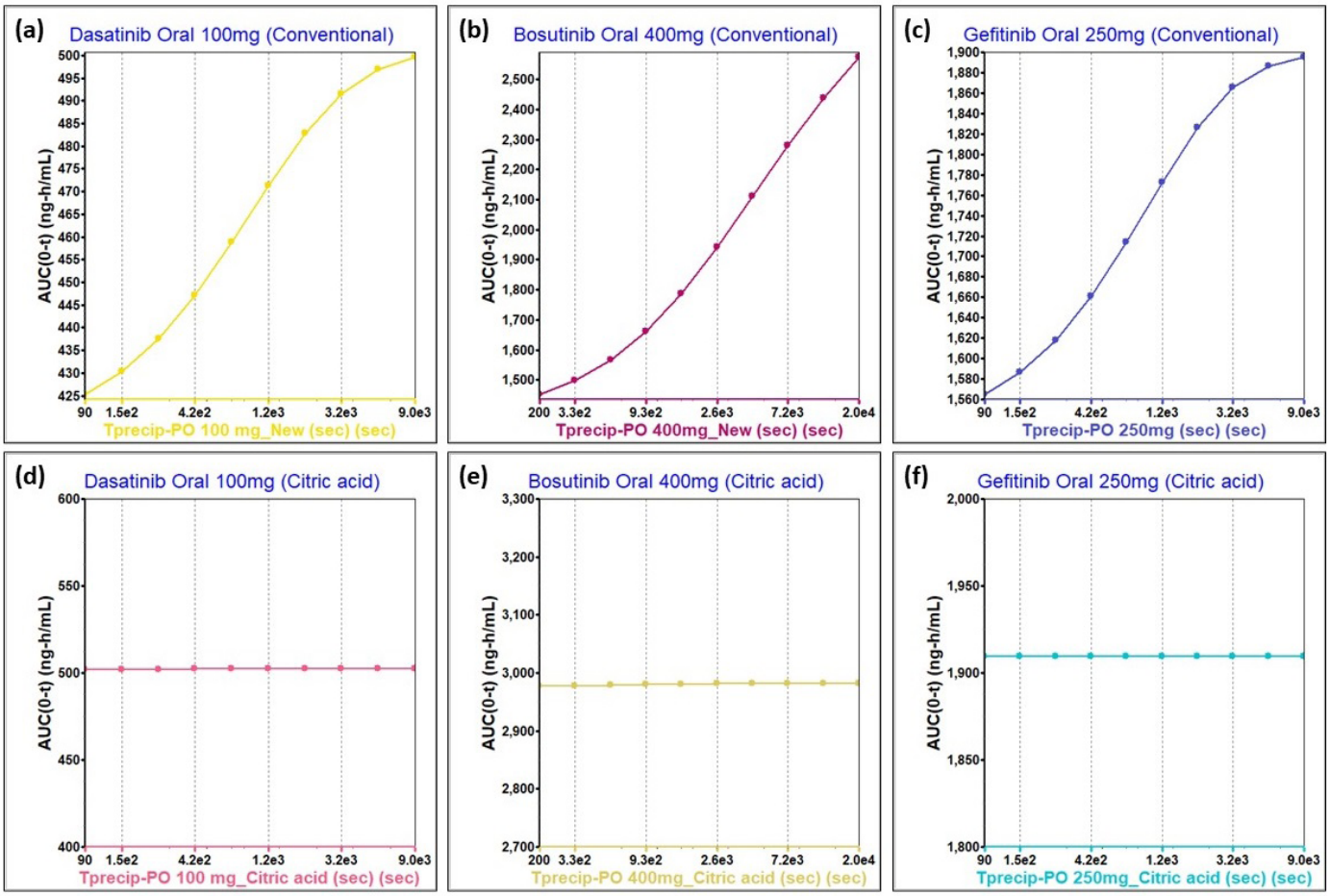

Figure 7. Parametric sensitivity analysis (precipitation time *vs*. AUC) (a) and (c) dasatinib oral 100 mg with and without citric acid (b) and (d) bosutinib oral 400 mg with and without citric acid (c) and (e) gefitinib oral 250 mg with and without citric acid. Horizontal access: precipitation time, vertical access: predicted parameter value.

of precipitation time on AUC when citric acid-based solubility was used. This aspect clearly demonstrates the nullified *in vivo* precipitation when solubility is enhanced in the range of pH 4.5–6.8 for all the drugs.

Possible reduction in the dose

Due to solubility enhancement in the presence of citric acid, possibility of dose reduction for all drugs has been studied and the results are portrayed in Table 6. When AUC values generated with citric acid solubility is compared against conventional solubility, a fold's increase of 1.08 1.60, and 1.10 was observed for dasatinib, bosutinib, and gefitinib resulting in dose reduction possibility by 7%, 37.5% and 8.8% respectively, owing to enhancement in solubility. These values represent mean reduction in doses and the ranges, confidence intervals of the dose adjustments can be estimated in the future based on the population simulations as described in the discussion section. Further, the reduced doses are deemed to yield bioequivalence against innovator formulation and thus similar clinical response is anticipated yet providing flexibility in dose administration with ARAs.

DISCUSSION

TKIs have demonstrated significant efficacy against various types of cancers including breast cancer, colon cancer, lung cancer, and so on, due to molecular targeting

mechanisms. Over the past two decades, more than 100 TKIs have been approved thereby portraying the extensive research done in medical oncology. Even though TKIs are efficient in various types of cancers through molecular targeting mechanisms, they are victims of administration challenges [13]. The TKIs are weakly basic in nature and thus are prone to precipitation in the intestinal condition, thereby leading to pharmacokinetic variability as they exhibit pH-dependent dissolution. Additionally, there has been inconsistent labeling practices observed for TKIs and despite positive food effects for many agents, these agents are administered in fasting conditions [48–50]. This aspect may be justifiable from a safety perspective, but administration in fasting conditions despite positive food effects may yield sub-optimal exposures leading to lower or insignificant therapeutic efficacy. Another important consideration in TKIs administration is the number of pills wherein some agents such as vemurafenib may require eight pills per day and neratinib require six pills per day [51,52]. Additionally, some of the agents require administration at multiple frequencies in a day (e.g., icotinib is administered three times a day) thereby possessing challenges to adhere to administration schemes.

Another important challenge in the administration of TKIs is the impact of ARAs on reduced exposures. Within ARA, there are further sub-classes of agents like antacids, H_2RA, PPIs, and so on. Although all these agents reduce the exposure of TKIs due to increased stomach pH, PPIs represent the worst case due to their long-lasting effect of increased stomach pH [53,54]. The DDIs with PPIs may happen at the systemic level (due to inhibition or induction of metabolizing enzymes) or at the absorption level (due to increased stomach pH). In case the TKIs represent pH-dependent solubility, then the later type of interactions is prevalent. Administration of ARA during TKI treatment is necessary to avoid gastrointestinal issues and to prevent mucosal damage caused by cytotoxic treatment. Raoul *et al*. [55] studied the oncology drug records of approximately 872 and observed that more than one quarter of patients regularly use PPIs. Uchiyama *et al*. [56] reviewed the impact of PPI on the efficacy of oncology treatment and concluded that due to impaired efficacy, it was suggested to limit unnecessary over usage of PPIs. Lee *et al*. [57] studied the impact of PPI on the efficacy of palbociclib treatment in patients with breast cancer. It was concluded that overall survival in concomitant PPI group was shorter than that of the non-concomitant PPI group. These examples clearly indicate the clinically significant impact of ARA on the TKI treatment efficacy. While the PPIs cannot be completely avoided, alternatives to mitigate the DDI were studied in the literature. Buti *et al*. [58] indicated that refraining the PPIs could be an option but other approaches such as dose staggering can be evaluated to mitigate DDI. As indicated in Table 1, dose staggering is allowed in a few cases for all three drugs, depending on the extent of interaction observed and the type of ARA.

To further understand the mechanism of DDI of TKIs with ARAs, further investigation has been performed in the literature. Buddha *et al*. [59] studied the clinical literature of 15 TKIs exhibiting DDIs with ARA and concluded that the interaction is maximum in cases where the solubility varies over the range of pH 1–4. As the TKIs are weakly basic in nature and exhibit pH-dependent solubility, the more the difference between solubility between pH 1 and 4, the more the possibility of interaction expected. Thus, the higher the steepness of the pH solubility curve, more is the interaction expected. Among the studied molecules in the present work, bosutinib has a lower steepness of the pH versus solubility curve and thus, a lower interaction of 17% reduction is seen for this molecule as compared to dasatinib and gefitinib (Table 3). Various approaches to increase the solubility in the range of pH 4.5–6.8 have been evaluated for TKIs to reduce the ARA impact and to relax the labeling schemes to allow staggering or co-administration. Hofmann *et al*. [24] portrayed the use of dasatinib anhydrate with improved solubility in the range of pH 4.5–6.8 as compared to monohydrate thereby enabling the staggered administration as compared to complete avoidance. Similarly, Larfors *et al*. [60] came up with a novel solid dispersion of dasatinib that has improved solubility throughout pH range thereby providing the possibility of co-administration of dasatinib with ARA. However, the development of such formulations requires multiple iterations and significant effort and thus, approaches such as PBBM offers attractive alternatives to extensive formulation experiments and clinical trials.

The use of PBBM to predict the DDI between TKI and ARA has been evaluated in the literature. Dodd *et al*. [47] use the modeling approach at the drug discovery and interface to demonstrate the utility of modeling approach to predict the DDI based on structure or based on minimum solubility data wherein a pH value of 5 is considered for simulations with ARAs. Mitra *et al*. [61] described the industry case studies wherein pH-dependent DDIs were evaluated by PBBM approach for weakly basic drugs. Based on the case studies described, a pragmatic PBBM workflow for the evaluation of such DDIs has been suggested. Although these case studies highlight the importance of PBBM in predicting DDIs between TKI and ARA accurately, PBBM utility to mitigate the risk of DDI using formulation intervention to proactively identify the mitigation was not discussed in detail. We could find only few publications wherein PBBM was used to predict pH-dependent DDI and one of such publication is Parrott *et al*. [62] wherein PBBM was used to explore gastric pH changes on the pharmacokinetics of entrectinib. It was indicated that the presence of acidifying agent in the formulation reduced the effect of gastric pH changes.

In the present manuscript, we attempted to demonstrate the use of PBBM not only to predict, but to mitigate the DDI risk through the addition of acidifying agent in the formulation to enhance solubility in the region of pH 4.5–6.8. The highlight and novelty of this present study is two folds: (1) To avoid DDI between TKI and ARA using suitable formulation intervention and (2) Use of PBPK modeling approach to predict and mitigate such interaction. Three drugs were selected namely dasatinib, bosutinib, and gefitinib for which label administration clearly indicates avoidance or staggering with ARA agents. While dasatinib and gefitinib represent the worst case in the case of ARA DDI (>35% reduction in AUC), bosutinib represents milder interaction (17% reduction in AUC). Citric acid has been chosen as an acidifying agent to provide microenvironment and subsequent enhancement in solubility. Although there are no

formulations made in the current study, the impact of citric acid on the solubilization behavior was performed through solubility experiments. Considering the average tablet weight of 500 mg with citric acid amount around 10% w/w in the formulation, the concentration of citric acid in the gastric fluid is calculated to be around 0.2 mg/ml considering 250 ml volume. As the pH-dependent DDIs mainly happens at stomach condition, this concentration is deemed to be relevant from *in vivo* perspective. This concentration was used in the solubility experiments to evaluate the impact of citric acid on the solubility enhancement of the studied drugs. As indicated in Table 3, citric acid significantly enhanced the solubility especially in the range of pH 4.5–6.8 thereby confirming hypothesis of acidic microenvironment. To further evaluate the impact of the enhanced solubility on the *in vivo* behavior, PBBM were developed for all the studied drugs (Fig. 1). Using the approach mentioned in Figure 1, all the models were successfully developed in the present work.

Physiological models were successfully developed for all the cases using the physicochemical properties (Tables 2 and 3). Elimination parameters were defined appropriately for bosutinib and gefitinib using intravenous data whereas oral data after bioavailability correction was used in case of dasatinib. Similar approach was followed for dasatinib by Heimbach *et al*. [63] wherein elimination parameters were determined for dasatinib after correcting the bioavailability. The developed models were successfully validated against both intravenous as well as oral pharmacokinetic data and the PEs and folds error were within acceptable limits (Figs. 2 and 3; Table 4). As per the data presented in Figures 2 and 3, the model validation was deemed to be successful. Further, the model's capability to predict the clinically reported ARA DDI were evaluated and by altering the stomach pH to 5 in the physiology, the models predicted the DDI that are closer to the observed clinical data as per label (Table 1) for all the three drugs. Further, using the enhanced solubility in presence of citric acid, the models were further evaluated to mitigate the ARA impact for all the selected drugs. It is evident from the simulations that due to enhancement in solubility in the range of pH 4.5–6.8, the models for all the studied drugs demonstrated almost nullified ARA DDI (Fig. 5). The outcome from Figure 5 indicates that there is a good probability of nullification of DDI arising from TKI and DDI with introduction of acidifying agent in the formulation. From the *in vivo* dissolution profiles (Fig. 6) and from the PSA of precipitation time (Fig. 7), it is evident that enhanced solubility in the presence of citric acid has reduced the precipitation and nullified the *in vivo* dissolution difference between normal stomach (pH 1.3) and altered physiology representing ARA administration (pH 5). The data in Figures 6 and 7 indicates that there is possibility of reduced precipitation and enhanced *in vivo* dissolution with help of citric acid. Thus, using the acidifying microenvironment, the absence of ARA impact is demonstrated for all the studied drugs. Overall, this work demonstrates the use of formulation intervention and PBBM to mitigate the DDI between ARA and TKI.

We feel that our work is very significant in dealing with the pertinent problem of DDI between ARA and TKIs. As indicated in previous sections, avoidance of ARA is completely not possible during the treatment to avoid gastric events as well as to prevent mucosal damage. Thus, the only possibility is to add acidifying agents in the formulation to mitigate the ARA impact. Although our work achieved its required objective, there are few limitations of the present work that the simulations are based on the *in vitro* solubility data but not based on the actual formulation that is manufactured with citric acid. To further extend this work, we plan to manufacture actual formulations with citric acid in the future and evaluate them in human study to support the observations in this work and the simulations performed. Further, there are few dissolution medias identified that mimic ARA administration in the fasting condition [64–66]. We further plan to evaluate the prepared formulations in these medias and subsequently shall input in the developed PBBM together with solubility to strengthen the prediction outcomes. Further, model-based predictions are always associated with *in vivo* variability. In the current modeling exercise, we could not perform population simulations with variability due to unavailability of individual subject data. Once the human study results become available, the variability (e.g., gastric pH variations) can be incorporated into the model to obtain variability in the predictions. Further, development of formulations with acidifying agents is possible and one of such reported formulation is palbociclib tablets wherein succinic acid is included in tablet to provide acidic microenvironment, thereby circumventing impact of ARAs. In the present case as well, for the selected agents, manufacturing formulations with citric acid is feasible and the stability can be evaluated subsequently [67]. We believe that the above-mentioned subsequent research in this area will complement observations in our article and we certainly plan to publish our additional research findings in future publications.

CONCLUSION

The work presented in this article demonstrates the utility of PBBM in predicting and circumventing the DDI arising from TKI and ARA interactions. Three TKIs namely dasatinib, bosutinib, and gefitinib were selected in this study, whose labels indicated restrictions with respect to ARA administration due to clinically relevant DDIs. The PBBM for all the drugs was developed and validated successfully across the formulations and doses. Further, the predictability of PBBM to simulate the observed clinical DDI was demonstrated through appropriate physiological modifications in the stomach. Further, the addition of citric acid to successfully circumvent the ARA TKI DDI was demonstrated using the developed models. Citric acid provided microenvironmental pH and subsequently reduced the precipitation and thus nullified *in vivo* dissolution differences between pH 1.3 and 5 thereby indicating the possibility of nullifying DDI. Overall, this work demonstrated approaches to mitigate the pertinent challenge of TKI administration, i.e., DDI with ARA and provided a way forward for successful formulation intervention. Such model-based approaches aid significant value to drug development by speeding up the formulation development and avoidance of unnecessary human clinical studies. Further areas of research include *in vitro* dissolution evaluation to confirm the role of citric acid and further final confirmatory human clinical study to relax the label recommendations with respect to ARA administration.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be authors as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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Hepatotoxicity 5.3 Embryo-fetal toxicity 6 Adverse reactions 6.1 Clinical trials experience 7 Drug interactions 7.1 Effect of other drugs on NERLYNX 7.2 Effect of NERLYNX on other. 2017 [cited 2024 Dec 22]; Available from: www.fda.gov/medwatch

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