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Model integrated evidence approach for rational and safe formulation development: case of alfuzosin prolonged-release tablets

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ABSTRACT

The model integrated evidence (MIE) approach aims to utilize simulation tools like physiologically based biopharmaceutic model (PBBM) or physiologically based pharmacokinetic (PBPK) model for the development of new drugs and generic formulations. In the current case, MIE is utilized for developing rational and safe formulations for alfuzosin prolonged-release tablets. Due to the side effects of postural hypotension, it is required to develop a formulation that can have lesser yet bioequivalent Cmax. To support this, the PBBM model was developed using physicochemical, disposition, and dissolution data in 0.01N HCl and pH 4.5 acetate buffer. The model was validated using literature reported *in vitro in vivo* correlation. Bioequivalence predictions indicated that in-house generic formulation is bioequivalent to reference and thus enabled direct pivotal study. The outcome from the pivotal bioequivalence study yielded Cmax T/R ratio, although lower (by 13%) it is bioequivalent to the reference formulation. The results matched with predictions and demonstrated the significance of MIE in formulation development. Comparison of generic formulation with other brands A, B, and C indicated that generic formulation is superior over others in terms of *in vitro* similarity and *in vivo* bioequivalence. Overall, this work signifies the novel use of MIE in rational formulation development that can reduce the expensive human clinical studies and enable faster approvals.

INTRODUCTION

The model integrated evidence (MIE) approach aims to utilize modeling and simulation tools such as physiologically based biopharmaceutic (PBBM) model or physiologically based pharmacokinetic model (PBPK) model for the development of formulations for both new drug and generic development [1]. Such modeling approaches fall under the category of quantitative methods and modeling (QMM) and are increasingly recognized for their applications in drug development [2]. Such modeling approaches are routinely utilized for model-guided formulation development and also are submitted as a part of regulatory dossiers. Application of such modeling approaches during new drug development includes a prediction of first-in-human exposures, efficacious dose estimation, formulation bridging, pediatric dose and exposure predictions, drug–drug interactions predictions, and so on [3–5]. The FDA Modernization Act in 2022 is a testimony to encouraging the use of such *in silico* tools to avoid extensive preclinical testing during innovative drug development [6]. At generic formulation development, model-integrated evidence yields a plethora of opportunities ranging from bioequivalence predictions, bioequivalence risk assessment, virtual bioequivalence, dissolution specifications justification, biowaivers, justification of f2 mismatch, and so on [7–12]. Model-based approaches are of greater use in the case of complex formulations such as locally acting drug products, complex injectable liposomal formulations, modified release

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formulations, and so on. For these complex formulations, QMM aided in the development of *in vitro*-based bioequivalence approaches, risk evaluations, critical bioavailability attributes assessment, novel bioequivalence methodologies, optimization of study designs, and estimation of a number of volunteers for successful bioequivalence outcome [13]. Considering these plethoras of opportunities, regulatory agencies such as USFDA and EMA came up with regulatory guidance in the area of modeling and simulations and also encouraged generic companies to use these approaches as a part of the MIE pilot program. These aspects also have been topics of discussion during the recent workshops and seminars, thereby further stressing the significance of these tools [14,15].

Modified release (MR) formulations possess complexity due to the interplay of formulation, API, and physiological factors governing the *in vivo* behavior. Designing an MR formulation against immediate release (IR) or innovator MR formulation can be considered with a biopharmaceutical risk of medium to high depending on formulation complexity [11]. As MR formulation navigates from the stomach to later parts of the intestine depending on the release profile, it might be often challenging to assess *in vivo* behavior solely based on the *in vitro* dissolution. In such cases, MIE approaches can be of significant aid due to their ability to predict regional absorption, and pharmacokinetic behavior in comparison with reference formulation [16]. Such approaches can be utilized to rationally design formulation with the intended objective. For example, if an MR formulation being developed against a traditional IR formulation for dosage frequency reduction, MIE can help to identify a suitable target dissolution profile. If MR formulation being developed to reduce C_{max}-related safety events, MIE can help to assess the target *in vitro* release that can result in the intended objective [17]. If MR formulation is intended to be delivered at a specific location in GIT, MIE can help to assess suitable T_{lag} that can help in achieving the desired release at a specific site. Thus, utilizing MIE approaches can reduce development timelines, enable early success, and help in faster regulatory approvals.

In this context, the present manuscript portrays the utility of MIE in developing a rational and safe formulation for alfuzosin, which is used to treat enlargement of the prostate [18]. The molecule belongs to BCS class III (high solubility, low permeability), and exhibits a half-life of 10 hours and Tmax of 8–10 hours. It comes as HCl salt and as a prolonged-release formulation and acts as a selective antagonist of post-synaptic alpha1-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. The dose is 10 mg and is to be taken immediately after a meal on each day, as its absorption is 50% lower in fasting conditions [19]. The prolonged-release formulation comes as a round, three-layer tablet (one white layer between two yellow layers) under the brand name of Xatral XL. Upon administration, maximum plasma concentrations (C_{max}) are achieved within 8 hours and exhibit linear pharmacokinetics up to 30 mg. A prominent adverse event that has been reported for Xatral XL is postural hypotension, and hence, care should be taken in patients with symptomatic hypertension. This side effect has been correlated with the $C_{max,}$ and thus, reduction of C_{max} can help to reduce the risk of postural hypertension. However, as the efficacy of the treatment is driven through AUC, it is important that any generic formulation should be bioequivalent to the reference formulation with respect to AUC followed by C_{max}.

In this context, the objective of the current manuscript is to describe the utility of MIE to drive formulation development for alfuzosin generic formulation with reduced C_{max} (yet bioequivalent) and equivalent AUC as compared to the marketed reference product Xatral XL. In the present case, we have utilized the MIE approach to rationally develop a formulation with reduced C_{max} for Alfuzosin. A typical side effect of alfuzosin is postural hypotension, and thus, it is desirable to have lesser C_{max} as compared to marketed formulation. Formulations were intentionally designed to have slower release, and MIE was used to predict the C_{max}. From a generic formulation perspective, considering the patent restrictions around three-layer innovator formulation, we have come up with the monolayer dual matrix formulation that is bioequivalent to innovator formulation. The MIE approach has been utilized to derive *in vitro* dissolution of generic formulations that can yield bioequivalence with that of innovator formulation with reduced C_{max} to avoid the risk of postural hypertension. The PBBM model has been developed using physicochemical, pharmacokinetic properties, and validated against literature-reported pharmacokinetic data. The model has been validated to establish literature-reported *in vitro in vivo* correlation (IVIVC). Subsequently, the model has been utilized to predict *in vivo* behavior of slower generic formulation against slightly faster innovator formulation. Considering the confidence gained from modeling and simulations, finally *in vivo* bioequivalence study has been performed in fed condition that has resulted in formulation with desired objectives of bioequivalence and lower C_{max}. Further, the generic formulation has been compared against other companies' brands A, B, and C to demonstrate the superiority of the current formulation as compared to others from a safety perspective. Overall, this work signifies the utility of MIE approaches in rational and safe formulation development which will be of benefit to the patients.

MATERIALS AND METHODS

Materials

Alfuzosin hydrochloride API was procured from MSN Laboratories Prv Ltd., Hyderabad. The reference product for dissolution evaluation and bioequivalence evaluation Xatral XL was procured from Aventis Pharma Limited, United Kingdom. Additionally, the products from other companies brands A, B, and C were procured from the local market for dissolution studies. The generic product was manufactured in-house and used for dissolution and bioequivalence against Xatral XL reference formulation.

GastroPlus® (hereafter called Gastroplus) version 9.8.011 (Simulations Plus Inc., Lancaster, California), a commercially available software to simulate pharmacokinetics of drugs through Advanced Compartmental Absorption and Transit (ACAT™) model and its ADMET® predictor, PKPlus™

and IVIVC™ modules were used during modeling exercise. Published literature was used to develop and validate the model and *in vitro* dissolution data were used for model applications. The literature reported dissolution and plasma concentration profiles were digitally extracted using Plot Digitizer, version 1.9 (Department of Physics, University of South Alabama). DDSolver, an add-in for Microsoft Excel was used to calculate similarity factor (f2) for the dissolution profiles comparison [20].

In vitro studies

Solubility

The equilibrium solubility of Alfuzosin hydrochloride was measured in the media's pH 2, pH 6, pH 6.8, and pH 7.4 buffers. Triplicate samples were prepared, and estimations were performed at 37°C. The samples were mixed for 24 hours and filtered through a 0.45 µm filter and supernatant was analyzed for drug content. Average solubility was determined and used for modeling and simulations together with the final pH at the time of sample collection.

Dissolution

The *in vitro* dissolution profiles of reference formulation Xatral XL, generic product, marketed formulations of Brands A, B and C were generated in multimedia dissolution conditions (0.01N HCl pH 2 representing fasting condition and pH 4.5 acetate buffer representing fed condition) using the following dissolution conditions: 900 ml, 37°C, apparatus II (paddle), USP, 75 rpm with n = 12 units to enable similarity factor (f2) calculations and modeling using Gastroplus. For the determination of the dissolved API in dissolution samples, the HPLC-based analytical method was used. The analytical method consisted of Inertsil ODS-2column with UV determination at 254 nm. Isocratic elution was used for HPLC analysis with a combination of mobile phase consisting of 70% perchloric acid and acetonitrile (80:20, %v/v). The samples during the dissolution testing were collected at 1, 2, 4, 6, 8, 10, 16, 20, and 24 hours and >85% of the drug was released at the end of dissolution. The LOD and LOQ of the HPLC method are 0.05 µg/ml and 0.3 µg/ml, respectively. The calibration curve range was 1.85 µg/ml to 33.35 µg/ml with a coefficient of determination of 0.98.

The dissolution similarity factor or f2 metric was utilized to determine the similarity between reference formulation Xatral XL against generic products and brands A, B, and C. Dissolution profiles are considered to be similar if the f2 is more than 50 [21,22]. The f2 similarity factor is calculated using the formula provided below.

$$f2 = 100 - 25log\ (1 + \frac{1}{p}\sum_{i=1}^{p}(\bar{X}Ti - \bar{X}Ri)^2) \quad (1)$$

wherein p represents the number of time points, $\bar{X}$Ti and $\bar{X}$Ri are the mean dissolved percentage at ith time point of various samples of test and reference, respectively.

Formulation development

The aim of current development is to develop bioequivalent prolonged-release formulation to that of the innovator product Xatral XL. Innovator Xatral XL is a triple-layer product wherein the drug layer is embedded between two different inert layers [23]. Generic formulation development targeted to development of a monolayer dual matrix tablet that can exhibit bioequivalence to that of the reference product. The monolayer dual matrix is defined as a tablet consisting of a hydrophilic active matrix core containing alfuzosin hydrochloride and a combination of two different hydrophilic controlled release cellulose polymers whose functions are to control the hydration and swelling rate of the core, thereby slowing down and linearizing the dissolution profile of active substance. Dual matrix tablets have the advantage of better release and dissolution control as compared to matrix with only hydrophilic or hydrophobic polymers.

Initial formulation trials consisted of developing a generic formulation that can yield similar dissolution profiles as that of Xatral XL using a combination of polymers. However, as postural hyportension has been reported for innovator Xatral XL formulation, efforts were made to formulate a drug product that can yield lower yet bioequivalent C_{max} to that of the reference product to reduce the probability of postural hypotension. Hence, efforts were made to slow down release in both 0.01N HCl and pH 4.5 media at T_{max} region (8–16 hours) as compared to the reference formulation. The impact of this slowdown of dissolution on *in vivo* performance was evaluated through PBBM simulations as described in later parts of the manuscript. With a validated PBBM approach, the dissolution data of 0.01N HCl and pH 4.5 were incorporated into the model and upon confirmation of low risk of bioequivalence, *in vivo* pivotal study was undertaken in fed condition.

In vivo studies

Data from *in vivo* studies from the literature reported data were obtained for oral administration of prolonged-release formulation of 10 mg for the purpose of model development and validation. Further, innovators have developed IVIVC for prolonged-release formulations with different release rates using HCl media [24]. The *in vitro* release and *in vivo* plasma concentration-time profiles of these formulations with different release rates were digitized using a plot digitizer and used for model validation to get further confidence in the developed PBBM model.

The in-house bioequivalence study between reference formulation Xatral XL and Generic formulation was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover oral bioequivalence study in 42 volunteers (completed 40) human subjects under fed condition. Inclusion criteria included: age 18–45 years, weight not less than 50 kg, normal health history, and male subjects who are non-smokers and non-alcoholic. Exclusion criteria included: subjects having hypersensitivity to study medications, presence of other medical conditions such as cardiovascular diseases, and history of QTc prolongation. Blood samples were collected at 0 hour (pre-dose), 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 16, 24, 36, and 48 hours following drug administration in each period by means of intravenous cannulation/vein puncture and transferred into pre-labeled vacutainers, containing K_3EDTA as an anticoagulant. The blood samples were centrifuged at 4,000

rpm for 5 minutes at 4°C to separate plasma. The separated plasma samples were transferred to pre-labeled polypropylene tubes in two aliquots and stored in the freezer (−70 ± 10°C) until analysis. The plasma samples were extracted by liquid-liquid extraction and analyzed by LC-MS/MS technique. The calibration curve ranged from 0.100 ng/ml to 40.216 ng/ml with long-term stability established over 112 days. The processed samples were chromatographed using Supelco Discovery C18, 10 cm × 4.6 mm, 5 µm column using a mobile phase consisting of acetonitrile: 5 mM ammonium formate (60:40 ratio). Column oven temperature was 40°C with a total run time of 3.0 minutes. The fed bioequivalence study was performed for regulatory submission was conducted in full accordance with the requirements of the current version of the International Conference on Harmonization "Guidelines for Good Clinical Practices," "Ethical Guidelines for Biomedical Research on Human Subjects" published by Indian Council of Medical Research, New Delhi and "CGP" guidelines set up by Central Drugs Standard Control Organization and the principles enunciated in the Declaration of Helsinki (WMA General Assembly, Seoul, October 2008). Study protocol and informed consent were reviewed, approved and were permitted by the independent Institutional Review Board before the study initiation [25–28]. All subjects were provided about the study conduct and written informed consent before any treatment was administered. The bioequivalence calculations are pre-defined in the protocol and are based on standard bioequivalence guidelines.

Modeling approach

Gastroplus was used to build the PBBM model for alfuzosin to describe human pharmacokinetics in fed conditions. The model utilizes ACAT™ physiology that integrates local solubility, dissolution, precipitation, absorption, and metabolism of API in each segment of the gastrointestinal tract. Several modules of Gastroplus namely ADMET Predictor™ (to obtain in silico estimates based on structure), PKPlus™ (to determine elimination parameters), optimization (to optimize model inputs), IVIVCPlus™ (*in vitro-in vivo* correlation module) were utilized during the modeling process. The workflow utilized for PBBM simulations is provided in Figure 1 and model input parameters are provided in Table 1.

Physicochemical and biopharmaceutic properties

The physicochemical and biopharmaceutics properties in the model are defined using a combination of in-house data, literature data, and data generated from *in silico* estimates with ADMET predictor module available in Gastroplus that predicts parameters based on structure. A summary of these parameters is provided in Table 1. Solubility estimates were used from in-house experimental data and permeability predicted from ADMET predictor was utilized. Default values of mean precipitation time and particle size were utilized. CR integral is used as dosage form considering prolonged-release formulation behavior. A dosing volume of 250 ml is used for all simulations and this volume is added to the stomach volume at the beginning of the simulations.

Dissolution model

The dissolution data obtained from media such as 0.01N HCl and pH 4.5 were utilized for the prediction of *in vivo* behavior of Xatral XL, Generic product, and brands A, B, and C (Table 2). The 0.01N HCl media was reported to be IVIVC media based on innovator literature and considering the pH-independent solubility behavior of alfuzosin, this media was utilized for fed simulations. Second, as pH 4.5 mimics the *in vivo* stomach condition after food administration, this media

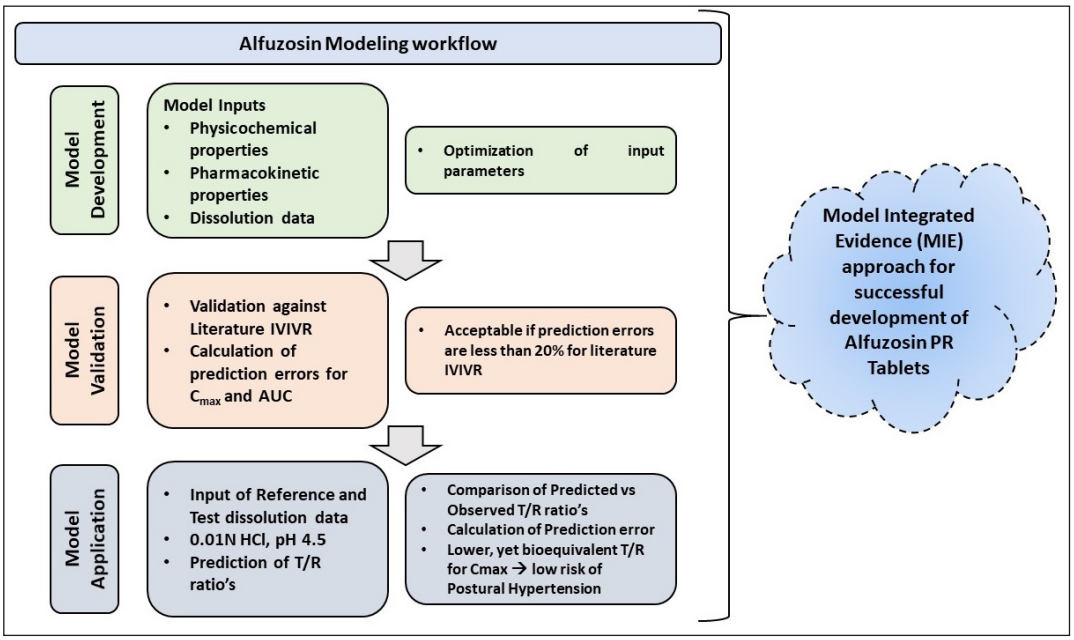

Figure 1. PBBM modeling workflow.

Table 1. Physicochemical, biopharmaceutical, disposition kinetics used in modeling and simulations.

Property	Value	References
Molecular weight	389.46 (Free base)	Literature [19]
Log *P*	1.75	ADMET predictor predicted value was used
pKa	7.48, 0.92, −0.72, −1.6	ADMET predictor predicted value was used, however pKa vs solubility fitting wasn't performed and only solubility data (.spd) file was used for simulations
Solubility data (mg/ml)	pH 2.2–176 mg/ml, pH 5.98–172 mg/ml, pH 6.6–235 mg/ml, pH 7.2–243 mg/ml	In-house generated data. pH 6.6 data was used as reference solubility
Human effective permeability (P_{eff})	0.96×10^{-4} cm/second	ADMET predictor predicted value was used
Mean precipitation time	900 seconds	Gastroplus default
Physiology	Fed	-
Pharmacokinetic disposition parameters	CL (L/hour/kg)—0.75, Vc (L/kg)—7.0, T1/2 (hour)—22.04 hours	One compartmental disposition parameters were used to define elimination of molecule. Calculated from literature oral plasma conc time profiles [24]
Blood to plasma ratio	0.76	ADMET
Plasma protein binding (F_{up}%, unbound)	82%–90%	Literature value [19]
Adjusted F_{up}%, unbound	19.96%	Calculated value from Gastroplus
Dosage form	CR integral tablet	Considering ER formulation

Table 2. Comparative dissolution profiles for Reference product and generic product with other approved brands.

Media	0.01N HCl					pH 4.5 Acetate buffer				
Time (hour)	Xatral XL	Generic product	Brand A	Brand B	Brand C	Xatral XL	Generic product	Brand A	Brand B	Brand C
1	19	16	17	15	21	18	15	12	14	19
2	27	25	26	24	33	26	23	18	22	31
4	39	39	39	38	52	38	36	29	34	48
6	50	50	50	49	67	48	47	37	45	61
8	61	60	58	57	78	58	57	45	53	72
10	72	69	64	66	87	69	65	52	60	81
16	93	85	80	83	102	91	83	69	78	97
20	97	91	87	90	104	96	91	77	85	101
24	99	97	92	95	104	98	95	84	91	103
F2 Similarity factor	-	71	59	64	47	-	70	42	56	52

was also utilized for predictions. During the PBBM model development, efforts were made to match the T_{max} accurately with that of the observed *in vivo* data. Hence, to predict *in vivo* T_{max} accurately, the time scaling approach was utilized on the *in vitro* dissolution data [29]. The time points of dissolutions were multiplied with a specific factor and were inputted into the model to match *in vivo* T_{max} accurately. Based on the optimization exercise, a time scaling factor of 0.6 was deemed to be acceptable as it has resulted in acceptable T_{max} prediction. The time scaling equation that has been utilized for scaling *in vitro* dissolution profiles is as follows. After time scaling, the dissolution profile is directly utilized in the model for *in vivo* prediction.

in vivo dissolution time (hour) = 0.6 x *in vitro* dissolution time (hour) (2)

Elimination kinetics

The literature reported *in vivo* plasma concentration data of Xatral XL was utilized to estimate elimination parameters such as clearance, volume of distribution, and subsequently half-life. From literature-reported data, the oral plasma concentration-time profiles of extended-release formulation for reference products were extracted, and PK parameters were calculated with one compartmental model. The calculated PK parameters were subsequently used in the model for simulation purposes as described in Table 1.

Physiology

Under the gut physiology tab of Gastroplus, the "Human-physiological-fed" and the default absorption scaling factor model (Opt Log D Model SA/V 6.1) were utilized as the

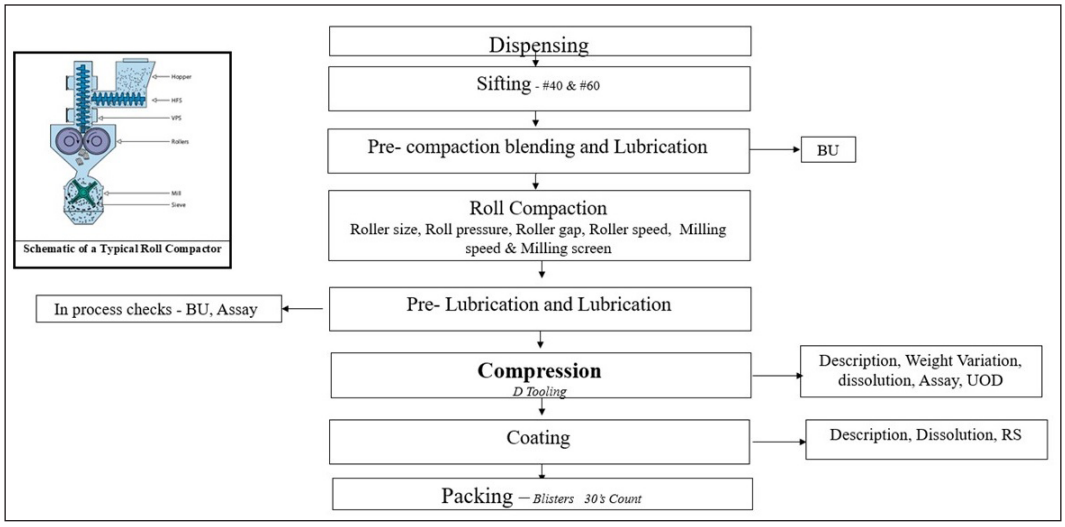

Figure 2. Manufacturing workflow for generic product.

physiological parameters. The mechanistic absorption model used was passive diffusion (transcellular and paracellular) with no carrier-mediated transport. A permeability (Peff) value of 0.96×10^{-4}cm/second from ADMET predictor was used for all gastrointestinal tract segments during simulations. Although ADMET predictor predicted value is used, this P_{eff} value appropriately described the *in vivo* T_{max} of alfuzosin thereby confirming its suitability of this parameter in the model.

Model validation

The model validation exercise has been performed to demonstrate the model's ability to establish a correlation between *in vitro* and *in vivo* behavior using innovator data. For this purpose, data from literature has been used where the *in vitro* dissolution and *in vivo* plasma concentration time profiles were extracted. The dissolution data were generated in acid media and for reference and test formulations, the data were extracted and used as input into the model. Further the plasma concertation time data of reference and test formulations were also inputted into the model and subsequently mechanistic IVIVC has been performed using the IVIVC module in Gastroplus. The mechanistic IVIVC integrates all the physiological processes into the simulations and yields output of *in vitro* vs *in vivo* dissolution based on inputs provided. For both reference and test formulations, IVIVC has been established using deconvolution using a single Weibull function followed by correlation. Furthermore, a convolution exercise has been performed for both formulations and the IVIVC was deemed to be acceptable if the %PE for C_{max} and AUC for both parameters C_{max} and AUC are within 20% [30].

Model application

After successful model validation, the model has been applied to predict the *in vivo* behavior of Xatral XL, Generic formulation, and brands A, B, and C obtained from the local market. For this purpose, the dissolution data after time scaling has been incorporated into the model as described above. Using the dissolution data of both 0.01N HCl and pH 4.5, the predictions were performed for C_{max} and AUC for all formulations and they were compared against reference formulation Xatral XL. Further, the T/R ratios for C_{max} and AUC were calculated for all formulations against reference formulation Xatral XL to assess the comparability of various formulations. Additionally, the T/R ratio's obtained for generic formulation has been compared against that of the *in vivo* bioequivalence study to assess the model's predictability.

RESULTS

Solubility data

The solubility data has been generated in pH 2 (final pH 2.2), pH 6 (final pH 5.98), pH 6.8 (final pH 6.6), and pH 7.4 (final pH 7.2) and the data is presented in Table 1. The same data has been utilized as input into the PBBM model. The solubility data indicates that across the pH conditions, the solubility is more than 170 mg/ml. When the dose of 10 mg of alfuzosin is compared against the solubility data, it is imperative that the molecule belongs to the high solubility categorization.

Formulation development

To achieve prolonged release profiles, a polymer blend was utilized for generic formulation. The objective of the formulation development was to achieve release over 24 hours yet a slightly slower profile as compared to reference formulation with the objective of achieving lower C_{max} as compared to reference. High-viscosity cellulose polymers were selected for dual matrix based on practical experience with other formulations. On the other hand, a precise selection of polymer blend composition was evaluated during the course of development with a high viscosity grade of cellulose polymers with dissolution profile as a parameter for screening. Apart from the polymers used, other standard excipients such as fillers, lubricants, and glidants were utilized for processibility. The manufacturing workflow for generic product is depicted in Figure 2. All the dissolution screening experiments of prototypes were performed in 0.01N HCl and

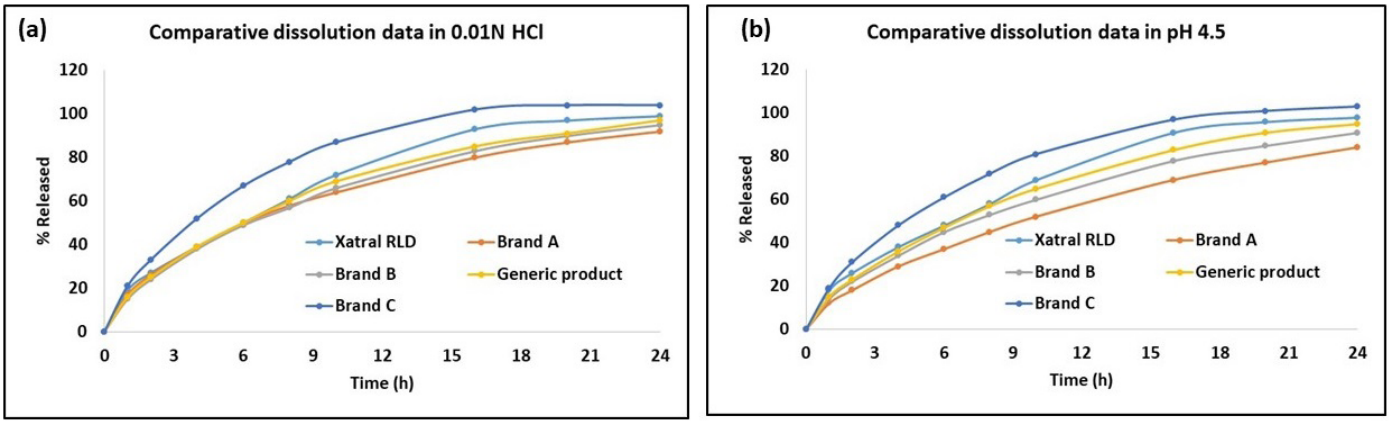

Figure 3. Comparative *in vitro* dissolutions of generic product against innovator and other brands.

pH 4.5 considering innovator reported data and biorelevancy. Initial prototypes matched release in these two media with that of the reference product; however, for the final prototype, the release was made slower to ensure that it can achieve lower yet bioequivalent C_{max}. It was also ensured that the final prototype meets dissolution similarity in both of the media's as described in a later section. Before proceeding with the pivotal bioequivalence study, confidence in bioequivalence has been obtained using PBBM modeling as described in later sections. Based on formulation optimization trials, the final polymer blend concentration ratio of high-viscosity cellulose polymers was selected.

Dissolution data

The dissolution data of reference product Xatral XL, Generic formulation, brands A, B, and C procured from the local market is provided in Table 2 and in Figure 3. The data in both pH conditions 0.01N HCl and pH 4.5 indicates that the dissolution is controlled over a period of 16–24 hours across formulations. It can be observed that the generic formulation is intentionally manufactured to be slower as compared to reference formulation Xatral XL and is evident in both dissolution conditions of 0.01N HCl and pH 4.5, especially at 10–20 hour time points. These data are further used in the PBBM model for simulating *in vivo* behavior and the results are presented in subsequent sections. Although slightly slower, the generic formulation is similar to that of the reference formulation in both pH conditions of 0.01N HCl and pH 4.5 as indicated by f2 values of 71 and 70, respectively.

Along with generic formulation, other brands A, B, and C were compared against reference formulation Xatral in both pH conditions. It can be observed from Table 2 that brands A and B formulations are significantly slower than reference formulation Xatral XL in both pH conditions and resulted in lesser dissolution similarity (lower f2) as compared to generic formulation. Moreover, brand A in pH 4.5 resulted in dissolution dissimilarity against the Xatral XL formulation. Brand C showed extremely faster dissolution profiles in both pH conditions as compared to Xatral XL formulation, and resulting in dissolution dissimilarity with f2 values of 47 and borderline f2 of 52, respectively. Overall, it can be concluded that even though the generic formulation is intentionally manufactured to be slightly slower to have reduced and bioequivalent C_{max}, it behaved with superior dissolution similarity as compared to other brands in the market.

Table 3. Bioequivalence study results of generic formulation against Xatral XL in fed condition ($N = 40$).

PK parameter	T/R ratio (%)	90% Confidence interval (%)	Power (%)	Intra-subject variability (ISCV, %)
C_{max}	87.73	81.24–94.75	99.86	20.62
AUC_{0-t}	99.55	91.42–108.41	99.52	22.90
AUC_{0-inf}	97.75	89.38–106.89	99.20	24.06

***In vivo* bioequivalence study**

The results of the bioequivalence study that has been performed in the fed condition are presented in Table 3. The study was planned in 42 subjects and a total of 40 subjects were included in statistical analysis. There were no adverse events observed in the entire duration of the study for both reference and test products. Therefore, the safety of the test and reference formulation were considered to be comparable. The results from Table 3 indicate that bioequivalence has been achieved comfortably for all parameters such as C_{max}, AUCt, and AUCinf. The power of the study was close to 100% for all parameters and ISCV was found to be moderate as observed in the literature. Thus, a power of >99% for Cmax and AUC indicates that 40 subjects is sufficient to confirm the adequacy of the study. Most importantly, the C_{max} T/R ratio is around 88% as per the rationale and objective of the formulation development to reduce postural hypotension. Although the C_{max} T/R is lower, it was found to be bioequivalent to the reference formulation as both T/R and 90% confidence intervals for C_{max} are within 80%–125%. For AUCt and AUCinf, bioequivalence has been achieved comfortably as the T/R ratios are close to 100%.

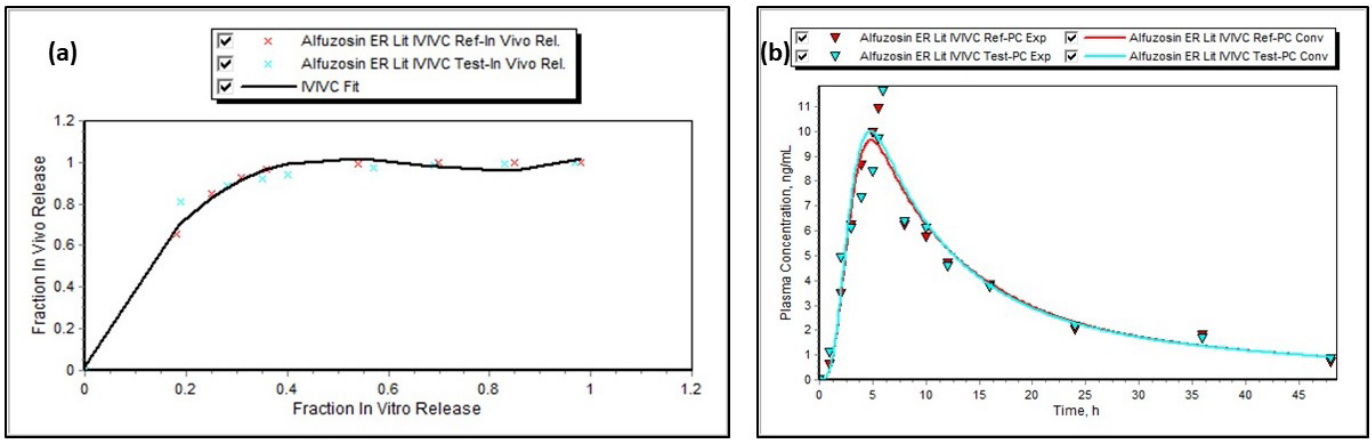

Figure 4. Literature based mechanistic IVIVC using PBBM model.

Table 4. Literature reported IVIVC simulations.

Strength	Literature IVIVC reference			Literature IVIVC test		
PK parameter	**Observed data**	**Simulated data**	**% PE**	**Observed data**	**Simulated data**	**% PE**
C_{max}	11.61	9.64	16.91	11.60	10.00	13.85
AUC_{0-t}	152.4	152.30	0.06	151.3	153.7	−1.59

PBBM modeling

In the present case, PBBM modeling has been utilized successfully for developing safe and rational formulations for alfuzosin prolonged release tablets. The details of model validation and application are presented in subsequent sections.

PBBM model validation

Before utilizing the model for bioequivalence risk assessment and predictions, extensive model validation has been performed using literature-reported data. For this purpose, mechanistic IVIVC was used based on literature-reported reference and test product data. As the current formulation is prolonged release and *in vivo* behavior is governed by release, it is important to ensure that the model is sensitive to dissolution and thus the establishment of IVIVC was necessary to demonstrate credibility of the model. The results from IVIVC are presented in Figure 4 and in Table 4. The data from Figure 4a indicates that using mechanistic dissolution, a strong correlation has been obtained between *in vitro* and *in vivo* release. Traditional IVIVC correlates *in vitro* release with that of *in vivo* fraction absorbed whereas mechanistic IVIVC correlates *in vitro* release with that of *in vivo* release and thus more reliable. Moreover, for prolonged release formulations, *in vivo* release is of more relevance as after release the drug gets absorbed, distributed, and eliminated and thus these processes cannot be controlled by formulation. The obtained mechanistic IVIVC equation is presented below:

$$y = 0.022 + 4.953 * x + -7.907 * (x)^2 + 3.972 * (x)^3 \quad (3)$$

where y is *in vivo* fraction released and x is *in vitro* fraction released. The R^2 value of this correlation was found to be 0.94, and thus confirming that the correlation is reliable. Moreover, the AIC criteria 39.12 and thus found to be lower and it provided the best fit for the model. Further, a convolution exercise has been performed for both literature-reported reference and test formulations and the data are presented in Table 4. The results from convolution indicates that for both C_{max} and AUC for both reference and test formulations, the %PE values were less than 20% thereby confirming the validity of the IVIVC. Overall, the developed model was found to be sensitive to dissolution and demonstrated acceptable IVIVC and thus can be utilized for model predictions for bioequivalence assessment.

Table 5. Generic product observed bioequivalence data and PBBM simulations using 0.01N HCl and pH 4.5 media data.

PK parameter	Pivotal test (Generic product) Observed BE ratios (CI limits)	Pivotal test predicted BE ratios (0.01N HCL data)	Pivotal test predicted BE ratios (pH 4.5 data)
C_{max}	87.73 (81.24–94.75)	94.1 (87.6–100.6)	95.0 (88.5–101.5)
AUC_{0-t}	99.55 (91.42–108.41)	99.4 (90.4–108.4)	99.1 (90.1–108.1)
AUC_{0-inf}	97.75 (89.38–106.89)	99.5 (90.5–108.5)	99.2 (90.2–108.2)

PBBM model application

The validated model was utilized to predict *in vivo* plasma exposures and bioequivalence T/R ratio's between the Generic formulation and reference formulation Xatral XL before initiating the pivotal study. As we intentionally manufactured formulation with slower behavior with the objective of achieving lower C_{max}, it was important that the bioequivalence risk is appropriately nullified before the pivotal study. For

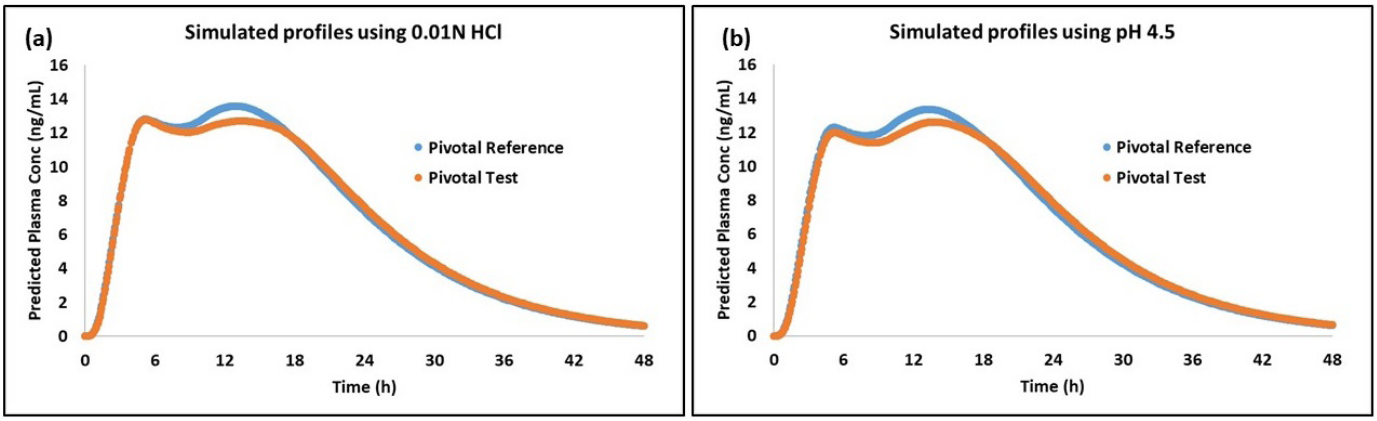

Figure 5. Model predictions for bioequivalence of generic product against innovator product.

this purpose, the MIE approach has been utilized where the T/R ratios were predicted before the pivotal study initiation to gain confidence in the drug product. The predicted T/R ratio's using both 0.01N HCl and pH 4.5 media's for pivotal reference and test formulations are presented in Table 5 and in Figure 5. The predictions indicated that using both media's, the T/R ratios were closer to 100% for AUC whereas for C_{max}, the T/R ratio's predicted were ~95%, which is in line with the slower dissolution of the generic formulation. Additionally, the 90% confidence intervals determined based on actual clinical study variability indicated that the confidence intervals as well as T/R ratio's met the bioequivalence limits of 80%–125% and thus confirming bioequivalence. Moreover, from the dissolution data demonstrated in Table 2, the variability was found to be less than 20% at initial time points and less than 10% at later time points. These values indicate that the variability in the dissolution is controlled and within acceptable limits and thus may not have impact on *in vivo* performance.

With the confidence obtained from MIE approach, pivotal study has been completed and the results indicated that there is good agreement between observed and predicted T/R ratios for both C_{max} and AUC. The model predicted T/R ratio's for AUC closer to 100% and the observed T/R matched with that of predictions. For C_{max}, the model predicted T/R of 95% and results indicated lower yet bioequivalent trend for C_{max} with T/R ratio of 88%. Overall, the model guided formulation development with integration of dissolution data, and the clinical study yielded results as per expectation.

Further, the same model also has been utilized to predict T/R ratios of different brands A, B, and C against reference formulation, and the results are presented in Table 6. It can be seen that for brands A and B, as the dissolution profiles were slower, they have resulted in inferior T/R ratio's for C_{max} as compared to the current generic product. Considering *in vivo* variability, there is a high chance and probability that the 90% lower T/R for C_{max} may be out of limits of 80%–125% and thus may yield bio-inequivalence for brand A and B. Moreover, the f2 values from dissolution similarity were also on the lower side as compared to current generic product. Similarly, brand C as higher dissolution was observed, the predicted T/R ratio's clearly indicate that there will be a risk for C_{max} parameter where the T/R ratios are as high as 116.3% and 125%. Considering the high T/R ratio's, there is a high chance and probability that the 90% upper T/R for C_{max} may be out of limits of 80%–125% and thus may yield bio-inequivalence for brand C. Moreover, the f2 values resulted in dissolution dissimilarity in 0.01N HCl (47) and near to dissimilarity in pH 4.5 (52). Overall, it can be concluded that the current generic product is superior over all the other brands available in the market. Moreover, lower C_{max} of the current generic product is of benefit to the patients to have a lower risk of postural hypotension.

Table 6. Generic product and other brands *in vivo* predicted ratios and f2 similarity factor against reference product using 0.01N HCl and pH 4.5 media data.

PK parameter	Generic product	Brand A	Brand B	Brand C
0.01N HCl predictions				
C_{max}	94.1	92.8	92.0	125.0
AUC_{0-t}	99.4	98.8	98.8	104.6
F2 Similarity factor	71	59	64	47
pH 4.5 Acetate buffer predictions				
C_{max}	95.0	82.3	88.8	116.3
AUC_{0-t}	99.1	95.3	97.9	103.6
F2 Similarity factor	70	42	56	52

DISCUSSION

The MIE approach has gained tremendous impact in recent times due to its ability to help in rationale formulation design. The literature review indicated that this has been a topic of discussion among regulatory workshops due to its plethora of applications. As the MIE approach is based on physiological aspects, it can integrate all *in vivo* processes accurately thereby helps in understanding formulation behavior *in vivo*. In the present case, we have successfully utilized MIE approach for rational and safe development of alfuzosin prolonged-release tablets. The innovator prescribing information mentions postural hypotension as one of the risk factors for patients taking the medication. The main adverse events associated with α1-blockers such as

alfuzosin are related to the vasodilatory properties of the drug. Caution is also advised that when alpha adrenergic antagonists are co-administered with PDE5 inhibitors, the risk of low blood pressure is more pronounced [31]. Alfuzosin 10 mg once a daily formulation has been developed with the intention to demonstrate less vasodilatory effects compared to alfuzosin 2.5 mg t.i.d. However, even with a 10 mg prolonged-release formulation, vasodilatory effects were seen and these were correlated with peak plasma concentrations.

With the intention to develop a bioequivalent, yet safer formulation with reduced possibility of vasodialtory effect and postural hypotension, it is imperative that the generic formulation should release slower as compared to the innovator formulation Xatral XL. To achieve this purpose, formulation development has been intentionally performed to have a slower release, yet comparable f2 against reference formulation. However, slower release can result in bio-inequivalence especially for C_{max} parameter and thus risk exists for the slower formulation. In order to mitigate the risk of bio-inequivalence, prior to initiating the study, the MIE approach based on PBBM modeling was utilized.

The model integrated physicochemical, dissolution, and elimination kinetics. As the *in vivo* behavior in the present case is driven by dissolution and release, it is important that the model is sensitive to dissolution. This has been demonstrated by extensive literature-based validation using innovator data in acidic media. The IVIVC exercise has demonstrated that the model is able to link *in vitro* with that of *in vivo* release; hence, model sensitivity towards dissolution is confirmed. The mechanistic IVIVC was found to be acceptable with high R^2 and AIC criteria and was superior to the traditional IVIVC. The validated model was subsequently utilized to predict T/R ratios before initiating the bioequivalence study and has provided confidence into the generic formulation. This has enabled us to go for a direct pivotal study without pilot studies and resulted in a successful bioequivalence outcome. Thus, this approach has saved time and cost of skipping pilot studies and enabled faster approval and launch for the drug product. Moreover, the observed bioequivalence outcome is in accordance with the predicted for both C_{max} and AUC parameters. As anticipated, a lower yet bioequivalent T/R for C_{max} has been obtained which is in line with expectations of rationale and safe formulation development. Thus, in the present case, MIE has proven its strength in rational formulation design, avoidance of unnecessary human studies, and enabled faster approvals. In the present case, for alfuzosin, the efficacy is driven by AUC and not the Cmax parameter. Thus, reduced Cmax does not have impact on the efficacy of the drug product. Moreover, bioequivalence has been achieved against the reference formulation as indicated in Table 5.

An additional exercise has been carried out where the *in vitro* and *in vivo* behavior of generic products is compared against other brands in the market. Comparative dissolution data in 0.01N HCl and pH 4.5 indicated that the generic product has superior f2 values as compared to other brands thereby demonstrating its closeness with that of innovator. Further, the *in vivo* bioequivalence has been predicted for all brands using a validated PBBM model that demonstrated bioequivalence risk clearly for brands A, B (risk of lower T/R for C_{max}) and for brand C (risk of higher T/R for C_{max}). Thus, the validated PBBM model also helped in demonstrating the superiority of generic formulation as compared to other brands in the market. Overall, this case study highlights the use of MIE in rationale formulation design. In the present case, if one would like to reduce the Cmax to reduce postural hypotension, it may require multiple experiments to optimize the dissolution profile and further multiple bioequivalence studies to come up with an optimized formulation. Through the MIE approach, the number of experiments and need for human bioequivalence studies are reduced. Thus, the MIE approach provides significant advantages as compared to the traditional approach. This approach brings a balance between a number of experiments and the actual clinical studies required. Moreover, this methodology can be used for other drugs that require a reduction in C_{max} to avoid side effects. For those specific drugs, PBBM needs to be developed, validated against bioequivalence studies and then can be and used for specific applications.

CONCLUSION

Overall, the work performed in this manuscript demonstrates the utility of the MIE approach in rational formulation development. We aimed at manufacturing a generic formulation that is bioequivalent yet more safer as compared to the innovator formulation. Thus, to reduce the risk of postural hypertension, formulation development has been initiated to have slower release profiles as compared to reference products. As slower profiles may yield in bio-inequivalence, the risk has been mitigated through the MIE approach. Using a validated PBBM model, bioequivalence has been predicted for generic formulation and thus enabled direct pivotal study. The results were found to be as per expectations where observed T/R correlated with that of predicted. Moreover, the validated PBBM model was used to demonstrate the superiority of generic formulation as compared to other brands in the market. Overall, MIE approaches can be of significant use for rational formulation design, to design drug products that can result in desired therapeutic outcome. Such models have the potential utility to avoid unnecessary human studies and can enable faster regulatory approvals and product launches. This study advances pharmaceutical formulation development by reducing the experiments and need for clinical bioequivalence studies. In this way, this study advances to bring medicines to the market at rapid pace. Further, the observations from this simulation exercise can be extrapolated to real world scenarios through post marketing surveillance studies to ensure that the drug product achieves the desired objective of reduced side effects.

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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.

CONFLICT OF INTEREST

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

ETHICAL APPROVAL

The study protocol was approved by the Maarg Independent Ethics Committee, Hyderabad, India (Protocol No.: BE-018-2022 and Date: 21 Apr2022).

DATA AVAILABILITY

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

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

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

REFERENCES

1. Wu D, Sanghavi M, Kollipara S, Ahmed T, Saini AK, Heimbach T. Physiologically based pharmacokinetics modeling in biopharmaceutics: case studies for establishing the bioequivalence safe space for innovator and generic drugs. Pharm Res. 2023 Feb;40(2):337–57. doi: https://doi.org/10.1007/s11095-022-03319-6
2. Yoon M, Babiskin A, Hu M, Wu F, Raney SG, Fang L, et al. Increasing impact of quantitative methods and modeling in establishment of bioequivalence and characterization of drug delivery. CPT Pharmacometrics Syst Pharmacol. 2023 May;12(5):552–5. doi: https://doi.org/10.1002/psp4.12930
3. Miller NA, Reddy MB, Heikkinen AT, Lukacova V, Parrott N. Physiologically based pharmacokinetic modelling for first-in-human predictions: an updated model building strategy illustrated with challenging industry case studies. Clin Pharmacokinet. 2019 Jun;58(6):727–46. doi: https://doi.org/10.1007/s40262-019-00741-9
4. Kollipara S, Ahmed T, Praveen S. Physiologically based pharmacokinetic modelling to predict drug-drug interactions for encorafenib. Part I. Model building, validation, and prospective predictions with enzyme inhibitors, inducers, and transporter inhibitors. Xenobiotica. 2023 May;53(5):366–81. doi: https://doi.org/10.1080/00498254.2023.2250856
5. Kollipara S, Ahmed T, Praveen S. Physiologically based pharmacokinetic modeling (PBPK) to predict drug-drug interactions for encorafenib. Part II. Prospective predictions in hepatic and renal impaired populations with clinical inhibitors and inducers. Xenobiotica. 2023 May;53(5):339–56. doi: https://doi.org/10.1080/00498254.2023.2246153
6. Zushin PH, Mukherjee S, Wu JC. FDA Modernization Act 2.0: transitioning beyond animal models with human cells, organoids, and AI/ML-based approaches. J Clin Invest. 2023 Nov 1;133(21):e175824. doi: https://doi.org/10.1172/JCI175824
7. Jaiswal S, Ahmed T, Kollipara S, Bhargava M, Chachad S. Development, validation and application of physiologically based biopharmaceutics model to justify the change in dissolution specifications for DRL ABC extended release tablets. Drug Dev Ind Pharm. 2021 May;47(5):778–89. doi: https://doi.org/10.1080/03639045.2021.1934870
8. Yuvaneshwari K, Kollipara S, Ahmed T, Chachad S. Applications of PBPK/PBBM modeling in generic product development: an industry perspective, J Drug Del Sci Technol. 2022;69:103152
9. Bhattiprolu AK, Kollipara S, Ahmed T, Boddu R, Chachad S. Utility of physiologically based biopharmaceutics modeling (PBBM) in regulatory perspective: application to supersede f2, enabling biowaivers & creation of dissolution safe space. J Pharm Sci. 2022 Dec;111(12):3397–410. doi: https://doi.org/10.1016/j.xphs.2022.09.003
10. Heimbach T, Kesisoglou F, Novakovic J, Tistaert C, Mueller-Zsigmondy M, Kollipara S, et al. Establishing the bioequivalence safe space for immediate-release oral dosage forms using physiologically based biopharmaceutics modeling (PBBM): case studies. J Pharm Sci. 2021 Dec;110(12):3896–906. doi: https://doi.org/10.1016/j.xphs.2021.09.017
11. Ahmed T, Kollipara S, Boddu R, Bhattiprolu AK. Biopharmaceutics risk assessment-connecting critical bioavailability attributes with *in vitro, in vivo* properties and physiologically based biopharmaceutics modeling to enable generic regulatory submissions. AAPS J. 2023 Jul 27;25(5):77. doi: https://doi.org/10.1208/s12248-023-00837-y
12. Boddu R, Kollipara S, Vijaywargi G, Ahmed T. Power of integrating PBPK with PBBM (PBPK-BM): a single model predicting food effect, gender impact, drug-drug interactions and bioequivalence in fasting & fed conditions. Xenobiotica. 2023 Apr;53(4):260–78. doi: https://doi.org/10.1080/00498254.2023.2238048
13. Zhao L, Kim MJ, Zhang L, Lionberger R. Generating model integrated evidence for generic drug development and assessment. Clin Pharmacol Ther. 2019 Feb;105(2):338–49. doi: https://doi.org/10.1002/cpt.1282
14. Wu F, Mousa Y, Jereb R, Batchelor H, Chakraborty S, Heimbach T, et al. Using mechanistic modeling approaches to support bioequivalence assessments for oral products. AAPS J. 2024;26:. doi: https://doi.org/10.1208/s12248-024-00886-x
15. Tsakalozou E, Fang L, Bi Y, van den Heuvel M, Ahmed T, Tsang YC, et al. Experience learned and perspectives on using model-integrated evidence in the regulatory context for generic drug products—a meeting report. AAPS J. 2024;26:14. doi: https://doi.org/10.1208/s12248-023-00884-5
16. Madabushi R, Seo P, Zhao L, Tegenge M, Zhu H. Review: role of model-informed drug development approaches in the lifecycle of drug development and regulatory decision-making. Pharm Res. 2022 Aug;39(8):1669–80. doi: https://doi.org/10.1007/s11095-022-03288-w
17. Boddu R, Kollipara S, Bhattiprolu AK, Ahmed T. Novel application of PBBM to justify impact of faster dissolution on safety and pharmacokinetics—a case study and utility in regulatory justifications. Xenobiotica. 2023 Oct-Nov;53(10-11):587–602. doi: https://doi.org/10.1080/00498254.2023.2289160
18. MacDonald R, Wilt TJ. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. Urology. 2005 Oct;66(4):780–8. doi: https://doi.org/10.1016/j.urology.2005.05.001
19. Uroxatral FDA label, [internet]. [cited 2024 Feb 05]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021287s013lbl.pdf
20. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, et al. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. AAPS J. 2010 Sep;12(3):263–71. doi: https://doi.org/10.1208/s12248-010-9185-1
21. Kollipara S, Boddu R, Ahmed T, Chachad S. Simplified model-dependent and model-independent approaches for dissolution profile comparison for oral products: regulatory perspective for generic product development. AAPS PharmSciTech. 2022 Jan 13;23(1):53. doi: https://doi.org/10.1208/s12249-021-02203-7
22. Boddu R, Kollipara S, Bhattiprolu AK, et al. Dissolution profiles comparison using conventional and bias corrected and accelerated f2 bootstrap approaches with different software's: impact of variability,

sample size and number of bootstraps. AAPS PharmSciTech. 2024;25:5. doi: https://doi.org/10.1208/s12249-023-02710-9
23. Park JB, Hwang CH, Noh HG, Chae YB, Song JW, Kang CY. Zero-order delivery of alfuzosin hydrochloride with hydrophilic polymers. J Pharm Invest. 2010;40(5): 285–9.
24. Sanki UK, Mandal BK. *In vitro-in vivo* correlation evaluation of generic alfuzosin modified release tablets. ISRN Toxicol. 2012 Nov 20;2012:813836. doi: https://doi.org/10.5402/2012/813836
25. EMA. Guideline for good clinical practice E6(R2). EMA/CHMP/ICH/135/1995. Committee for Human Medicinal Products. [Internet]. [cited 2024 Feb 05]. 2016. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf
26. Declaration of Helsinki. Ethical principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the WMA General Assembly, Seoul, Korea. [Internet]. [cited 2024 Feb 05]. 2008. Available from: https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2008.pdf
27. Good Clinical Practices for Clinical Research in India. Central Drugs Standard Control Organization. Ministry of Health and Family Welfare, Government of India. [Internet]. [citec 2024 Feb 05]. 2013. Available from: https://rgcb.res.in/documents/Good-Clinical-Practice-Guideline.pdf
28. National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. Indian Council of Medical Research. [Internet]. [cited 2024 Feb 05]. 2017. Available from: https://ethics.ncdirindia.org//asset/pdf/ICMR_National_Ethical_Guidelines.pdf
29. Kollipara S, Bhattiprolu AK, Boddu R, Ahmed T, Chachad S. Best practices for integration of dissolution data into physiologically based biopharmaceutics models (PBBM): a biopharmaceutics modeling scientist perspective. AAPS PharmSciTech. 2023 Feb 9;24(2):59. doi: https://doi.org/10.1208/s12249-023-02521-y
30. USFDA guidance for industry, IVIVC. [Internet]. [cited 2024 Feb 05]. 1997. Available from: https://www.fda.gov/media/70939/download
31. USFDA dossier for Xatral XL, [Internet]. [cited 2024 Feb 05]. 2003. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/021287_uroxatral_toc.cfm

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