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RESEARCH ARTICLE

Application of Physiologically Based Biopharmaceutics Modeling (PBBM) to Establish Clinically Relevant Dissolution Specifications for a Prolonged Release Tablet Formulation of Verapamil, a BCS Class I Drug

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Abstract

Our work aimed at setting clinically relevant dissolution specifications for a prolonged release formulation of verapamil, a BCS Class I drug. We have used a two-pronged approach- a Level A IVIVC correlation supplemented with virtual bioequivalence assessment using Physiologically based biopharmaceutics modelling (PBBM). Dissolution studies were performed for two batches, Medium-release (BE batch) and Slow-release (non-BE batch), using a biorelevant method. Mechanistic absorption deconvolution method was used to obtain the *in vivo* release profiles and correlate with the respective *in vitro* release profiles to develop the IVIVC. Theoretical dissolution profiles for upper and lower limits were generated and used for convolution and calculation of Percent prediction errors (%PE). This was supplemented with virtual bioequivalence (VBE) assessments at each level to select clinically relevant dissolution specifications. A two-step deconvolution-correlation method resulted in a linear Level A IVIVC with $R^2 = 0.951$ which was internally and externally validated. Percent prediction errors (%PE) for C_{max} and AUC were calculated for each level to accept/reject the limits. VBE trials showed that the 90% CI fell within the acceptable limits of 80–125% for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ for the lower dissolution specification limit 5 and for the upper specification limit 3. The current investigation demonstrates new opportunities offered by mechanistic modelling and how this two-pronged approach (IVIVC and IVIVR-VBE) can be used to define clinically relevant dissolution specifications and the BE safe space, which can support post-approval changes for waiving bioequivalence studies and ensuring commercial product quality over the years.

Keywords Bioequivalence (BE) safe space · biowaiver · clinically relevant dissolution specification · *in vitro-in vivo* (IVIVC) correlation(s) · mechanistic modelling · physiologically based biopharmaceutics modelling (PBBM)

Introduction

Evaluating the dissolution rate and the amount of drug released from the dosage form is the current key attribute used for product quality and process control. A comparative and consistent release profile ensures batch-to-batch similarity and *in vivo* performance. For immediate release products, dissolution can be used to support waiver of *in vivo* bioequivalence studies (biowaiver) of BCS Class I/III drugs (under specific conditions) following post-approval product or manufacturing changes [1]. For extended-release dosage forms that show a rate-limited absorption, an *in vitro-in vivo* correlation (IVIVC) can be constructed. This is a quantitative framework that links the *in vivo* absorption and the *in vitro* dissolution [2]. IVIVC can be of different types such as Levels A, B, C and multiple level C [3]. A direct one-to-one relationship between *in vitro* and *in vivo* release rate is presented by Level A correlation [4], and is highly recommended by U.S. Food and Drug Administration (USFDA) and European Medicines Agency (EMA) to support biowaivers [5, 6]. A validated Level A IVIVC is useful for setting clinically relevant dissolution limits, and as a tool to distinguish between acceptable and unacceptable drug products. The pharmacokinetics of drug product can be

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predicted using its *in vitro* release and can serve as a substitute for clinical bioequivalence (BE) studies to support biowaivers.

Physiologically based pharmacokinetic modeling (PBPK) has emerged as an essential tool to support drug product quality attributes and bridging of formulations [7]. The USFDA has recently published a draft guidance that provides general recommendations on the development, evaluation, and use of PBPK analysis for biopharmaceutics applications [8]. Regulatory authorities encourage use of modeling approaches for demonstrating bioequivalence (BE), allowing the pharmaceutical industry to save development time and resources by avoiding unnecessary clinical trials [9]. Physiologically based biopharmaceutics modeling (PBBM), which combines physicochemical properties of drug, *in vitro* dissolution, and mechanistic absorption with PBPK models can serve as a powerful aid to establish a dissolution "safe space" and widen dissolution specifications [10].

An IVIVC uses deconvolution to derive an '*in vivo* absorption/dissolution profile' for comparison with the '*in vitro* dissolution data'. Traditional deconvolution methods such as Wagner-Nelson [11], Loo-Reigelman [12] or Numerical Deconvolution [13] are used to determine the rate at which a compound enters the central compartment. These are more suitable for drugs that show good absorption throughout the GI tract and have linear pharmacokinetics [14]. Their utility gradually reduces for products with decreasing rate of dissolution and increasing rate of transit [15]. A PBBM model allows the use of Mechanistic Absorption Deconvolution (MAD), which incorporates processes related to drug release, dissolution and precipitation, permeation, transit time and so forth to directly deconvolute the *in vivo* release rate [16]. This method allows incorporation of site-specific absorption, transporter interactions, saturable metabolism pathways, and other factors that offers greater flexibility in setting up a Level A IVIVC [17].

Under certain circumstances, it is challenging to build and/or validate a Level A IVIVC using the conventional approaches. In such cases, the use of mechanistic absorption modeling to build *In vitro-In vivo* Relationship (IVIVR) and virtual BE (VBE) analysis to confirm BE and non-BE batches and define a safe space has gained confidence [18]. The BE safe space approach provides an understanding of product quality attributes (formulation and process parameters) to set the upper and lower dissolution specifications, within which all manufactured products are anticipated to be bioequivalent to the pivotal clinical trial batch(es) permitting biowaivers. It rejects batches beyond these specifications that would not be bioequivalent [19].

In the current investigation, we have used a two-pronged approach (IVIVC and IVIVR-VBE) to evaluate and define clinically relevant dissolution specifications and the BE safe space for a prolonged-release tablet formulation of verapamil, a non-narrow therapeutic index, BCS Class I drug. Verapamil is a phenyl alkylamine calcium channel blocker belonging to the class IV antiarrhythmics, widely used in the management of hypertension, ischemic heart disease such as angina pectoris, myocardial infarction and arrhythmias [20]. Verapamil is a weak base with a pKa of 8.46, a log P of 4.45 and is classified as a BCS Class I compound. Following oral administration, T_{max} is reached between 1–2 h for its immediate release formulation and approximately 7 h for the prolonged release (PR) formulation [21]. More than 90% of the orally administered dose of the parent drug is absorbed from the small intestine. The oral bioavailability ranges from 20 to 35% [22] due to first-pass metabolism. It has an elimination half-life of 3–7 h [23]. Typical therapeutic plasma levels of parent drug are low and range from 80 to 400 ng/mL. Steady state after multiple once daily oral dosing is reached after three to four days [24]. For a continuous high dose infusion of 0.40 mg/kg/h, plasma concentrations of 1500 to 2500 ng/mL have been reported without life-threatening toxicity [25], providing insight in the broad therapeutic range of the drug.

Verapamil exhibits a high solubility and high intestinal permeability but shows a large intra- and inter-subject variability [26–29]. Therefore, a PBBM-based mechanistic IVIVC approach followed by VBE that incorporates pharmacokinetic variability was used to derive the BE safe space. Products with two release rates and oral PK data from a pivotal BE study (BE batch) and a pilot PK study (non-BE batch) were used to build a Level A IVIVC. The IVIVC was internally and externally validated, and the limits for lower and upper dissolution were defined using percent prediction errors (%PE) for AUC and C_{max}. This was followed by validation of the limits using VBE evaluations to derive a BE safe space and support the dissolution acceptance criteria (Fig. 1).

Materials and Methods

Drug Product

PR 240 mg tablets of verapamil with two different release rates of the drug were prepared using varying concentrations of sodium alginate, a pH-dependent, water-soluble release controlling agent in a hydrophilic matrix, using wet granulation, compression, and coating processes. The *in vitro* release rates differed by > 10% and are termed Medium (Pivotal BE batch) and Slow (Non-BE batch) for the purpose of IVIVC.

In Vitro Dissolution Studies

In vitro drug release profiles from the Medium (commercially available product) and Slow-release tablet formulations and a third batch (External validation batch for IVIVC) were determined (n = 12) using biorelevant media in USP Apparatus

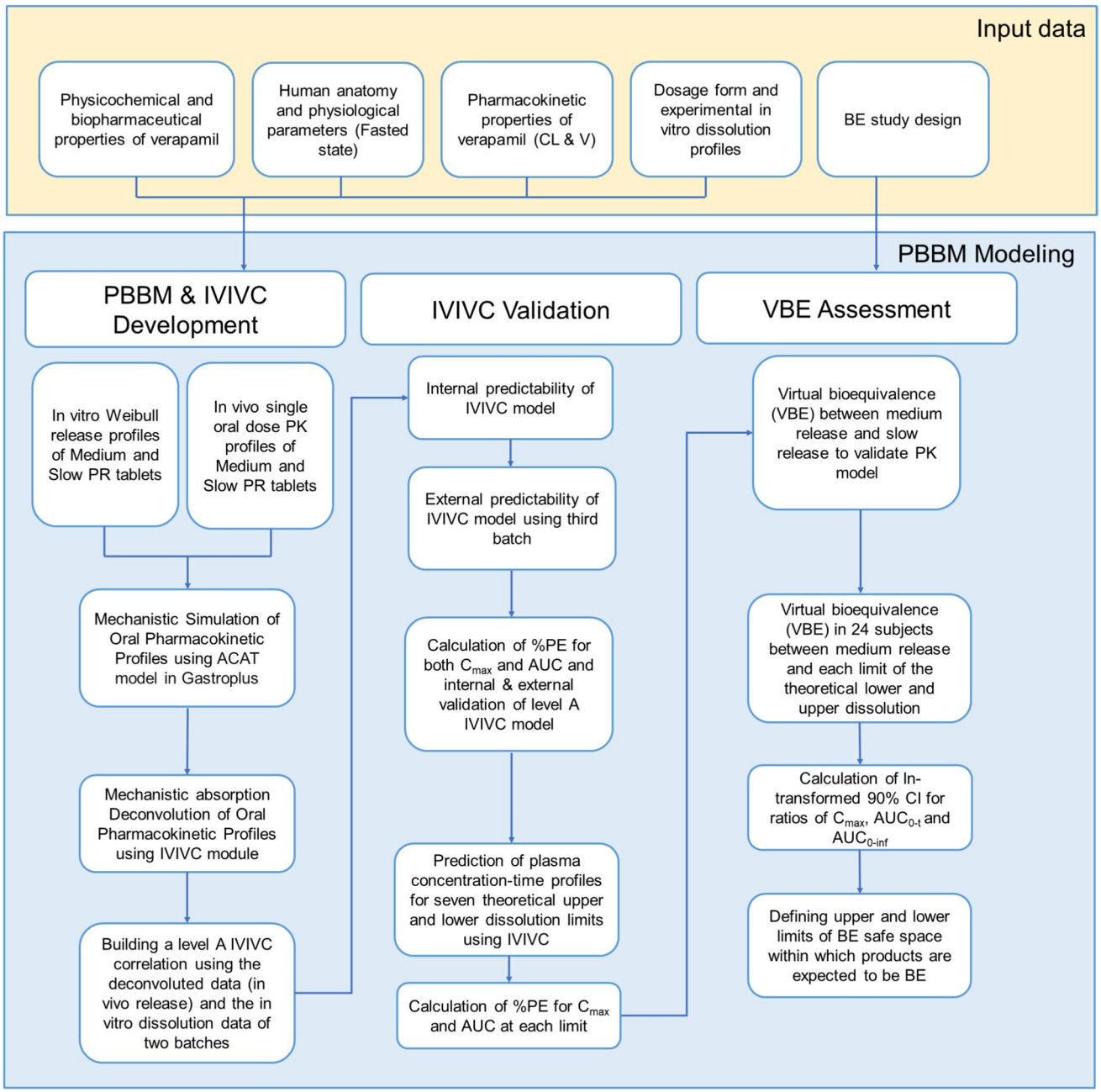

Fig. 1 Workflow of Physiologically Based Biopharmaceutics Modeling (PBBM) to Establish Clinically Relevant Dissolution Specifications

II (paddle method) [30]. The external validation batch was similar to the Medium-release formulation with no changes in manufacturing process but with a different batch number. Each tablet was wrapped in a wire helix (to prevent the tablets from floating) and placed in a vessel containing 900 mL of simulated gastric fluid TS without enzyme (0.15 M of NaCl and 0.01 M of HCl, pH = 1.5–2). The dissolution apparatus was operated at 50 rpm for 1 h in the acid stage. After 1 h, a sample was withdrawn for analysis, and the dosage form was carefully transferred, including the wire helix, to a vessel containing 900 mL of simulated intestinal fluid TS without enzyme (0.05 M Phosphate buffer, pH = 6.8), previously warmed to 37 ± 0.5 °C. This stage of the test was conducted for 11 h. The paddles were operated at a speed of 50 rpm. Samples of dissolution medium were removed at defined time points of 1, 2, 3, 4, 5, 6, 7 and 8 h. Additionally, samples were collected at 9, 10 and 12 h to achieve more than 85% release for the Slow-release formulation. All samples were further diluted appropriately and analyzed for drug content by ultraviolet spectrophotometry at 278 nm. Percent dissolution at each time point was calculated.

In Vivo Pharmacokinetic Studies

Pharmacokinetic data were obtained from single dose studies with the Medium, Slow-release and External validation batch formulations. The studies used healthy male volunteers (n = 24) in an open label, randomized, design. The subjects received single oral doses of the treatments on Study Day 1 of each period as close as possible to 8:00 a.m. together with 240 mL of water on empty stomach after a 10 h fast. Four hours after drug administration, a standardized lunch was given and 10 h post-administration a standardized dinner was served. Except for the water required for drug administration, drinking water was prohibited from 1 h predose to 1 h post-dose. The wash-out time between periods was 1 week. Blood samples were collected just before drug administration (time −5 to 0 min) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 20, 24, 30, 36 and 48 h post-administration in lithium heparin containing tubes. Immediately afterwards, the samples were cooled and centrifuged at 4 °C at 1500*g for 15 min. The plasma was then transferred into polypropylene tubes and stored below −20 °C until bioanalytical evaluation. A validated HPLC method developed with lower limit of quantification (LOQ) of 1 µg/L was used for drug analysis.

These studies were approved by the Institutional Review Board. All clinical measures carried out within the framework of this study were subject to Good Clinical Practice (GCP). The ethics committee's approval was obtained before the study began. All subjects provided written informed consent.

Level A IVIVC Model: Development and Validation

Mechanistic Simulation of Oral Pharmacokinetic Profile

The Advanced Compartmental Absorption and Transit (ACAT) model in GastroPlus® (v9.0; Simulations Plus, Lancaster, CA) was used to simulate the drug's intestinal absorption. The human PK parameters, clearance and volume of distribution, were obtained by fitting the intravenous (IV) pharmacokinetic data [31] to a two compartmental pharmacokinetic model in PKPlus™ (Simulations Plus, Lancaster, CA). For simulating the oral pharmacokinetic profile of 240 mg PR tablet, the physicochemical properties of the drug (Table I) and optimized CL/F and V/F were used. The experimental *in vitro* dissolution profile was loaded as an *.dsd file in ACAT model with human fasted physiology. The Weibull release function was then used to fit the *in vitro* dissolution data. The resulting Weibull release profile (regarded as dissolution profile) was further incorporated in the model as an *.crd file. The default physiological parameters were used for simulation. The oral pharmacokinetic profile was then predicted using the dosage form CR integral tablet and an*.crd file. The resulting simulated concentration *versus* time curve was compared with the observed data from the pharmacokinetic study.

Deconvolution of Oral Pharmacokinetic Data

A mechanistic absorption deconvolution method in the IVIVC module of GastroPlus® software was used. This

Table I Key Input Physicochemical and Biopharmaceutical Parameters Used for Simulating the Oral Absorption Profile in GastroPlus®

Parameter	Value/Method	Reference
Mol. Wt. (g/mol)	454.61	Measured
Log of the octanol–water partition coefficient (LogP)	4.45	Predicted by ADMET Predictor®
Acid dissociation constant (pKa)	Base: 8.46	Predicted by ADMET Predictor®
Reference solubility, mg/mL	46 @ pH 6.54	[32]
Formulation	CR: Integral tablet	Used for simulation
Dose volume, mL	250	GastroPlus® default value
Human effective jejunal permeability (P*eff*), cm/s	4.5574×10^{-4}	[32]
Diffusion coefficient, cm^2/s	0.55×10^{-5}	GastroPlus® default value
Drug particle density, g/mL	1.2	GastroPlus® default value
Particle size, µm	25	GastroPlus® default value
Dissolution model	Johnson	GastroPlus® default value
Physiology	Human-Physiological-Fasted	Used for simulation
ASF (model)	Opt LogD Model SA/V 6.1	Used for simulation
Fraction unbound in plasma (fup)	7.13%	Predicted by ADMET Predictor®
Blood:plasma concentration ratio (Rbp)	0.68	Predicted by ADMET Predictor®
Adjusted plasma fup	3.60%	GastroPlus® algorithm
First pass extraction (FPE)- liver	79.8%	Optimized
First pass extraction (FPE)- intestinal	11.2%	Optimized

method uses the drug's available physical and chemical characteristics, *in vitro* permeability and solubility, physiological parameters**,** and *in vivo* information to separate the *in vivo* release from intestinal drug uptake and first-pass extraction [17]. The pharmacokinetic profiles of the Medium and Slow formulations were loaded, followed by deconvolution to obtain the *in vivo* dissolution of the drug from respective formulations.

Development and Validation of a Level A IVIVC

A Level A IVIVC was constructed by importing the *in vitro* release profiles into the IVIVC module of GastroPlus® software. A linear Level A relationship was established between the deconvoluted data and the *in vitro* release using R^2. To estimate the predictive performance of the established Level A correlation, the initial data of the BE formulation (Medium release) used to define the IVIVC model were used for convolution and internal validation of the IVIVC model. To evaluate external predictability, a formulation (External validation batch) not used in the development of the IVIVC model was used for convolution and prediction of plasma concentration–time profile. The percent prediction errors (%PE) for AUC and C_{max} were computed and analysed in relation to the observed data to validate the model internally and externally using the following formula:

$$\%PE = \frac{PK_{obs} - PK_{pred}}{PK_{obs}} * 100$$

where PK is either C_{max} or AUC.

Setting of Clinically Relevant Dissolution Specifications

Seven theoretical upper and lower dissolution limits for the test product were generated using the Weibull function in GastroPlus®, with differences from the Medium release formulation as shown in Fig. 5a. The plasma-concentration–time profiles for these theoretical dissolution profiles were convoluted using the established Level A IVIVC model, and the corresponding bioavailability parameters C_{max} and AUC were estimated. The predicted C_{max} and AUC at these specification limits were then compared with the observed data and %PE was calculated. The upper and lower dissolution specifications were acceptable if the %PE was 20% or less for both C_{max} and AUC. These criteria are consistent with the USFDA guidance on IVIVCs for modified-release oral dosage forms [5].

Virtual bioequivalence (VBE) trials

VBE were performed using the population simulator in GastroPlus®, which generates virtual subjects by random sampling of selected variables such as formulation, physiological, and PK parameters. The VBE trials used a body weight of 70 kg, 24 subjects, fasted condition and a crossover design like the original clinical study protocol. In the population simulator, the percent coefficient of variation (CV%) was optimized for some parameters like primary permeability and liver first pass extraction (identified using parameter sensitivity analysis) to capture pharmacokinetic variability observed in the clinical studies. The dissolution profiles of the test (Slow) and reference (Medium) products were provided as input for validation of VBE assessment. Further VBE trials were conducted at each lower and upper theoretical dissolution limit with the Medium release. The trial was considered as 'Pass' if the population simulation results of the ln-transformed 90% confidence interval for the ratios of C_{max}, AUC_{0-t} and AUC_{0-inf} values were within the 80–125% interval.

Results

In Vitro Dissolution

The mean cumulative fraction of verapamil dissolved from the Medium and Slow formulations (used to build the IVIVC model) and the External validation batch is presented in Fig. 2a. The dissolution method used was discriminatory and predicted the pharmacokinetic profile accurately. The CV% associated with the dissolution for each formulation was < 10% at every time interval. The f_2 values calculated for Medium *vs*. Slow, Medium *vs*. External validation and External validation *vs*. Slow were 41.9, 71.26 and 46.39, respectively. An f_2 value between 50–100 indicates similarity between two dissolution profiles whereas an f_2 value below 50 suggests that two profiles are dissimilar.

In Vivo Pharmacokinetics

Twenty-four healthy male adults aged 23–43 years and body weight range 60–92 kg (median 70 kg) were enrolled and completed the clinical studies. The geometric mean plasma concentration–time profiles obtained for all treatments are shown in Fig. 2b. The Medium-release formulation achieved a higher mean peak plasma concentration than the Slow-release formulation but a similar AUC_{0-t}. The 90% CIs for the ratios of adjusted geometric means (Slow-release *vs* Medium-release) were 81.83–103.65% for AUC and 68.96–97.90% for C_{max}, indicating that the two batches were not bioequivalent for C_{max}. The external validation batch showed a C_{max} and AUC_{0-t} like the Medium/Slow release formulation used in the first study (Fig. 2b). All formulations achieved T_{max} with a median value of 5 h.

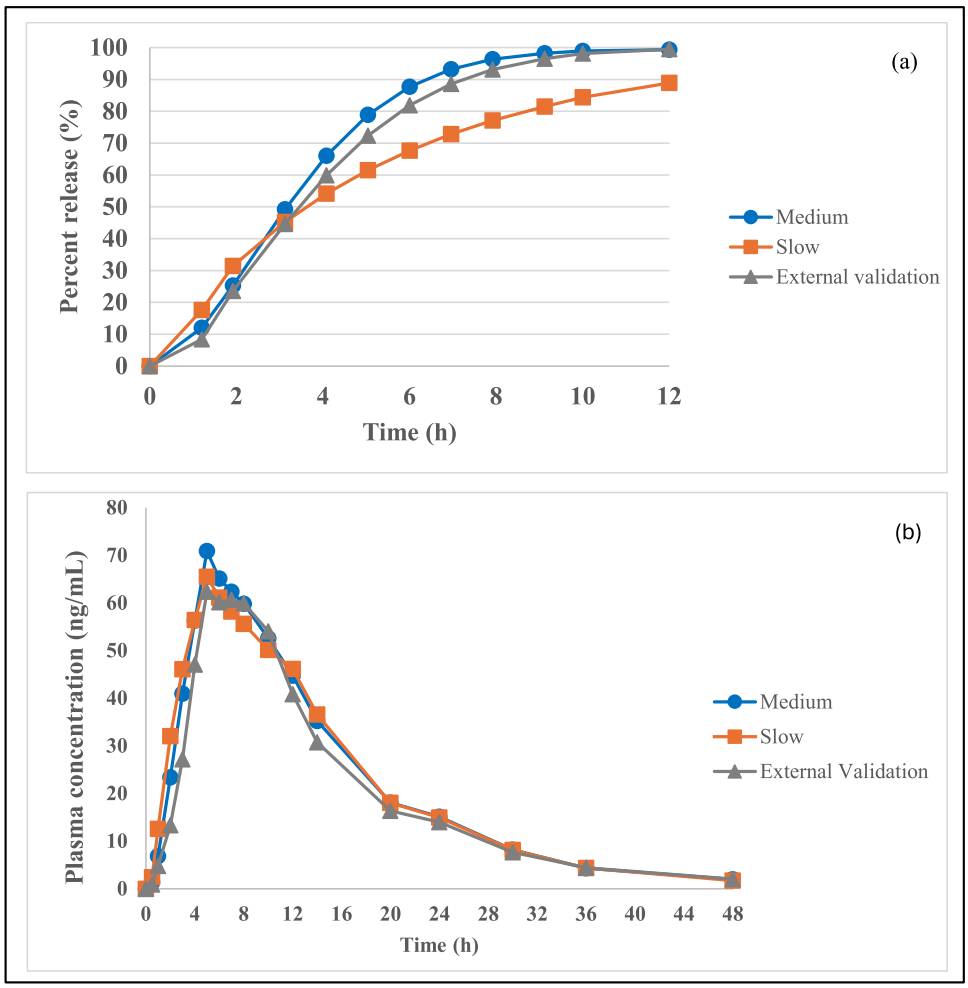

Fig. 2 **a** *In vitro* dissolution data for the Medium, Slow and External validation formulations using USP Apparatus II, 50 rpm. **b** Mean plasma concentration–time profiles following administration of single dose of Medium, Slow and External validation Formulations to healthy male volunteers

PK Model Development and Validation

The physicochemical and biopharmaceutical parameters used for simulation of the oral pharmacokinetic profile of the 240 mg PR tablet are given in Table I. Optimized human PK parameters (V/F = 0.53177 L/kg, CL/F = 0.61126 L/h/kg, K12 = 14.449 h^{-1}, K21 = 1.3765 h^{-1}) were used. The resulting simulated concentration *versus* time curve (Fig. 3) was compared with the observed data and was found successful as the mean C_{max} and $AUC_{0\text{-}t}$ were within 15% of the observed values.

IVIVC Model Building and Validation

The *in vivo* release profiles obtained from mechanistic absorption deconvolution of the Medium and Slow-release formulations showed a linear relationship with their *in vitro* dissolution profiles, with a slope of 1.171, and $R^2 = 0.951$, as shown in Fig. 4a. The %PE for both C_{max} and AUC were within 10% for both internal prediction and external prediction (Table II). By visual inspection, the simulated pharmacokinetic profiles following convolution were comparable to the observed data (Fig. 4b and c), and the prediction errors were within acceptable limits which established the validity of the Level A IVIVC model.

Establishment of Clinically Relevant Dissolution Specifications

Dissolution Specifications Based on IVIVC

Seven upper and lower theoretical dissolution profiles generated using the Weibull function were used for convolution. The corresponding bioavailability parameters C_{max} and AUC were estimated for these dissolution profiles following convolution using the Level A IVIVC. The %PE for these parameters is given in Table III. The %PE for the predicted C_{max} and AUC were within 20% for the lower dissolution specification until limit 6 and for the upper specification until limit 4.

Dissolution Safe Space Based on VBE

After modifying CV% in the population simulator, the intra-subject PK variability of 25–28% observed in the clinical

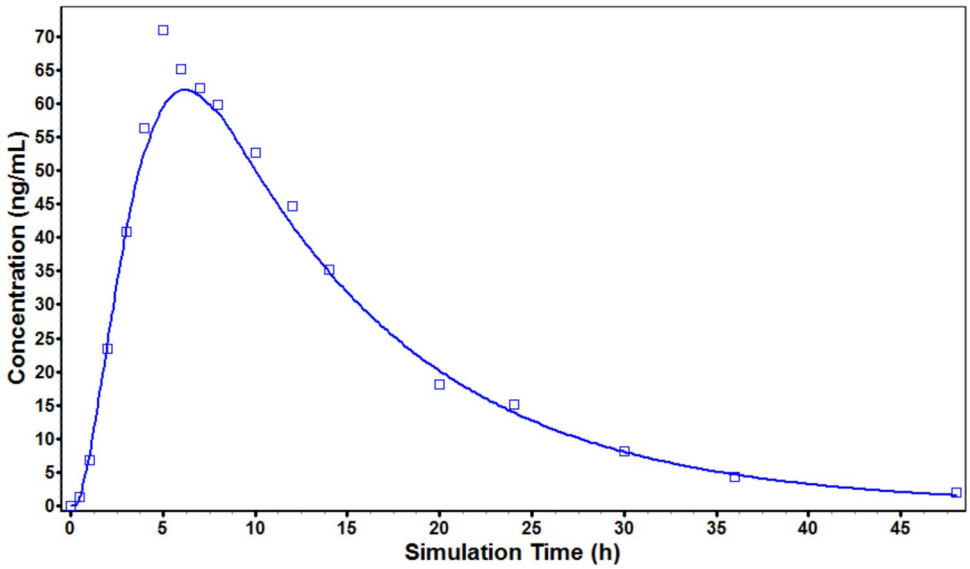

Fig. 3 Observed (squares) and simulated (solid line) plasma concentration–time profiles of single oral dose of 240 mg prolonged release used in PK model building

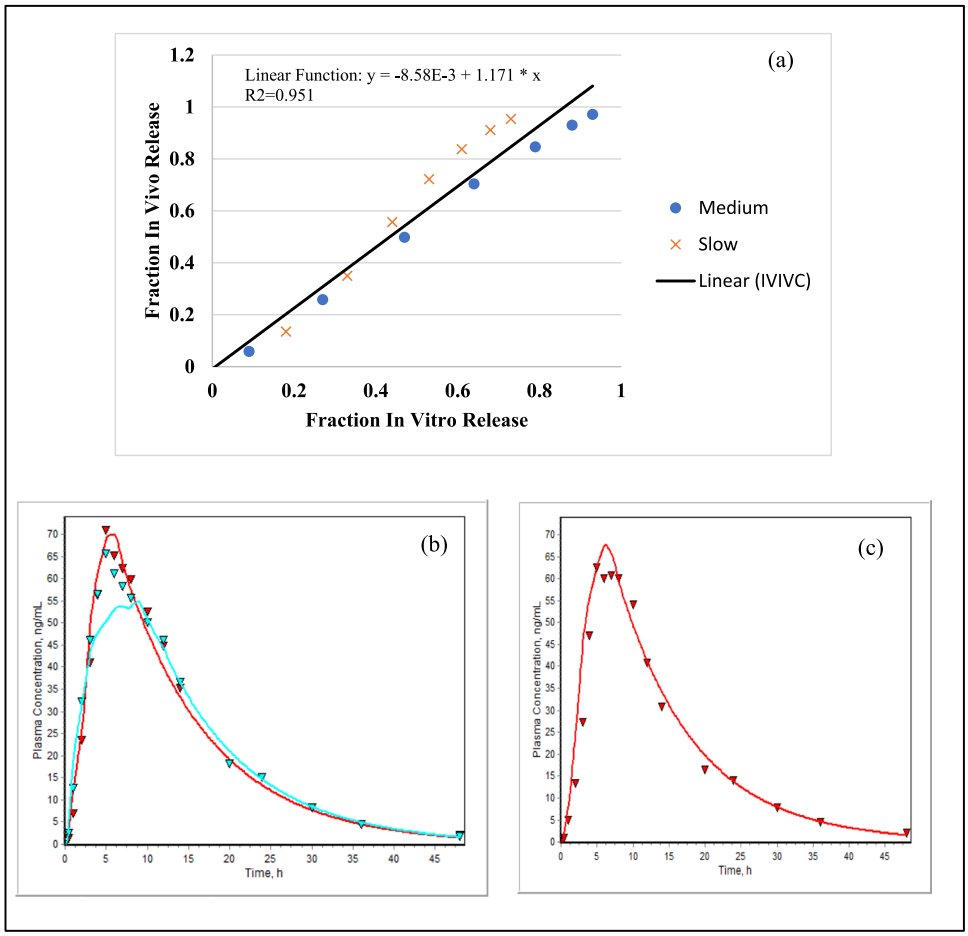

Fig. 4 **a** *In vivo* release *vs*. *in vitro* release relationship for the Medium and Slow-Release Formulations resulting in Level A IVIVC, **b** Convoluted plasma concentration–time profiles of Medium and Slow-release formulations used for internal validation and **c** Convoluted plasma concentration–time profile of batch used for external validation

studies was reasonably captured. These settings were able to reproduce and prove non-bioequivalence between the Medium and Slow formulations seen in the clinical study (Fig. 5b). Using these settings further VBE trials were carried out between **the** Medium formulation and at each limit of the theoretical lower and upper dissolution profiles. The point estimates and 90% CI for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ fell within the acceptable limits of 80–125% for the lower dissolution

Table II Internal and External validation results for the Level A IVIVC

Validation	Formulation	Mean C_{max} (ng/mL)			Mean AUC (ng/mL*h)		
		Obs	Pred	% Pred. Error	Obs	Pred	% Pred. Error
Internal	Medium	70.88	70.54	0.478	1005.7	987.8	1.78
	Slow	65.51	55.72	14.95	1006.1	984.9	2.099
External	External validation	62.38	68.16	−9.269	917.6	987.2	−7.587

Table III Predicted PK Parameters and %PE for Lower and Upper Limits of Theoretical Dissolution Profiles

Specification	Limit	C_{max} (ng/mL)			AUC (ng.h/mL)		
		Obs	Pred	% Prediction Error	Obs	Pred	% Prediction Error
Lower Specification	1	70.88	70.11	1.09	1005.7	987.5	1.805
Upper Specification		70.88	71.56	−0.96	1005.7	988.2	1.741
Lower Specification	2	70.88	67.54	4.714	1005.7	987.1	1.851
Upper Specification		70.88	73.49	−3.683	1005.7	988.5	1.708
Lower Specification	3	70.88	67.79	4.353	1005.7	986.6	1.895
Upper Specification		70.88	73.19	−3.257	1005.7	988.9	1.672
Lower Specification	4	70.88	65.45	7.66	1005.7	985.9	1.97
Upper Specification		70.88	76.34	−7.7	1005.7	989.3	1.631
Lower Specification	5	70.88	65.79	7.177	1005.7	985	2.054
Upper Specification		70.88	78.18	**−10.29***	1005.7	989.7	1.595
Lower Specification	6	70.88	63.89	9.857	1005.7	983.8	2.181
Upper Specification		70.88	82.28	**−16.08***	1005.7	990.1	1.553
Lower Specification	7	70.88	63.65	**10.21***	1005.7	982.3	2.324
Upper Specification		70.88	85.11	**−20.08***	1005.7	990.5	1.512

*Out of acceptance criteria

specification until limit 5 and for the upper specification until limit 3 (Fig. 5c and 5 d), indicating this is the BE safe space.

Discussion

The USFDA released guidelines for the development, evaluation, and application of IVIVC for extended-release products over twenty-five years ago [5]. Validated IVIVCs enable setting of dissolution limits that can be utilized as a surrogate for *in vivo* bioequivalence studies to support certain post-approval formulation, equipment, process, and manufacturing site changes. A Level A IVIVC correlation is predominantly used for this purpose and represents 87% of the total IVIVC studies submitted to the regulatory agency. Level B and C correlations do not reveal much information regarding the overall plasma concentration–time profiles, which limits their regulatory application [12]. Thus, in the current investigation a Level A IVIVC was used which is the most informative and is recommended for setting dissolution specifications based on the USFDA guidance [5].

A typical prerequisite for developing an IVIVC is the development of formulations with sufficient difference in the rates of release (measured as f_2 values < 50 between the drug release profiles) [13]. This was achieved by quantitatively modulating the release controlling agent in the formulation to obtain the Medium and Slow-release rate formulations that showed an $f_2 = 41.9$. A dissolution method utilizing biorelevant media, SGF followed by SIF, was employed that showed > 80% release of drug after ~6 h corresponding to the *in vivo* T_{max} and delayed absorption of Medium-release formulation. A rank order correlation in dissolution data and peak plasma concentrations of formulations demonstrated the discriminatory power and *in vivo* predictability of the dissolution method, achieving an IVIVR.

A mechanistic absorption model was used for deconvolution of the Medium and Slow-release PK profiles to obtain the intestinal drug release rates. The IVIVC showed a linear correlation ($R^2 = 0.951$) and was successfully validated internally and externally as the average absolute prediction errors for C_{max} and AUC were < 10%. Visual inspection of the convoluted profiles showed that the entire concentration–time curve was well predicted. Using this validated IVIVC and limit of %PE < 20%, the lower dissolution specification was obtained at theoretical limit 6 and the upper dissolution specification at theoretical limit 4.

The above IVIVC-based dissolution specifications were derived using two release rates and thus could limit

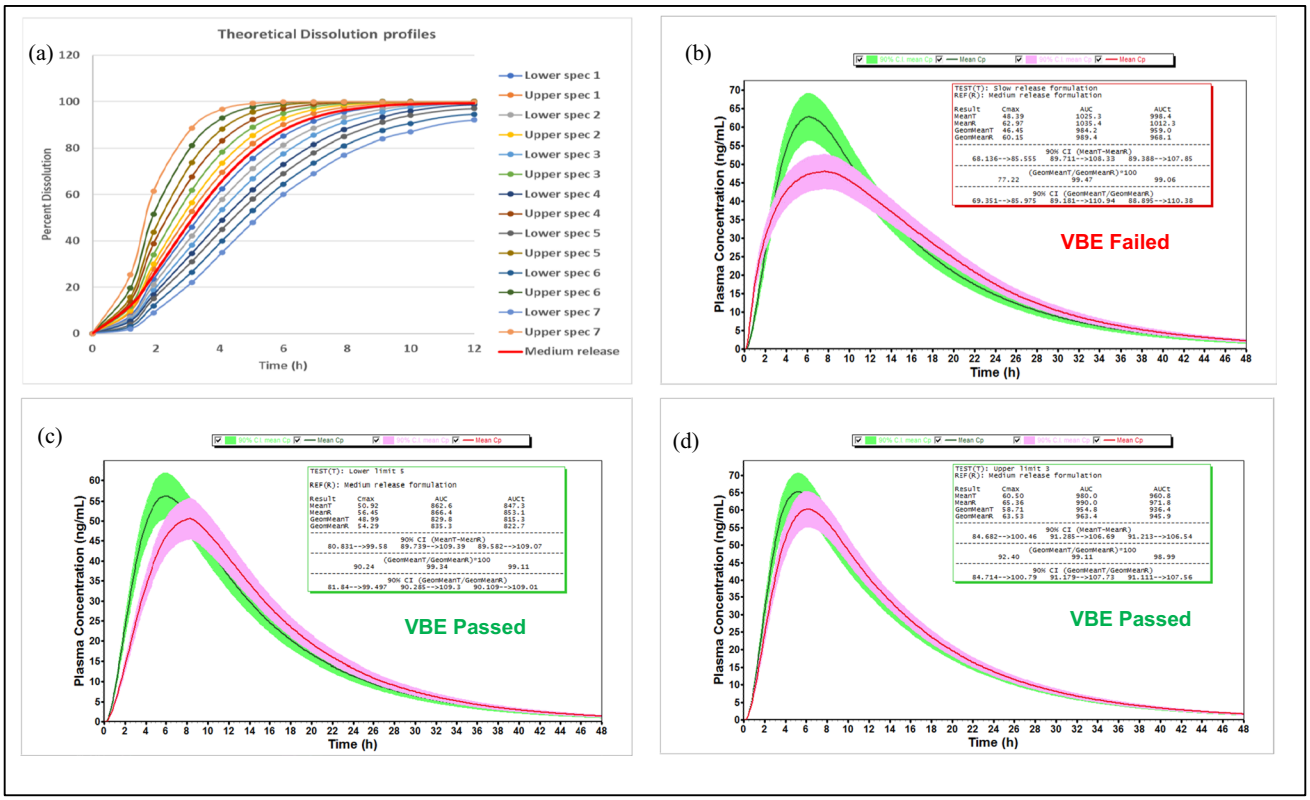

Fig. 5 **a** Theoretical dissolution profiles for Seven Upper and Lower specification. Virtual bioequivalence (VBE) between **b** Medium release (green) and Slow-release formulation (pink) **c** Medium release formulation (green) and Lower limit 5 (pink) and **d** Medium release formulation (green) and Upper limit 3 (pink)

regulatory applications as per the IVIVC guidance [32, 33]. Thus, to gain confidence in the defined dissolution specifications, we supplemented this with the IVIVR-VBE approach to derive clinically relevant dissolution specifications. In recent years this approach has been increasingly used as it enables an *in vitro- in vivo* link to assess the clinical impact of CQAs (critical product quality attributes) namely CMAs (critical material attributes), CPPs (critical process parameters) and CFVs (critical formulation variables) on bioequivalence [34–39]. For deriving clinically relevant dissolution specifications, the PBBM model is further combined with VBE assessments that allows incorporation of population variability [40]. Including observed clinical data from a BE and a non-BE batch in this validation tests the model sensitivity to *in vitro* dissolution and permits setting of a BE safe space bounded by the upper and lower specifications [41].

Few examples utilizing this approach have been reported in literature. Laisney *et al.* [42] demonstrated similar *in vivo* performance between immediate release tablet and capsule formulations of ribociclib that shows a permeation-controlled absorption and defined clinically relevant specifications and BE safe-space, superseding dissolution similarity f_2 criteria. Miranda dos Santos *et al.* [43] used the PBBM strategy and bioequivalence safe space to develop an extended release mini-tablet formulation of cyclobenzaprine that was virtually bioequivalent to the reference drug product, even though it failed the f_2 test. A dissolution safe space was established for fevipiprant by Kourentas *et al.* [44] using the observed clinical intravenous and oral PK data from BE and non-BE formulations that allowed for a wider than 10% dissolution difference for bioequivalent batches, superseding f_2 similarity analyses. Cheng *et al.* [45] developed a fasted and fed PBPK model of oral warfarin sodium, a narrow therapeutic index drug, and used it to predict bioequivalence and develop a dissolution safe space. Application of PBBM to support drug product quality is evolving and the interest from industry and regulators is growing especially for drug products that are not covered by BCS-based or IVIVC-based biowaivers, or that failed in a comparative dissolution study in respect to f_2 similarity [46–48].

As IVIVC in the current investigation was built using data from a BE and a non-BE batch, it was suitable to set the BE safe space using this IVIVR-VBE approach. As observed in the clinical study, the VBE estimations were able to reject the non-BE batch (Slow release) which provided confidence to run VBE at each level of the theoretical dissolutions. The 90% CI fell within the acceptable limits of 80–125% for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ for the lower dissolution specification until limit 5 and for the upper specification until limit

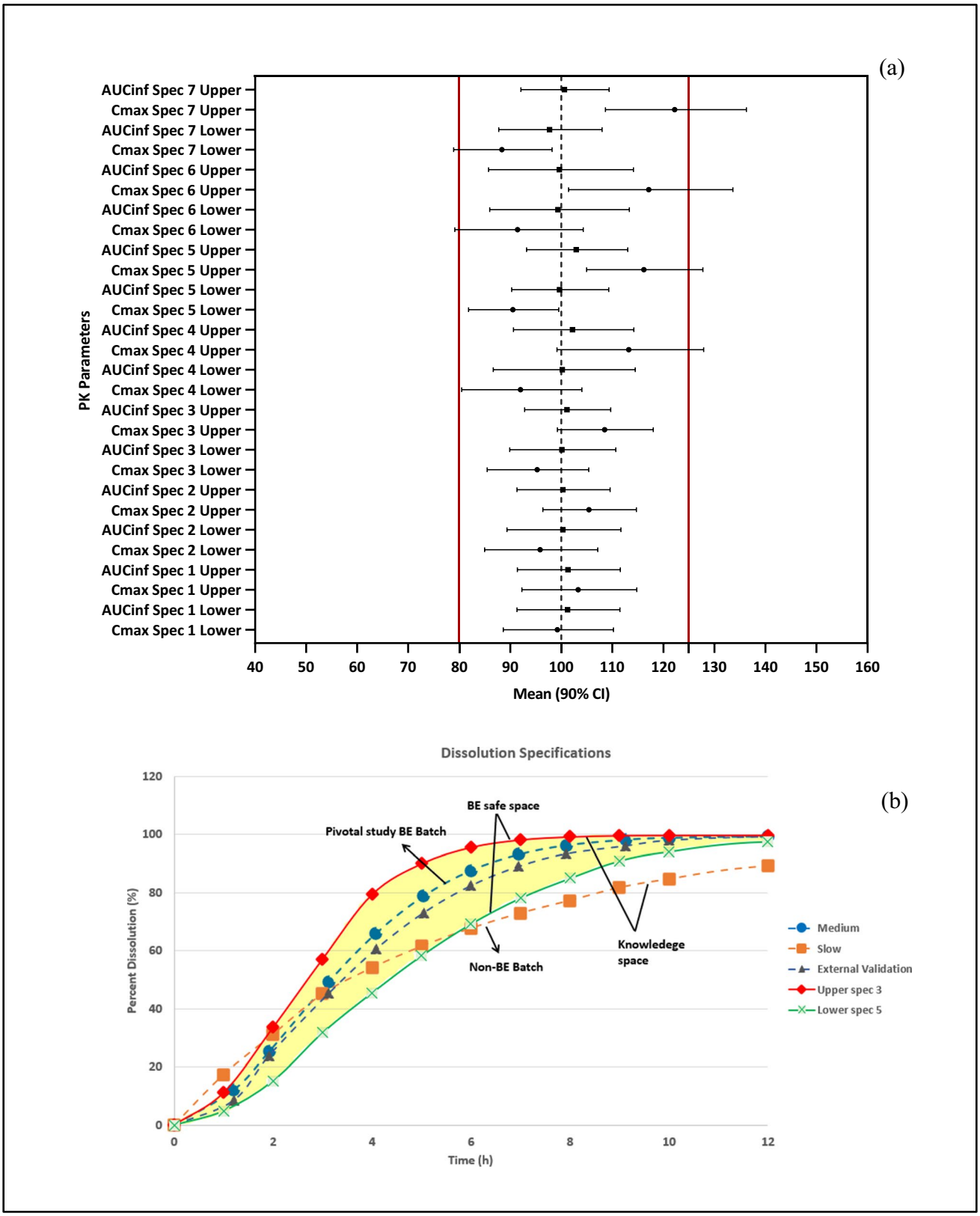

Fig. 6 **a** Geometric mean Cmax and AUC (90% CI) values determined at each level of the Lower and Upper theoretical dissolution limits. **b** BE safe space determined for prolonged release formulation

3 (Fig. 6a). Based on these evaluations, the BE safe space was more stringent than that derived by IVIVC modeling due to incorporation of population variability and allowed a wider i.e. > 10% dissolution difference with the BE Medium-release batch, overriding the f_2 similarity analysis (Fig. 6b). These clinically relevant dissolution specifications can be used for quality control of the product and can serve as a surrogate to support scale-up and post-approval manufacturing or product changes, eliminating the need for expensive and time-consuming clinical studies throughout the product lifecycle [49]. A more consistent therapeutic effect, resulting in optimal benefit for the patient is ensured by clinically relevant specifications. Additionally, wider dissolution specifications than the traditional approach will reduce the probability of rejecting batches that are deemed acceptable from a safety and efficacy point of view [50, 51].

As technology advances and regulatory expectations evolve, PBBM must adapt to ensure consistent application. Despite significant progress, predicting complex *in vivo* drug behaviors remains challenging, especially for compounds with extensive metabolism or non-linear pharmacokinetics. Future research should focus on integrating PBBM with complementary models like PBPK, QSP, and machine learning to enhance predictive accuracy. Developing standardized guidelines for PBBM application and validation is crucial for regulatory acceptance. Automation and artificial intelligence can expedite model development, reduce errors, and allow real-time adjustments. Expanding PBBM applications to innovative drug delivery methods and incorporating real-world data can improve clinical relevance and predictive capacity.

Conclusion

A PBBM model was successfully developed and validated for a prolonged release formulation of BCS Class I drug, verapamil. Two batches of the formulation variant (a BE and a non-BE batch) with f_2 values < 50 in the drug release profiles were used to build a Level A IVIVC, which was validated internally and externally. The IVIVC was used to calculate the lower and upper dissolution specification limits. To confirm these specifications and incorporate population variability, an IVIVR-VBE approach was used. This led to more stringent but wider lower and upper limits that defined the BE safe space. The current investigation demonstrates new opportunities offered by mechanistic modelling and how this two-pronged approach (IVIVC and IVIVR-VBE) can be used to define clinically relevant dissolution specifications and the BE safe space, which can support post-approval changes for waiving bioequivalence studies and ensuring commercial product quality over the years. This approach could facilitate regulatory acceptance of biowaivers, enhancing efficiency in drug development.

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Declarations

Conflicts of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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