Establishing the Dissolution Bioequivalence Safe Space for Immediate Release Formulation of Baclofen using Physiologically based Biopharmaceutics Modeling

Anuj K. Saini,[1,2]*, Mukesh Gupta[1] and Ajay Lale [2]
[1]*School of Pharmacy, Lords University, Alwar, Rajasthan*
[2]*Department of Biopharmaceutics and Clinical Development, Pharmaceutical Technology Center, Zydus Lifesciences Limited, Ahmedabad*

*__Address for correspondence__:
Anuj K. Saini,
School of Pharmacy, Lords University, Alwar, Rajasthan - 301028
E-mail: anuj.niper@gmail.com

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ABSTRACT
1. Clinical bioequivalence assessment is one of the critical aspects in the product development, since these studies are helpful in establishing the equivalence between a generic product and its reference-listed drug as per regulatory requirements. Physiologically based biopharmaceutics modeling (PBBM) can be a useful tool to assess potential bioequivalence risks and predict the outcome of bioequivalence studies. 2. In this study, GastroPlus® was used for virtual bioequivalence (BE) assessments, which required defining a clinically relevant dissolution safe space for Baclofen Tablets 20 mg USP. The purpose was to investigate if bioequivalence can be achieved *in silico* with the help of a PBB model developed using in-house *in vitro* and *in vivo* data. This study successfully predicted the pharmacokinetics of the theoretically slower dissolving batch compared with the pivotal test and reference formulations. 3. Ultimately, if there is confidence in such models, they can be used as a biowaiver approach for different products. Systemically applying these models to set clinically relevant specifications can greatly reduce product development timelines and costs, minimize drug exposure to healthy volunteers, and ensure product quality.

Introduction

In the realm of clinical pharmacology and drug product development, bioequivalence (BE) studies are crucial. They play a pivotal role in facilitating formulation alterations during the late stage of development, such as preapproval modifications, shifts in manufacturing sites, and adjustments to dissolution specifications. Beyond this, BE studies are essential for adhering to SUPAC guidelines for post-approval changes in new drug applications (NDAs) or abbreviated new drug applications (ANDAs). Moreover, these studies are essential in establishing the equivalence between a generic product and its reference-listed drug in ANDA submissions.(Jereb et al. 2020)

Recent findings from a pharmaceutical industry survey indicate that physiologically based pharmacokinetic/biopharmaceutics (PBPK/PBBM) modeling has become a widely used tool to be applied during drug development to tackle biopharmaceutics-related challenges. PBBM aids in predicting the cumulative effects of

various factors that influence oral drug absorption. These factors include the characteristics of the active compounds, the type of formulation, dosage, administration route, in vitro release/dissolution profile, metabolism, and disposition properties of any specific molecule. Additionally, it accounts for the gastrointestinal (GI) tract's physiology which potentially impacts the absorption and metabolism-related mechanisms of dosage forms. This modeling approach amalgamates discrete *in vitro* measurements and physiological phenomena to thoroughly evaluate the biopharmaceutics risks.(Pepin et al. 2016; Jaiswal et al. 2021; Lale et al. 2024)

By establishing a connection between bio-predictive *in vitro* dissolution profiles and *in vivo* pharmacokinetic performance using mechanistic oral absorption modeling, it becomes possible to exempt the clinical studies for oral formulations. This can be achieved through conducting virtual bioequivalence (VBE) trials that account for population variability and allow for the establishment or justification of broader dissolution specifications or their adjustments while assessing the feasibility of achieving BE. As a result, discriminatory dissolution becomes a crucial input parameter for modeling, as it captures both the rate and extent of drug release *in vivo*.(Bermejo et al. 2020; Jaiswal et al. 2021)

Baclofen, a muscle relaxant and antispastic agent, is particularly effective in alleviating symptoms of spasticity due to multiple sclerosis. It helps reduce flexor spasms, associated pain, clonus, and muscular rigidity. Baclofen exhibits high solubility that varies with pH across the physiological range and is rapidly and almost completely absorbed from the gastrointestinal tract. Approximately 15% of the dose undergoes hepatic metabolism, primarily through deamination. Between 70-80% of the administered dose is getting recovered unchanged or as metabolites in urine, with the remainder being excreted in faeces. The elimination half-life of Baclofen is approximately 2.5 to 4 hours. According to the Biopharmaceutics Classification System, Baclofen is classified as a Class I compound, indicating both high solubility and high permeability.(Agarwal et al. 2014; Schmitz et al. 2017)

This study investigates the application of PBBM in virtual BE assessments, demonstrating its capability to predict successful BE outcomes. The main objective was to predict the plasma concentrations of Baclofen Tablet USP, examine the impact of change in *in vitro* dissolution on *in vivo* absorption, and determine the potential bioequivalence of formulation with theoretically 20% slower dissolution rate compared to both the pivotal study test and reference products. Establishing confidence in these models and predictions could potentially justify the exemption of clinical BE studies for certain SUPAC-level modifications. The insights gained from this approach could be applied in other scenarios during various stages of product development.

Materials and Methods

Materials

The details of batches used in the modeling exercise have been given in Table 1.

Software

All *in vivo* pharmacokinetic simulations of Baclofen tablets were conducted using GastroPlus® (Version 9.9; Simulations Plus, Inc., Lancaster, California, USA). Additionally, PKPlus™ was utilized to perform compartmental modeling with oral plasma concentration-time data, generating pharmacokinetic parameters for the simulations.

In vitro dissolution studies

The dissolution profiles for both the Baclofen generic product and the reference product were assessed using the OGD-recommended method with the USP Apparatus II,

maintained at 37 ± 0.5 °C with an agitation speed of 50 rpm. The dissolution medium used in this study consisted of 1000 mL of 0.01 N hydrochloric acid. During the experimentation, 5 mL samples were collected and decided time intervals and replenished with the fresh medium. The samples were then filtered and diluted to determine the concentration of Baclofen spectrophotometrically at 334 nm. All experiments were performed in triplicate and reported as their means.

Pharmacokinetics of bioequivalence batches

An open-label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single-dose oral bioequivalence study was conducted in healthy adult human subjects under fasting conditions to compare and evaluate the oral bioavailability of the test formulation against the reference formulation.(Dewan and Chimata 2010)The study involved 28 subjects, all of whom completed the study adhering to the protocol. In each study period, following at least 10 hours fast (overnight), a single 20 mg oral dose of test or reference product was administered to the subjects in a seated position with approximately 240 mL of water at room temperature, under the supervision of trained personnel. The subjects received both the test and reference products according to the randomization schedule. The washout period between the doses was 7 days. Blood samples were collected at pre-dose (0.0 hours) and at various predetermined intervals up to 24 hours post-dose. Plasma samples from all subjects were sent to Cliantha Research Limited, Ahmedabad, India, for bio-analysis. Statistical analysis of the pharmacokinetic data was performed by to compare the relative oral bioavailability of the test formulation to the reference formulation. Bioequivalence was assessed through a statistical comparison of Cmax, AUCt, and AUCi for the test and reference products.

Overview of modeling strategy

The PBB Model of Baclofen was built using GastroPlus® which appropriately describes its clinical pharmacokinetics. Intravenous and oral administration for the dose of 15 mg and 20 mg was considered respectively. The experimentally determined values of physicochemical and biopharmaceutics properties were incorporated and some values from the literature and default GastroPlus® values were considered for the properties not experimentally determined.(Jaiswal et al. 2021)(Jaiswal et al. 2021) With the help of this information, the ACAT™ model in the GastroPlus® simulated the absorption of active pharmaceutical ingredient (API) i.e. Baclofen after p.o. administration. Entire modeling strategy is presented in Figure 1.

With the help of in-house generated *in vitro* data and the data available in the literature, the physicochemical and biopharmaceutical properties of Baclofen were defined.(Bhattiprolu et al. 2022)(Bhattiprolu et al. 2022) Table 2 summarizes those defined parameters.

Intestinal absorption of Baclofen

In each compartment of the intestinal tract, the ACAT™ model defined the site-specific solubility and dissolution impacting the absorption of Baclofen. With this, it also described the absorption and metabolism of Baclofen in the intestinal region. For intravenous dose, data was taken from the literature in which Baclofen was administered as an intravenous infusion. Since, Baclofen tablet is an Immediate-Release formulation; Takano's Z-factor model was fitted to *in vitro* dissolution data and the resulting Z-factor was further incorporated into the model.(Hofsäss and Dressman 2020) In the GastroPlus® the default fasted state physiology in humans was used for constructing the model. The drug-specific parameters such as reference aqueous solubility, pKa, bile salt solubilization ratio, solubility factor; and physiology-specific parameters such as pH and concentration of bile salts calculated the compartment-specific solubility and effective

diffusion coefficient of Baclofen automatically. Regarding the permeability, passive diffusion was considered. With the help of Baclofen-specific (molecular size and ionization) and system-specific (pore size, pore density, electrical potential gradient) parameters, the GastroPlus® built-in model predicted the contribution of paracellular pathway to overall absorption in each intestinal compartment. The absorption rate coefficients in individual intestinal compartments are calculated from effective permeability and absorption scale factors (ASFs). The default ASF model (Opt Log D Model SA/V 6.1) was used to calculate ASFs in all compartments of gastrointestinal tract.(Jaiswal et al. 2021)

Pharmacokinetics of Baclofen

Disposition parameters of Baclofen were obtained from the intravenous PK profile reported in the literature. One compartment PK parameters were exported to the ACAT™ model. Based on the metabolism data reported in the literature, it was assumed that first-pass metabolism has a minor impact on absolute bioavailability. Therefore, it was not considered for the model building.

Selection of dosage form and dose volume in the GastroPlus®

The simulations for i.v. infusion and IR tablets of Baclofen were performed in adherence to the study-specific protocol of dose and time. A default dose volume of 250 mL was used in the simulation. At the start of the simulation, the combination of dose-volume and stomach fluid volume impacts the fluid volume in the stomach.

Hypothetical slower dissolution profile

In vitro dissolution studies of reference and test pivotal formulations were completed in-house for IR tablets of 20 mg strength. Along with that, a new drug record for a theoretical batch with 20% slower dissolution was created.

Virtual trial execution

The default population parameters and their variabilities were used in the simulations. GastroPlus® calculated geometric means for the endpoints (Cmax and AUC0-inf) from the concentration-time profiles simulated in the virtual trials.

Model Optimization

Human jejunum permeability has been manually optimized to $2.4*10^{-4}$ cm/sec considering rapid and complete absorption of Baclofen. Based on the mass balance study, approx. 80% unchanged drug is excreted in urine.

Model Validation

For validating the ACAT™ model, dissolution of reference formulation (lot 2961056**)** was incorporated which contains the same model input parameters. Simulations were performed the same as the Test compound. Predicted plasma concentration data has been compared with the observed plasma concentration-time profile for exhibit batch test formulation (Internal validation) and reference formulation (External validations) [Lot #2961056 and Batch No. ZE78058] under fasting study.(Kollipara et al. 2024)

Parameter Sensitivity Analysis

A sensitivity analysis was conducted to assess the impact of dissolution on Baclofen Pharmacokinetics. Sensitivity analyses are important components for the verification of model, especially for the parameters that have the potential to impact simulation results.

Model Application: Virtual Bioequivalence Simulation

Once the model was validated, dissolution space was explored. Additional simulations were performed using theoretical formulation with 20% slower dissolution profile to check the impact of reduced dissolution compared to the observed data for the exhibit batch formulation.

The population simulator has been used to run several virtual BE trials following

scenario. The exhibit batch formulation and 20% theoretically slower formulations considering two ways cross over trials, (n=28 subjects). The cross-over virtual trial feature of GastroPlus® was used loading population for different formulations. Due to the low intra-subject variability (ISCV) observed in the pivotal BE studies, population parameters were kept default. The incorporation of *z factor* for the exhibit batch, (considered as a reference) and Test product (20% theoretical slower formulation) was different in both simulations. Mean and 90% confidence interval (CI) for PK parameters such as C_{max} and AUC were calculated in all virtual BE simulations. If all the BE parameters passed the BE criteria (CI between 80% and 125%), the trial was considered as 'pass'; otherwise, it was considered as 'fail'.(Kollipara et al. 2024)

Results

In vitro dissolution

Dissolution profiles were measured using the OGD recommended method in which the USP Type II apparatus setup was maintained at 37 ± 0.5 °C at 50 rpm. The dissolution medium for this product is 0.01 N hydrochloric acid and the volume of the medium was 1000 mL.(Li et al. 2019)(Li et al. 2019) Based on the observed dissolution profile of test formulation, a profile of theoretical formulation with 20% slower dissolution was calculated needed for the dissolution safe space finding. The comparative dissolution profiles are presented in Table 3.

Pharmacokinetics of bioequivalence study batches

Pharmacokinetics of Baclofen was characterized in a clinical bioequivalence study comparing test formulation (Batch No. ZE78058) and reference formulation (Lot #2961056). The outcomes of the study are presented in Table 4.

Modeling

Construction of PBB model and its validation

The PBB model of Baclofen in human was developed with the help of parameters presented in Table 2. Those parameters were measured *in vitro* or considered from the literature of observed intravenous PK profile.(Jaiswal et al. 2021)(Jaiswal et al. 2021) Using the observed PK profile, disposition parameters were calculated using PKPlus™ module of GastroPlus and parameters for one compartmental model were exported to the GastroPlus®.

Then, for the oral dosage form for the test product (Batch No. ZE78058) simulation was run suggesting a good fit of the simulated PK profile with the observed PK profile (%PE for AUCt and Cmax were 3.24% and -4.92% respectively) as shown in Figure 2.

After getting a good fit of simulated PK profile with the observed PK profile of Test formulation, the built model was validated using *in vivo* PK data of reference formulation.

In order to validate the developed model, Z-factor for dissolution profile of reference formulation was calculated and similar procedures were followed as the simulation for test formulation.(Bhattiprolu et al. 2022)(Bhattiprolu et al. 2022) From the simulation, it was found that prediction error for it was -9.7% and 0.36% for Cmax and AUCt respectively, suggesting the good fit with observed PK profile, resulting the validation of the developed model. (Figure. 3)

Similarly, Z-factor was calculated for this theoretically 20% slower dissolution profile as previously calculated for test and reference formulations.

Sensitivity Analysis

The Parameter Sensitivity Analysis (PSA) data for Baclofen test formulation are presented for Cmax and AUC0−t in Figure. 5.

To evaluate the assumptions of model parameters, sensitivity analyses were performed by individually adjusting predicted and arbitrarily assigned parameters within a realistic range, while keeping all other parameters fixed. The resulting pharmacokinetic (PK) metrics from each simulation were collected (as shown in Figure. 5). These results were then assessed by comparing each metric's value for a given parameter to its value in the baseline simulation.

This sensitivity analysis showed that critical parameters for test formulation such as precipitation time, diffusion coefficient, particle density, particle radius, and dissolution factor do not have an impact on both Cmax and AUC(0-t).

Model application

In the application of the developed model, virtual bioequivalence trials were run for different formulations. Initially, the test and reference formulations run in the virtual BE trials considering the parameters presented in the Table 5.

The output of representative virtual BE of 10 executed trials are presented in Figure. 5 and Table 6. The test formulation with 20% slower dissolution profile was concluded as bioequivalent in all ten trials compared to the pivotal test and reference formulations.

Discussion

Fasting condition is more discriminative to reflect the impact of the dissolution differences on bioequivalence.(Wu et al. 2023) (Wu et al. 2023) Hence, 'Human physiology fasting' was considered for the simulation. Simulation has been performed till 12 h, as the concentration at the last time point is 5% of the Cmax and hence, excluded from the simulation to capture the proper elimination phase. It should be noted that sampling has been done till 24h in the submitted pivotal bioequivalence study. The absorption of Baclofen from the GI tract is not variable and displays approximately <20% of intra-subject variability. Hence mean plasma concentration profile has been considered in the simulation.

Acceptance Criteria for PBB Model:

The acceptance criteria for model were defined as Percent Prediction Error (%PE) should be less than or equal to 20% in comparison with observed PK parameters including Cmax and AUC. It was calculated using following equation.(Wang et al. 2024)

Prediction error (PE) was calculated as : $PE\% = (\text{simulated} - \text{observed}) / (\text{observed}) \times 100$

Model applications were conducted only after the fulfilment of this acceptance criteria.

Virtual Bioequivalence

Because of the dynamic conditions within the gastrointestinal tract of humans, demonstrating bioequivalence can be challenging. Relying on a single simulation may lead to misleading conclusions about a BE outcome. Therefore, predicting the BE outcome with an appropriate number of subjects necessitates population virtual bioequivalence simulations. This study thus conducted ten crossover virtual trial simulations, each involving 28 randomly selected subjects. For these trials, the %CV for PK parameters were considered from the pivotal BE study since the variability affects the bioequivalence outcomes.

The obtained predictions inferred that the formulation with theoretically 20% slower dissolution is bioequivalent to the pivotal test and reference formulations both in all 10 virtual BE trials.

From Figure 5.A, it can be observed that the information box has got the green border, concluding that the trial is passed and the test formulation is bioequivalent with the reference formulation with 90% CI within the range of 80-125%. It was observed in

the *in vivo* pivotal BE study conducted earlier.

After comparing the test formulation with the reference, a test formulation with theoretically 20% slower dissolution was compared with the reference through virtual BE trials with the same parameters mentioned in Table 5. Their outcomes suggested that the test batch with a 20% slower dissolution profile is comparable with the reference formulation. It is presented in Figure 5.B.

After completing the above trials, to establish the robustness of the developed model, a test formulation with a theoretically 20% slower dissolution profile was run for virtual BE against the pivotal test formulation.(Wu et al. 2023) Figure 5.C explains the virtual BE results of this comparative study. The detailed outcomes for all above mentioned virtual BE trials are presented in Table 6.

Conclusion

A Physiology-Based Biopharmaceutics Model (PBBM) was utilized to extend the dissolution safe space for the immediate-release (IR) tablets of Baclofen. By using *in vitro* dissolution profiles as a discriminatory input parameter for BE study simulations virtually, the model predicted the likelihood of achieving bioequivalence between the test and reference formulations. This included a theoretical formulation with a 20% slower dissolution rate, which helped define a clinically relevant dissolution safe space extending beyond the clinically defined parameters. The Baclofen case study illustrates that PBBM can achieve comparable *in vivo* results following formulation modifications. This approach fills the gaps for drug products that are not eligible for BCS-based biowaivers, or those that do not pass comparative dissolution tests using f2 similarity.

In recent years, the use of PBB models alongside virtual BE simulations has become increasingly prevalent. Systemically applying these models to set clinically relevant specifications can greatly reduce product development timelines and costs, minimize drug exposure to healthy volunteers, and ensure product quality.

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Authors' contributions

Participated in research design, conducted virtual trials, performed data analysis, wrote and contributed to the writing of the manuscript: Anuj Saini and Ajay Lale
Reviewed the manuscript: Mukesh Gupta

Disclosure statement

Authors also report that there are no potential conflicts of interest.

Data availability statement

The authors declare that all the data supporting the findings of this study are available within the paper.

Additional information

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Table 1. Batches of Reference and test drug products used for Model building and validation

S.No.	Drug Product	Mfg. by/ Mfg for	Lot /Batch no.
1	Baclofen Tablets USP (Reference product)	Mfg. by: PLIVA HRVATSKA d.o.o. Zagreb, Croatia Mfg for: TEVA PHARMACEUTICALS USA INC., North Wales, PA 19454	2961056
2	Baclofen Tablets USP (Test product)	Cadila Healthcare Ltd. Ahmedabad, India	ZE78058

Table 2. Physicochemical properties of Baclofen used as input parameters in the model

Physiochemical Properties	Values	Reference
Molecular weight (g/mol)	213.66	)(Schmitz et al. 2017)
pKa	3.9 (Strongest Acidic) 9.6 (Strongest Basic)	(Product Monograph) (Product Monograph)
Human jejunum Permeability ($cm/sec*10^{-4}$)	2.4	optimized
log P	-0.82	(Product Monograph)
Dosage form	"IR: Tablet"	(Product Monograph)
Dose (mg)	20	(Product Monograph)
Dose volume (mL)	250	Default values in GastroPlus®
Mean Precipitation Time (sec)	900	Default values in GastroPlus®
Diffusion coefficient (cm/sec^2)	0.75×10^{-5}	Default values in GastroPlus®
Drug particle density (g/mL)	1.2	Default values in GastroPlus®
Precipitation time (sec)	900	Default values in GastroPlus®
Solubility profile for test formulation	**Media** / **Solubility** (mg/mL) 0.01 N HCl: 7.98 0.1 N HCl: 26.12 pH 4.5 Acetate Buffer: 6.06 pH 6.8 Phosphate Buffer: 5.85	Experimental In-house
Dissolution profile	Table 4	Experimental In-house
Dissolution Model	Z factor (Takano's Model)	IR: Tablet" dissolution rate controlled by z factor
Z factor (ml/mg/sec)-Test	$8.12*10^{-4}$	

Table 3. *In vitro* dissolution profiles of Test, Reference, and 20% slower theoretical formulations of Baclofen Tablets USP

Time (min)	Baclofen Tablets USP 20 mg Reference (2961056)	Baclofen Tablets USP 20 mg Test (ZE78058) *	Baclofen Tablets USP 20 mg Test (with theoretical 20% slower dissolution rate)
5	94.0	91.9	73.52
10	95.3	97.7	78.16
15	96.0	99.5	79.6
30	96.4	99.7	79.76
45	97.2	100.0	80.0
60	98.1	100.4	80.32

Table 4. Outcomes of in vivo clinical BE study of test and reference Baclofen Tablets USP 20 mg

Parameter	Unit	RefGeo LSM	TestGeo LSM	Ratio of Geometric Means	90% Confidence Interval	Intra-subject CV%
Ln(Cmax)	ng/mL	5.84	5.88	104.60%	(99.18%;110.31%)	11.70
Ln(AUClast)	hr*ng/mL	7.73	7.74	101.47%	(95.9%;107.37)	12.44
Ln(AUCINF_obs)	hr*ng/mL	7.78	7.81	102.36%	(97.64%;107.30%)	10.37

Table 5. Parameters considered for Virtual BE trials

Parameter	Details
Route of administration	Oral
Dosage form	IR: Tablet
Fasting/Fed	Fasting
Simulation duration (h)	12
Demographics of the virtual population	GastroPlus® product manual (version 9.9)
Simulation trials	10
Number of virtual subjects in each simulation trial	28
Intra-subject variability (ISCV)	12% for both Cmax and AUC as observed in *in vivo* bioequivalence study

Table 6. Outcomes of Virtual BE trials

Formulation	Predicted T/R (%)	90% CI	Predicted T/R (%)	90% CI	Predicted T/R (%)	90% CI
	C_{max}		$AUC_{(0-t)}$		$AUC_{(0-inf)}$	
20 % slower formulation vs. Batch No. ZE78058	101.0	93.8 – 108.7	98.10	89.6 – 107.4	98.11	88.4 – 108.9

20 % slower formulation vs. Lot #2961056	97.77	90.1 – 106.0	98.61	89.3 – 108.9	98.63	88.1 – 110.5
Test Batch no- ZE78058 and RLD- Lot #2961056	96.82	89.3 – 104.9	100.5	91.1 – 111.0	100.5	89.8– 112.6

Figure 1. PBB modeling strategy for Baclofen Tablets 20 mg USP

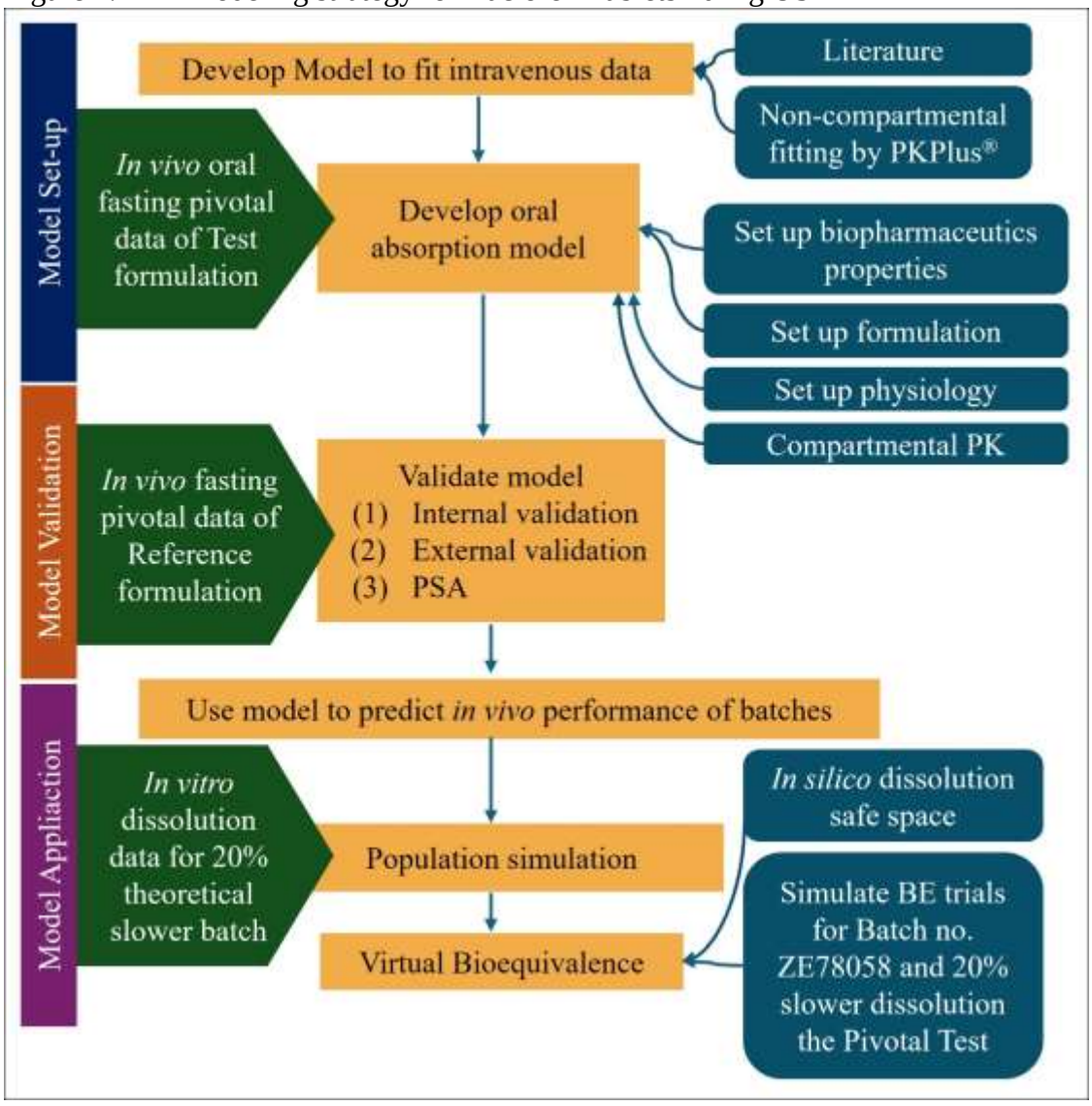


Figure 2. Simulated and observed plasma concentration-time profile of Baclofen Tablets USP 300 mg, pivotal test formulation. The solid line indicates simulated profile, whereas square boxes represent the observed concentrations at specific time.

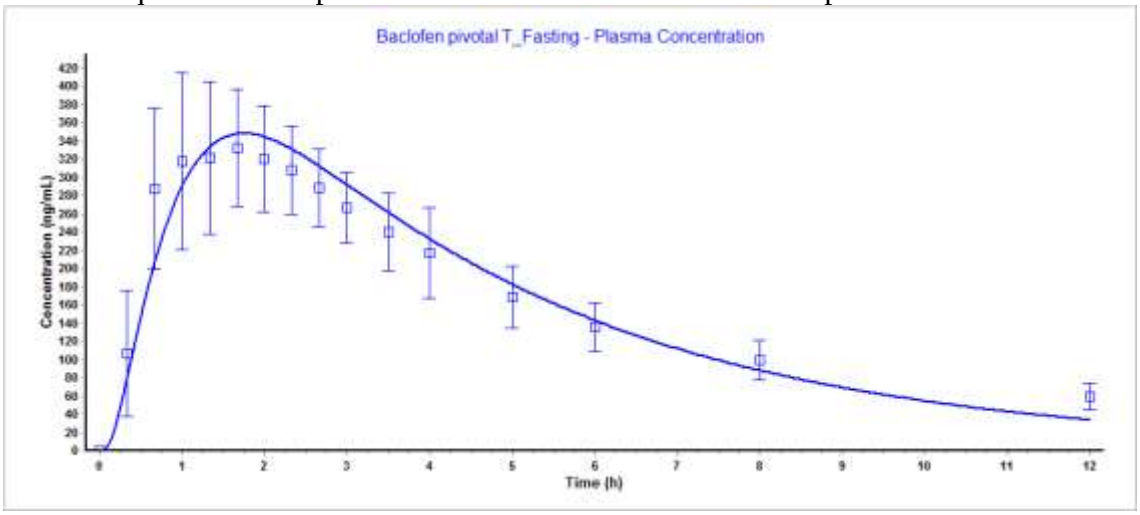


Figure 3. Simulated and observed plasma concentration-time profile of Baclofen Tablets USP 300 mg, reference formulation. The solid line indicates the simulated profile, whereas square boxes represent the observed concentrations at specific time points.

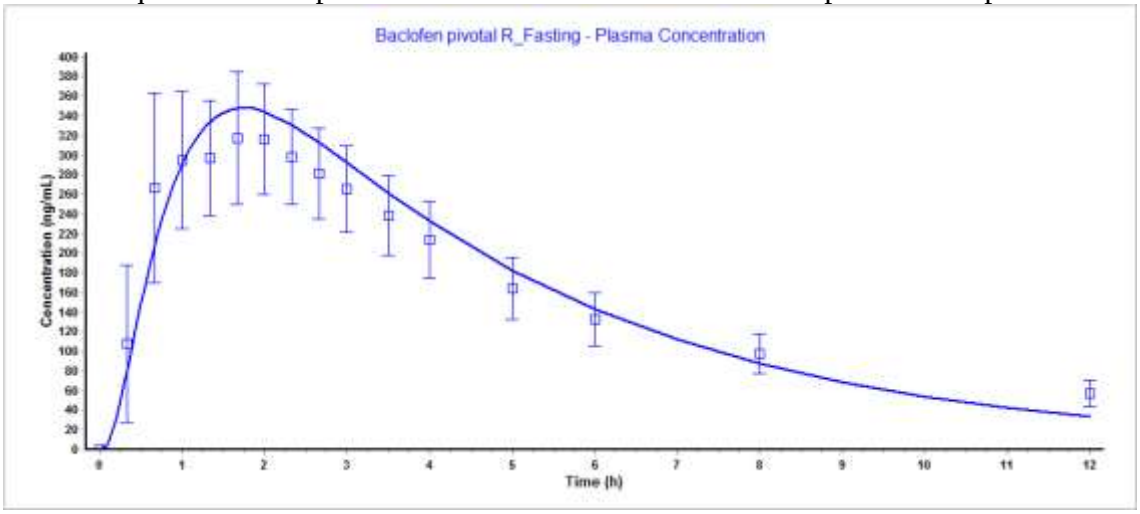


Figure 4. Parameter sensitivity analysis for Baclofen Tablets 20 mg USP, where the parameters present on the X-axis (precipitation time, diffusion coefficient, drug particle density, particle radius and dissolution factor) are presented for their impact on Cmax and AUC(0-t) respectively

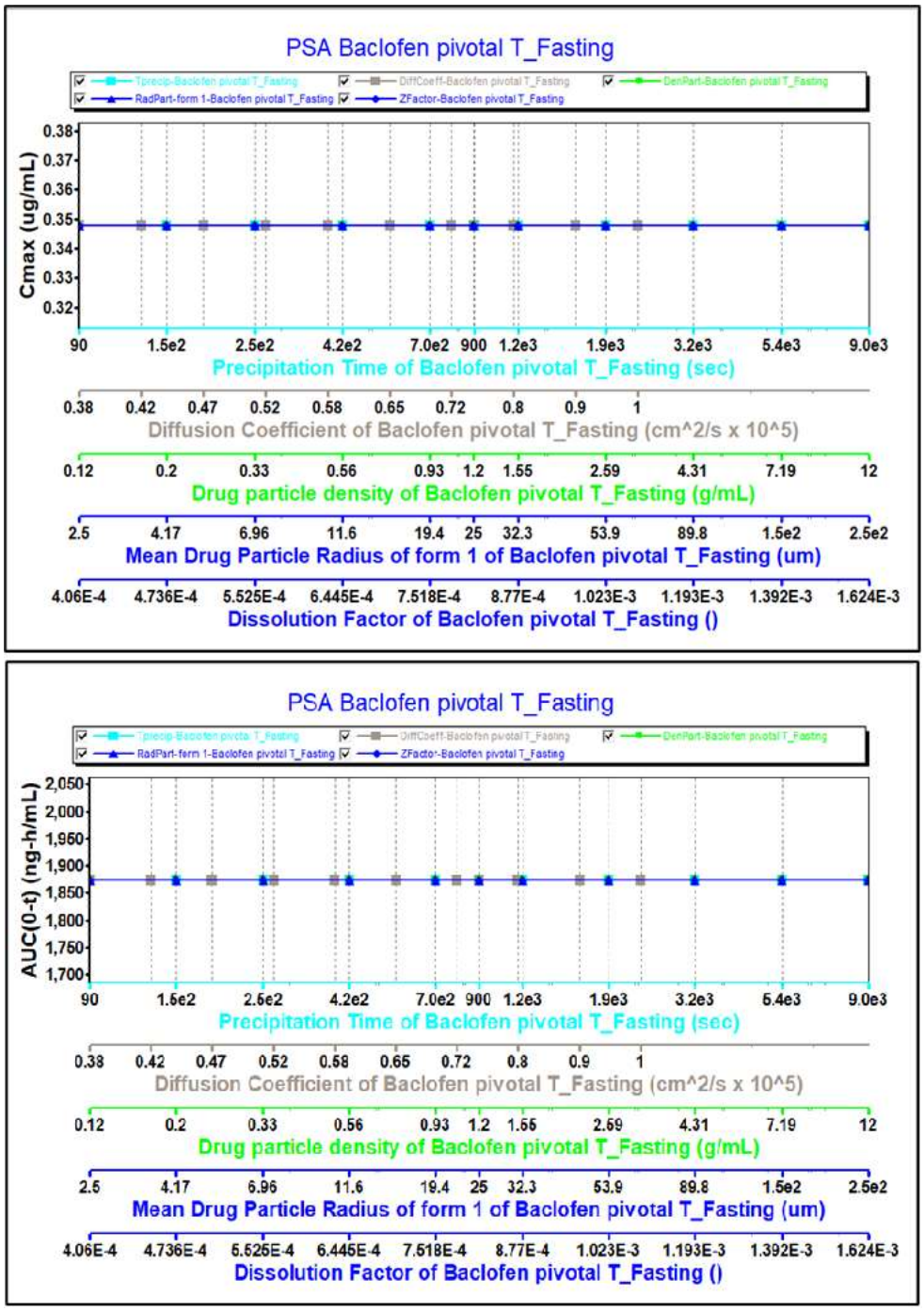
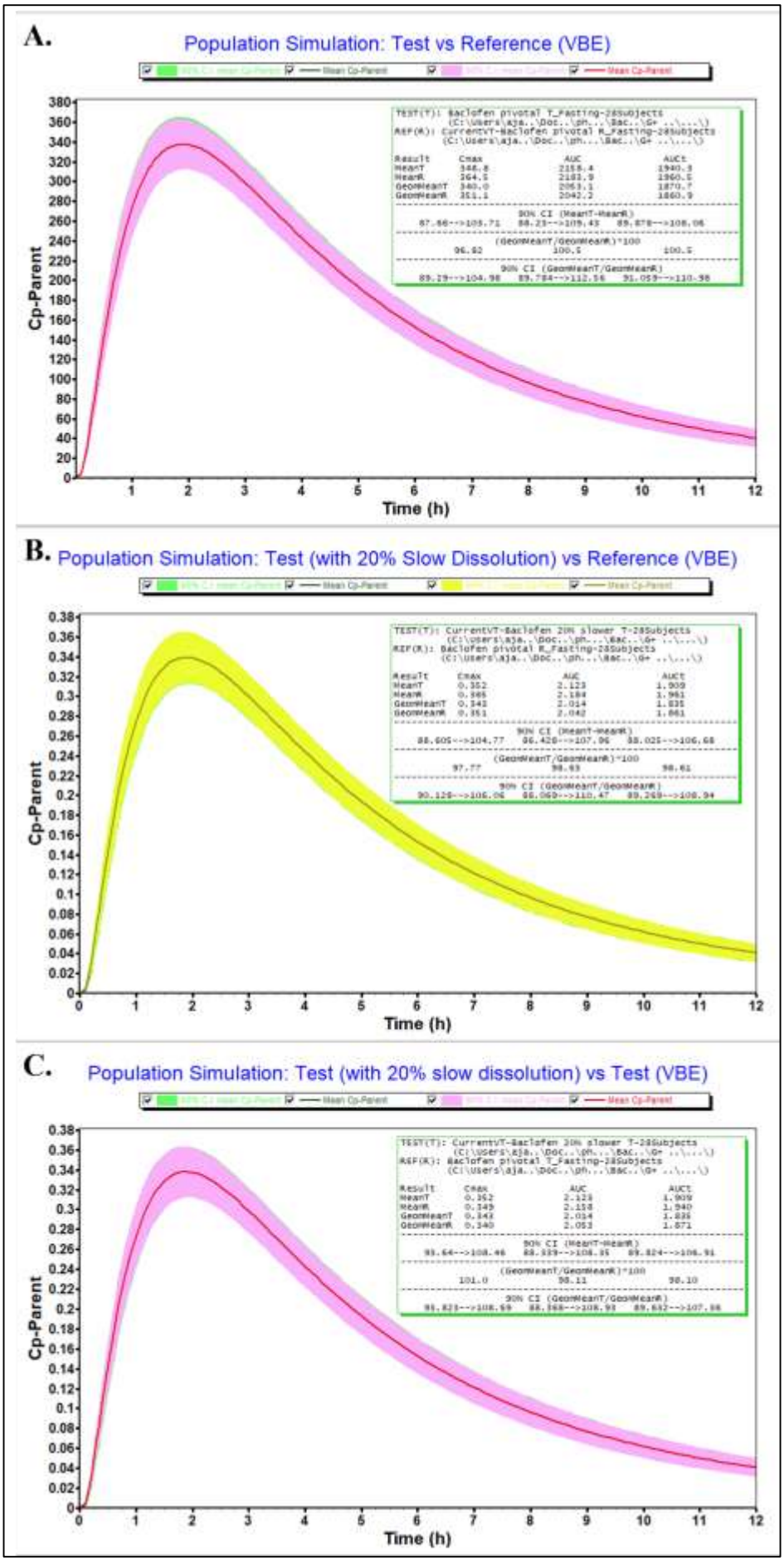


Figure 5. The outcome of virtual BE trials between a. Test and Reference, b. Test (with 20% slower dissolution) and Reference, and c. Test (with 20% slower dissolution) and Test formulation


A.
Population Simulation: Test vs Reference (VBE)
Cp-Parent
Time (h)
B.
Population Simulation: Test (with 20% Slow Dissolution) vs Reference (VBE)
Cp-Parent
Time (h)
C.
Population Simulation: Test (with 20% slow dissolution) vs Test (VBE)
Cp-Parent
Time (h)

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