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Research paper

Physiologically based absorption modeling to predict bioequivalence of controlled release and immediate release oral products

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ABSTRACT

Physiologically based absorption modeling was conducted to predict bioequivalence (BE) for immediate release (IR) and controlled release (CR) formulations. In case of the CR formulation of a BCS class 1 drug, sensitivity analyses were conducted to investigate the impact of gastrointestinal (GI) transit time and absorption scaling factors in caecum and colon on formulation PK. The regional absorption profiles of the test and reference formulations were compared to provide additional confidence on the BE predictions. For IR formulation of BCS class 2b drug, the sensitivity of dissolution rate, precipitation time and human permeability were evaluated. Finally for both cases, population simulations were conducted in crossover manner to investigate BE between formulations, and compared with the observed data. These case studies highlight the utility of absorption modeling in prediction of BE. Such modeling can be used for development of innovator and generic products, as well as to address questions arising during regulatory reviews.

1. Introduction

The application of physiologically based absorption modeling to predict oral absorption [1], support formulation development [2], and preclinical to clinical translation [3] has been widely reported. In addition, these models are now being used routinely for regulatory review and decision making [4–6]. Infact US FDA has now finalized a guidance on format and content of physiologically based PK (PBPK) model reports [7], and EMA has published a draft guidance on qualification and reporting of PBPK models [8]. These recent guidances from FDA and EMA demonstrate the acceptance of PBPK modeling by regulatory agencies. FDA has also published and presented several examples of applications of oral absorption modeling in formulation development and bioequivalence assessment in regulatory submissions [6,9]. These models can integrate key *in vitro* properties of the drug and formulation, and the GI tract physiology to predict the overall pharmacokinetics. As a result these models can be used as a biopharmaceutics risk assessment tool during formulation development.

Bioequivalence (BE) studies are routinely used during product development such as to support comparison of early and late clinical trial formulations (i.e. preapproval changes), and to support Scale-Up and Post Approval Changes (SUPAC) requirements during post-approval changes in a new drug application (NDA) or abbreviated new drug application (ANDA). Also, BE studies are pivotal in showing similarity between a pharmaceutically equivalent generic formulation and the reference listed drug (RLD) in ANDA submission. Due to the importance of BE studies in drug product development, successful application of absorption modeling to predict BE outcome will be helpful in guiding formulation development based on mechanistic understanding of factors impacting drug absorption, streamline generic product development, design BE studies, and support biowaiver argument on a case-by-case basis, to name a few.

In this manuscript, we report two case studies attempting to highlight successes and challenges in utilizing physiologically based absorption models to assess BE for CR product of a BCS class 1 compound (Compound A) and IR product of a BCS class 2b compound (Compound B). In these case studies the application of virtual clinical trials conducted to predict BE between the test and reference formulations are described. In addition, appropriate incorporation of *in vitro* dissolution data for CR and IR formulations into these models and parameter sensitivity analyses of critical parameters to demonstrate BE are also discussed.

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2. Materials and methods

2.1. Software used

GastroPlus™ v 9.5 (Simulations Plus, Lancaster, CA, USA) was used for absorption modeling in both case studies.

2.2. Case study 1: BE prediction for controlled release (CR) formulation of a BCS class 1 compound

2.2.1. Compound A physicochemical properties

The following key compound properties were used in building the model – molecular weight 260 g/mol, log P 1.9, pKa 8.8, density 1.2 g/mL, calculated human effective permeability (based on Caco-2 data, data on file) was 2.1×10^{-4} cm/s and diffusion coefficient was calculated based on molecular weight. The following pH-solubility data was input as .spd - 0.82 mg/mL (pH 1), 0.8 mg/mL (pH 3), 0.79 mg/mL (pH 4), 0.82 (pH 5), 0.86 (pH 7.5). This pH-solubility data was used directly in GastroPlus with linear interpolation, as this is highly soluble neutral compound. Diffusion coefficient and solubility was adjusted in GastroPlus™ to account for bile salt concentration changes across the GI tract. This was done automatically in the software using the in-built model based on the FaSSIF (0.96 mg/mL) and FeSSIF (1.31 mg/mL) solubility input. The fitted solubilization ratio was 2113.7. The precipitation time was fixed at the default value of 900 s, as no effect of precipitation time on the model outcome had been observed. The blood to plasma ratio was 1.15. Fraction unbound in plasma was 0.12.

2.2.2. Dosage form and dissolution data input

CR integral tablet was chosen as the formulation option in GastroPlus™, to model the CR formulations. USP-2 dissolution data for the CR formulations in pH 6.8 buffer were fitted to a double Weibull function and was used as *in vivo* dissolution in all the simulations. The use of double Weibull function is justified in this case because the solubility of compound A is not affected by pH.

2.2.3. Physiology

The default human fasted & fed physiological model in GastroPlus™ (Opt logD SA/v6.1) was used in these simulations, except that the ascending colon ASF was decreased to 0.9 to better fit the observed data.

2.2.4. Pharmacokinetic (PK) parameters

Human PK parameters were estimated by fitting 5 mg IV (10 min infusion) data to a two-compartment model in PK-plus. The model was selected based on best fitting of the PK profile as judged by the AIC value. The mean PK parameters used in these simulations were CL = 0.7 L/h/kg and Vc = 0.51 L/kg, $k_{12} = 5.4\,h^{-1}$, and $k_{21} = 2.1\,h^{-1}$. Single dose escalation studies had demonstrated linear increase in AUC and C_{max} up to 500 mg. Since the current BE predictions were at a dose in the linear range, the PK parameters used were appropriate.

2.2.5. Simulations

The model was built using 50 mg solution and 200 mg CR formulation human PK data. Single simulations were conducted to predict the mean PK profiles and parameters and compared with the observed data. Subsequently, data from a crossover relative bioavailability study comparing test CR formulations with 3 different release rates (fast, medium, slow) and the reference product was used to refine the fasted and fed absorption models, specifically the ascending colon ASF had to be reduced to better fit the observed PK profiles and parameters. Parameter sensitivity analyses (PSA) were conducted to assess the impact of colon and caecum absorption scaling factor (ASF) and transit time, on AUC and C_{max} under fasted and fed states. Finally, this model was used to predict the outcome of a BE study using the test and reference product dissolution data. Twenty crossover virtual trial simulations were conducted with 40 randomly selected subjects in each trial, to assess BE between the test and reference formulations. The number of subjects used in the virtual trial were chosen based on study design for previous relative bioavailability study conducted for this product. The crossover trials were conducted by loading the same selected population for both test and reference formulations in each trial. The default population mean parameter and %CV in GastroPlus™ was used in these simulations. However, the mean values and % CV for PK parameters specific to compound A, were changed to the measured values for all formulation records, based on previous clinical data. The geometric mean ratio (GMR) and 90% confidence interval (90% CI) were calculated in Phoenix® (Pharsight, a Certara Company) using the Bioequivalence workflow.

2.3. Case study 2: BE prediction for Immediate Release (IR) formulation of a BCS class 2b compound

2.3.1. Compound B physicochemical properties

The following key compound properties were used in building the model – molecular weight 356, density 1.2 g/mL, log P = 2.3, and diffusion coefficient was calculated based on molecular weight. The calculated human effective permeability (P_{eff}) from absorption rate constant (ka) was 3.25×10^{-4} cm/s. It is noted that given this is a low solubility compound, dissolution rate limited absorption can confound correct estimation of P_{eff}. However, there was good confidence in the estimated human P_{eff} (3.25×10^{-4} cm/s) from the ka, as it was close to the human P_{eff} (3.46×10^{-4} cm/s) estimated from rat intestinal perfusion data (data on file). The following pH-solubility data was input as .spd – 10.4 mg/mL (pH 1.36), 7.75 mg/mL (pH 1.55), 2.46 mg/mL (pH 2.0), 0.23 mg/mL (pH 2.36), 0.016 mg/mL (pH 6.07), 0.0047 mg/mL (pH 6.84) and 0.0004 mg/mL (pH 7.58). This pH-solubility data was used directly in GastroPlus with linear interpolation. Diffusion coefficient and solubility was adjusted in GastroPlus™ to account for bile salt concentration changes across the GI tract. This was done automatically in the software using the in-built theoretical model, since solubility in biorelevant media (SGF, FaSSIF or FeSSIF) was not available. The fitted solubilization ratio was 2590. The precipitation time was fixed at the default value of 900 s. The following API particle size distribution (PSD) were input as .psd in the model, d10 = 0.39 μm, d50 = 3.1 μm, d90 = 8.4 μm. However, as Z-factor dissolution was used (as described below), in this case PSD was not used. The blood to plasma ratio was 0.91. Fraction unbound in plasma was 0.03. Intestinal first pass extraction (FPE) was estimated to be 16%, based on available human ADME and absolute bioavailability data.

2.3.2. Dissolution data input

Dissolution data for test and reference formulations generated in pH 2.0, 4.5 and 6.8 media were fit simultaneously to Z-factor in GastroPlus™. The Z-factor vs. pH profile for each formulation were then used for further modeling. The solubility data used for fitting of the profiles were derived from the respective dissolution data. These solubility values were in agreement with the pH-solubility profile shown above. The Johnson model (using API PSD data) and effective PSDs model were also evaluated as part of the model building.

2.3.3. Physiology

The default human fasted physiological model in GastroPlus™ (Opt logD SA/v6.1) was modified by increasing the percent fluid in small intestine to 50% to better fit the observed PK.

2.3.4. Pharmacokinetic (PK) parameters

Human PK parameters were estimated by fitting the human IV data to a one-compartment model in PK-plus. The model was selected based on best fitting of the PK profile as judged by the AIC value. The mean PK parameters used in these simulations were CL = 0.034 L/h/kg and Vc = 0.29 L/kg. Single dose escalation studies had demonstrated linear

increase in AUC and C_{max} upto 60 mg. Since the current BE predictions were at a dose in the linear range, the PK parameters used were appropriate.

2.3.5. Simulations

The model was built using single ascending dose PK data in healthy subjects. Simulations were conducted to predict the mean PK profiles and parameters and compared with the observed data. Parameter sensitivity analyses (PSA) were conducted to assess the impact of human P_{eff}, Z-factor, and precipitation time on AUC and C_{max}. Finally, this model was used to predict the outcome of a pivotal BE study, using the test and reference product dissolution data. Twenty crossover virtual trial simulations were conducted with 42 randomly selected subjects in each trial, to assess BE between the test and reference formulations. The crossover trials were conducted by loading the same selected population for both test and reference formulations in each trial. The number of subjects used in the virtual trial were chosen based on study design for previous relative bioavailability study conducted for this product. The default population parameter values and %CV in GastroPlus™ was used in these simulations. However, the mean values and % CV for PK parameters specific to compound B, were changed to the measured values for all formulation records, based on previous clinical data. The geometric mean ratio (GMR) and 90% confidence interval (90% CI) were calculated in Phoenix® (Pharsight, a Certara Company) using the Bioequivalence workflow.

3. Results

3.1. Case study 1: BE prediction for Controlled Release (CR) formulation of a BCS class 1 compound

The simulated PK profile and parameters from the model built using the parameters listed above was compared to the observed human data from a solution formulation. The simulated plasma concentration vs. time profiles and comparison to observed data are summarized in Fig. 1A, which shows that the model was able to predict the observed

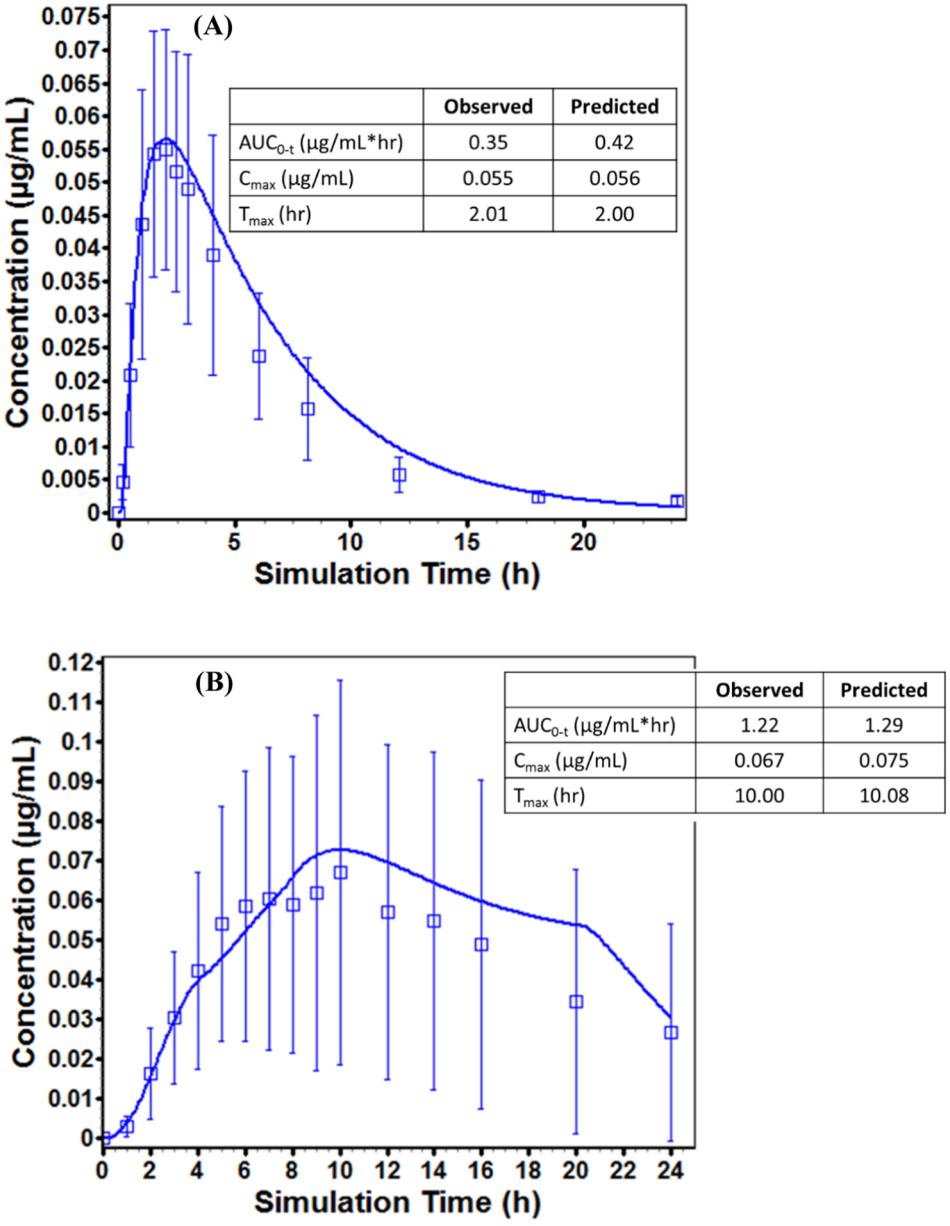

Fig. 1. Simulated plasma concentration vs. time profiles for solution formulation (A), and CR formulation (B) of compound A. The observed plasma concentration vs. time profiles are shown for comparison.

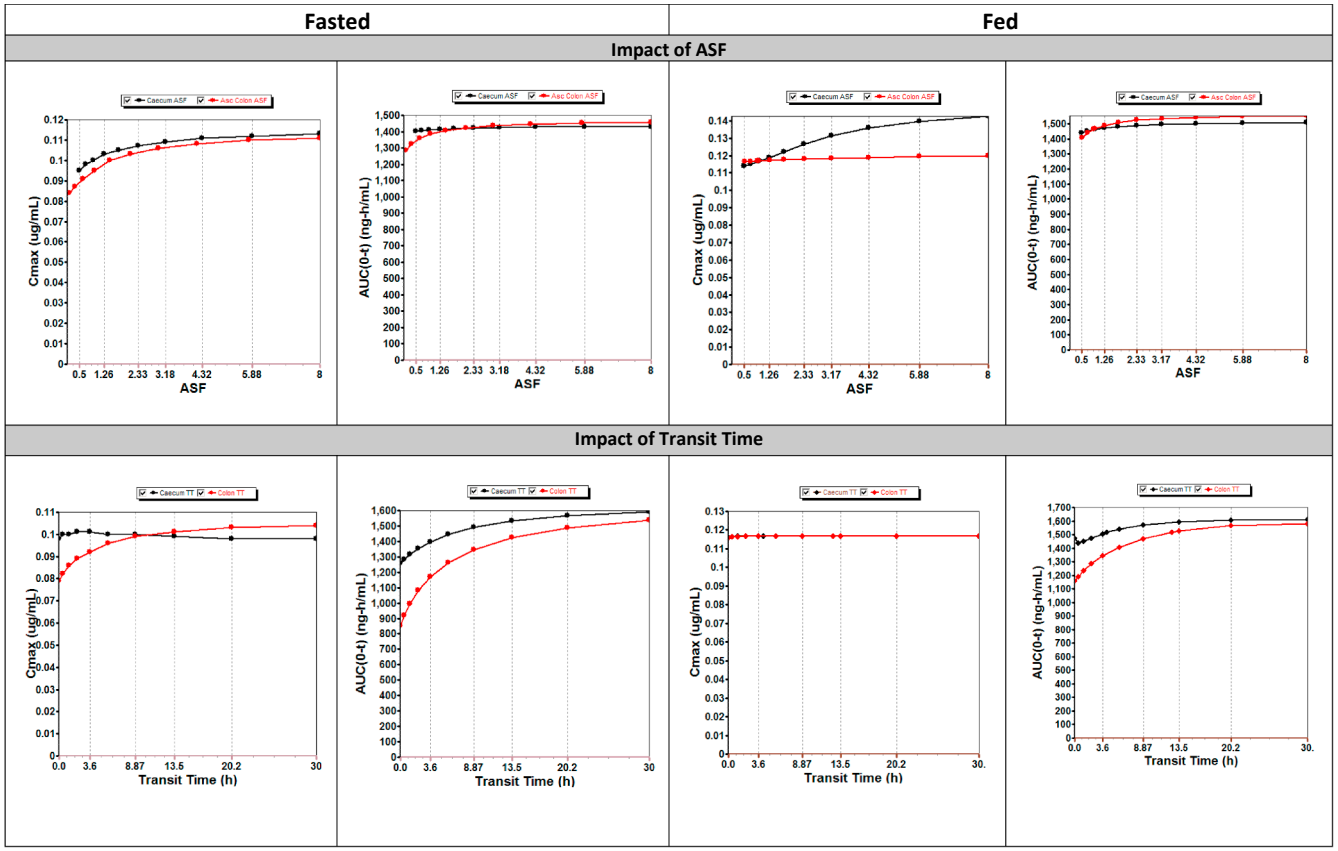

Fig. 2. Effect of changes in caecum and colon ASF and transit time on AUC and C_{max} of CR formulation of compound A, in fasted and fed states.

data reasonably well. Since this was a non-precipitating solution formulation, good prediction for this formulation gives confidence that the human P_{eff} and PK parameters were estimated accurately. The model also suggested that this compound was completely absorbed (> 99%) at this dose, which is expected given that this is a BCS class 1 molecule, which was dosed as a solution. Next, the PK of the CR formulation was predicted using this model and compared with the observed data (Fig. 1B). This comparison showed that the model with revised ASF value in the colon was able to predict the observed PK of the CR formulation well i.e. within variability of the observed data. Hence, this model could be used for subsequent BE predictions.

PSA demonstrated that while there was some impact of changing caecum and colon ASF on C_{max}, the effect on AUC was negligible. As shown in Fig. 2, changing the ASF by 16-fold (0.5 to 8) only changed AUC and C_{max} by approx. 10% and 25%, respectively, under both fasted and fed states. Sensitivity analysis also showed that caecum and colon transit time had no impact on C_{max}. Caecum and colon transit time did show an impact on AUC, with AUC increasing approximately 25–60% as transit time was increased.

Subsequently, the model was used to conduct crossover virtual trials in 30 subjects to predict the data from relative bioavailability studies comparing three test formulations with different release rates with the reference formulation, under fasted and fed conditions. As shown in Fig. 3A and B, the simulations were able to predict the trends in bioperformance of the three test formulations reasonably accurately, with the medium release rate formulation showing the closest PK to the reference, under both fasted and fed conditions. In addition comparison of predicted and observed data, demonstrated the model was able to predict the GMR between the test and reference formulations reasonably well (data not shown). It should be noted that this was a relative bioavailability study and the study was not powered to demonstrate BE between the formulations. The model was clearly able to predict the impact of dissolution differences on relative bioavailability, with the slow formulation showing the lowest relative BA as compared to reference formulation. Thus the model was considered acceptable for the purpose of predicting the probability of success of showing BE of the final formulation based on its dissolution data. In addition, comparison of the regional absorption outputs (Fig. 3C and D) from the model demonstrated that the total fraction absorbed decreased as the dissolution rate decreased, as expected. Also, high fraction absorbed in the lower GI (caecum and colon) were observed for these formulations, as the CR product was designed to maximize absorption in the lower GI so as not to lose significant bioavailability. In addition these simulations also demonstrated that the medium release rate test formulation had similar absorption profile across the GI tract as the reference in both fasted and fed states. These outcome gave confidence in the model performance for application in prediction of the pivotal BE study. Finally, the available dissolution data for the final test and reference formulations were used to conduct 20 virtual crossover trials with 40 subjects in each trial in-order to simulate the BE outcome. These results are summarized in Table 1, which clearly demonstrates that the model was able to accurately predict both GMR and 90%CI, as compared to the observed data.

3.2. Case study 2: BE prediction for Immediate Release (IR) formulation of a BCS class 2b compound

The simulated plasma concentration vs. time profiles are shown in Fig. 4, for the single ascending dose study. The observed data are shown for comparison. Overall, the model was able to predict observed human PK data with reasonable accuracy demonstrating that this model could be used for simulation of the pivotal BE study. The PSA results are summarized in Fig. 5. PSA demonstrated that there was minimal impact

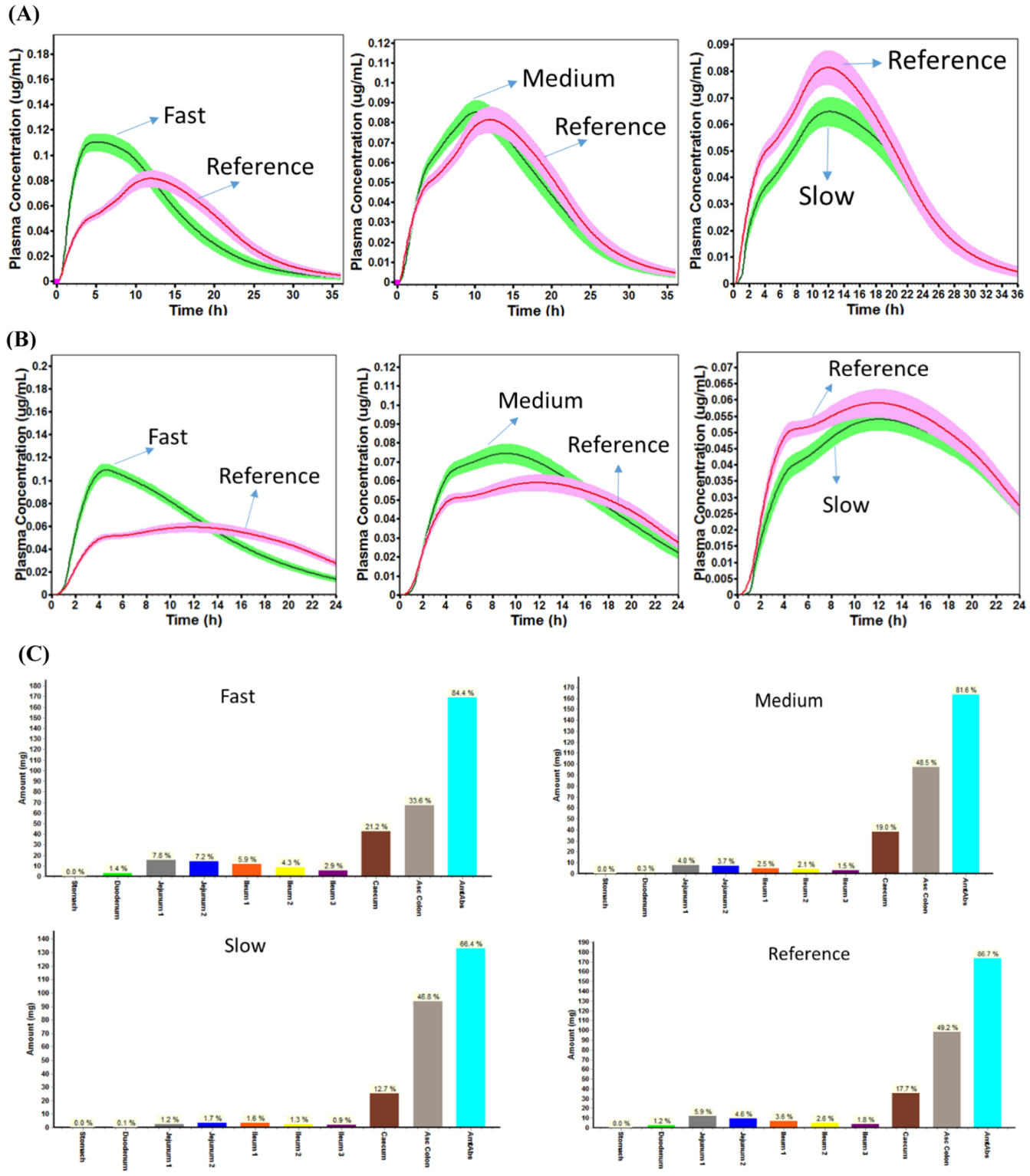

Fig. 3. Simulations of CR formulations of compound A. (A) Representative virtual trial outputs comparing with three different release rates to the reference formulation under fasted state. (B) Representative virtual trial outputs comparing with three different release rates to the reference formulation under fed state. The shaded area in the figures are 90% confidence interval. (C) Regional absorption under fasted state. (D) Regional absorption under fed state.

of P_{eff} on AUC. However increase in P_{eff} did result in an increase in C_{max}. There was good confidence in the estimated human P_{eff} (3.25×10^{-4} cm/s) from the absorption rate constant (ka), as it was close to the human P_{eff} (3.46×10^{-4} cm/s) estimated from rat intestinal data. PSA also demonstrated that the dissolution rate would have minimal effect on the bioperformance of the tablet formulation. This is likely because of the high solubility of compound B in gastric pH, which results in complete solubilization of the dose (i.e. dose number < 1). Similarly, precipitation time was predicted to have minimal impact on AUC or C_{max} because the low dose of compound B results in low dose number (approx. 10) even in the intestinal pH, which would mean less propensity of the drug to precipitate *in vivo*. The

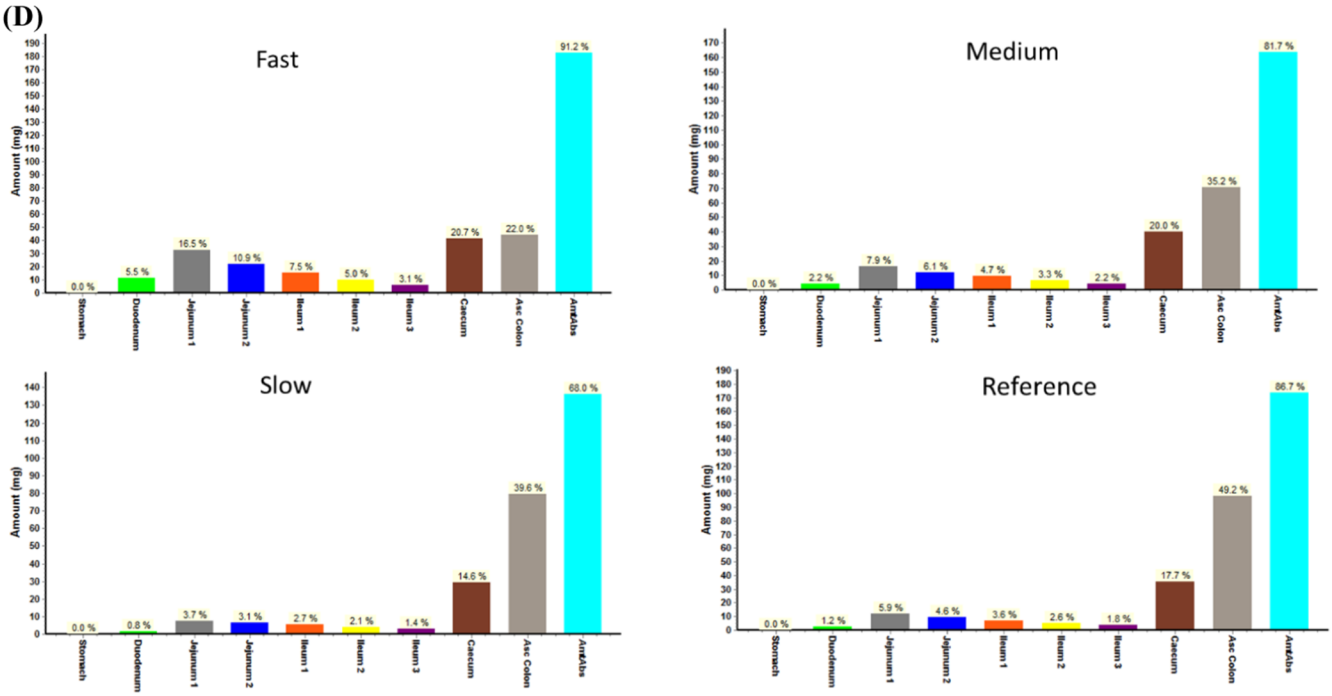

Fig. 3. (*continued*)

Table 1
Predicted and observed GMR and 90% CI for CR formulation of compound A for pivotal BE study in fasted and fed states.

	AUC_{0-t} GMR (90% CI)	Cmax GMR (90% CI)	AUC_{0-t} GMR (90% CI)	Cmax GMR (90% CI)
	Observed (test/reference)		Predicted (test/reference)	
Fasted	0.85 (0.81–0.90)	0.90 (0.86–0.95)	0.86 (0.81–0.99)	0.88 (0.83–1.10)
Fed	1.00 (0.94–1.07)	0.99 (0.93–1.08)	0.99 (0.90–1.09)	1.01 (0.88–1.13)

lack of precipitation was also observed in 2-stage (SGF to FaSSIF) dissolution studies (data not shown). It is acknowledged that the 50% SI fluid volume used here is higher than the volumes reported in literature (20). There could be an interplay between the SI fluid volume and precipitation time for BCS-2 weak base, such that increasing the fluid volume might decrease the precipitation rate. However, in the case of compound B because of the low dose number the likelihood of this happening is low. A 3-dimensional PSA conducted to understand the interplay of SI fluid volume and precipitation time, demonstrated that both of these parameters had no effect on fraction absorbed (data not shown). Additional 3-dimensional PSA conducted to understand the interplay of stomach pH and stomach transit time, also demonstrated that there was no effect on AUC and C_{max} (data not shown). This further demonstrated that due to low dose number throughout the GI tract

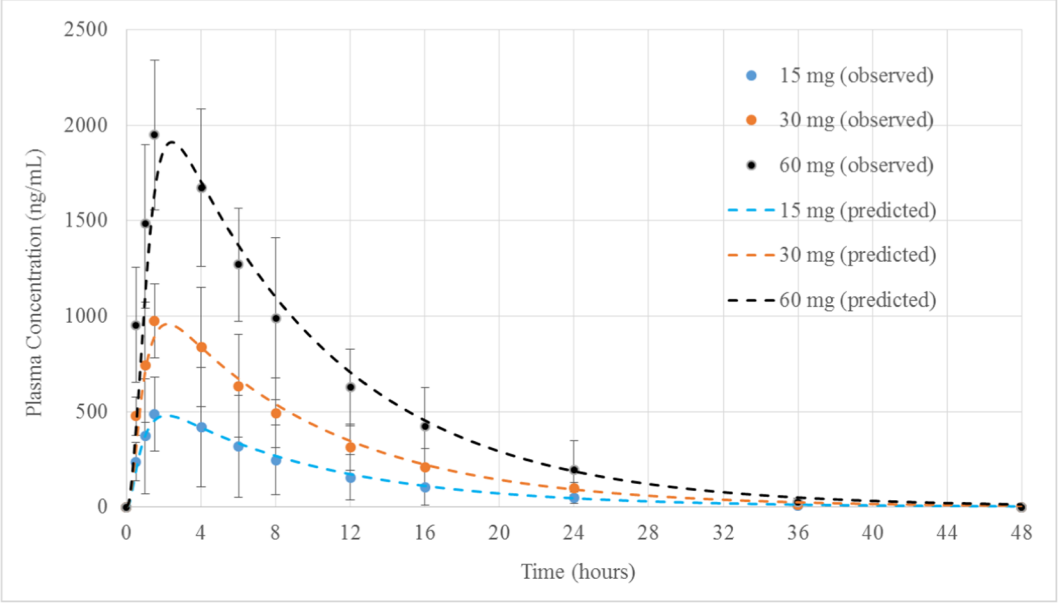

Fig. 4. Simulated and observed pharmacokinetic profiles for three doses of IR formulation of compound B in fasted state.

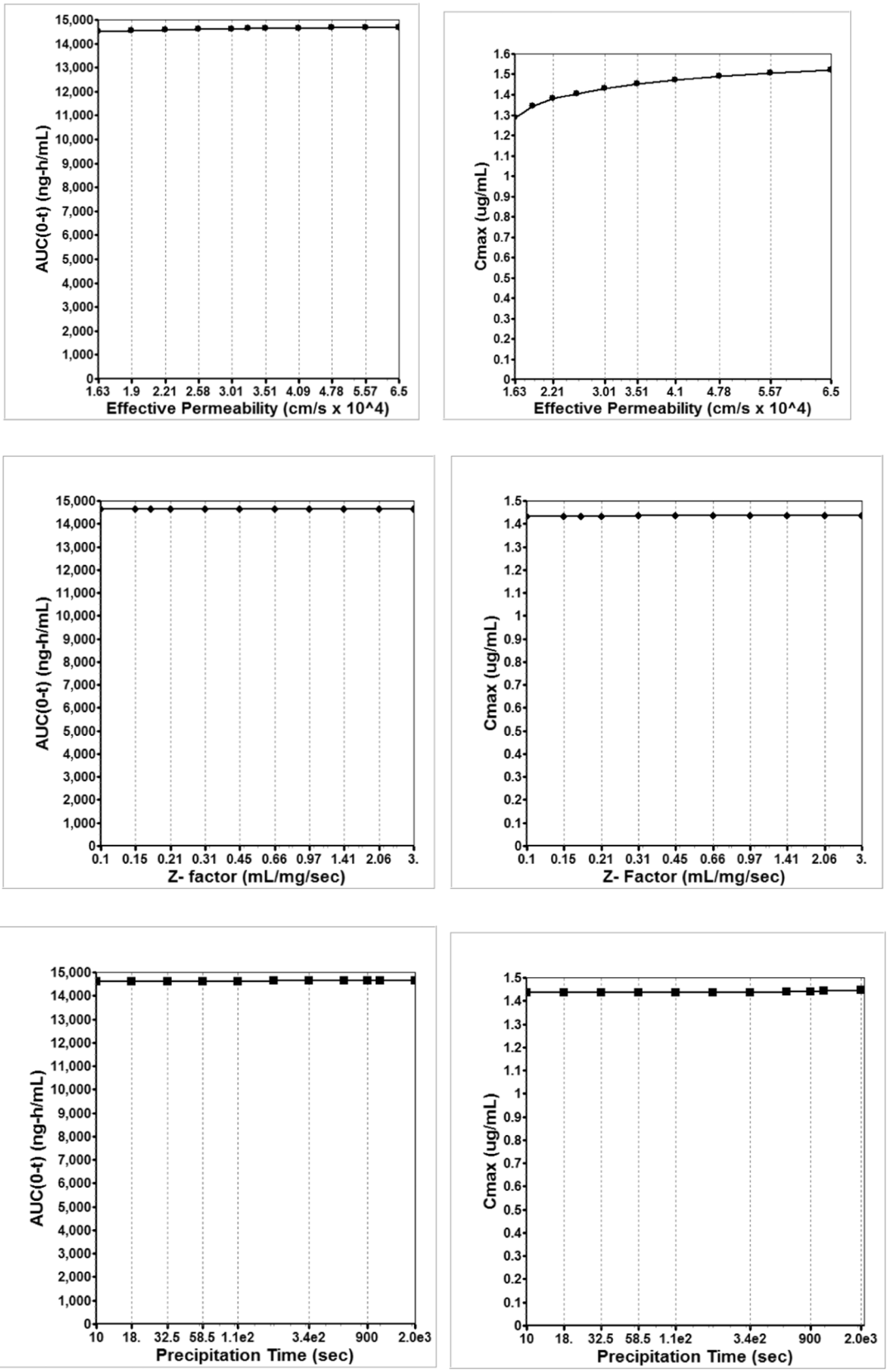

Fig. 5. Effect of changes in effective permeability, dissolution rate (Z-factor) and precipitation time on AUC and C_{max} of IR tablet of compound B in fasted state.

there is minimal impact of gastric physiology on PK of compound B.

Finally, the available dissolution data for the final test and reference formulations were used to conduct 20 virtual crossover trials with 42 subjects in each trial in-order to simulate the pivotal BE study outcome. The outcome of the virtual BE simulations and comparison with the observed data are summarized in Table 2. These data clearly

Table 2
Predicted and observed pharmacokinetic parameters, GMR and 90% CI for IR formulation of compound B for pivotal BE study in fasted state.

	Observed			Simulated		
	AUC_{0-48} (ng/mL*hr)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-48} (ng/mL*h)	C_{max} (ng/mL)	T_{max} (hr)
Reference	14020	1388	2.2	14193	1412	2.6
Test	14441	1360	2.1	14931	1442	2.5
	AUC	C_{max}		AUC	C_{max}	
GMR (T/R)	1.03	0.98		1.05	1.02	
90% CI	0.97–1.09	0.92–1.06		0.98–1.06	0.93–1.04	

demonstrate that the model was able to accurately predict GMR and 90%CI, as compared to the observed data.

4. Discussion

Physiologically based absorption modeling has been used to address several aspects of drug product development [2,10–13]. In this paper, we report the use of absorption modeling in prediction of BE of formulations. Two case studies are reported here, one each for CR and IR product for BCS class 1 and class 2b drug, respectively. In both these cases, modeling was an integral part of the product development activities and was used iteratively to guide formulation selection as clinical data were available and ultimately to apriori predict probability of success (POS) of target formulations to be bioequivalent to the reference. The model was used to help with formulation screening and formulation selection for the pivotal BE study. These are examples of the significant role modeling can play in decision making in pharmaceutical product development, specifically with respect to BE predictions in this particular case.

In case study 1, the development and application of an absorption model for predicting BE of a CR formulation was described. In this case of a BCS class 1 drug, where GI physiology was expected to have minimal impact on the absorption of the drug, Weibull function was able to describe the dissolution profiles accurately and could be used in the model. Such success with Weibull fitting of dissolution profiles has been reported for CR formulations of several BCS class 1 compounds [2,14]. Since CR products rely of absorption in the lower GI tract (i.e. caecum and colon, Fig. 3C and D) to achieve adequate bioperformance, it is imperative that any mechanistic absorption model is able to accurately capture drug absorption from these formulations in the lower GI tract. However, even with significant strides in understanding of processes impacting drug absorption in the GI tract [15–17], there are still several unknowns about the lower intestine [18–20], which makes it difficult to build truly mechanistic models of the lower GI tract. In GastroPlus™, ASFs are used for the different sections of the GI tract to scale the effective permeability based on physiological changes across the GI tract. So it is frequently observed that for CR products the ASFs in caecum and/or colon needed to be adjusted to better fit the observed PK [2,14]. This was also the case for compound A, where the ascending colon ASF had to be reduced to better fit the PK and regional absorption profile in lower GI tract. Given the very low fluid volumes in the colon, reduced dissolution and absorption is expected here. As a result decreasing the ASF in the colon to account for higher absorption there, is reasonable. As observed from the parameter sensitivity analysis (Fig. 2), changing the ASF in caecum and colon had an impact on the C_{max} under both fasted and fed states. This was due to significant absorption in the lower GI, as evidenced from the 10–15 h T_{max} (Fig. 3A and B), and regional absorption profiles (Fig. 3C and D). However, the impact on AUC was negligible due to almost complete absorption of compound A. This lack of effect of lower GI ASF on AUC for BCS class 1 compound has been reported before [14]. The increase in AUC with increasing the colon transit time (Fig. 2), is expected since increasing the transit time allows more time for absorption of compound A in the lower GI tract.

In case study 2, the development and application of an absorption model for predicting BE of an IR formulation was described. Given that this was a BCS class 2b compound, dissolution rate limited absorption was expected and hence during product development several formulations with varying dissolution profiles were investigated using this model (data not shown). Based on the outcome of those analyses a final test formulation was selected which was predicted to have the highest probability to demonstrate BE to the reference product, using the Z-factor dissolution input. In this case of a BCS class 2 drug, proper incorporation of *in vitro* dissolution data to be representative of *in vivo* dissolution is imperative, since in case of low solubility drugs GI fluid volume, solubility and dose can have significant impact on dissolution [2,21]. Several dissolution models (Z-factor, Johnson and effective PSD) were investigated during model building. Ultimately the Z-factor model was found to give the best fit, where the *in vitro* dissolution data was fitted to Z-factor for each formulation factoring in the media volume, solubility, pH and doses used in the dissolution experiment. These pH vs. Z-factor values were then used as input in model as *.zfd support file for each formulation, to calculate *in vivo* dissolution using the physiologically relevant volumes, pH, and transit times in the ACAT model. This option of incorporating the dissolution data, takes into consideration the changes in solubility and volumes in the GI tract and modifies the dissolution rate as per changes in the GI tract environment. Indeed there are reports of successful application of Z-factor model for poorly soluble drugs, where the authors were able to use the fitted Z-factor for incorporation of dissolution into the absorption model [22].

In both cases the absorption models were built and optimized based on the available clinical data. In particular, the availability of crossover relative BA and single dose studies helped in setting up the virtual trial simulations in both case studies. It should be noted that the CVs for each parameter in the virtual trial populations were treated as intrasubject CVs. This assumption is imperative for treating the virtual trials as crossover studies and for calculation of average BE metrics. However, since intrasubject CVs are rarely available for all the physiological parameters, though there are some reports with such physiological data [23,24], there is room for further improvement of these commercial available modeling platforms by generating and incorporating intrasubject CVs for the key parameters. In case study 1 given the complexity of the CR formulation, the reasonably accurate simulations of the relative BA studies using the crossover virtual trial simulations gave confidence that these models could be used in simulations of the pivotal BE studies. The in-silico prediction of BE using mechanistic absorption models can provide significant advantage in drug product development, where the available dissolution data can be used to iteratively guide formulation development, design BE studies as well as give confidence in the outcome of the BE studies. These models can be applied to new drug development (e.g. in case of formulation changes during late stage clinical development, post approval changes beyond biowaiver limits, and set dissolution specifications to name a few) as well as in generic product development where the primary goal is to develop formulation that would achieve BE to the reference listed drug (RLD). The use of virtual trials to predict BE has been reported previously to support SUPAC based biowaiver for IR product [22], support dissolution specification [21], and generic product evaluation [6]. In our opinion such modeling could be used to support biowaiver of CR formulations and insoluble compounds depending on the physicochemical, biopharmaceutic, and PK properties, as well as depending on the regulatory acceptability of such applications. In this paper, we have provided further evidence of the applicability of these models to assess BE of both CR and IR products. However, it is incumbent on the modeler to ensure that for any specific case the model is built robustly and validated against an independent clinical dataset such that there is enough confidence in the BE predictions.

5. Conclusion

In conclusion, on a case-by-case basis the use of *in vitro* dissolution profiles in absorption model can be used to predict BE of both CR and IR products. As exemplified in the two case studies shown here, such models are key tools in robust development of drug products as well as derisking clinical studies. These absorption PBPK model can be used not only for development of innovator and generic products, but also to address questions arising during regulatory reviews. However, it is also acknowledged that there are areas in these models that need further improvement, such as incorporation of intrasubject variability of physiological parameters in virtual trials, and better colonic absorption model (water volume and permeability).

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