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Physiologically based pharmacokinetic modeling and simulations to inform dissolution specifications and clinical relevance of release rates on elagolix exposure

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Abstract

The aim of this analysis was to use a physiologically based pharmacokinetic (PBPK) model to predict the impact of changes in dissolution rates on elagolix exposures and define clinically relevant acceptance criteria for dissolution. Varying in vitro dissolution profiles were utilized in a PBPK model to describe the absorption profiles of elagolix formulations used in Phase 3 clinical trials and for the to be marketed commercial formulations. Single dose studies of 200 mg elagolix formulations were used for model verification under fasted conditions. Additional dissolution scenarios were evaluated to assess the impact of dissolution rates on elagolix exposures. Compared to the Phase 3 clinical trial formulation, sensitivity analysis on dissolution rates suggested that a hypothetical scenario of ~75% slower dissolution rate would result in 14% lower predicted elagolix plasma exposures, however, the predicted exposures are still within the bioequivalence boundaries of 0.8–1.25 for both C_{max} and AUC. A clinically verified PBPK model of elagolix was utilized to evaluate the impact of wider dissolution specifications on elagolix plasma exposures. The simulation results indicated that a slower in vitro dissolution profile, would not have a clinically significant impact on elagolix exposures. These model results informed the setting of wider dissolution specifications without requiring in vivo studies.

KEYWORDS
biopharmaceutics, dissolution specifications, PBPK modeling

1 | INTRODUCTION

Elagolix is a non-peptide, oral gonadotropin-releasing hormone (GnRH) receptor antagonist recently approved for the management of moderate-to-severe pain associated with endometriosis and for heavy menstrual bleeding associated with uterine fibroids. Phase 3 clinical studies of elagolix demonstrated that elagolix 150 mg once daily (QD) and 200 mg twice daily (BID) produce clinically meaningful pain reduction, including dysmenorrhea and non-menstrual pelvic pain in premenopausal women with moderate-to-severe

endometriosis-associated pain (Ng et al., 2017). Elagolix Phase 3 clinical trials formulation and the approved commercial product (elagolix commercial formulation) consisted of immediate release (IR) 150 and 200 mg elagolix tablets (Shebley et al., 2020).

Model informed drug development is rapidly emerging as a tool for clinical drug development to aid in regulatory decision making in lieu of clinical studies (Grimstein et al., 2019; Zhao et al., 2011). Physiologically based pharmacokinetics (PBPK) modeling is an evolving tool capable of filling the gap between in vitro physico-chemical knowledge and physiological factors that determine systemic exposure of a drug product (Grimstein et al., 2019). PBPK modeling is a valuable quantitative approach which is accepted by regulatory authorities to inform and manage the potential risk of drug-drug interactions (Grimstein et al., 2019; Zhao et al., 2011). The US Food and Drug Administration (US FDA) advocates for the use of biopharmaceutical tools such as the Biopharmaceutics Classification System (BCS), in vitro dissolution testing, risk-based assessment, and bioavailability (BA)/bioequivalence (BE) assessments in addition to translational modeling strategies such as PBPK modeling to support drug product quality during development as well as for marketed products (FDA, 1997, 2017). More recently efforts to extend the application of PBPK to drug absorption processes have shown promise in guiding biopharmaceutic applications such as formulation development, setting design space, predicting food-effect, determining the impact of changes in gastric pH, and achieving biowaivers for scale up and post-approval changes (Wu et al., 2021). In this field of applications, PBPK modeling is often known as PBBM (physiologically based biopharmaceutic modeling), though the essential techniques for the development and validation of such models remain the same. In vitro dissolution testing for IR solid dosage forms can be used to evaluate lot-to-lot differences in the release characteristics of drug product, guide formulation development, and ensure product quality (FDA, 1995). Development of a discriminatory dissolution method and establishing relevant acceptance criteria are important aspects of this strategy for quality control. Coupled with clinically verified PBPK/PBBM models, in vitro dissolution data can be used to prospectively predict the performance of lots not tested clinically and can be used to set dissolution acceptance criteria.

Elagolix has high aqueous solubility and low-to-moderate in vitro permeability. It is also rapidly absorbed in the gastrointestinal tract with time to observed maximum plasma concentration (T_{max}) of approximately 1 h, and food has no clinically meaningful impact on the efficacy of elagolix (Shebley et al., 2020). The elagolix commercial drug product for endometriosis is supplied as either a 150 mg or 200 mg tablet (AbbVie, 2018). The dissolution specifications for the elagolix 200 mg tablets in the elagolix new drug application (FDA, 2018a) were set and justified based on the physico-chemical properties of the drug substance as well as other release and stability data for available tablet batches. Statistical analysis of the dissolution data and its variability indicated that, based on characteristics of the drug substance, a wider dissolution acceptance criterion could still result in acceptable clinical performance of the drug

product within specification and without risk of dissolution test failure. This work describes how in vitro dissolution testing was coupled with PBPK modeling to justify wider dissolution acceptance criteria. A PBPK model for elagolix was developed to mechanistically capture all of the known disposition mechanisms of elagolix (i.e. quantify the interplay between metabolism by CYP3A, hepatic uptake by OATP1B1, and efflux by P-gp), and to support drug-drug interaction (DDI) dosing recommendations for the co-administration of elagolix with other drugs such as midazolam (CYP3A substrate) and digoxin (P-gp substrate) (Chiney et al., 2020). The objectives of this work were to use a model-based approach to assess the impact of dissolution profile on elagolix exposures and provide evidence to support the expansion of dissolution specifications that would still ensure bioequivalent elagolix exposures for all the batches released in the market.

2 | MATERIALS AND METHODS

2.1 | In vitro dissolution

In vitro dissolution data (mean of 12 units) was obtained using the proposed commercial dissolution method (USP apparatus II (paddle), 50 RPM, 900 mL of 0.05 M sodium phosphate buffer at pH 6.8). Batches of elagolix IR tablets used in the Phase 3 clinical trials were studied using the above method. This method was developed because these conditions provided maximum discriminating power to detect differences among formulations. The medium in the vessel was kept at 37°C. For generating the dissolution profiles, the sample was taken from the vessel with an automatic sampling system equipped with a membrane filter (0.45 μm pore size) at intervals of 5, 10, 15, 20, 30, 45, and 60 min. The dissolution tests were performed using a USP apparatus system: Agilent 708-DS dissolution apparatus equipped with an 8000 dissolution sampling station. The analytical finish was conducted using an Agilent 1100 series HPLC system. The dissolution data for the clinical batches did not show any meaningful differences compared to the stability and commercial batches; thus, data from clinical and commercial batches were used in this analysis. Some of the clinical batches were re-tested to obtain dissolution profiles with a higher density of sampling intervals.

2.2 | In vivo studies

In vivo data from two bioequivalence studies (denoted by Study 1 & Study 2 in this article) were used in this work for the purpose of model validation. Study 1 was a Phase 1, single dose, randomized, open-label bioequivalence study conducted according to a 4-period crossover design in 23 healthy adult premenopausal females (FDA, 2018b). This BE study bridged the 200 mg tablet of the elagolix Phase 3 formulation to the reference elagolix 200 mg tablet. Study 2 (FDA, 2018b; Shebley et al., 2020) was a Phase 1, single dose, randomized, open-label bioequivalence study conducted

according to a 3-period crossover design in 54 healthy adult pre-menopausal females. It was a pivotal bioequivalence study to bridge the commercial 200 mg elagolix formulation to the reference elagolix 200 mg tablets (FDA, 2018b). Table 1 shows a summary of the two trials used in this work. The bioequivalence trials were selected to assess model validation using both Phase 3 and commercial 200 mg tablets of elagolix.

2.3 | PBPK model development

Figure 1 shows the overall strategy that was used for the PBPK model-based analysis in this work. A prior full PBPK model for elagolix was developed using Simcyp® (V15.0.86.0, Sheffield, UK) (Chiney et al., 2020). The model was based on physico-chemical parameters, in vitro ADME information, and clinical data from elagolix single ascending dose, multiple ascending doses, and DDI studies. The absorption of elagolix was modeled using the advanced dissolution absorption and metabolism (ADAM) model in Simcyp (Jamei et al., 2009) which represents a mechanistic description of the gastrointestinal physiology. Kinetic processes in drug absorption are reflected in the PBPK model such as drug release from the formulation, transit of the solid drug, dissolution into gastrointestinal fluid, and absorption of the drug across the epithelium. The interplay between physiologic factors such as gastric emptying time, gastrointestinal transit time, fluid turnover, blood flow, drug metabolism enzymes and transporters are considered. The previously developed and published elagolix PBPK model (Chiney et al., 2020) considered elagolix as a solution due to its moderately high solubility (0.89 mg/mL) which would result in a 200 mg dose taken with 200 mL of water being fully dissolved in the GI tract. In this work, the model was modified to reflect input of a solid dosage form by directly entering the in vitro mean % release (N = 12) data (shown in Figure 2) for two manufacturing lots that were evaluated in the relative bioavailability clinical studies. In vitro dissolution data, as a function of time for elagolix manufacturing lots that were tested clinically, were used as direct input into the PBPK model and the formulation was represented as an IR solid formulation. No other modifications were made to the disposition or distribution parameters in the original PBPK model, to enable examination of the impact of different dissolution rates on the absorption profile of elagolix. The published PBPK model (Chiney et al., 2020) which was developed in Simcyp V15, was

TABLE 1 Summary of elagolix single dose clinical studies under fasting conditions used in this work

Brief description	Dose (mg)	N	Age (year)	% Female	Formulation
Study 1—relative bioavailability study of the elagolix Phase 3 formulation	200	23	35.4 ± 6.1 (24–46)	100	Elagolix Phase 3 formulation and elagolix reference tablet
Study 2—relative bioavailability study of the elagolix commercial formulation	200	54	34.1 ± 8.6 (20–50)	100	Elagolix commercial formulation and elagolix reference tablet

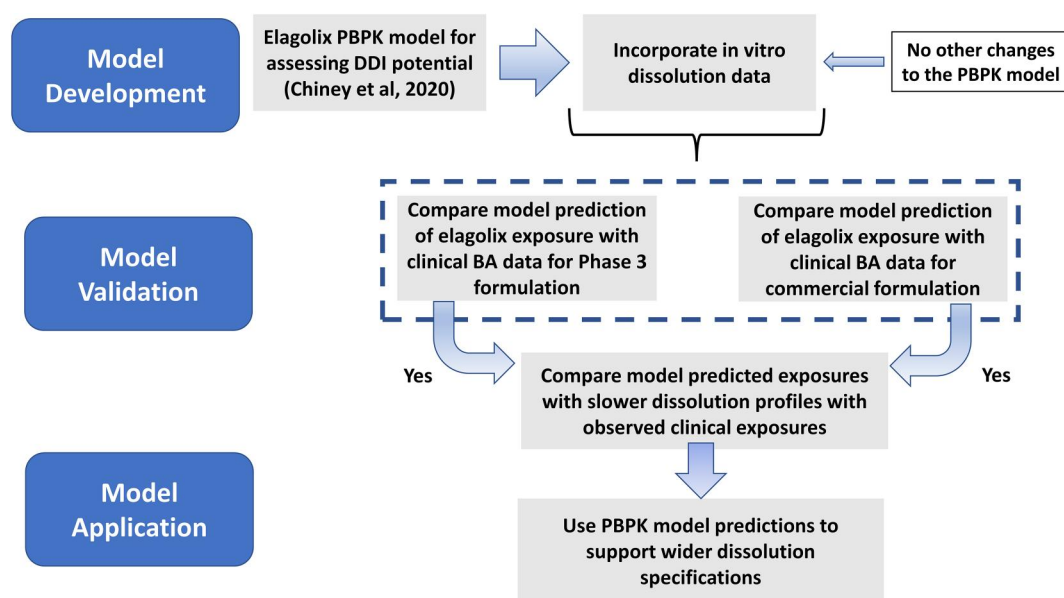*Note*: Age presented as mean ± SD (range).

FIGURE 1 Schematic showing PBPK model development, verification, and application for the demonstration of the impact of wider dissolution specifications for elagolix

transferred to a more recent software version (Simcyp V16) in order to leverage the improvements and updates made in the absorption module of the software particularly in relation to entero-hepatic recirculation (FDA, 2018b). Elagolix is a substrate of P-gp transporter-mediated biliary efflux and thus entero-hepatic recirculation and reabsorption from the GI tract might affect the overall fraction of elagolix absorbed. A model version control was conducted to compare the two versions of software, and this is summarized in Table 2.

2.4 | PBPK model validation

PBPK model simulations were performed using the default 'Sim-Healthy Volunteers' implemented as a population representative (Howgate et al., 2006). The study design (dose, route of administration, and study duration) used for simulations were matched to the clinical study design for each study as shown in Table 1. Model-predicted C_{max}, T_{max} and AUC_{inf} were compared to
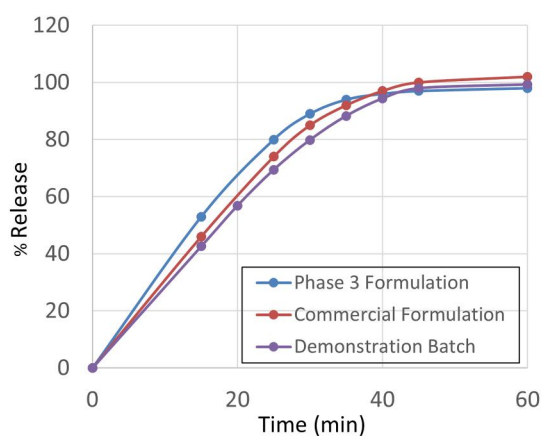
FIGURE 2 In vitro dissolution data (mean of 12 units) from the proposed commercial dissolution method for elagolix IR formulations

observed elagolix exposures. The pre-specified acceptance criteria to evaluate the predictive performance of the model was set to the bioequivalence boundaries of 0.80–1.25, for the ratio of predicted to observed exposure. The model prediction acceptance criteria are shown below:

$$0.80 \leq \frac{Predicted\ PK\ parameter}{Observed\ PK\ parameter} \leq 1.25$$

Various acceptance criteria (25%–100% prediction error) are widely used for the evaluation of model prediction accuracy. In this case stricter acceptance criteria were selected based on the bioequivalence criteria to assess model appropriateness for detecting potential non-BE exposures in vivo. In addition, a visual inspection of the overlay of the population representative and the observed elagolix plasma concentration versus time data was performed to ensure acceptable model performance. The ability of the PBPK model to predict the observed plasma exposure was evaluated after incorporation of the in vitro dissolution data, to predict elagolix exposures at 200 mg dose under fasting conditions. This evaluation counts as model validation (based on accepted PBPK model best practices) (Shebley et al., 2018), since no model parameters were optimized or changed from the original PBPK model and the evaluation was done with external in vivo data (not used for model calibration).

2.5 | PBPK model application

After validation of the PBPK model, the elagolix PBPK model was used to predict elagolix exposures (C_{max} and AUC_{inf}) for tablet lots that exhibited a slower dissolution profile and define a dissolution threshold that may result in exposures outside of the bioequivalence limits. Model predictions were compared to the observed exposures using bioequivalence limits of 0.80–1.25 to assess the significance of slower dissolution rates. Model simulations were conducted using in vitro dissolution profile from a simulated batch (Figure 3) which was generated for this purpose. Simulations were also conducted using

TABLE 2 Software version control: comparison of model-predicted pharmacokinetic parameters of elagolix in Simcyp V16 versus Simcyp V15

Pharmacokinetic parameter (units)		150 mg QD			200 mg BID		
		Simcyp V15[a]	Simcyp V16	%Change	Simcyp V15[a]	Simcyp V16	% Change
Day 1							
C_{max}	(ng/mL)	524	516	1.5	779	691	11
T_{max}	(hr)	0.95	0.95	0.0	0.95	0.95	0.0
AUC_{τ}	(ng•hr/mL)	1321	1313	0.0	1756	1701	3.1
Day 21							
C_{max}	(ng/mL)	524	463	12	680	616	9.4
AUC_{τ}	(ng•hr/mL)	1213	1199	1.2	1518	1478	2.6

Note: AUC_{τ} where τ (tau) is the dosing interval (i.e., 12 h for BID, 24 h for QD).
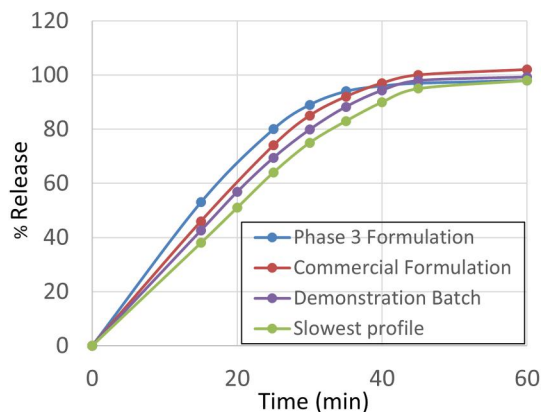
[a]Chiney et al., 2020.

FIGURE 3 Observed (in vitro) dissolution rates for different elagolix formulations, including the slowest observed dissolution profile

the slowest dissolution profile (Figure 3) from the simulated batch to explore the impact of dissolution differences on elagolix exposures. To evaluate the impact of wider dissolution specifications for the elagolix tablet on in vivo exposure, a sensitivity analysis was conducted to investigate the impact of dissolution rates on the predicted in vivo PK of elagolix. For the sensitivity analysis, hypothetical dissolution profiles were generated which were slower or faster than the dissolution profile for the commercial elagolix tablet. A total of eight hypothetical scenarios were simulated which corresponded to both slower (10%, 20%, 30%, 40% 50% & 75% slower) and faster (20%, 50% faster) dissolution rates compared to that observed for the commercial 200 mg tablet (reference formulation). To generate the hypothetical dissolution profiles, the time values (in minutes) were scaled by the appropriate percentage, using the formula: $T_{i,x} = T_i(1 + x/100)$, where $T_{i,x}$ is the ith time point (in minutes) for the hypothetical profile x% slower than the reference profile and T_i is the ith time point for the reference profile. Similarly, the time points for the faster hypothetical profiles were generated using $T_{i,x} = T_i(1 - x/100)$.

This method ensured that the hypothetical profiles maintained the overall shape of the dissolution kinetic profile while producing progressively slower profiles. These hypothetical profiles define a wider in vitro dissolution specification that will ensure acceptance of majority of manufacturing lots using the dissolution method. In addition, the impact of the slowest dissolving lots was studied using the slowest dissolution profile from the demonstration batch to simulate in vivo exposures as a representation of a worst-case scenario.

3 | RESULTS

3.1 | In vitro dissolution results

Figure 2 shows the mean in vitro dissolution profiles for the elagolix tablets (elagolix Phase 3 formulation) used for the Phase 3 clinical

trials and the tablets of elagolix commercial formulation. Also presented in Figure 2, are the dissolution data for a simulated batch of elagolix tablets which was generated to study the impact of wider dissolution specifications. The simulated batch was not used in any of the clinical trials of elagolix but was generated to bracket the proposed wider dissolution specifications.

3.2 | PBPK model development and validation

Simulation results from the PBPK model in Simcyp V16 were compared to that from Simcyp V15 (FDA, 2018b). This software version comparison revealed a maximum of 12% difference in the predicted PK for the 150 mg QD and 200 mg BID doses of elagolix between the two software versions (Table 2). Consequently, Simcyp V16 was used in all the modeling results presented in this work. The ability of the PBPK model to predict the exposures of elagolix, following incorporation of in vitro dissolution data (Figure 2) in the mechanistic ADAM model, was evaluated by comparing the model-predicted elagolix exposures to those observed for the 200 mg elagolix tablets used in pivotal Phase 3 clinical trials and 200 mg commercial elagolix tablets (summarized in Table 3). For the Phase 3 formulation, the model-predicted mean C_{max} and AUC_{inf} of 743 ng/mL and 1788 ng-h/mL, were in good agreement with the observed mean C_{max} and AUC_{inf} of 789 ng/mL and 2069 ng-h/mL, respectively (FDA, 2018b). For the commercial formulation, the model-predicted mean C_{max} and AUC_{inf} of 768 ng/mL and 1830 ng-h/mL, were also in good agreement with the observed mean C_{max} and AUC_{inf} of 734 ng/mL and 1908 ng-h/mL, respectively (Shebley et al., 2020). For both formulations, the ratio of predicted PK parameters to observed PK parameters was between 0.80 and 1.25 (Table 3). In addition to the comparison of PK parameters, a visual predictive check of the predicted and observed elagolix plasma concentration-time profiles for the commercial formulation (Figure 4a,b) indicated close agreement between the model predictions and the overall shape of the elagolix pharmacokinetic profiles. This represents external model validation since the model predictions were able to capture clinical data from studies which were not used for model development or model verification. In line with PBPK modeling best practices (Shebley et al., 2018), external validation of PBPK models provides increased confidence in their use for applications which were not initially intended for the model.

Figure 5 shows a comparison of the pooled clinical data from two studies (Study 1 and Study 2) with elagolix and model prediction with dissolution kinetics of the simulated batch. The comparison provides visual confirmation that the simulated batch, despite having different dissolution kinetics, results in predicted in vivo PK profiles which are virtually superimposed on the observed clinical PK profiles. The dissolution profile for the elagolix simulated batch resulted in a model-predicted mean C_{max} and AUC_{inf} of 758 ng/mL and 1805 ng-h/mL, respectively, which were no more than 13% lower than observed elagolix exposures (Table 3). The predicted

TABLE 3 PBPK model-predicted and observed (mean ± SD) elagolix exposures following a single 200 mg dose under fasting conditions with input from observed dissolution profiles corresponding to clinical batches (elagolix Phase 3 formulation and elagolix commercial formulation), the demonstration batch and slowest observed in vitro dissolution profile

Dissolution input[a]	PK parameter	Clinical scenario with Phase 3 formulation			Clinical scenario with commercial formulation		
		Predicted	Observed (study 1)	Ratio (Pred/Obs)	Predicted	Observed (study 2)	Ratio (Pred/Obs)
In vitro dissolution	C_{max} (ng/mL)	743	789	0.94	768	734	1.05
	T_{max} (hr)	1.02	1.0	1.02	1.02	1.0[b]	1.02
	AUC_{inf} (ng-hr/mL)	1788	2069	0.86	1830	1908	0.96
Dissolution profile of demonstration batch	C_{max} (ng/mL)	758	789	0.96	758	734	1.03
	T_{max} (hr)[b]	1.05	1.0	1.05	1.05	1.0	1.05
	AUC_{inf} (ng-hr/mL)	1805	2069	0.87	1805	1908	0.95
Slowest observed dissolution profile	C_{max} (ng/mL)	742	789	0.94	742	734	1.01
	T_{max} (hr)[b]	1.07	1.0	1.07	1.07	1.0	1.07
	AUC_{inf} (ng-hr/mL)	1775	2069	0.86	1775	1908	0.93
Slowest hypothetical dissolution profile	C_{max} (ng/mL)	711	789	0.90	711	734	0.97
	T_{max} (hr)[b]	1.32	1.0	1.32	1.32	1.0	1.32
	AUC_{inf} (ng-hr/mL)	1787	2069	0.86	1787	1908	0.94

Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; C_{max}, observed maximum concentration; obs, observed; pred, predicted; SD, standard deviation; T_{max}, time of observed maximum concentration.

[a]Simulation results based on input of different dissolution profiles to describe the absorption of elagolix.

[b]Median.

plasma concentration-time profile from this slower dissolution rate suggested that no change would be expected in the plasma exposure in comparison to the observed data from the two clinical studies (Figure 5). The PBPK model was also used to predict the exposure of elagolix under the slowest observed profile from the repeated measurements performed with the commercial formulation. The model-predicted exposure metrics C_{max} and AUC_{inf} for this dissolution profile, were also bioequivalent to exposures from two independent clinical studies (Table 3).

3.3 | Sensitivity analysis

A local sensitivity analysis was conducted on the dissolution rate of elagolix to evaluate its impact on the exposure of elagolix (Figure 6). Sensitivity of dissolution rates were evaluated by using the observed in vitro dissolution profiles for the elagolix commercial formulation to generate hypothetical dissolution profiles which were slower than the observed dissolution rates. For the elagolix 200 mg tablet using a hypothetical 75% slower in vitro dissolution (Figure 6), the PBPK model-predicted C_{max}, T_{max}, and AUC_{inf} were 711 ng/mL, 1.32 h, and 1787 ng-h/mL (Table 3). This slower hypothetical elagolix in vitro dissolution profile was predicted to delay T_{max} by 0.3 h and reduce C_{max} by 7% and AUC_{inf} by 2%. These hypothetical slower dissolution profiles (Figure 6) would lead to a less strict dissolution specification, but still ensure bioequivalent exposures in patients taking the elagolix 200 mg IR tablet.

4 | DISCUSSION

The simulation work presented in this paper shows that PBPK modeling can be a useful tool in the area of biopharmaceutics as it can allow decision making on in vivo consequences using in vitro data. The ability to use a base PBPK model that was used to predict DDIs was demonstrated by incorporating the in vitro dissolution profiles as an input into the model and predicting the corresponding plasma concentration-time profiles. The predictive power of the corresponding model was demonstrated by the model's ability to predict the plasma concentration-time profiles for both the clinical pivotal Phase 3 formulation as well as the commercial formulation with a prediction error of less than 25% for both C_{max} and AUC.

The use of physiologically based models will alleviate regulatory burden by decreasing the number of in vivo studies needed to approve and maintain a drug product on the market. The ability to determine an in vivo outcome from in vitro dissolution data facilitates biowaivers and bioequivalence assessments using virtual bioequivalence studies (FDA, 2020). Establishing a link between the in vitro release characteristics and the in vivo bioavailability would allow the impact of differences in release characteristics on the plasma concentration profile of the drug to be assessed and consequently establish clinically relevant acceptance criteria that will ensure therapeutic benefit to the patient despite inter- and intra-lot variability. Regulatory recommendations (FDA, 2018c) provide guidance for the setting of dissolution specifications of oral dosage forms with API of high solubility. For compounds which
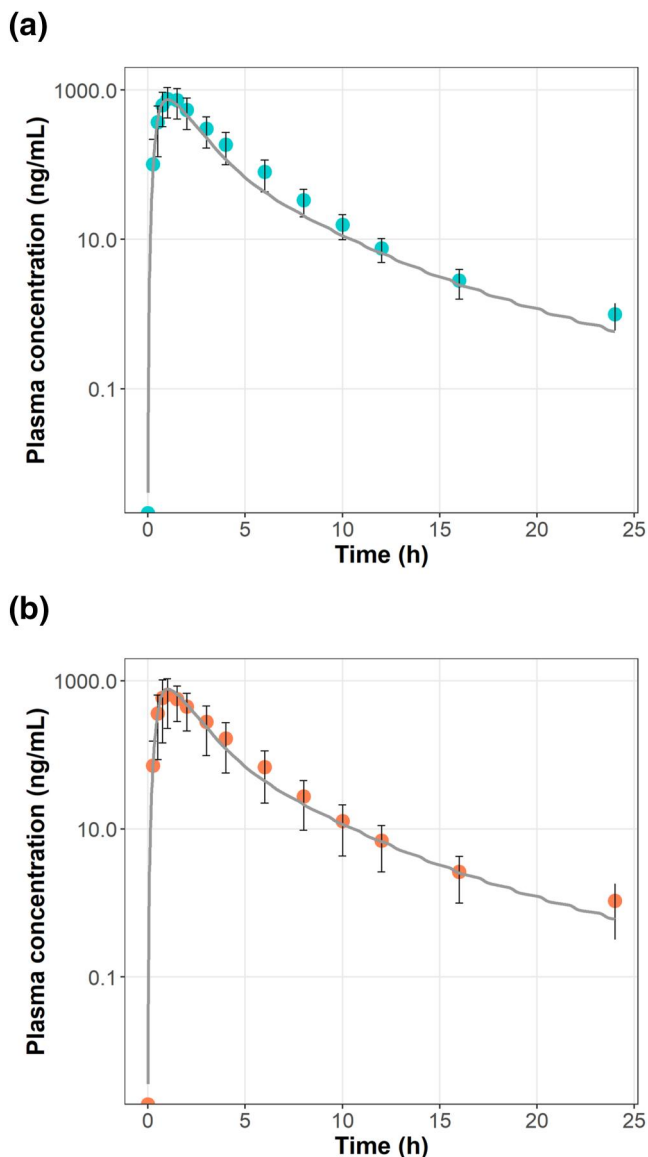
(a)

(b)

FIGURE 4 Comparison of PBPK model-predicted elagolix plasma concentration (solid line) after a single 200 mg dose of reference elagolix tablet with clinical data from a relative BA study with the (a) elagolix Phase 3 formulation and (b) the commercial elagolix formulation. Dots represent the mean and error bars, the standard deviations of clinical observations

FIGURE 5 Comparison of PBPK model-predicted elagolix plasma concentration (solid line) after a single 200 mg dose of elagolix tablet using the dissolution profile for the demonstration batch with pooled clinical data from two relative BA studies shown in Table 1. Dots represent the mean and error bars, the standard deviations of clinical observations

meet the criteria of good solubility, a suitable dissolution criterion can be set using in vitro dissolution studies without the need for in silico modeling. However, in that case the compound has to demonstrate good solubility in the entire pH range of 1–6.8 which was not the case for elagolix. Elagolix has moderate to low permeability, is a substrate for P-gp mediated efflux in the GI tract, undergoes entero-hepatic recirculation due to biliary excretion, and is not considered a rapidly dissolving drug. Therefore, supplementing the comparative in vitro dissolution data with mechanistic PBPK modeling was essential to demonstrate that the rate limiting step in elagolix absorption is permeability and not dissolution. Consistent with this approach, the draft guidance from the US FDA on the use
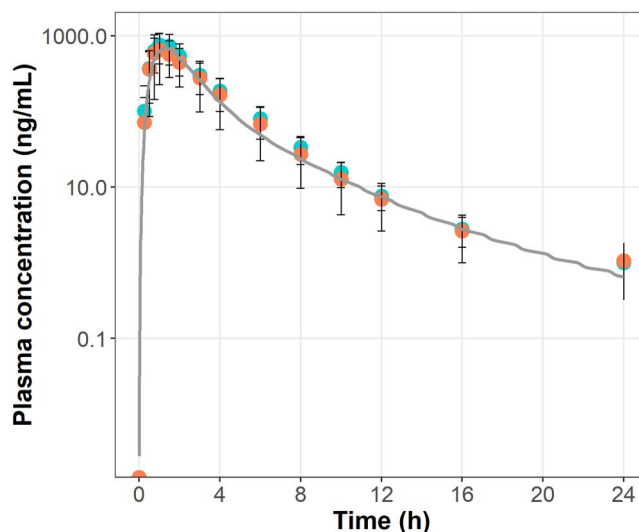
of PBPK modeling (FDA, 2020) to address biopharmaceutics applications, summarizes cases where such in silico modeling can be appropriately used.

To build a successful model, a thorough understanding of the physico-chemical characteristics of the drug, the formulation attributes that are critical to the in vivo bioavailability of the drug, and the in vivo ADME characteristics of the drug moiety are required. Likewise, a sensitive and discriminating dissolution method is needed to identify differences in release characteristics among the different formulations. One of the assumptions in this analysis was that in vitro dissolution was incorporated directly into a PBPK model. This implies that the in vitro dissolution rate was similar to the in vivo dissolution rate and that an identical dissolution rate was applied to all the segments of the gastrointestinal tract. Incorporation of in vitro dissolution data using the proposed method from an USP apparatus into a PBPK model can be approached in different ways, such as fitting a Weibull function of dissolution kinetics, fitting a Weibull function for release kinetics, or using the SIVA (Simcyp InVitro Analysis) toolkit (Pathak et al., 2019). The last method involves optimization of a relevant dissolution specific parameter (such as disintegration rate or dissolution rate scalar) based on the USP dissolution data. This is similar to the method involving calibration of the Z-factor used in GastroPlus® (Li et al., 2019). Each of these methods enables the description of various dissolution processes and mechanisms to a different degree and might be important for compounds with low solubility and permeability, especially where complex mechanisms can be attributed to its dissolution, precipitation, and absorption. Utilizing in vitro dissolution into PBPK models has been demonstrated using various approaches and there have been efforts
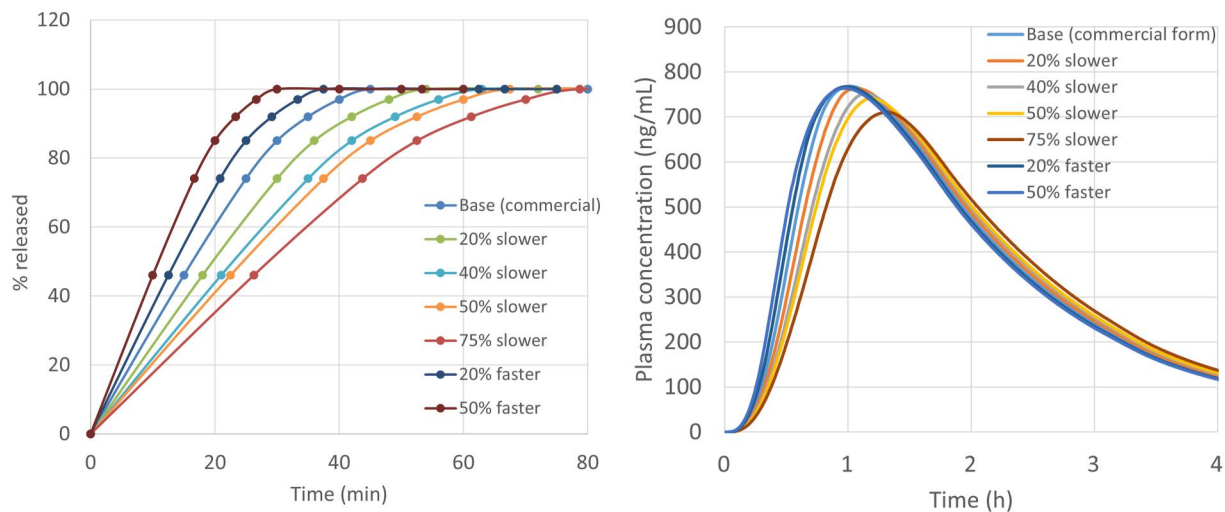
FIGURE 6 Sensitivity analysis of dissolution rates on the pharmacokinetics of elagolix

across industry, academia, and regulatory agencies to harmonize these methods (McAllister et al., 2019). It has been concluded that each method has its merits and limitations and there cannot be one prescriptive method to achieve this (McAllister et al., 2019). The choice of complexity of the absorption module used in the PBPK model would depend on the nature of the compound. For BCS 2 or 4 compounds, it is recommended to use a fully mechanistic absorption model (Mistry et al., 2016) (e.g ADAM model in Simcyp® or ACAT model in GastroPlus®) to capture the effect of differential pH solubility, precipitation, supersaturation, and the interplay of solubility and permeability. Direct input of a dissolution or release profile for a formulation is often a viable method (particularly for BCS I or III compounds) in cases where solubility is not a limiting factor in drug absorption (Loisios-Konstantinidis et al., 2020). The dissolution or release profile can also be input using predefined mathematical functions (e,g. a Weibull function). Often in vitro dissolution profiles are used to define a particular critical material attribute (CMA) or a critical process parameter (CPP) and the impact of these CMA or CPP on in vivo drug pharmacokinetics is desired. This approach can facilitate the incorporation of clinical relevance in product quality from initial development through marketing approval to lifecycle management and thereby minimize the need to conduct additional in vivo BE studies, leading to reducing cost in product development and supporting regulatory decisions. In these cases, the appropriate CPP or CMA should be included in a mechanistic fashion within the absorption module of the PBPK model. In this case, a simple approach was considered because elagolix is limited by permeability and not by dissolution rate; thus, the inclusion of more complexities for capturing dissolution was not the focus of this analysis. This was further supported by the simulation results that various in vitro dissolution rates did not significantly affect the simulated in vivo outcome.

5 | CONCLUSIONS

The PBPK model that was developed by incorporating dissolution data as an input into the model was predictive of the in vivo performance of elagolix as it was able to predict the plasma levels of both the pivotal elagolix Phase 3 formulation and the proposed elagolix commercial formulation with prediction errors of less than 25% for C_{max} and AUC. The developed model also showed that a decrease of up to 30% in the dissolution rate of elagolix would still result in plasma concentration-time profiles that are deemed to be bioequivalent to the reference commercial formulation. This model was successfully submitted to the regulatory agency in support of widening the dissolution acceptance criteria for elagolix (FDA, 2018b). The regulatory review concluded that "overall, the submitted PBPK model is acceptable. This PBPK model-predicted a similar elagolix exposure for batches with slower dissolution rate compared to the clinical batches." The newly approved acceptance criteria provided a wider manufacturing space without compromising the clinical benefit to the patient as it allowed the approval of lots with up to 30% slower release compared to the elagolix commercial formulation but were still deemed to be bioequivalent to the reference formulation.

CONFLICT OF INTEREST

INFORMED CONSENT STATEMENT

This work did not use any original clinical data only referenced published data.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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