Physiologically Based Pharmacokinetic Modeling for Substitutability Analysis of Venlafaxine Hydrochloride Extended-Release Formulations Using Different Release Mechanisms: Osmotic Pump versus Openable Matrix

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Abstract

An FDA-approved generic oral product of venlafaxine HCl ER tablets has employed a release mechanism based on an openable matrix, which is different from the push-pull osmotic pump system of its reference listed drug. In an extreme case, a delay in the bursting of the openable matrix may be considered a product failure mode that alters the intended profile of systemic exposure. A PBPK absorption model was established and verified to simulate the PK profiles after a single-dose oral administration of ER venlafaxine HCl tablets based on an osmotic pump or openable matrix design. This model adequately predicted the observed mean PK metrics human with less than 20% difference between the predicted and observed data. Based on the modeling and simulation results, C_{max} and AUC_t of the venlafaxine openable matrix tablets were entirely within the bioequivalence acceptance limits (*i.e.* 80% to 125%) when the lag time varied from 0 to 4 hrs and using drug release profiles under most dissolution conditions. The results indicated that a bioinequivalence risk is minimal for a delayed onset of drug release from the approved generic venlafaxine HCl ER tablets with an openable matrix design, supporting its substitutability to the reference product.

Keywords: Physiologically based pharmacokinetic modelling; osmotic pumps; controlled release; oral drug delivery; bioequivalence

1. Introduction

The mechanisms used to achieve a controlled release in oral drug delivery systems are based on diverse and complex principles such as dissolution, diffusion, osmosis, swelling, and erosion. The development of push-pull osmotic pump systems and diffusion- or dissolution-controlled monolithic devices or reservoir systems has been widely applied to many extended-release (ER) oral dosage forms¹. For the matrix-based ER formulations of Biopharmaceutics Classification System (BCS) Class I (*i.e.* high solubility, high permeability) drugs, common technical challenges include reducing the initial burst release, minimizing dose dumping, and achieving a constant release profile^{2,3}. To overcome the issue of initial burst release³⁻⁷, one promising approach is to delay the onset of drug release by employing an openable layer in a formulation design known as a “wrap matrix” or “openable matrix”⁸, which can be found in several generic oral ER drug products such as venlafaxine hydrochloride (HCl) and levetiracetam⁹.

As illustrated in Figures 1A and 1B, the drug release from an osmotic pump is driven by the gradual swelling of a push layer upon ingress of the aqueous medium, whereas the swelling of an openable layer bursts open the wrap matrix, exposing the drug-release surface to the dissolution medium. For an openable matrix design, the core bi-layer tablet is coated with functional porous materials, using a mixture of insoluble (*e.g.* ethylcellulose) and soluble pore-forming excipients. In contrast to an osmotic pump design which has been thoroughly reviewed^{10,11}, there have been relatively few investigations on the formulation-associated risk of an openable matrix which contains multiple compartments coated by a semi-permeable membrane.

Although ER tablets using the wrap matrix technology may accommodate various design modifications for different pharmaceutical requirements (Figure 1D), the drug release is governed by the same principle in which the swelling of the openable layer opens the matrix to expose the surface of the

drug layer, facilitating a zero-order release due to a constant surface area. It is noteworthy that the time required to open the tablet counteracts the potential burst effect as commonly encountered in matrix-based ER tablets of freely water-soluble drugs as demonstrated in the hypothetical dissolution curves of Figure 1C. In this case, the onset of matrix breakage (*i.e.* a lag time of drug release) depends on the composition and thickness of functional coating of the openable layer and other factors such as pharmaceutical quality of coating film and a potential food effect. For instance, controlling a precise coating thickness of an openable matrix often poses technical challenges during the manufacturing process. Moreover, the effects of the openable layer composition and the *in vivo* micro-environment in the GI tract on the resulting breakage time of openable matrix tablets are not well understood.

At times, the generic products are designed using different release mechanisms from the reference listed drug (RLD) products. For example, a generic version of venlafaxine HCl ER tablets manufactured by Sun Pharmaceutical Industries Ltd. (Sun) adopted the “openable matrix” design⁸ while the RLD is designed as an osmotic pump¹². Venlafaxine is a serotonin and norepinephrine reuptake inhibitor which has been formulated as IR and ER dosage forms for the treatment of depression among other neurological disorders¹³. Considering that the manufacturing variability of functional coating may affect the lag time of drug release from an openable matrix, setting suitable quality specifications to ensure consistent therapeutic performance is often under dispute. Hence, there is an imminent need of assessing the associated risk of the ER drug products using an openable matrix in order to establish clinically relevant specifications for quality control and to ensure consistent clinical performance.

Currently, there are two reference listed drug (RLD) products of oral ER venlafaxine hydrochloride based on diffusion-controlled coated beads encapsulated in capsules (Effexor XR by Wyeth Pharmaceuticals Inc. (now Pfizer), approved in 1997) and osmotic pump tablets (venlafaxine HCl ER tablets by Osmotica Pharmaceutical Corp., approved in 2008) on the U.S. market. In 2005, the

Food and Drug Administration (FDA) approved a suitability petition submitted by Sun, requesting to develop a venlafaxine hydrochloride ER tablet dosage form using Effexor XR capsules as its RLD¹⁴. In this case, Sun adopted a formulation design using an openable matrix to achieve a sustained release of venlafaxine as previously described. After Sun has submitted its abbreviated new drug application (ANDA), Osmotica appealed that all pending ANDAs including Sun's application for venlafaxine hydrochloride ER tablets should cite Osmotica's drug product as the designated RLD via a citizen petition in 2008¹⁵. Given the regulatory, legal, and scientific considerations, the Agency determined that Sun's pending ANDA must be withdrawn and a new ANDA should be submitted to reference Osmotica's venlafaxine hydrochloride ER tablets¹⁶. Sun's generic venlafaxine hydrochloride ER tablets were eventually approved in August 2010, based on its demonstrated bioequivalence to Osmotica's product.

Physiologically based absorption modeling and simulation has been demonstrated to be powerful tools to assess *in vivo* performance and bioequivalence¹⁷ and has been applied in generic drug post-marketing surveillance and bioequivalence evaluation¹⁸⁻²⁰. Using venlafaxine HCl as a model drug, the objective is to conduct physiologically based pharmacokinetic (PBPK) analysis to investigate the effect of different drug release profiles of an openable matrix on the resulting *in vivo* pharmacokinetic (PK) profiles compared with those of the RLD product using an osmotic pump. Based on the validated PBPK model for venlafaxine HCl ER products, simulations will be employed to evaluate the associated risks of various lag times and release profiles of an openable matrix design for oral ER dosage forms. The study results will not only confirm a minimal risk related to the lag-time effect of the generic version of venlafaxine HCl ER tablets based on an openable matrix, but also shed new lights on the risk assessment for this category of ER drug products.

2. Methods

2.1 Modeling and simulation strategy

The development of the PBPK models, which simulate the plasma concentrations of venlafaxine and its major active metabolite, o-desmethylvenlafaxine (ODV), is based on the previously described methodology^{18,19}. As illustrated in Figure 2, the modeling and simulation strategy begins with fitting compartmental models to the plasma concentration vs. time data following an IV administration of both venlafaxine and ODV to obtain the parameters describing the *in vivo* distribution, metabolism, and elimination kinetic processes. Next, the absorption models describing immediate-release (IR) venlafaxine HCl capsules (Effexor) were developed. Finally, the full physiologically based absorption models were established to predict the plasma concentrations of ER venlafaxine HCl capsules based on coated beads, tablets based on osmotic pumps, and tablets based on openable matrices.

2.2 Human *in vivo* pharmacokinetic data

Unless otherwise specified, all input parameters, dissolution profiles, and PK information were collected from multiple New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs). The observed clinical PK data of venlafaxine HCl ER capsules at 75 mg and osmotic pump ER tablets at 75 mg can be found in the clinical pharmacology biopharmaceutics reviews of the new drug application²¹. The individual PK data points for IV venlafaxine, venlafaxine HCl osmotic pump tablets, and venlafaxine HCl openable matrix tablets are not available to the public.

2.3 Model drug substances

Venlafaxine is freely soluble in water with a measured aqueous solubility of 534 mg/mL²² and is considered a BCS Class I drug^{23,24}. The major active metabolite (*i.e.* ODV), which is also freely soluble

in water²⁵, can be formed via cytochrome P450 (CYP) enzymes of CYP 2D6, 2C9, 2C19, and 3A4 in which the metabolic clearance through 2D6 is predominant²⁶⁻²⁹. The values for Vmax and Km used as a parameter input were obtained by *in vitro* and *in vivo* extrapolation²⁹. The scaling factors for liver Vmax were obtained through model optimization while the Km value was kept the same as obtained in liver microsomes. All the physiochemical properties are summarized in Table 1.

2.4 Pharmacokinetic models

The PK data after an IV infusion of both venlafaxine and ODV were fitted in a one-, two-, or three- compartment model with linear and non-linear elimination in the PKPlus™ module of GastroPlus™. The Hooke-and-Jeeves-Pattern-Search optimization and a unity weighting of the objective function were used to determine optimal compartmental model, clearance and distribution related parameters.

2.5 Absorption/Advanced Compartmental Absorption and Transit (ACAT) models

All the physiological parameters except those described below are model default values¹⁸. The conventional PK model from PKPlus™ module was re-optimized in the context of the Advanced Compartmental Absorption and Transit (ACAT) model built in GastroPlus™ (version 8.6 00034, Simulations Plus Inc. Lancaster, CA) in which the clearance parameters from PKPlus™ were replaced by Vmax and Km values for CYP 2D6, 2C9, 2C19, and 3A4. In addition, the effective human permeability (P_{eff}) was obtained by fitting the model against the PK data of IR venlafaxine HCl tablets. The “Opt log D Model SA/V6.1” option was selected for determining the absorption scale factor.

The inputted PK parameters were fixed throughout all simulation trials, except for clearance of venlafaxine because the values are estimated based on trials conducted in different populations. Renal

clearance was fixed in all models, considering its minimal role in drug elimination. The major route of clearance of venlafaxine was modeled by the gut and liver metabolism in which the individual values V_{max} and K_m for CYP 2D6, 2C9, 2C19, and 3A4 reported by Fogelman et al²⁹ were used to establish the ACAT model for IV and oral dosage forms. V_{max} values in liver were optimized by adjusting V_{max} scaling factor per study population. In addition, the default values of enzyme distributions and expression levels were used in GastroPlusTM.

Moreover, the dosage forms “IR: Tablet”, “CR: Dispersed”, and “Integral Tablet” were selected for immediate-release tablets, extended-release capsules, and extended-release tablets (including osmotic pumps and openable matrices), respectively, in GastroPlusTM. A Weibull function describing the observed *in vitro* dissolution profiles for each ER formulation was used as the input function of *in vitro* dissolution during the simulation. Various dissolution profiles were tested in the PBPK models in order to select an optimal dissolution profile that best predicts the PK data of ER dosage forms. The dissolution profile which gives the highest value of R^2 (coefficient of determination) was chosen to as the baseline value to predict the PK profiles, considering that R^2 indicates how well the simulation predicts the observed data. Since venlafaxine oral dosage forms should be administered with food according to the drug label¹³, the observed PK profiles used for modeling and simulation here were collected from PK studies in healthy volunteers under fed conditions. Hence, a customized human fed physiology was optimized in GastroPlusTM in which absorption scaling factors (ASFs) for caecum and ascending colon were set to be the same as default values of physiological parameters in the ilium. As such, this allows for an appropriate description of plasma concentrations to reflect the late-stage absorption from caecum and colon.

2.6 Parameter sensitivity analysis (PSA)

To assess the impact of critical and uncertain parameters on *in vivo* performance, PSA was performed by varying one parameter at a time while keeping all other model parameters constant at the same time. PK metrics were calculated from the simulated plasma concentration-time profiles. In this case, PSA results were evaluated by comparing the value of each PK metric (C_{max} or AUC_t) associated with a parameter value to that of the corresponding metric in the baseline simulation. In addition, a Three-dimensional (3-D) PSA was conducted to assess the effect of tablet-opening time (*i.e.* a lag time of drug release) with respect to the sensitivity of a range of other input parameters. In such a 3-D PSA, two parameters including the lag time (*e.g.* 0, 1, 2, 3, 4 hrs) and the parameters of interest (*i.e.* V_c, k₁₂, k₂₁, k₁₃, k₃₁, V_{max} (gut), K_m (gut), V_{max} (liver), K_m (liver), plasma unbound, blood plasma ratio, hepatic flow, stomach empty time, P_{eff}, and drug solubility) were simultaneously tested for their impact on the resulting PK metrics (C_{max} and AUC_t), while all other model parameters remained constant. This simulation tested the *in vivo* pharmacokinetics of an openable matrix tablet formulation (reflected in the lag time) in a wide range of populations (reflected in the physiological and PK parameters).

3. Results

3.1 Modeling and simulation of PK profiles after single-dose oral administration of IR and ER venlafaxine HCl formulations

Following the modeling and simulation steps illustrated in Figure 2, the observed and simulated PK profiles for drug products containing venlafaxine or o-desmethylvenlafaxine (ODV) are shown in Figure 3. The mean observed IV data for plasma concentrations of venlafaxine (10 mg) and ODV (50 mg)³² were separately fitted using PKPlusTM (Figures 3A and B). In this case, three- and two-compartmental models could adequately predict the mean PK profiles for venlafaxine and ODV, respectively. The simulated data for venlafaxine HCl IR tablets are not shown here.

Next, PK profiles were simulated for three oral ER dosage forms including ER capsules (Figure 3C), ER tablets based on an osmotic pump at 75 and 150 mg (Figures 3D and E) and an openable matrix at 150 mg (Figure 3F). Several *in vitro* dissolution profiles (Figure 4) under different dissolution conditions (Table 2) were tested for best fitting the observed PK profiles of venlafaxine ER tablets in clinical studies. In this case, profile No. 4 (Figure 4 and Table 2) using a two-stage dissolution method was eventually selected as the input *in vitro* dissolution data owing to an accurate prediction of observed clinical PK data as well as its physiological relevance. As can be seen in Figures 3D and E, the predicted PK profiles of venlafaxine HCl osmotic pump ER tablets at 150 mg are fairly consistent with those of the observed PK data, using both the dissolution profile No. 4 and the metabolism and elimination kinetics based on the IV infusion data of venlafaxine and ODV.

Nevertheless, the predicted PK metrics (*i.e.* C_{max} and AUC_t) of the parent drug (venlafaxine) are within 20% of the observed mean C_{max} and AUC_t for all simulation (Figure 3). In addition, the general trend of venlafaxine PK profiles agrees well between the experimental data and model prediction as shown in Figures 3B, C, and D. The PK parameters for the metabolite ODV (*e.g.* volume

of distribution, clearance, k_{12} , k_{21}), estimated from the ODV IV infusion data, were kept constant without further optimization across all study populations. This may, in part, account for the underestimated C_{max} and AUC_t of ODV PK profiles as shown in Figures 3C and 3D. It is understood that the PK parameters describing the metabolism and elimination processes of ODV in a specific population may not be equivalent to those from a different population. Considering that the BE requirement criteria of venlafaxine HCl ER tablets is based on the parent drug, the underestimated PK metrics for ODV should not affect the current BE assessment.

3.2 Effect of in vivo dissolution profile on bioequivalence

As illustrated in Figure 4, the drug release profiles of venlafaxine HCl ER tablets based on an osmotic pump are similar under different dissolution conditions (No. 1 – 3 solid lines). In contrast, the release profiles of venlafaxine HCl ER tablets based on an openable matrix (No. 4 – No. 8 dashed lines in Figure 4) show a greater variation under different dissolution conditions (*e.g.* various medium pH and composition) compared to that of osmotic pumps. The findings are consistent with the fact that drug release from a tablet formulation based on an osmotic pump design into the GI lumen is independent of pH or gastric motility^{10,11}.

The dissolution profile of openable matrix venlafaxine HCl ER tablets using a two-stage dissolution method (acidic condition followed by the pH 6.8 medium) was chosen as the baseline input dissolution in the established PBPK models as it can reasonably predict the observed PK profiles (Figure 3F). To evaluate the influence of various dissolution profiles on bioequivalence, the PK metrics of the resulting simulated concentration-time curves using dissolution profiles under different conditions (Figure 4) were compared with those using the dissolution profile using the two-stage method (No. 4). As shown in Table 2, the simulated $\%C_{max}$ and $\%AUC_t$ using majority dissolution profiles fall within

the bioequivalence acceptance limits of 80% (lower) and 125% (upper), except for %C_{max} of the PK profile based on dissolution profile No. 5 (pH 1.2). However, this should not be a concern as it is unrealistic for the tablet to be exposed to such a low pH in the entire GI tract. Furthermore, two dissolution profiles plotted in black dots in Figure 4 represent the limits of 80% (lower) and 125% C_{max} compared to that of Sun's venlafaxine HCl ER tablets using the baseline dissolution profile (No. 4). To this end, the dissolution variations of the venlafaxine HCl ER tablets based on an openable matrix formulation have a minimal risk of bioinequivalence based on the established PBPK absorption model.

3.3 Effect of lag time on bioequivalence

To evaluate the impact of lag time of an openable layer on resulting simulated *in vivo* PK and bioequivalence, dissolution profiles with various lag times from 0 (baseline) to 4 hrs in a Weibull function (parameters derived from two stage dissolution profile with lag time set to zero) were generated as shown in Figure 5. After inputting the hypothetical dissolution profiles into the established PBPK models, the resulting virtual trial shows that the longer it takes the openable layer to burst open, the lower the C_{max} and AUC_t due to a delayed onset of *in vivo* drug release (see Figure 6). Nevertheless, when the lag time varies from 0 to 4 hrs, the simulated results show that the PK metrics (*i.e.* C_{max} and AUC_t) are entirely within the bioequivalence acceptance limits of 80% to 125%. In this regard, the impact of the opening time of openable matrix venlafaxine HCl ER tablets on bioequivalence should have a minimal risk. Moreover, 3-D sensitivity analyses using a lag time of 0, 1, 2, 3, and 4 hrs as the 1st dimension and various input parameters as the 2nd dimension were conducted to review the risks associated with the lag time in simulated PK profiles (Table 3). The predictions show no dramatic change of C_{max} and AUC_t within the range tested, indicating that the lag time of drug release for an

openable matrix is not considered a crucial factor affecting the resulting simulated bioequivalence for venlafaxine HCl ER tablets.

4. Discussion

Physiologically based pharmacokinetic (PBPK) modeling has been utilized to assess the food effect^{33,34}, drug-drug interaction³⁵⁻³⁷, inter-batch quality variation³⁸, *in vivo* performance in sub-population¹⁸, and bioequivalence for generic drug evaluation^{18,38,39}. In the current study, we extended such a PBPK approach to assess the *in vivo* PK and bioequivalence associated with formulation release mechanism change for oral ER venlafaxine HCl dosage forms based on an openable matrix design. The development of an absorption model for venlafaxine was built in GastroPlus™ to predict the PK and bioequivalence outcome of matrix-based ER tablets. As illustrated in Figure 3, the predicted PK profiles of venlafaxine were reasonably consistent with the observed data after IV infusion of venlafaxine (10 mg) and a single oral administration of ER capsules (75 mg) and ER tablets based on both osmotic pump (75 and 150 mg) and openable matrix (150 mg). Based on the model validation against the human PK data, the established absorption model was deemed sufficiently robust for the prediction of C_{max} (predicted/observed value, 98% – 116.2%) and AUC_t (predicted/observed value, 80.3% – 95.8%) for all the ER dosage forms. It is noteworthy that the systemic exposure was slightly underestimated probably due to the incomplete drug release as indicated by the *in vitro* dissolution profiles (Figure 4).

The current product-specific guidance on venlafaxine HCl ER oral dosage forms recommends ANDA applicants to conduct a 2-way crossover bioequivalence study at equivalent 150 mg base in healthy volunteers under fed conditions due to a safety concern of administration of venlafaxine under fasting condition^{40,41}. The simulation conditions specified in the *Methods* section are consistent with the current bioequivalence recommendations. In this case, Office of Generic Drugs recommends that both the parent drug (venlafaxine) and its metabolite (ODV) to be measured in plasma. The bioequivalence is recommended to be demonstrated based on the parent drug per the guidance. The similarity between the predicted and observed C_{max} and AUC_t for both venlafaxine and ODV (Figures 3B, C and D) shows

that the established physiologically based absorption models can properly simulate the observed clinical PK data of venlafaxine HCl ER oral drug products.

Subsequently, several PBPK simulations were conducted to critically assess the potential risks of varying *in vitro* dissolution profiles and lag times of drug release for the venlafaxine HCl ER tablets using an openable matrix design. In contrast to drug release from osmotic pump systems¹¹, factors such as gastric pH, food effect, and other physiological parameters (*e.g.* gastric emptying rate) may influence drug release from conventional controlled-release systems (*e.g.* coated beads and matrix). Thus, it is not surprising that the dissolution profiles of the venlafaxine ER openable matrix (No. 4 – No. 8 in Figure 4) under different dissolution conditions show a higher variability in comparison to those of the venlafaxine ER osmotic pumps (No. 1 – No. 3 in Figure 4). When inputting these dissolution data into the established PBPK model, the predicted PK parameters after administering a single dose of venlafaxine HCl ER tablets based on an openable matrix are shown to be bioequivalent to that using the two-stage dissolution method (*i.e.* the most physiologically relevant and accurately predicting the PK profiles), except for profile No. 5. In this case, venlafaxine initial release from an openable matrix tablet is slower in an acidic buffer (profile No. 5) than that of two-stage buffer (profile No. 4), resulting the simulated C_{max} (64.3%) falling outside of the bioequivalence requirement.

Moreover, PBPK simulations demonstrate that the lag time in which an openable matrix bursts open for the onset of venlafaxine release has a minimal effect on C_{max} and a relatively small effect on AUC_t (Figure 6) up to 4 hrs of lag time. In this instance, a delayed onset of drug release for venlafaxine HCl ER tablets does not significantly influence the C_{max} values for a single-dose bioequivalence study although the T_{max} is clearly delayed. Considering that the plasma concentrations do not return to the baseline for more than 40 hrs and the half-life is approximately 10.7 hrs for venlafaxine HCl ER tablets¹³, PBPK simulations predict that the systemic exposure of an openable matrix with 4-hr lag time

is approximately 80% of that with no lag time, conforming with the bioequivalence requirements for oral generic drug products. In addition, a minimal risk of bioinequivalence was confirmed in a 3-D sensitivity analysis using lag time (0-4 hrs) and various input parameters (Table 3). To this end, the modeling and simulation results have verified the delayed opening and various drug release profiles do not significantly alter the resulting PK metrics (C_{max} and AUC_t) of the generic version of venlafaxine HCl ER tablets based on an openable matrix. We also noticed that the delayed onset of drug release will shift the PK profiles (Figure 6) suggesting that trough concentration at a steady state could be changed. However, in the absence of evidence suggesting that the trough venlafaxine concentration of the PK profile in an exposure-response relationship is associated with efficacy or safety in patients with panic disorder, a multiple-dose simulation was therefore not performed.

A question that arises with establishing a PBPK absorption model is related to choosing an adequate *in vitro* drug release profile as a model dissolution input for *in vivo* drug release. In the current study, it is expected that the *in vitro* release profile of venlafaxine HCl ER tablets can be used to sufficiently predict the *in vivo* PK profiles, considering that venlafaxine HCl is a highly soluble and highly permeable drug with a moderate half-life. In the case of osmotic pump ER tablets, the dissolution conditions (*e.g.* medium pH) do not significantly affect the drug release during *in vitro* dissolution, leading to similar dissolution profiles under different conditions (Figure 4) generating a reasonable PK prediction (Figures 3D and E). In the case of openable matrix ER tablets, the selection of a bio-relevant *in vitro* dissolution profile as the model input is more complicated as drug release from an openable matrix is affected by a number of factors such as pH and residency time in each segment of the GI tract. For instance, Figure 4 shows that the dissolution rate of the openable matrix venlafaxine HCl ER tablets increases with an increasing pH of dissolution media. With this in mind, a dissolution condition based on the two-stage method (pH 1.5 followed by pH 6.8) was eventually selected because it is considered

the most *in vivo* relevant and predictive to model the PK profiles for openable matrix venlafaxine HCl ER tablets (Figure 3F). Given above scientific rationales, determining an appropriate dissolution profile for establishing PBPK absorption models should be based on the physicochemical properties of the drug substance and factors which may affect both *in vitro* and *in vivo* drug release of matrix-based tablet formulations.

5. Conclusion

To summarize, we developed a PBPK absorption model for venlafaxine HCl ER formulations using the *in vitro* drug release profiles based on a two-stage method as the dissolution input to predict the PK profiles after a single-dose oral administration of venlafaxine HCl openable matrix and osmotic pump ER tablets. The established models were used to investigate a bioinequivalence risk associated with the potential delayed opening time of the openable matrix venlafaxine HCl ER tablets. Based on the single-dose PK simulations, a delayed onset of venlafaxine release up to 4 hrs conforms to the bioequivalence requirements of PK metrics (*i.e.* C_{max} and AUC_t), although the T_{max} is expected to be delayed. Virtual clinical trials based on PBPK modeling and simulation can be a powerful tool to critically evaluate quality-associated risks on resulting formulation, drug release, pharmacokinetics and bioequivalence for generic drug products.

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Disclaimer

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Figure/Table Legends

Figure 1. Schematic illustration of drug release mechanisms from the formulations based on (A) an osmotic pump and (B) an openable matrix; (C) their corresponding kinetics of drug release; and (D) different formulation designs of the openable matrix drug delivery.

Figure 2. Schematic illustration of modeling and simulation strategy. The boxes of the same color represent the studies conducted in the same clinical trial.

Figure 3. Observed (refer to Section 2.1 for PK data collection) and predicted PK profiles for drug products containing venlafaxine or ODV for (A) venlafaxine IV infusion (0.5 hr) at 10 mg, and (B) ODV IV infusion (1 hr) at 50 mg³², (C) venlafaxine HCl ER capsules at 75 mg²¹, (D) venlafaxine HCl osmotic pump ER tablets at 75 mg²¹, (E) venlafaxine HCl osmotic pump ER tablets at 150 mg, and (F) venlafaxine HCl openable matrix ER tablets at 150 mg. Red: venlafaxine; blue: ODV; solid lines: simulated plasma concentrations; circle symbols: mean observed plasma concentrations. Inset: The C_{max} (in ng/mL) and AUC_t (ng hr/mL) values of observed and predicted pharmacokinetic profiles for venlafaxine are presented in (A), (C), (D), (E) and (F), and for ODV in (B).

Figure 4. The reported mean *in vitro* dissolution profiles (No. 1 – 3 solid lines for osmotic pump and No. 4 – 8 dashed lines for openable matrix) using (1) pH 1.2, (2) pH 4.5, (3) water, (4) two-stage (pH 1.5 for 1.5 hr and pH 6.8 for 22.5 hr), (5) pH 1.2, (6) pH 4.5, (7) pH 7.4, and (8) water, buffers as dissolution media in a USP II apparatus at an agitation rate of 50 rpm. By adjusting the parameters in a

Weibull function of input dissolution profiles, two dissolution profiles plotted in black dots represent the lower and upper limits of 80% and 125% C_{max} compared to that of Sun's venlafaxine hydrochloride ER tablets using dissolution profile No. 4.

Figure 5. Hypothetical dissolution profiles generated to test the effect of lag time on PK metrics (C_{max} and AUC_t) through a Weibull function with a lag time of 0 (baseline), 1, 2, 3, and 4 hr, while the rest of Weibull parameters were kept constant.

Figure 6. Effect of lag time (0 – 4 hr) on simulated PK profiles based on the established PBPK models. Inset: Fractional C_{max} and AUC_t of each simulated PK profile compared to that with zero lag time.

Table 1. Summary of input parameters for venlafaxine and o-desmethylvenlafaxine (ODV) ACAT simulations

Table 2: Summary of %C_{max} and %AUC_t of simulated pharmacokinetic profiles using inputs of various *in vitro* dissolution profiles presented in Figure 3, compared to that using dissolution profile No. 4 for openable matrix venlafaxine HCl ER tablets.

Table 3: 3-D PSA using a lag time of 0, 1, 2, 3, 4 hr (1st dimension) against various input parameters (10 test conditions with a uniform spacing) (2nd dimension) with total of 50 combinations per pair of parameters. For any particular test condition in 2nd dimension, simulated C_{max} or AUC_t were compared

to those generated from the conditions paired with a 0-hr lag time. The range of %Cmax and %AUC_t (minimum and maximum out of 40 results per pair of parameters) were reported in the table.

Table 1. Summary of input parameters for venlafaxine and o-desmethylvenlafaxine (ODV) ACAT simulations

Drug or Drug product	ODV IV Infusion	Venlafaxine IV Infusion	Effexor	Effexor XR	ER tablet (Osmotica)	ER tablet (Sun)
Molecule	ODV	Venlafaxine	Venlafaxine	Venlafaxine	Venlafaxine	Venlafaxine
Route of administration	IV infusion 1h	IV infusion 0.5 h	oral	oral	oral	oral
Dose (mg)	50	10	50	75	75 or 150	150
Dosage form ^a	IV: Infusion	IV: Infusion	IR: Tablet	CR: Dispersed	CR: Integral Tablet	CR: Integral Tablet
Dissolution model	N/A	N/A	N/A	Weibull	Weibull	Weibull
Dose volume (ml)	N/A	N/A	240	240	240	240
Particle density (g/ml) ^a	N/A	N/A	1.2	1.2	1.2	1.2
MW (g/mol)	263.38	277.41				
logP	2.62 ^b	2.8 ²⁸				
Solubility (mg/ml)	34.6 (pH 6.5)	572 (pH 7) ^c				
pKa ^a	8.86 (base) 10.25 (acid)	8.94 (base)				
Diffusion coefficient (cm ² /s x 10 ⁻⁵) ^a	0.75	0.72				
f _{up} (%) ^d	70	73				
R _{bp}	1.2 ^b	1 ^e				
Permeability (x10 ⁻⁴ cm/s)	1.28 ^b	1.668 ^f				
Central Volume (L/Kg) ^f	1.2648	0.45939				
K ₁₂ (1/h) ^f	3.1166	12.756				
K ₂₁ (1/h) ^f	2.1747	2.6796				
K ₁₃ (1/h) ^f	0	0.25792				
K ₃₁ (1/h) ^f	0	0.04089				
Clearance (L/h/Kg) ^f	0.25542	0				
Renal clearance (L/h/Kg) ²⁹	0	0.054				
CYP2C19 O-demethylation ²⁷	Vmax: 0; Km: 0		Vmax: 0.17 mg/s/mg-enzyme; Km: 59.34 mg/L			
CYP2C19 N-demethylation ²⁷	Vmax: 0; Km: 0		Vmax: 0.33 mg/s/mg-enzyme; Km: 80.6 mg/L			
CYP2C9 O-demethylation ²⁷	Vmax: 0; Km: 0		Vmax: 0.13 mg/s/mg-enzyme; Km: 631.6 mg/L			
CYP2C9 N-demethylation ²⁷	Vmax: 0; Km: 0		Vmax: 2.38 mg/s/mg-enzyme; Km: 455.7 mg/L			
CYP2D6 O-demethylation ²⁷	Vmax: 0; Km: 0		Vmax: 0.16 mg/s/mg-enzyme; Km: 4.698 mg/L			
CYP3A4 N-demethylation ²⁷	Vmax: 0; Km: 0		Vmax: 0.43 mg/s/mg-enzyme; Km: 112.6 mg/L			

^a Dose form selected in GastroPlus

^b Predicted by ADME predictor or default values in GastroPlus

^c Reported in reviews from Drug@FDA

^d Fraction of the drug unbound reported in drug labels

^e The blood-to-plasma partition coefficient²⁹

^f Optimized values

Table 2: Summary of %C_{max} and %AUC_t of simulated pharmacokinetic profiles using inputs of various *in vitro* dissolution profiles presented in Figure 3, compared to that using dissolution profile No. 4 for openable matrix venlafaxine HCl ER tablets.

Dissolution profile	Dosage form	Dissolution medium	%C _{max} compared to two-stage dissolution	%AUC _t compared to two-stage dissolution
No. 1	Osmotic pump	pH 1.2 HCl	101.1	92.2
No. 2	Osmotic pump	pH 4.5 buffer	104.0	92.7
No. 3	Osmotic pump	Water	111.0	97.3
No. 4	Openable matrix	two-stage (pH 1.5 for 1.5 hr; pH 6.8 for 22.5 hr)	100.0	100.0
No. 5	Openable matrix	pH 1.2 HCl	64.3	83.0
No. 6	Openable matrix	pH 4.5 buffer	83.4	90.3
No. 7	Openable matrix	pH 7.4 buffer	97.5	99.6
No. 8	Openable matrix	Water	83.0	91.6

Table 3: 3-D PSA using a lag time of 0, 1, 2, 3, 4 hr (1st dimension) against various input parameters (10 test conditions with a uniform spacing) (2nd dimension) with total of 50 combinations per pair of parameters. For any particular test condition in 2nd dimension, simulated C_{max} or AUC_t were compared to those generated from the conditions paired with a 0-hr lag time. The range of %C_{max} and %AUC_t (minimum and maximum out of 40 results per pair of parameters) were reported in the table.

1 st dimension 2 nd dimension	Lag time of 1, 2, 3, 4 hr / lag time 0 hr	
	C _{max} (%)	AUC _t (%)
0.1-10X V _c	93-100	96-100
0.1-10X k ₁₂	93-102	97-100
0.1-10X k ₂₁	93-100	97-100
0.1-10X k ₁₃	96-99	97-100
0.1-10X k ₃₁	97-99	99-100
0.1-10X V _{max} (gut)	94-101	95-103
1-10X K _m (gut)	95-105	96-110
0.2-17X V _{max} (liver)	87-99	95-99
0.1-10X K _m (liver)	97-100	97-100
Plasma unbound (1-100%)	97-101	96-100
0.5-10X Blood plasma ratio	96-100	98-100
Hepatic flow (0.25-2.5X)	96-99	98-100
Stomach empty time (0.5-10 hr)	86-112	96-100
0.1-10X P _{eff}	93-99	95-100