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Research Article

Application of Physiologically Based Absorption Modeling to Formulation Development of a Low Solubility, Low Permeability Weak Base: Mechanistic Investigation of Food Effect

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Abstract. Physiologically based pharmacokinetic (PBPK) modeling has been broadly used to facilitate drug development, hereby we developed a PBPK model to systematically investigate the underlying mechanisms of the observed positive food effect of compound X (cpd X) and to strategically explore the feasible approaches to mitigate the food effect. Cpd X is a weak base with pH-dependent solubility; the compound displays significant and dose-dependent food effect in humans, leading to a nonadherence of drug administration. A GastroPlus Opt logD Model was selected for pharmacokinetic simulation under both fasted and fed conditions, where the biopharmaceutic parameters (e.g., solubility and permeability) for cpd X were determined *in vitro*, and human pharmacokinetic disposition properties were predicted from preclinical data and then optimized with clinical pharmacokinetic data. A parameter sensitivity analysis was performed to evaluate the effect of particle size on the cpd X absorption. A PBPK model was successfully developed for cpd X; its pharmacokinetic parameters (e.g., C_{max}, AUC_{inf}, and t_{max}) predicted at different oral doses were within ±25% of the observed mean values. The *in vivo* solubility (in duodenum) and mean precipitation time under fed conditions were estimated to be 7.4- and 3.4-fold higher than those under fasted conditions, respectively. The PBPK modeling analysis provided a reasonable explanation for the underlying mechanism for the observed positive food effect of the cpd X in humans. Oral absorption of the cpd X can be increased by reducing the particle size (<100 nm) of an active pharmaceutical ingredient under fasted conditions and therefore, reduce the cpd X food effect correspondingly.

KEY WORDS: GastroPlus; particle size; physiologically based pharmacokinetics; precipitation; solubility.

INTRODUCTION

Physiologically based pharmacokinetic (PBPK) models establish a physiological environment to estimate drug absorption and distribution using a series of mathematical equations. GastroPlus™ (Simulation Plus, Inc., Lancaster, CA) is a commercial PBPK modeling tool based on compartmental absorption and transit (CAT) model originally proposed by Amidon *et al.* (1), which was later expanded to the advanced CAT or ACAT model (2). The model contains nine compartments in sequence representing anatomic segments of the gastrointestinal (GI) tract, namely stomach, duodenum, jejunum (two compartments), ileum (three compartments), caecum, and ascending colon. Default physiological conditions such as pH values and transit time for each compartment are incorporated in the model. The absorption processes of compounds throughout GI tract can be estimated based on specific physicochemical properties such as pK_a, partition coefficient, and particle size of the compounds, as well as related dosing regimen. Transmembrane passage of the compound in each GI segment is estimated based on the permeability and concentration gradient across the membrane in that GI compartment. The absorption in each segment following first-pass metabolism is subsequently estimated, accumulated, and convoluted with disposition kinetics to generate drug pharmacokinetic profiles.

Compound X (Cpd X) is a lipophilic compound displaying a low, pH-dependent aqueous solubility and moderate intestinal

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ABBREVIATIONS: ACAT, advanced compartmental absorption and transit; AUC, area under the plasma concentration–time curve; BCS, Biopharmaceutics Classification System; CAT, compartmental absorption and transit; C_{max}, maximum plasma concentration; ECG, electrocardiogram; FaSSIF, fasted-state simulating intestinal fluid; FeSSIF, fed-state simulating intestinal fluid; GI, gastrointestinal; IR, immediate release; PBPK, physiologically based pharmacokinetics; PSA, parameter sensitivity analysis; PK, pharmacokinetics; SGF, simulated gastric fluid; t_{max}, time to reach maximum concentration; F_a, fraction of absorption; API, active pharmaceutical ingredients; NFE, Nanoparticle factor effect.

permeability. The compound demonstrates properties consistent with the Biopharmaceutics Classification System (BCS) class II (or IV) category (3). The absorption of cpd X in humans has been investigated in a mass-balance study following a single oral dose of 400 mg C^{14}-labeled cpd X. Majority of the dose (~70%) was recovered in feces as parent drug with large individual variability, suggesting a low oral absorption under fasted conditions. Metabolism occurs primarily in the liver via hydroxylation and oxidation mediated by the *CYP*3A4 enzyme. Unchanged cpd X form is the main circulating drug component in the serum and primarily responsible for the drug's pharmacologic activities.

The cpd X is currently marketed as an immediate release (IR) capsule formulation. The systemic exposure of the cpd X is increased when given with food. Compared to the fasted state, the mean systemic exposure of cpd X (400 mg single dose) measured from an area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}) were increased by 29% and 55%, respectively, when dosed 30 min after a light meal, and increased by 82% and 112%, respectively, after a high fat meal. While absolute oral bioavailability of cpd X has not been determined due to the lack of a suitable intravenous formulation, it has been estimated to be less than 30%.

Food may interact with drug absorption via mechanisms including delay in gastric emptying, change in GI pH and bile excretion. The relationship of food effect with physicochemical properties of compounds has been reported by Fleisher *et al.* (4), lipophilic compounds with poor aqueous solubility mostly exhibit a positive food effect (increase in exposure after food intake) because of improved solubilization due to high bile salt concentration (5). These findings were confirmed by Gu *et al.* who investigated food effects of 92 compounds which correlated with physicochemical properties (6); nearly 71% of the BCS class II compounds (low solubility and high permeability) displayed a positive food effect.

Physiologically based pharmacokinetic models have been used to quantitatively predict oral drug absorption and food effects for poorly soluble drugs, based on *in vitro* biorelevant solubility and dissolution results, as well as investigation in animal models (7–9). The current study applied a similar PBPK approach to understand the underlying mechanism of food effects on the absorption of a low solubility compound and to explore potential formulation solutions to overcome the food effects.

MATERIALS AND METHODS

Clinical Food Effect Studies of Compound X

Pharmacokinetic data from four Novartis clinical studies conducted from 2005 to 2012 were analyzed. Healthy adult male and sterile or postmenopausal female subjects with ages from 18 to 65 years participated in these studies. All study participants were required to provide written informed consent prior to study initiation. Marketed capsule formulation was selected to investigate drug absorption with or without meal. Fasted state was defined as overnight fasting for 10 h before dosing and fed state as dosing within 30 min following ingestion of high fat meal (approximately 1,000 calories with 50% from fat content). Study details and demographic information of participants are shown in Table I.

Data Analysis of Clinical Studies

The PK profiles of cpd X were determined by collecting series of blood samples at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, and 72 h post-dose. Plasma concentrations of the cpd X were measured using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay. The plasma concentration *versus* time data were analyzed with non-compartmental analysis (NCA) methods to calculate PK parameters (e.g., AUC, C_{max}, t_{max}, CL/F, etc.) using WinNonlin Version 5.0.1 (Pharsight Corporation, Mountain View, CA). In addition, arithmetic mean plasma concentrations at each sampling time were calculated, and the mean plasma concentration *versus* time profiles at 200, 300, 400, and 600 mg were individually transferred to the GastroPlus™ software database for simulation.

Modeling and Simulations

Disposition Pharmacokinetics of Compound X in Humans

The PK of cpd X following intravenous administration has never been investigated in humans. The key disposition parameters in humans used in this study (e.g., clearance and volume of distribution) were collected from literature based on a verified model, with minor modifications according to the CL/F values obtained following NCA (Table II).

Prediction of Human Plasma Concentration–Time Profiles and Estimation of Food Effect

The GastroPlus™ (Version 8, Simulation Plus, Inc., CA) was used to simulate oral pharmacokinetic profiles of cpd X following a single dose administration under both fasted and high fat meal conditions. The default human physiology model (Opt LogD model SA/V 6.1) was selected, and fraction of absorption was estimated following simulation. Experimentally measured physicochemical properties of the cpd X, including pK_a, LogP, pH-dependent aqueous solubility, and permeability are shown in Table II. The apparent permeability measured across Caco-2 cell layers (P_{app}, apical to basolateral at 30 μM, 2.7×10^{-6} cm/s) was converted to a human effective permeability (P_{eff}, 1.5×10^{-4} cm/s) using a reported correlative equation (10).

Estimation of In Vivo Solubility and Dissolution Profiles

The cpd X is a weak base with two pK_a values (pK_{a1}=3.0 and pK_{a2}=6.2) displaying high solubility under acidic conditions (1.81 mg/ml at pH 1). The solubility is sharply reduced with increasing pH (0.3 mg/mL at pH 2 and 0.001 mg/mL at pH 6.8) (Table II). Therefore, the *in vivo* dissolution kinetics of cpd X is expected to be altered accordingly with physiological pH changes in the GI tract following a meal intake. To estimate the *in vivo* solubility of the cpd X, the solubility in biorelevant media including a simulated gastric fluid (SGF), a fasted simulated small intestinal fluid (FaSSIF), and a fed simulated small intestinal fluid (FeSSIF) was measured.

Table I. Clinical Studies of Cpd X at Various Doses

Study number	Dose (mg)	Physiological conditions	Number of subjects	Body weight of participants (kg) (mean±SD)	Ages of participants (year) (mean±SD)
C2105	200	Fasted and fed	20	76.5±9.4	55.2±8.6
C2118	300	Fasted	58	76.8±13.2	44.1±7.4
A2106	400	Fasted and fed	44	79.4±12.6	37.0±9.0
A2108	600	Fasted	18	73.1±8.6	39.9±11.0

These solubility values, together with other biopharmaceutic properties of cpd X, such as diffusion coefficient and particle size were utilized to generate *in vivo* dissolution profiles under fasted and fed conditions in the model using a modified Noyes–Whitney equation (11). The *in vivo* precipitation time used in this *in silico* model was adjusted to best fit the *in vivo* human pharmacokinetic profiles, because no feasible method was currently available to quantitatively determine the precipitation time. An *in vitro* two-step dissolution test in the SGF/FaSSIF and SGF/FeSSIF was investigated and referenced to provide useful insights of drug precipitation.

Estimation of pH Values in Stomach

The pH value in stomach was reported to be time dependent within subjects and variables during the digestion process following food intake (12). This value, however, was constant in the current ACAT model (pH=4.9) and failed to reflect a dynamic change of the gastric acidity. In this study, human stomach pH was switched to a set of sequential values following meal intake, similar to the values reported by Gardner *et al.* and Dressman *et al.* (12,13) (Table III).

Table II. Physicochemical Parameters, Default Physiological Values, and Pharmacokinetic Parameter Used in the Simulation at Various Doses

Parameters	Value(s)
Compound parameters	
M_w: g/mol	>475
cLogP:	>4
pK_a (base):	3.2, 6.2
Dosage:	IR capsule
Solubility (mg/mL):	1.8 (pH 1), 0.3 (pH 2), 0.001 (pH 6.8)
Biorelevant solubility (mg/mL) :	0.023 (fasted); 0.190 (fed)
Mean precipitation time (s) :	450 s (fasted); 2,000 s (fed)
Effective permeability (cm/s):	1.48×10^{-4}
Particle radius of API (μm):	19
Physiological parameters	
Stomach pH	1.2 (Fasted); 1.2–4.9 (Fed)
Duodenum/jejunum pH	6.0–6.4 (Fasted); 5.4–6.0 (Fed)
Ileum pH	6.6–7.4 (Fasted); 6.6–7.4 (Fed)
Cecum–colon pH	6.4–6.8
Stomach transit time (h)	2.0 (Fasted); 5.4 (Fed)
Small intestine transit time (h)	3.3
Cecum transit time (h)	4.2
Ascending colon transit time (h)	12.6
Pharmacokinetics	
First pass extraction (%):	9.0
Blood/plasma ratio:	0.68
Plasma unbound (%):	1.6
Clearance (L/h/kg)	0.070
V_c (L/kg)	0.4
k_{12} (1/h)	0.64
k_{21} (1/h)	0.17
V_t (L/kg)	1.5

IMPACT OF DRUG PARTICLE SIZE ON DRUG ABSORPTION AND PARAMETER SENSITIVITY ANALYSIS

For the solid active pharmaceutical ingredients (API), the dissolution rate is proportional to drug solubility and the surface area of drug particles according to a modified Noyes–Whitney equation and therefore, inversely proportional to the particle size. In addition, drug solubility is inversely proportional to the particle size according to Frudlich–Ostwald equation (Eq. 1) (14).

$$C_{s,r} = C_{s,\infty}\exp\left(\frac{2\gamma M_w}{r\rho RT}\right) \quad (1)$$

where $C_{s,r}$ is the solubility of drug particle of radius r, $C_{s,\infty}$ is the solubility of the same drug with no curvature at temperature T, r is the particle radius, R is the gas constant (8.314 J/K/mol), ρ is the density, M_w is the molecular weight, and γ is the interfacial tension. Drug particles less than 1 μm are easily trapped in apical microvilli of the intestinal wall, leading to an abnormally higher concentration gradient across intestinal wall and higher permeation rate. When the particle size is within nanoscale range, the Noyes–Whitney dissolution equation is modified by taking consideration of the nanoparticle factor effect (NFE), which serves as a solubility scaling factor of $C_{s,r}$ to describe the increased dissolution rate of nanoparticles (Eq. 2),

$$\frac{dM_D}{dt} = k_{diss} \times \left(C_{s,r} \times NFE - C_l\right) \times M_{u,t} \quad (2)$$

where dM_D/dt is the dissolution rate, k_{diss} is the dissolution rate constant, Cl is the total drug concentration in the lumen

Table III. Stomach pH and ACAT Physiology Models under High Fat Fed Conditions

Time after dose (h)	Stomach pH	ACAT physiology model
0–3	4.9	Human physiological fed
4–5	3.5	Human physiological fed
4–4.5	2.0	Human physiological fed
>4.5	1.2	Human physiological fasted

of the compartment, *MD* is the amount of dissolved drug, and $M_{u,t}$ is the undissolved amount at time of *t*.

To investigate the correlation of the particle size with fraction of absorption at various doses, a parameter sensitivity analysis (PSA) was conducted. A three-dimension surface response plot was generated to elucidate the interactive effect of particle sizes and doses on the extent of cpd X absorption under both fasted and fed condition. In addition, the positive food effects, represented by $AUC_{0\text{-inf}}$ ratio of fed *versus* fasted, was estimated based on the predicted AUC values in the PSA.

RESULTS

Observed Pharmacokinetics of Compound X

The cpd X was rapidly absorbed with measurable plasma concentrations at 0.5 h post-dose, and t_{max} occurred at approximately 4 h post-dose under fasted conditions. The AUC and C_{max} of the cpd X were increased with increasing doses in an under dose-proportional manner (Table IV). The Cpd X displayed significant and dose-dependent food effects. After dosing with high-fat food, the t_{max} was prolonged to 5 h, and AUC_{inf} was increased by 49.6% and 74.3% at 200 and 400 mg dose levels, respectively (Fig. 1 and Table IV).

Modeling and Simulations

Prediction of Concentration–Time Profiles and Pharmacokinetic Parameters

Simulation results of cpd X at 200 and 400 mg under both fasted and fed conditions are shown in Fig. 1. The modeling was evaluated by comparing predicted pharmacokinetic parameters including C_{max}, AUC_{inf}, and t_{max} to those mean values calculated from observed clinical data. The predicted pharmacokinetic values were observed to be within ±25% of the observed mean values at various doses under both meal conditions (Table IV).

Gastrointestinal Dissolution and Absorption of Compound X under Fasted and Fed Conditions

Absorption of the cpd X in different GI regions was estimated by the calculated fraction absorbed (F_a) (Fig. 2). The cpd X was primarily absorbed in the upper GI tract including duodenum and jejunum. The absorption in ileum was minimal, and less than 5% absorption occurred in colon

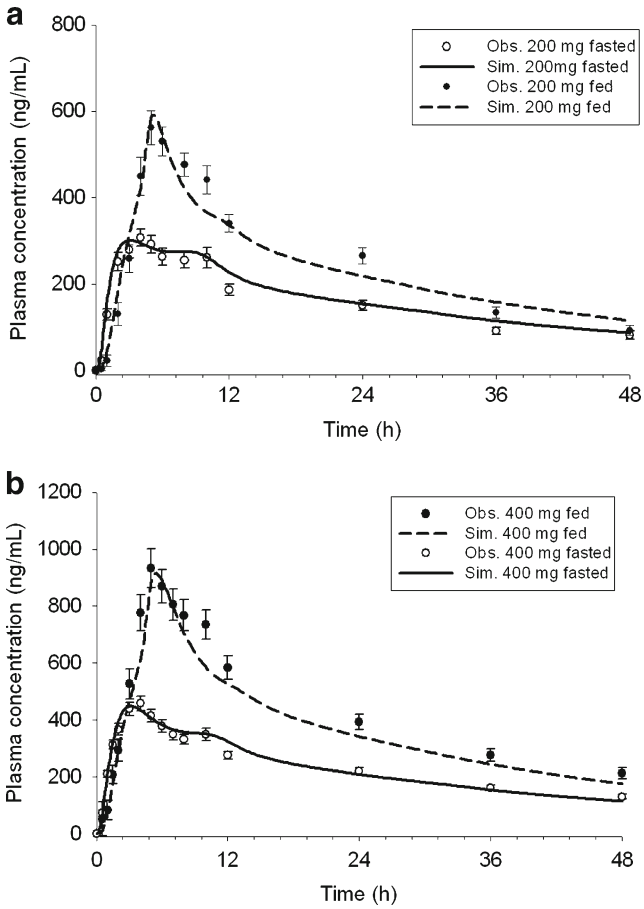

Fig. 1. Mean clinically observed (*solid circles* with standard error) and model-simulated plasma concentration *versus* time profiles of cpd X after a single oral dose of **a** 200 mg or **b** 400 mg cpd X under fasted and fed condition

over the dose range from 200 to 600 mg under both meal conditions, likely due to the limited solubility at elevated pH in ileum and colonic regions. The cpd X displayed dose-dependent absorption, and F_a decreased with increasing doses. For example, F_a decreased from 29.7% to 15.6% when the dose was increased from 200 to 600 mg under fasted conditions and decreased from 41.8% to 33.2% when the dose was increased from 200 to 400 mg under fed conditions (Table IV). The *in vivo* dissolution profiles of cpd X were derived following simulations (Fig. 3). Under fasted conditions, cpd X achieved rapid dissolution in the stomach within the first hour post-dose and then, proceeded with rapid precipitation when

Table IV. Calculated and Predicted Pharmacokinetic Parameters of Cpd X at Various Dose Levels under Both Fasted and Fed Conditions

		C_{max}(ng/ml)		AUC_{inf} (ng×h/ml)		t_{max} (h)		F_a (%)	F (%)
Dose (mg)	Meal condition	Observed	Predicted	Observed	Predicted	Observed	Predicted	Predicted	Predicted
200	Fasted	320	302	8,595	11,170	4.0	3.1	29.7	27.4
200	Fed	601	547	12,857	15,555	5.0	5.5	41.8	38.0
300	Fasted	451	387	11,486	13,080	4.0	3.0	24.0	22.1
400	Fasted	508	449	14,656	15,920	4.0	3.1	20.3	18.7
400	Fed	1068	892	25,542	25,010	5.0	6.1	33.2	30.6
600	Fasted	453	529	14,576	18,840	4.0	3.6	15.6	14.4

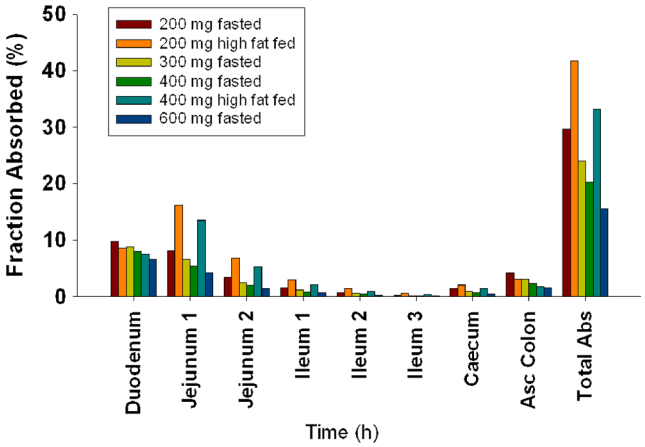

Fig. 2. Fraction of regional absorption under fasted and fed conditions in healthy volunteers after a single dose of cpd X

accessing intestinal tract with relatively high pH values. The fraction of amount of drug dissolved (as% of dose), dropped from 30% to 20% when the dose was increased from 200 to 400 mg under fasted conditions. In contrast, slow but gradually enhanced dissolution was observed for the cpd X under fed conditions and faster dissolution of the cpd X occurred 3 h after meal when gastric pH decreased from 4.9 to 3.5. The simulated triphasic dissolution profile indicated that drug dissolution rate was correlated to the time-dependent gastric pH variation after a high fat meal. In addition, drug precipitation appeared to be delayed with minimal impact on drug absorption.

Parameter Sensitivity Analysis

The PSA was conducted using three-dimensional surface response plots to investigate the sensitivity of F_a to mean drug particle radius in the range from 0.01 to 1 μm at doses ranging from 200 to 800 mg under fasted and fed conditions. Under fasted condition (Fig. 4a), a steep drop in F_a was observed over the therapeutic dose range from 200 to 400 mg when the particle radius was increased above 0.05 μm. In addition, the plot suggested that 60–80% F_a can be achieved by reducing the particle radius to less than 0.1 μm for the dose ranging from 200 to 400 mg (therapeutic dose range) under fasted conditions. Under fed condition (Fig. 4b), drug absorption was nearly complete (>85%) if the particle radius is less than 0.1 μm, regardless of doses in the selected range (200–800 mg). The F_a was reduced to 35–80% if the particle radius was in the range of 0.1–1 μm and the reduction of F_a increased when the dose increased from 200 to 800 mg. Comparing the surface response plots under fasted and fed condition, the F_a between fasted and fed state was still large if the particle radius was greater than 0.1 μm, whereas such difference was significantly reduced when the particle radius was in nanoparticle range (0.1–1 μm).

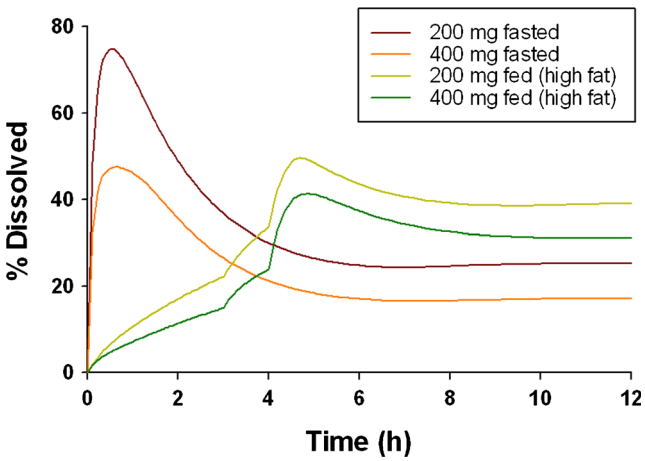

Fig. 3. Percentage of dissolved cpd X in healthy volunteers after single 200 and 400 mg cpd X doses with and without receiving a high fat meal 30 min prior to the dose

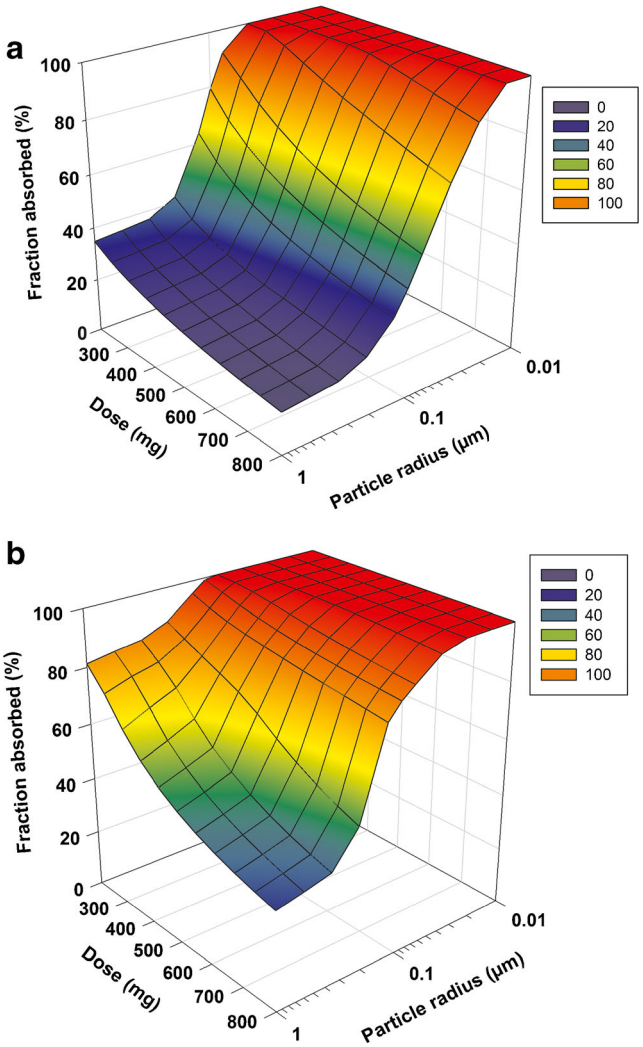

Fig. 4. Surface response plot describing interactive effect of particle size and dose on fraction absorbed (F_a) of cpd X under fasted (**a**) and fed (**b**) conditions

DISCUSSION

Food may significantly impact drug absorption and distribution by various mechanisms including changing the physiological conditions or direct drug–food interactions. Positive food effects have been commonly observed for BCS class II/

IV compounds displaying low solubility within the GI tract. These compounds are primarily lipophilic and weak bases with pH-dependent solubility profiles (15), exhibiting decreased solubility and are thus susceptible to precipitation with increased pH in the intestine. The precipitated drug will exists as aggregates of fine particles and will only partially redissolve in the GI tract due to limited solubility under the conditions with elevated pH, leading to incomplete absorption under fasted conditions. Following food intake, these compounds are retained in the stomach with prolonged dissolution resulting in an improved absorption. In addition, the intestinal solubility of the cpd X increases remarkably in the presence of bile salts that are secreted following the food intake, leading to the additional enhancement in absorption of the cpd X.

A rapid and significant precipitation was observed for the cpd X under fasted conditions. In comparison, the precipitation was significantly delayed under fed conditions (Fig. 3), suggesting that precipitation was prevented in the presence of food. In addition, t_{max} of the cpd X under fed conditions was prolonged from 4 to 5 h at 400 mg, suggesting a continuous absorption in the downstream GI tract as a result of a sufficient concentration of the cpd X in the dissolved form. This is consistent with a previous report demonstrating that *in vivo* precipitation was delayed in the presence of a high fat meal due to a high degree of supersaturation in the secreted bile following a food stimulation (16). The true *in vivo* precipitation time, which is the mean time for particles to precipitate from a supersaturated state when the local concentration exceeds the drug solubility, is technically difficult to measure. In this study, the precipitation time was estimated via data-fitting of multiple pharmacokinetic datasets obtained from the clinical studies at various dose levels. The precipitation time of 2,000 and 450 s used in this model may reflect the realistic precipitation rates of the cpd X *in vivo* under fed and fasted conditions, respectively.

The reduced precipitation under fed conditions might be attributable to improved wettability of a drug substance with food content such as lipids, which reduces the interfacial surface energy between the cpd X drug particles and the GI fluids, thus enhancing the solubilization of the cpd X along the GI tract. Bile salt has been reported to increase drug absorption by enhancing drug solubility in the GI tract, which is a function of bile salt concentration expressed by the equation proposed by Mithani *et al.* (17). Solubility measurement in biorelevant media containing bile salts and lecithin provided a valuable information to estimate *in vivo* solubility under physiological conditions, enabling accurate estimation of absorption and bioavailability. The formulae of FaSSIF and FeSSIF were designed based on the most recent research evidence in humans. Nicolaides *et al.* suggested adding pepsin or lipase to improve correlations between *in vitro* solubility and *in vivo* absorption (18). In the case of the cpd X, the measured solubility in FaSSIF and FeSSIF, as expected, assisted to better predict the plasma levels.

A commonly accepted strategy to reduce positive food effects is to enhance drug absorption under fasted conditions, therefore reducing the gap in absorption between fasted and fed conditions. Wu *et al.* and Jinno *et al.* demonstrated suppression of food effect by improving drug absorption using drug particle size reduction strategies for two BCS II compounds (19,20). The cpd X exhibits similar pharmaceutical properties to those BCS II compounds suggesting that food effect may be mitigated using the same strategies. In general, if a compound has sufficient absorption (F_a>70%) under fasted state, positive food effect tends to be clinically insignificant because the extent of absorption increased by a meal will be limited. From the PSA, greater than 70% of F_a under fasted state can be achieved for a particle radius less than 0.1 μm at a dose up to 400 mg, and a particle size less than 0.05 μm is required to reach similar absorption at higher doses. Therefore, API particle size reduction to nanoparticle range appears to be an effective strategy to mitigate the food effect of cpd X.

Physiologically based absorption modeling has been recognized as a useful tool to understand the effects of API and formulation properties on bioavailability and explore specific mechanisms for drug absorption. The predictability of drug absorption using a dog absorption model to explore the correlation between particle size and bioavailability has been evaluated by Kesisoglou *et al.* (21). This model predicted the dependency of drug absorption extent on the particle radius for the particle size greater than 1.8 μm. However, for the particle size smaller than 500 nm, the predicted exposure deviated significantly from the observed results. These results suggest that NFE may play an essential role in the enhancement of solubility and should be considered in the model for nano-sized API. In this model, the NFE was incorporated in PBPK model and the PSA results clearly suggested a strong influence of nanoparticle effects on bioavailability.

CONCLUSION

A PBPK modeling was developed to elucidate the mechanism of food effect of cpd X, a weak base compound. The observed low bioavailability was primarily due to a significant precipitation under fasted conditions leading to incomplete absorption. The positive food effect of the cpd X was resulted from a prolonged precipitation time and increased *in vivo* solubility under fed conditions. The PBPK based model indicates that the oral absorption is sensitive to the particle size of API. The reduction of particle size may potentially improve absorption under fasted conditions and minimize differences in drug exposures observed under fasted and fed conditions.

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