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ORIGINAL ARTICLE

Mechanistic prediction of food effects for Compound A tablet using PBPK model

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Abstract Physiologically based pharmacokinetic (PBPK) modeling has been extensively used to study the factors of effect drug absorption, distribution, metabolize and extraction progress in human. In this study, Compound A(CPD A) is a BCS Class II drug, which has been extensive applied in clinical as lipid-lowering drug, administered orally after food, they displayed positive food effects in human, A PBPK model was built to mechanistic investigate the food effect of CPD A tablet in our study. By using gastroplus™ software, the PBPK models accurately predicted the results of food effects and predicted data were within 2-fold error of the observed results. The PBPK model mechanistic illuminated the changes of pharmacokinetic values for the positive food effects of the compound in human. Here in, the PBPK modeling which were combined with ACAT absorption models in it, successfully simulated the food effect in human of the drug. The simulation results were proved that PBPK model can be able to serve as a potential tool to predict the food effect on certain oral drugs.

1. Introduction

It is necessary to explore the effect of food on the pharmacokinetics of drugs, for many drugs, food effects may cause enhanced or reduced pharmacokinetic parameters in human. However, the estimation of quantitative food effect is difficult, because clinical food effect studies is expensive and time consuming, and is always limited by many pathologies, physiochemical, and formulation factors of drug development.

Food can change the drug pharmacokinetic parameters and produce negative, positive or not pronounced effect of plasma concentration in human (Custodio et al., 2008; Fleisher et al., 1999; Gu et al., 2007). It is for this reason that the Food and Drug Administration (FDA) stipulates the food-label for all prescription products, codified in the Product Labeling and

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affords a guidance for the industry entitled 'Food-effect bioavailability and fed bioequivalence studies' (FDA, 2002).

Food can influence the drug absorption through physicochemical (drug-meal interactions mediated by altering dissolution, degradation, and diffusion mechanisms) and/or physiological mechanisms (interactions mediated by altering the residence times, volumes, and content of gastric and intestinal secretions, as well as membrane transport mechanisms) (Fleisher et al., 1999; Charman et al., 1997).

The effect of food on drug pharmacokinetic is complex processor, there are many physiological and physicochemical factors influence drug absorption, distribution, metabolize and extraction. Some effects of food observed in animals cannot always be directly convert to human, because there are various physiological property exit in different species. In recently years, some published literatures have supported that PBPK models integrated with drug physicochemical property and physiological parameter of human can give similarly prediction of food effects (Fleisher et al., 1999; Gu et al., 2007; FDA, 2002; Charman et al., 1997; Rowland et al., 2011).

There are a kind of business computer software such as GastroPlus, PK-Sim, SimCyp Simulator, Stella, etc (Chaubal, 2004; Kuentz, 2008; Dressman et al., 2011), which were used to simulated drug PBPK modeling more and more. GastroPlus™ (Simulation Plus, Inc., Lancaster, CA) is a commercial PBPK modeling tool based on compartmental absorption and transit (CAT) model originally proposed by Heimbach et al. (2013). The ACAT model is the advanced CAT model (Wagner et al., 2012), 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.

Here in, adopting gastroplus™ (Simulation Plus, Inc., Lancaster, CA, version 9.0), a mathematic PBPK simulation software, which is based on ACAT model in absorption, and PBPK model in disposition simulation of drugs. Physiologically based pharmacokinetic (PBPK) models build a simulation environment to estimate drug absorption and distribution using a series of mathematical equations, such as Johnson (Lu, 1993), Wang-Flanagan (Wang, 1999), Takano (Takano, 2006), Gibbs (Gibbs and Schmelzer, 2010) etc. By inputting compound physicochemical parameters such as: lipophilicity (LogP), ionization (pKa), permeability data, and other parameters were required by software, our team predicted the effects of food on vivo pharmacokinetic process of the drug in human body.

Most of the BCS class II compounds (low solubility and high permeability) displayed a positive food effect (Gu et al., 2008). The present work describes and rationalizes the formulation development strategy utilized in overcoming the food effect on oral pharmacokinetics of a BCS Class II drug. This is a retrospective analysis to understand the primary pharmacokinetic variation for the food effect, and then research mitigation strategy could be minimize the influence of food act on drugs.

CPD A is a lipid-lowering agent which belongs to the statin class of medications for treatment of dyslipidemia. It is also used for primary and secondary prevention of cardiovascular disease. FDA approved in Aug 3, 2009. CPD A is a lipid-lowering compound used for the treatment of High cholesterol, familial high cholesterol. According to the Biopharmaceutics Classification System (BCS), CPD A is a BCS class II drug, characterized by low aqueous solubility and high intestinal permeability. It has been extensive applied in clinical, administered orally with food, they displayed positive food effects in human. The purpose of this study was to mechanistically interpret the oral food effect of CPD A tablet in fed state by designing a silico PBPK drug model which takes into account drug different biopharmaceutical properties as the pharmacokinetic characteristics of the gastrointestinal (GI) tract in pre- and post-food states.

2. Method

2.1. Chemicals and reagents

CPD A tablet was purchased from Xinan Pharmaceuticals Corporation (Kunming). Methanol (HPLC-grade) was purchased from Fisher Scienti-fic (Fair Lawn, USA), Distilled water, prepared from demineralized water, was used throughout the experiment. All the other chemicals were HPLC grade.

2.2. Computer software

Gastroplus™ (Simulation Plus, Inc., Lancaster, CA, version 9.0) was run on a Lenovo (i7-4790) computer. This software using the PBPK and ACAT models simulate drug disposition and absorption under both fasted and food conditions. Input parameters of the drugs, including solubility, permeability, LogP, pKa, and particle sizes, F_{up}, and other parameters were default values in gastroplus software. A summary of the input parameters employed for CPD A absorption simulation is given in Table 1.

2.3. GastroPlus™ model simulation

The model underlying GastroPlus™ is known as the Advanced Compartmental Absorption and Transit (ACAT) model (Agoram et al., 2001) and is based on the original CAT model described by Yu and Amidon (1999). The physiologically based ACAT model, consists of nine compartments corresponding to different segments of the digestive tract. The release, dissolution, degradation, metabolism, uptake and absorption of a compound as it transits through these compartments are modeled with a system of differential equa-

Table 1 Physicochemical Properties and BCS Classification of CPD A.

Compound	CPD A
MW (Da)	300–500
pKa (strongest acidic)	4.13
pKa (strongest basic)	4.86
log P	3.75/2.92
Plasma protein binding (%)	>99
Water solubility (mg/mL) (pH)	0.00394
Caco-2 permeability (cm/s × 10^{-6})	0.5135
Human formulation	Tablet
Transporter information	P-glycoprotein substrate
BCS	Ⅱ
Dose	2 mg

Table 2 ACAT model parameterization for physiological models of human gut.

Compartment	pH (fasted/fed)	Transit time (h)	Length (cm)
Stomach	1.30/4.90	0.25/1	29.19
Duodenum	6.0/5.4	0.26	14.58
Jejunum 1	6.2/5.4	0.94	60.26
Jejunum 2	6.4/6.0	0.74	60.26
Ileum 1	6.6	0.58	60.26
Ileum 2	6.9	0.42	60.26
Ileum 3	7.4	0.29	60.26
Cecum	6.4	4.36	13.5
Asc colon	6.8	13.07	28.35

tions. The software accepts a variety of in vitro and in silico input data such as solubility versus pH profile, permeability, particle size, logP, pKa and dose. Solubility increases with increased ionisation (calculated from the pKa values using the Henderson Hasselbalch equation) (Hasselbalch, 1916). Dissolution rate is calculated using the Noyes-Whitney equation (Noyes and Whitney, 1897). For permeability a generic logD model provided by Simulations Plus Inc. Adjusts absorption rate coefficients in each intestinal compartment according to pH and logD to explain the observed rate and extent of absorption for a training set of drugs. Special interest here are the descriptions of the fasted-state and fed-state physiology. The physiological changes in the GastroPlus™ model between fasted and fed states are described in Table 2. The oral pharmacokinetics of each drug was simulated under fasted conditions using the model. The effect of food was investigated by changing physiological model parameters and introducing the appropriate solubility data.

2.4. Food effect studies in healthy subjects

A study was conducted to evaluate the effect of food on pharmacokinetics after a single 2 mg oral dose of CPD A in healthy subjects. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol and informed consent forms were approved by the local institutional review board. CPD A tablet was taken orally 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 1000 calories with 50% from fat content). Study details and demographic information of participants are shown in Table 3.

The PK profiles of CPD A were determined by collecting series of blood samples at pre-dose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 8, 12, 24, 36, and 48 h post-dose. Plasma concentrations of the CPD A were measured by using a validated liquid chromatography tandem mass spectrometry (LC–MS/MS) assay. The plasma concentration versus time data were analyzed with noncompartmental analysis (NCA) methods to calculate PK parameters (e.g., AUC, C_{max}, t_{max}, CL/F, etc.) using WinNonlin Version 6.2 (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 2 mg was transferred to the GastroPlus™ software database for simulation.

2.5. Modeling analysis

A GastroPlus™ model was built for CPD A using the available parameters shown in Table 1. The required data regarding drug physicochemical and pharmacokinetic properties were obtained from available literature sources. The oral pharmacokinetics of CPD A tablet was simulated under fasted and food conditions using the models. The effects of food were investigated by changing physiological model parameters and introducing the appropriate solubility data. Predicted and observed plasma concentration time profiles were compared and analysis using WinNonlin Professional version 6.2. Area under the plasma concentration–time curve from time zero to the last measurable concentration ($AUC_{0\text{-}t}$) was calculated using the (linear up, logarithmic down) trapezoidal rule. Peak plasma concentration (C_{max}) was determined directly from the observed and predicted using WinNonlin Professional version 6.2. Area under the plasma concentration–time curve from time zero to the last measurable concentration ($AUC_{0\text{-}t}$) was determined respectively from the experiment and prediction plasma concentration–time profiles. The results were calculated in accordance with the following Eq. (1).

$$\text{Food effect(fed v fasted)} = AUC_{fed}/AUC_{fasted} \text{ or } C_{max(fed)}/C_{max(fasted)} \quad (1)$$

Table 3 Clinical studies of CPD A at single doses.

Compound name	Dose (mg)	Physiological conditions	Number of subjects	Body weight of participants (kg) (mean ± SD)	Ages of participants
CPD A	2	Fasted	24	63.6 ± 2.3	22.7 ± 1.9
	2	Fed	24	62.5 ± 2.0	23.3 ± 3.4

Table 4 Calculated and Predicted Pharmacokinetic Parameters of two drugs at study dose under both fasted and fed conditions.

Compound	Dose (mg)	Physiological conditions	C_{max} (ng/mL)		$AUC_{0\text{-}t}$ (ng·h/mL)		t_{max}(h)	
			Observed	Predicted	Observed	Predicted	Observed	Predicted
CPD A	2	Fasted	36.38 ± 15.66	37.45 ± 11.24	243.20 ± 132.06	216.75 ± 132.15	1.17 ± 0.36	1.32 ± 0.21
CPD A	2	Fed	46.53 ± 19.21	53.44 ± 14.25	292.16 ± 160.02	274.39 ± 171.23	1.13 ± 0.47	1.21 ± 0.55

All values are mean (±SD), Fold error value < 2.0.

Predicted data and observed food effects were compared to calculated the precision of the simulations. The results were calculated in accordance with the following Eq. (2).

$$\text{Fold-error} = \text{predicted}/\text{observed}, \text{ if predicted} > \text{observed} \quad (2.1)$$

$$\text{Fold-error} = \text{predicted}/\text{observed}, \text{ if observed} > \text{predicted} \quad (2.2)$$

3. Results

3.1. Properties of the studied drugs

The modeling described here applies the human ACAT models described in Table 1, and based on the physicochemical inputs listed in Table 2.

3.2. Results of clinical study

A two-way crossover study was conducted in 24 healthy volunteers to assess the effect of food on the exposure of CPD A. A obvious change (about 20% increase) in CPD A plasma exposure was observed in humans at 2 mg when it was administered with food (Table 4). This obvious food effect was predicted accurately (Table 4). As shown in Fig. 1, the simulated plasma concentration–time profiles in fasted and fed conditions captured the mean observed data reasonably well in humans.

3.3. Observed pharmacokinetics of compounds

The results from this study are shown in Fig. 1. The comparison of CPD A tablet between the fasted and the fed state clearly demonstrates a dramatic positive food effect, with much higher bioavailability absorption observed when the tablet is administered with food. The administration of the CPD A tablet with food resulted in an approximately 20 almost percentages increase in C_{max}, and $AUC_{0\text{-}t}$ values respectively, compared to the tablet administered while fasted state.

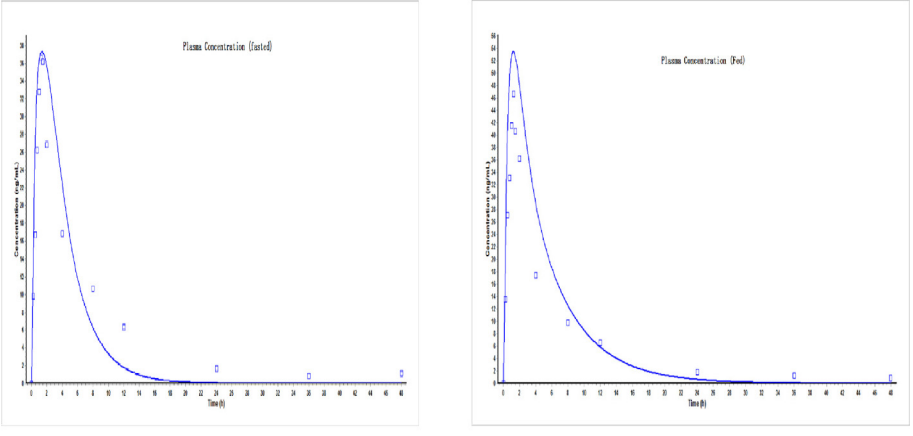
3.4. Development of a human ACAT model

The default GastroPlus™ human physiological models for fasted and fed states are given in Table 1. The pH, lengths, transit time and diameters for all compartments are based on published values (Dressman et al., 1998; Zwart et al., 1999). It should be noticed that the values in these standard GastroPlus™ fasted and fed-state models represent a time average of properties, which actual vary considerably after meal ingestion (Kalantzi et al., 2006). The volume of fluid in human intestines was set at 40% for the small intestine and 10% for the colon based on measurements made by Schiller et al. (2005).

3.5. Silico PBPK absorption model of food effect in human

The plasma concentration–time profile, simulated on the basis of inputing parameters in software, gave a good estimate of the CPD A oral absorption in the fasted state. The generated pharmacokinetic parameters were C_{max} = 37.45 ng/ml, t_{max} = 1.32 h, $AUC_{0\text{-}t}$ = 216.75 ng·h/ml and they agreed well with the values calculated from the in vivo observed data (36.38 ng/ml, 1.17 h, 243.20 ng·h/ml for C_{max}, t_{max} and $AUC_{0\text{-}t}$, respectively). The simulated pharmacokinetic parameters in fed state were C_{max} = 53.44 ng/ml, t_{max} = 1.21 h, $AUC_{0\text{-}t}$ = 274.39 ng·h/mL and they agreed well with the values calculated from the in vivo observed data C_{max} = 46.53 ng/ml, t_{max} = 1.13 h, $AUC_{0\text{-}t}$ = 292.16 ng·h/mL. Although the percent prediction errors for $AUC_{0\text{-}t}$, was a bit lower (more than 10%), the simulated values appear to be good estimates considering the variable in vivo pharmacokinetics of CPD A. It should be noted that the clinical data from different studies vary considerably, depending on age, sex and/or method of CPD A quantification, in addition to the large inter individual variability in drug pharmacokinetics.

The higher postprandial drug plasma concentrations observed in the in vivo study indicated that additional factors contribute to the positive food effect on CPD A absorption. The simulated pharmacokinetic parameters indicating about 20.0% increase in $AUC_{0\text{-}t}$ in the presence of food agreed well



a b

Fig. 1 In silico modeling of CPD A observed food effect using GastroPlus software. The solid circles corresponds to clinical data, whereas the solid line represents GastroPlus simulations predictions. (a) (fasted state), (b) (fed state).

with the value calculated from the mean in vivo observed data (about 17.0% increase in AUC_{0-t}), On the other hand, the percent increase in C_{max} (about 30.0%), calculated on the basis of the in silico generated values, slightly underestimated the in vivo observed decrease in C_{max} in the presence of food (about 22.0% increase). Also, the simulated t_{max} in the fed state was shifted to a mild higher values (1.21 h) in comparison with the mean in vivo observed value (1.13 h). However, considering the large inter individual variability in the rate and extent of CPD A absorption, individual values for C_{max} following the high-fat breakfast varied about 2-fold, which agrees with the findings of observation, the simulated values can be considered as reasonable estimates.

4. Discussion

Food can induce various changes in physiological conditions, such as delayed gastric emptying, blood flow, change of gastrointestinal (GI) pH, stimulation of bile flow, and interaction of intestinal influx or efflux transporters (Fleisher et al., 1999; Benet, 2006; Custodio et al., 2008; FDA, 2002). Especially, bile salt concentrations, which increase in the intestine after a meal from around 4–6 to 10–20 have been shown to increase the solubility and/or dissolution rate for numerous poorly soluble compounds (Charman et al., 1997; Fleisher et al., 1999; Humberstone et al., 1996; Nicolaides et al., 1999; Bates et al., 1966). These factors is always thought to be due to increased solubility via micellar solubilisation or improved wetting in vivo (Kostewicz et al., 2002).

Biopharmaceutical Classification System (BCS) developed by Amidon et al. (1995). It helps categorize drugs based on the drug aqueous solubility and GI permeability. Biopharmaceutics Drug Disposition Classification System (BDDCS) further categorized the drugs based on their solubility and metabolism rates (Custodio et al., 2008; Dahan et al., 2009; Wu and Benet, 2005). Guet al. regarding the generated model, high drug permeability across the intestinal epithelium, delayed gastric emptying time. It may be qualitatively predicted on the basis of the Biopharmaceutics Classification System (BCS). BCS class I drugs are highly-soluble and well absorbed throughout the intestine, and are unlikely to exhibit any food effects. Poorly soluble BCS class II drugs often show increased systemic exposure with food, and this phenomenon is attributable to improved drug solubilization due to higher bile salt concentrations. Negative food effects are mostly seen for highly-soluble, but poorly-permeable BCS class III drugs, especially if a drug possesses a narrow window of absorption. BCS class IV drugs show no clear trend, because the overall effect of food will be governed by either an increase in drug solubility or decrease in its permeability. So, positive food effects are commonly seen for Biopharmaceutics Classification System (BCS) Class II drugs which have low solubility and high permeability (Benet, 2006; Leeson and Springthorpe, 2007) and positive food effects occur when a higher systemic exposure is observed under fed conditions compared with the fasted state.

When a Class II drug is administered shortly after a meal is ingested, food may enhance the solubilization of drug in the intestinal lumen (e.g., via the formation of micelle) and inhibit the efflux transporters in the intestine, and thus improve the absorption. Conversely, food can delay gastric emptying and prolong intestinal transit time, resulting in a delayed t_{max} of the drug product.

This paper presents a case study of a BCS (Biopharmaceutics Classification System) Class II compound CPD A that was observed to have a dramatic positive food effect. It was reported positive food effect by some literatures when it was taken orally under food condition. Modeling techniques of In vitro, in vivo, and in silico were used to illuminate the primary mechanism behind the observed food effect and devise a formulation strategy to mitigate the food effect. According to the Biopharmaceutics Classification System (BCS), CPD A is a BCS class II drug, characterized by low aqueous solubility and high intestinal permeability. Due to the high permeability, and complex absorption pattern, the absolute bioavailability of CPD A tablet after oral administration is high and variable.

The before published studies about CPD A were conducted to identify the distinct phenomena that lead to increase in drug bioavailability in the presence of food, but none of them provided an inclusive interpretation of the positive food effect on CPD A absorption. The purpose of this study was to mechanistically interpret the oral absorption pattern of CPD A in fasted and fed states by designing a drug-specific in silico absorption model that takes into account all the relevant information regarding drug biopharmaceutical properties, along with the physiological characteristics of the gastrointestinal (GI) tract in pre-prandial and post-prandial states. In addition, the generated model served as a tool to demonstrate the combined mechanisms responsible for the positive food effect on CPD A oral absorption.

The generated pharmacokinetic parameters in fasted state were C_{max} = 37.45 ng/ml, t_{max} = 1.32 h, AUC_{0-t} = 216.75 ng·h/mL and they agreed well with the values calculated from the in vivo observed data C_{max} = 36.38 ng/ml, t_{max} = 1.17 h, AUC_{0-t} = 243.2 ng·h/mL. The generated pharmacokinetic parameters in fed state were C_{max} = 53.44 ng/ml, t_{max} = 1.21 h, AUC_{0-t} = 274.39 ng·h/mL and they agreed well with the values calculated from the in vivo observed data C_{max} = 46.53 ng/ml, t_{max} = 1.13 h, AUC_{0-t} = 292.16 ng·h/mL. The simulated values appear to be good estimates, considering the variable in vivo pharmacokinetics of CPD A. According to the obtained results, both models for the fasted and fed states gave good estimates of the CPD A plasma concentration after oral administration. The simulation outcomes coincided well with the values obtained in clinical studies and literature report, indicating that the selected input values adequately reflected the absorption pattern of orally administered CPD A.

The simulated results from this study are shown in Fig. 1. A comparison of two conditions between the fasted and the fed states clearly demonstrates a dramatic positive food effect. Such a strong positive food effect can be attributed to several factors: physicochemical based (solubilization of the drug, sensitivity to GI pH), altered permeability (bile and lipid-influenced influx or efflux), reduced GI emptying and transit, or other physiological changes such as increased splanchnic blood flow or altered gut metabolism (Mathias and Crison, 2012). 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. (1999), 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 (Parrott et al., 2009). These findings were confirmed by Gu et al. who investigated food effects of 92 compounds which correlated with physicochemical properties (Gu et al., 2008); nearly 71% of the BCS class II compounds (low solubility and high permeability) displayed a positive food effect.

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 (Benet et al., 2011), exhibiting decreased solubility and are thus susceptible to precipitation with increased pH in the intestine. 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 compound CPD A increases remarkably in the presence of bile salts that are secreted following the food intake, leading to the additional enhancement in absorption of the compound CPD A. 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. (1996). Solubility measurement in bio-relevant 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.

Food can alter drug absorption via a variety of mechanisms, including impact on GI physiology (e.g. food-induced changes in gastric emptying time, intestinal motility, regional pH values, intestinal fluid composition, hepatic blood flow, luminal metabolism, transporter effect), drug solubility and dissolution, drug permeation, and direct interactions between food components and drug molecules. In addition, food may act as a physical barrier, preventing drug diffusion to the site of absorption (Lentz, 2008; Welling, 1996; Yu et al., 2004). Additional factors is that food may significantly impact drug absorption and distribution by various mechanisms including changing the physiological conditions or direct drug-food interactions.

According to the obtained results, both models for the fasted and fed states gave good estimates of the CPD A plasma concentration after oral administration. The simulation outcomes coincided well with the values obtained in clinical studies, indicating that the selected input values adequately reflected the absorption pattern of orally administered CPD A tablet.

Physiologically based absorption modeling has been recognized as a useful tool to understand the effects of CPD A and formulation properties on bioavailability and explore specific mechanisms for drug absorption. The in silico generated absorption model estimated the in vivo observed increase in the CPD A plasma concentration–time profile, and the positive food effect on CPD A pharmacokinetic should be investigated further in future.

5. Conclusion

Predictions of food effect is necessary throughout the drug discovery and development process. This paper describe a case study of BCSII system drug CPD A that was observed to have dramatic positive food effects. We used gastroplus™ (version 9.0 software), by inputting compound physicochemical parameters such as structure of compound, solubility, permeability, lipophilicity, ionization, transporter data, to simulate food effects for CPD A. CPD A is extensively used in clinical for many years, it is important to notice that effect of food on drug oral way is complex and can change through uncertainties mechanism. The gastroplus™ software simulation technology used in this study afford precise prediction of food effect, an ACAT model as absorption modeling was established to answer the mechanism of food effect of compounds absorption. The positive food effect of the CPD A was resulted from prolonged precipitation time and increased solubility, permeability under fed conditions. This PBPK simulation approach should be applied to other BCS or BDDCS class II compounds with prediction of drug pharmacokinetics processor under food effect. Additionally, the simulated results relive that determination of solubility and permeability for BCSⅡ classification drugs in fed state is indispensable in drug developmental stages.

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