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The role of predictive biopharmaceutical modeling and simulation in drug development and regulatory evaluation☆

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ABSTRACT

Advances in predicting *in vivo* performance of drug products has the potential to change how drug products are developed and reviewed. Modeling and simulation methods are now more commonly used in drug product development and regulatory drug review. These applications include, but are not limited to: the development of biorelevant specifications, the determination of bioequivalence metrics for modified release products with rapid therapeutic onset, the design of *in vitro–in vivo* correlations in a mechanistic framework, and prediction of food effect. As new regulatory concepts such as quality by design require better application of biopharmaceutical modeling in drug product development, regulatory challenges in bioequivalence demonstration of complex drug products also present exciting opportunities for creative modeling and simulation approaches. A collaborative effort among academia, government and industry in modeling and simulation will result in improved safe and effective new/generic drugs to the American public.

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1. Introduction

The FDA encourages the implementation of quality by design (QbD) in the development of all pharmaceutical products, including generic drugs (Yu, 2008). The QbD paradigm is based on building quality into the final product by understanding and controlling formulation and manufacturing variables. Since formulation attributes and manufacturing processes can affect the bioavailability of the drug substance, application of QbD principles can help drug applicants ensure that the new formulation and manufacturing process will produce a bioequivalent product.

Formulation strategies are often based on trial and error and formulator experience. Modeling and simulation methods that predict the *in vivo* performance of drug products can greatly improve formulation strategy by aiding scientists in designing a rational approach to formulation development. FDA's "Critical Path Opportunities for Generic Drugs" recognized that the designing of better absorption models and the developing of *in vitro–in vivo* correlations (IVIVC) were critical modeling and simulation research areas. Predictive models of drug release profiles and the relationship between dissolution and bioavailability/bioequivalence can help guide drug applicants in the implementation of QbD (FDA, 2007; Lionberger, 2008).

One such modeling approach useful in predicting *in vivo* performance of formulations is physiologically based pharmacokinetic (PBPK) modeling. PBPK models have a broad scope and comprise three major components: system-specific properties, drug properties, and the structure model (Rowland et al., 2011). In this article we define PBPK models as the models having physiologically based structures for distribution and clearance that predict pharmacokinetics. Models with physiologically based structure for absorption but connected with an empirical distribution and clearance model were defined as physiologically based absorption models. Biopharmaceutical modeling includes physiologically based absorption models, but has a broader range that includes any models that study/evaluate/predict drug product performance from the physicochemical properties of the drug and the formulation properties of the formulation. Mechanism-based models generally indicate models derived following theoretical laws, such as Fick's laws of diffusion and mass balance. PBPK models, physiologically based absorption models, and some biopharmaceutical models are all different types of mechanism-based models. Mechanism-based models that integrate anatomical and physiological parameters, as well as the physicochemical properties of the drug substance, have been used to predict absorption (Willmann et al., 2003, 2004; Yu and Amidon, 1999), clearance (Watanabe et al., 2009), volume of distribution (Rodgers and Rowland, 2007), tissue distribution

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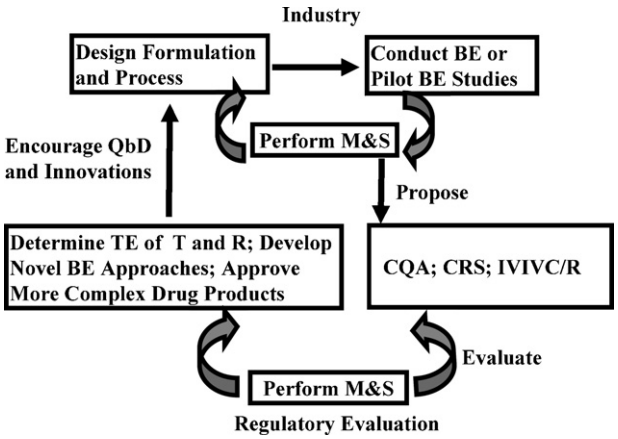

Fig. 1. Advances in predicting *in vivo* performance of drug products has the potential to change how drug products are developed and reviewed. Modeling and simulation can impact drug product development, and the implementation of regulatory concepts such as quality by design also requires advances in biopharmaceutical modeling. *Abbreviations*: M&S, modeling and simulation; BE, bioequivalence; QbD, quality by design; TE, therapeutic equivalence; T, test formulation; R, reference product; CQA, critical quality attributes; CRS, clinically relevant specifications; IVIVC/R, *in vitro* and *in vivo* correlation/relation.

(Baxter et al., 1995; Luttringer et al., 2003; Rodgers et al., 2005; Rodgers and Rowland, 2006; von Kleist and Huisinga, 2007), and drug–drug interaction in humans (Chenel et al., 2008a,b; Kato et al., 2008; Poirier et al., 2007; Vossen et al., 2007). PBPK models are increasingly used as important tools in drug development and regulatory review. FDA's first application of PBPK modeling was in the assessment of the risk of fetal exposure to tretinonin, the active ingredient of a highly teratogenic topical "wrinkle cream". From FDA's analysis, it was concluded that the risk of teratogenicity was minimal and the drug product (Renova®) was approved (Rowland et al., 2011). Today, FDA uses PBPK modeling and simulation in deciding upon the need to conduct specific clinical pharmacology studies, recommendations for specific study designs, and appropriate labeling language (Zhao et al., 2010).

In the context of formulation development, mechanism-based models that have integrated formulation properties as input parameters should yield lower costs and greater time savings. Much effort has been allocated to developing predictive models for oral absorption in various species since oral administration is still the major administration route (Willmann et al., 2003, 2004, 2007, 2010; Yu, 1999; Yu and Amidon, 1999; Yu et al., 1996). As many review articles have already summarized and presented detailed descriptions about how these models were developed and the features of each model (Agoram et al., 2001; Grass, 1997; Huang et al., 2009; Jamei et al., 2009; Norris et al., 2000; Parrott and Lave, 2002), we present here case studies of modeling and simulation-guided oral formulation development based on literature review, as well as drug review areas in which predictive models have been and can be applied.

Fig. 1 graphically illustrates the role of modeling and simulation in drug development and the regulatory review. The pharmaceutical industry and regulatory agency both benefit from incorporating modeling and simulation in the drug development and application review process. For drug companies, modeling and simulation can be helpful in the proper design and formulation of drug products and to propose critical quality attributes, clinically relevant specifications, and IVIVCs. A regulatory agency can employ a variety of modeling and simulation methods to evaluate the above-mentioned, with the objective of confirming the therapeutic equivalence of potential products to the reference product. In addition, modeling and simulation may aid in developing novel approaches to demonstrate bioequivalence, especially for complex drug products. Modeling and simulation efforts foster QbD practices and encourage innovation in drug development and regulatory policy.

In this review, we present examples of regulatory applications of biopharmaceutical modeling in drug review including the development of biorelevant specifications, the determination of bioequivalence (BE) metrics for modified release (MR) products with rapid therapeutic onset, the design of IVIVCs in a mechanistic framework, and the assessment of bioequivalence recommendations for drugs with safety concerns under fasting or fed conditions. Future challenges in drug development with the increasing number of complex drug products will continue to expand the role of modeling and simulation in regulatory science.

2. Modeling and simulation to guide formulation development and abbreviated new drug application (ANDA) review

Over the last two decades, there has been increased emphasis on applying physiologically based absorption models to drug development (Agoram et al., 2001; Parrott and Lave, 2002; Yu, 1999; Yu and Amidon, 1999; Yu et al., 1996). Some pharmaceutical companies use these tools routinely in the drug development chain for drug candidate selection (Brandl et al., 2008), to guide clinical formulation development (Dannenfelser et al., 2004; Kesisoglou and Wu, 2008; Kuentz, 2008; Kuentz et al., 2006), and to reduce the number of trial formulations to decrease development time and cost. Table 1 gives an overview of studies that investigated the impact of formulation properties on pharmacokinetics through physiologically based modeling.

2.1. Formulation development

One of the most frequently used applications of physiologically based absorption models is formulation design and optimization in drug development. This is because physiologically based absorption models integrate formulation properties as input parameters such as particle size distribution, solubility, solubility–pH profiles, and dissolution profiles.

The clinical dosage form development of LAB687 from Novartis is an example of using physiologically based absorption modeling in drug development (Dannenfelser et al., 2004). LAB687 is a poorly soluble and highly permeable compound with minimal first pass metabolism and active transport mechanisms. It has an aqueous solubility of 0.17 μg/mL. Its solubility increases 10-fold in the presence of 40 mM sodium glycocholate with 4 mM lecithin. Three formulations were developed for a dog study: a dry blend consisting of micronized drug, a solid dispersion, and an oral cosolvent–surfactant solution. All formulations were encapsulated and a dose of 50 mg was given to each dog. Before conducting an *in vivo* study, a dog absorption model was developed in GastroPlus™. The model predicted that the change in fraction absorbed is sensitive to changes in *in vivo* solubility and particle size. This suggested that modifying the formulation to improve solubility could increase bioavailability. In this case, modeling and simulation were useful in understanding relationships between absorption and its associated parameters and provided insight into the formulation development process and foresight regarding potential issues prior to formulation investment (Dannenfelser et al., 2004).

Another example of applying physiologically based absorption models in formulation development was published by Roche for R1315 (pK_a = 5.9), which is a poorly soluble (aqueous solubility < 1 μg/mL at pH values higher than 5) and highly permeable

Table 1
Overview of studies investigating the influence of formulation properties on pharmacokinetics in the context of physiologically based modeling.

Modeling and simulation purpose	Example	Property	Ref.
Formulation selection	LAB687, R1315	BCS II	Dannenfelser et al. (2004); Kuentz et al. (2006)
Risk assessment: assessment of API properties, e.g., salt vs. free form, different polymorphs, particle size, density, and surface area	Merck compounds, aprepitant	BCS II/IV	Kesisoglou and Wu (2008)
IVIVC	Glyburide, etoricoxib, carbamazepine, montelukast sodium	BCS I/II	Kovacevic et al. (2009); Okumu et al. (2008, 2009); Wei and Lobenberg (2006)
In support of biowaivers	Multiple compounds	BCS I–IV	Jantratid et al. (2006); Kortejarvi et al. (2010, 2007); Kovacevi et al. (2009); Tsume and Amidon (2010); Tubic-Grozdanis et al. (2008)

compound (Kuentz et al., 2006). Solubility was measured in various media and was found to be highest at 0.2 mg/mL at room temperature in simulated gastric fluid (SGF at pH 1.2). The drug exhibited supersaturation in the presence of mixed micelles. A physiologically based absorption model was constructed in GastroPlus™ for human subjects given an immediate release capsule with 160 mg dose. Parameter sensitivity analysis (PSA) was performed for solubility and particle size under two clinically relevant doses (Kuentz et al., 2006). The simulation results showed that particle size reduction or solubility enhancement by technological means would not lead to increased rate of absorption, which was consistent with the results of a later bioavailability study performed in dogs. Based on simulations and a well designed bioavailability experiment, a sophisticated drug delivery system was not investigated for R1315, contrary to what was initially planned for this biopharmaceutics classification system (BCS) Class II compound (Kuentz et al., 2006). Although this is an example showing how physiologically based absorption modeling can be used in drug development, we also need to understand the assumptions, limitations, and gaps in these models. When we perform physiologically based modeling, it is important to provide sufficient justification for the values used for the uncertain parameters. If justification cannot be provided based on current knowledge, then extensive exploration about the effects of these uncertain parameters on predicted responses is encouraged using parameter sensitivity analysis or Monte Carlo simulations. In this example, the role of dissolution versus solubility and the true impact of the degree of supersaturation and the duration of sustaining of supersaturation to achieve enhancement in the fraction of dose absorbed was not discussed and could be explored using multi-dimensional parameter sensitivity analysis or Monte Carlo simulations.

Application of absorption modeling in understanding the effects of drug substance properties on bioavailability was discussed by Kesisoglou and Wu (2008). Several case studies (BCS Class II/IV compounds) were provided to illustrate how absorption modeling was used to assess the impact of drug substance forms (salt vs. free form and different polymorphs) and bulk properties (particle size, density, and surface area). The absorption modeling served as a risk assessment tool in formulation development to quickly understand the interactions of drug substance properties and bioavailability and to increase confidence in the preclinical animal model data, thus facilitating the decision making process.

2.2. *In vitro–in vivo correlations/relation (IVIVC/R)*

Establishing IVIVCs for poorly soluble compounds is of great interest since an IVIVC may help develop predictive dissolution testing methods and support potential biowaivers (Polli et al., 2008). An IVIVC or IVIVR is possible when the pharmacokinetic properties of the drug product are controlled by the release of the drug from the dosage form. Physiologically based absorption models can extend the scope of possible IVIVCs by accounting for other factors (such as solubility, permeability, or metabolism) that also impact the observed pharmacokinetics. We note that several recent publications describe examples of the application of physiologically based absorption models to develop IVIVCs for Class II/IV compounds, such as glyburide (Wei and Lobenberg, 2006), etoricoxib (Okumu et al., 2009), carbamazepine (Kovacevic et al., 2009), and montelukast sodium (Okumu et al., 2008).

One approach to establishing IVIVCs via physiologically based absorption modeling is to measure solubility and dissolution rate in media with different pH values and compositions that reflect *in vivo* conditions. *In vitro* dissolution can also be calculated from drug particle size, solubility, and surface area using different dissolution models such as the Nernst–Brunner/Noyes–Whitney equation (Brunner, 1904; Nernst, 1904; Noyes and Whitney, 1897). Dissolution profiles under different conditions can be used as model inputs. The predicted pharmacokinetic (PK) profiles based on the physiologically based models can then be compared with the observed PK profile, and the condition that gives the most accurate prediction can be considered the most representative condition of *in vivo* dissolution. For example, the anti-diabetic drug glyburide is a BCS Class II compound with low aqueous solubility which is highly pH-dependent aqueous solubility (Wei and Lobenberg, 2006). The dissolution profiles for two glyburide formulations were tested in different media of either a single pH stage or in dynamic multiple pH stages (Wei and Lobenberg, 2006). Comparing the predictions using different *in vitro* dissolution profiles as the input function, the dynamic LQ-FaSSIF (low quality fasted state small intestinal fluid) media achieved the best prediction of the average AUC and Cmax for the clinically observed data for both test and reference formulations (Wei and Lobenberg, 2006). These results supported a conclusion that the dynamic LQ-FaSSIF dissolution testing was the *in vitro* condition which was most representative condition of glyburide's *in vivo* dissolution. Interestingly, dynamic LQ-FaSSIF was also the most discriminating *in vitro* dissolution test among all the media studied at pH 6.5 (Wei and Lobenberg, 2006). However, in this example, free drug concentrations solubilized in bile salt mixed micelles considered the major factor governing the absorption rate should be reported. In the case of developing an IVIVC for the leukotriene receptor antagonist montelukast sodium, dissolution profiles tested in the custom made flow-through cells gave the most accurate prediction, where the flow of the dynamic dissolution testing was designed to mimic the pH, transit time, and components of the human gastrointestinal (GI) tract (Okumu et al., 2008).

Another approach to establishing IVIVC is through deconvolution of PK profiles to obtain *in vivo* dissolution profiles and compare them with *in vitro* dissolution profiles tested under different conditions to identify the ones that fit closest to the *in vivo* profiles (Zhang

et al., 2011). Because the deconvoluted *in vivo* profiles depend on the relevance of the model to *in vivo* conditions, it is important to validate the model from different perspectives using as much data as possible to ensure that the model best represents *in vivo* conditions. Such limitations should be addressed as part of advancing the science of IVIVC or IVIVR. For example, in a recent modeling study for the anticonvulsant drug carbamazepine, we found that deconvolution of the PK profiles obtained after oral administration of extended release capsules under the GastroPlus™ Opt log *D* Model showed that the *in vitro* dissolution profile tested in media containing 0.1% SLS at a rotation speed of 75 rpm was the closest to the *in vivo* release profile (Zhang et al., 2011). After we obtained the PK parameters (clearance, volume of distribution, and rate constants between compartments) by fitting the compartmental model using immediate-release (IR) suspension data (the fastest releasing and dissolving formulation available), we used the Opt log *D* Model to predict the PK profile after administration of IR suspension. However, we found that the model could not capture the early Tmax, and so we fit the absorption scale factors (ASFs) using IR suspension data to capture the early Tmax. Further modeling deconvolution of PK profiles after administration of extended release capsules using the physiology model obtained from deconvolution of PK profiles after administration of IR suspension showed that the best relationship between *in vivo* and *in vitro* dissolution was at 50 rpm and 0.1% SLS. Thus, the utility of a predictive IVIVC model can be established by validating it under different conditions such as testing with different dosage forms, evaluating not only for traditional PK parameters (Cmax and AUC), but also for the profile similarity (such as Tmax).

2.3. Potential applications of biopharmaceutical modeling in drug development and regulatory review

These mechanism-based modeling approaches, particularly those used during the formulation development stage, can be of great help for development of generic drug product or 'follow-on' formulations. Drug applicants are encouraged to adopt such approaches to guide formulation development and set product specifications, since by the time that generic drug or 'follow-on' formulations are being developed, knowledge of PK properties, pharmacodynamic effects, and mechanism of action of the active ingredients are better understood than when these drugs were first developed as new molecular entities. By the time that a drug has reached the generic or 'follow-on' stage, uncertainties from drug distribution and clearance are most likely minimized and absorption models can be constructed with greater confidence.

An example of the opportunity for modeling and simulation in generic drug development is seen in developing a modified release product. For one example product, the applicant was attempting to adjust the level of release controlling polymer to match the PK profile of the brand drug, or reference listed drug (RLD). The polymer level was adjusted using trial and error to four different levels and each formulation was evaluated in a separate *in vivo* PK study. Because this drug also displayed highly variable PK, it was necessary to use replicate design studies to achieve adequate power to show bioequivalence (Davit et al., 2008; Haidar et al., 2008a,b). Overall, in this example there were 650 subjects dosed throughout development (which was probably 5–10 times the optimal). A modeling and simulation program might have been able to help with identification of optimal value of the critical parameter (release controlling polymer level) through a parameter sensitivity analysis or establishment of an IVIVC. Modeling of sources of variability and use of virtual trials would also lead to more optimal selection of study sizes.

Predictive biopharmaceutical models also have great potential uses in chemistry, manufacturing and control (CMC) review. For example, when there is a large difference in particle size distribution between the RLD and a new proposed generic formulation, a predictive absorption model could be employed to identify the risks in having a significant difference in particle size distribution. Another important application is to define biorelevant dissolution specifications. The first steps include constructing the model, validating the model from multiple aspects, and establishing IVIVC/R. The biorelevant dissolution specification can be identified by comparing the *in vivo* dissolution with the *in vitro* dissolution rate under different conditions.

3. Modeling and simulation to support bioequivalence recommendations

3.1. Partial AUC as a BE measure

The standard statistical measures of BE for orally administered drug products include AUC_{0-t}, $AUC_{0-\infty}$ and Cmax. The area under the plasma concentration–time curve (AUC) and maximum plasma concentration (Cmax) represent the extent and rate of drug absorption, respectively. Bioequivalence is confirmed when for each BE measure, the 90% confidence interval for the test (generic product) to reference (RLD) ratio lies between 80 and 125% for these two parameters. However, there exist multiphasic MR products for which there are concerns that the generic and the corresponding reference products may not be therapeutically equivalent despite being deemed bioequivalent based on the standard BE metrics. Many of these concerns are due to differing plasma concentration profiles between the two products (having one peak vs. multiple peaks, for example). In August 2009, the FDA posted the Draft Guidance for Zolpidem Extended Release (ER) Tablets to recommend the use of a partial area under the curve (pAUC; the area under the plasma concentration–time curve calculated between two specified time points) to establish bioequivalence between the generic and RLD, in addition to the traditional measures of AUC_{∞} and Cmax (FDA, 2009). Shortly after posting the guidance, the FDA's thinking on the pAUC requirements for Zolpidem ER Tablets was discussed at the Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting on April 2010 (FDA, 2010b). The Agency's comments on the use of pAUC in BE evaluation of potential generics to Zolpidem ER Tablets have been published on the federal docket (FDA, 2010a).

Ambien® CR (the RLD for the Zolpidem ER Tablet), used to treat insomnia, consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content. The resulting release mechanism from this formulation design shows biphasic absorption characteristics for Ambien CR, which is critical to the safety and efficacy of this drug product. In this case, the unique Zolpidem plasma profile of Ambien CR is important as there is a clear link between drug concentration and effect. FDA performed modeling and simulation studies to support the evaluation of the need for an additional BE metric and the subsequent identification of the appropriate BE metrics.

In brief, PK profiles were predicted for several investigative Zolpidem ER formulations that were evaluated in a pharmacodynamic (PD) study. Each formulation produced a different PD effect including undesirable outcomes such as residual post-awakening effects (psychomotor impairment) and the results of this study were used to select a formulation for further development. However, PK profiles were not obtained for the formulations used in the PD study. To address this issue, FDA estimated Zolpidem PK profiles for these formulations using IVIVC, deconvolution, and advanced compartmental absorption and transit model (ACAT) (Yu and Amidon, 1999) approaches. The simulations indicated that

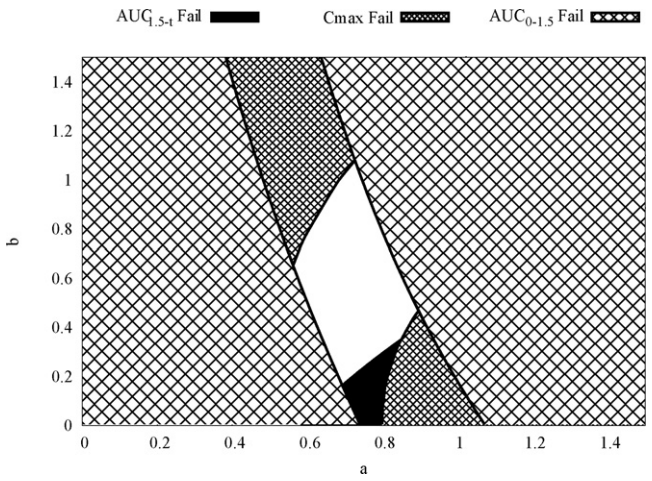

Fig. 2. Exploration of the space of potential generic formulations with *in vivo* release profiles described by Weibull parameters *a* and *b*. The white region indicates the passing space when a pAUC is added to the BE recommendation.

although the formulations had different PD effects, under a sufficiently powered PK study all formulations would be deemed bioequivalent when evaluated using AUC and Cmax. Therefore, results from this modeling study suggested that an additional BE criterion was needed to ensure that a potential generic product would be equivalent to Ambien CR with respect to PD characteristics.

Additional modeling and simulation studies were performed to determine the most effective additional BE measure. Since generic drug products referencing Ambien CR are permitted to use a different formulation design from the RLD, a wide design space encompassing a range of formulation designs was explored to predict the absorption characteristics of potential generic formulations. The Weibull model of drug release was combined with the ACAT model to simulate *in vivo* absorption profiles of the possible range in formulations. Fig. 2 depicts the design space of potential generic formulations with *in vivo* release profiles described by Weibull parameters *a* and *b*, and the passing region when a partial AUC (such as $AUC_{0-1.5\,h}$) is used. It was confirmed from in-house data that formulations within the passing region had formulations that most closely resembled the RLD, particularly in having release characteristics that contributed to early exposure. This finding is consistent with clinical data that supported the approval of Ambien CR, showing that at least 90% of subjects on active treatment were asleep 1.5 h after dosing. This analysis demonstrated that $AUC_{0-1.5\,h}$ was best at discriminating between formulations with respect to the desired response of sleep onset.

FDA anticipates that subsequently, it will be necessary to evaluate other potential generic MR products for which the corresponding RLD product was specifically formulated to accomplish a rapid onset of therapeutic effect. Generic industries may formulate the product using different mechanisms of release and still achieve BE under the standard requirement for Cmax and AUC. In considering the optimal bioequivalence study acceptance criteria for generic versions of multiphasic MR formulations, the FDA must consider how important the early PK profile is to the onset of response, and how important the formulation design is to the onset of response. In order to answer the first question, an established PK/PD relationship would be helpful. An established PK/PD relationship can be used to assess whether additional BE criteria are needed. In order to answer the second question, a mechanistic absorption model may be developed which integrates the dissolution profile as an input parameter. Thus, different formulations can be evaluated and reformulation recommendations can be made based on a well validated absorption model.

3.2. Quantitative prediction of food effect

Food can influence the rate and extent of drug absorption and bioequivalence between test and reference products. It is generally believed that food effects result from changes in drug solubility and other influencing factors that may "delay gastric emptying, stimulate bile flow, change gastrointestinal pH, increase splanchnic blood flow, change luminal metabolism of a drug substance, and physically or chemically interact with a dosage form or a drug substance" (FDA, 2002). In 2002, the FDA issued a guidance entitled, "Food-Effect Bioavailability and Fed Bioequivalence Studies"(FDA, 2002). In this guidance, in addition to a fasting BE study, a fed BE study is generally recommended for BCS Class II, III, or IV drugs in IR products and for all MR drug products in an ANDA submission (FDA, 2002).

However, it may not be feasible to conduct the full set of fasting and fed BE studies in healthy subjects or patients due to safety concerns or tolerability issues. Physiologically based pharmacokinetic models have been utilized to predict food effects quantitatively in humans (Yu and Amidon, 1999). Jones et al. (2006) incorporated biorelevant solubility data into the ACAT model to predict plasma profiles in fasted and fed humans for six molecules. For the majority of compounds, the observed plasma exposure in fasted, fed and high fat diet conditions was correctly predicted and the simulations captured well the magnitude of the food effect. It is stressed that a significant amount of prior verification work was needed including extensive animal and human data to establish confidence in the human absorption model.

The approach of using the ACAT model to quantitatively predict the food effect is particularly appealing for generic drug product development and review. At the stage of generic drug development, most food effect information is publicly available. Researchers are more interested in understanding quantitatively at which dose there would be a food effect and how to design fasting and fed BE studies appropriately. FDA has ongoing research projects to evaluate modeling and simulation in food effect predictions to aid bioequivalence study design. One example was using the ACAT model to predict food effect for a BCS II drug. The drug was formulated as an IR formulation. Pharmacokinetic (PK) data were extracted from a published report after single dose administration of 75 mg IR formulation. A two-compartment model was used to describe the data. The fitted PK parameters (CL, Vc, V2, K12, and K21) were used to model the distribution and elimination. Other input parameters for the absorption model, such as pK_a, log *P*, solubility, particle size and density, permeability were obtained from various sources, or estimated by parameter sensitivity analysis (PSA). Absorption modeling was conducted in GastroPlus™. We first simulated single-dose fasted and fed PK studies under different doses (ranged from 12.5 mg to 500 mg). Then we conducted PSA under fasted and fed conditions to study the sensitivity of PK profiles to formulation changes. The single-dose PK simulations showed that Cmax started to show non-linearity when the dose was greater than 200 mg under fasted but not fed condition (Fig. 3a). The fed/fasted ratio of Cmax was increased from 0.96 to 1.46 when the dose was increased from 100 mg to 500 mg (Fig. 3b). The fed/fasted ratio of AUC_t was increased less significantly, i.e. from 1.00 to 1.12 when dose was increased from 100 mg to 500 mg, suggesting that Cmax was more sensitive at detecting a food effect, and we will only observe food effect at higher doses (Fig. 3b). The simulated results were consistent with the observed trend. Comparison of PSA under fasted and fed conditions showed that PK is more sensitive to formulation parameters such as particle size and density under fasting condition assuming no variability associated with the studies (Fig. 3c and d).

We have seen successful examples showing that physiologically based models have better predictability for food effects compared

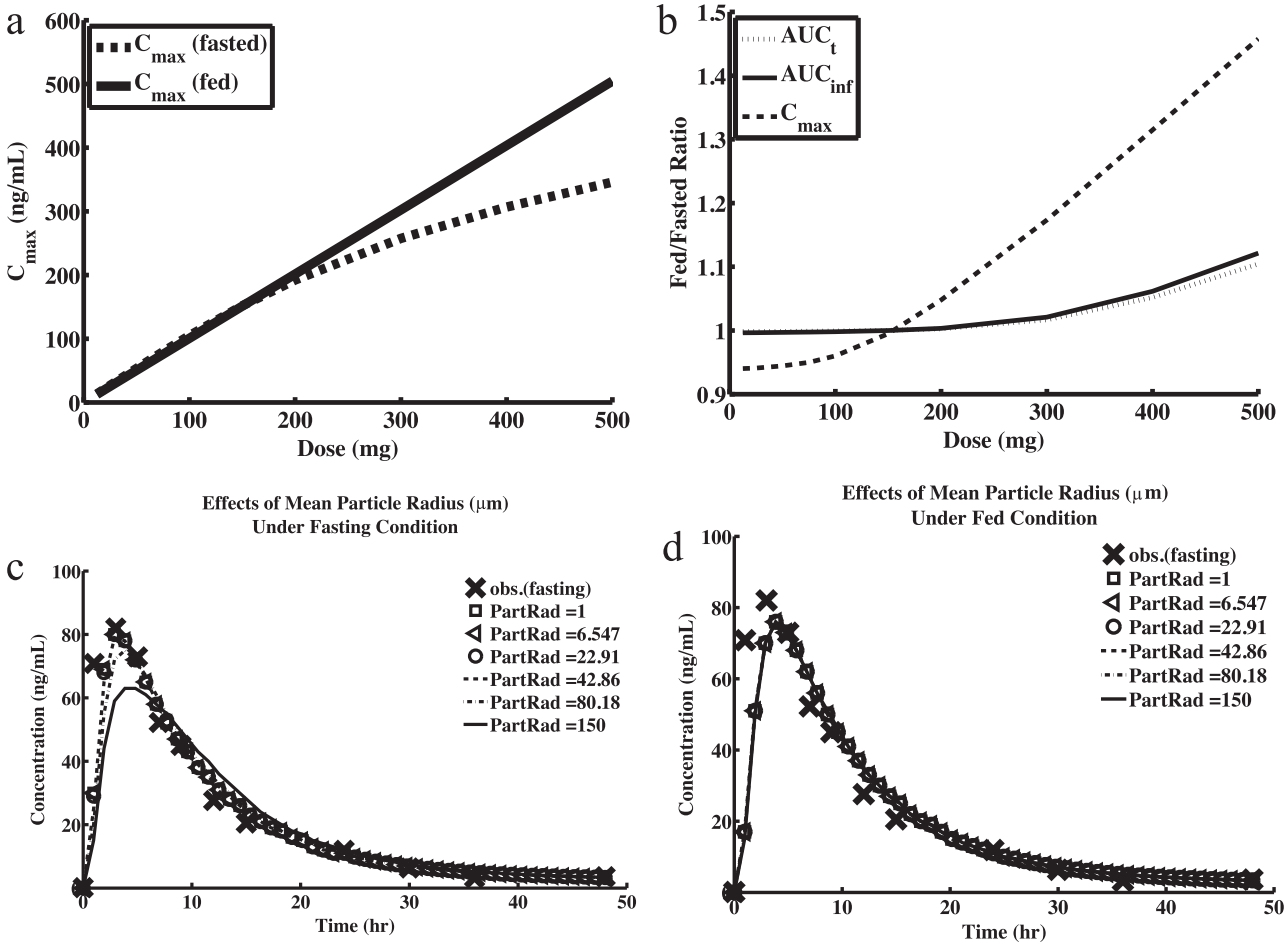

Fig. 3. Prediction of food effect for a BCS II drug: (a) prediction of the change of Cmax with increasing doses under fasting and fed condition, (b) food effect increases with increasing dose and Cmax is a more sensitive parameter to food effect, (c) PK profile changes with the change of particle radius under fasting state, and (d) PK profile changes with the change of particle radius under fed state.

to the dog model for some drugs (Jones et al., 2006; Parrott et al., 2009; Shono et al., 2009; Wei and Lobenberg, 2006) and we have also obtained promising results of physiologically based modeling from our internal studies.

4. Future opportunities and challenges in modeling and simulation

4.1. Biowaiver extension

Possible biowaiver extensions to other BCS Class II, Class III, and intermediate Class I/II compounds are under active discussion among regulators, industry representatives, and academicians within the pharmaceutical sciences community (Blume and Schug, 1999; Cheng et al., 2004; Kortejarvi et al., 2005; Polli et al., 2008; Rinaki et al., 2004; Vogelpoel et al., 2004; Yu et al., 2002), and are mentioned in FDA's critical path report for generic drugs. A recent BCS workshop summary indicated that robust and predictive dissolution methods along with additional simulation validation were needed in order to broadly recommend BCS-based biowaivers for Class II compounds (Polli et al., 2008). To support biowaivers, researchers are applying mechanistic models to justify biowaivers for BCS Class II (Kovacevic et al., 2009; Tubic-Grozdanis et al., 2008) and III (Jantratid et al., 2006; Kortejarvi et al., 2007; Tsume and Amidon, 2010) compounds. Two independent groups recently published articles describing the use of mechanism-based absorption models for BCS I drugs to support the argument that it is not necessary for a drug to be very rapidly dissolving (>85% dissolved in 15 min) in order to be eligible for a biowaiver for BCS Class I drugs (Kortejarvi et al., 2010; Kovacevi et al., 2009).

4.2. Virtual alcohol dose dumping

Unintended, rapid drug release of the entire amount or a significant fraction of the drug contained in a modified release dosage form within a short period of time is often referred to as "dose dumping" (Meyer and Hussain, 2005). One recent example of where QbD can be used in formulation development is the interaction of modified release formulations with alcohol (Meyer, 2005; Meyer and Hussain, 2005). Alcohol-induced dose dumping *in vivo* led to the removal of a hydromorphone [opioid] MR product (Palladone®) from the market. In some cases, conducting an alcohol-induced dose dumping BE study *in vivo* may put the subjects at high risk because alcohol may induce significantly high exposure to the drug. Establishing an *in vitro* test that can identify the risk of dose dumping and compare dose dumping between two products would aid in the development of safe and effective modified-release generic products. Computational modeling could help correlate formulation components and *in vitro* release profiles with *in vivo* PK. Modeling and simulation can help to answer key questions such as which *in vitro* condition would best represent *in vivo* performance, what alcohol concentrations should be used, and the potential pitfalls of not recommending an *in vivo* dose dumping study for a specific drug product.

4.3. Physiologically based modeling of nanosized drug products

Nanotechnology has been extensively applied in drug product development to improve drug targeting, bioavailability, or to decrease toxicity of a drug product when administered via different routes (Junghanns and Muller, 2008). Nanomaterials present significant regulatory challenges because properties of a material relevant to the safety and effectiveness, performance, or quality can change significantly and they can also be difficult to characterize as the particle size enters into the nanoscale range.

Currently, there are more than 20 FDA-approved new drug application (NDA) products which are based on various nanotechnology platforms including liposomes, micelles, nanocrystals, nanoparticles, nanotubes, and superparamagnetic iron oxide particles. Of these, nanocrystal technology has received the most attention as four oral products incorporating the nanocrystal technology are currently marketed in the United States and in other countries: Rapamune® (sirolimus, an immunosuppressant), Emend® (apripetant, an antiemetic), TriCor 145® (fenofibrate, a lipid regulating agent), and MegaceES® (megestrol acetate, a progestin used in oncology).

Nanocrystals, consisting of pure drugs with minimal surface active agents required for stabilization, are carrier-free submicron (10–1000 nm) colloidal drug particles that are further processed into oral and parenteral drug products. The decrease in drug particle size can be linked to both the dissolution rate of the formulation via the Nernst–Brunner equation and the solubility of the active ingredient via the Ostwald–Freundlich equations (Kesisoglou et al., 2007). Willmann et al. (2010) reported that a PBPK model for gastro-intestinal transit and absorption combined with a dissolution model of the Noyes–Whitney type for spherical particles could predict the influence of particle size on the rate and extent of cilostazol absorption under both fasted and fed conditions accurately using PK-Sim®. Shono et al. (2010) also demonstrated that a model based on STELLA software combined with dissolution data in biorelevant media successfully forecasts the *in vivo* performance of both nanosized and micronized formulations of aprepitant in the fed and fasted states. Some permeability restrictions are revealed for the absorption of nanosized formulations.

However, there are some technical challenges of measuring *in vitro* dissolution of nanoparticles as sub-micron particles can easily pass through a line filter, which may overestimate the dissolution rate (Jinno et al., 2006). In addition, currently available dissolution models may have limitations in describing the dissolution behavior of nanoparticles. One hypothesis is that a local "supersaturation" may be present when the nano-sized particles get trapped between apical microvilli. With further advancement in scientific understanding about nanoparticles and their interaction with GI tract, these predictive modeling approaches (Kesisoglou et al., 2007; Shono et al., 2010) may help FDA address some challenging regulatory questions concerning ANDAs utilizing nanotechnologies such as: what are the critical formulation attributes (particle size, particle surface physicochemical properties, etc.) that have the greatest impact on clinical outcome/pharmacokinetics? What are the appropriate specification limits?

For parenterally administered liposomes intended for targeted delivery, PBPK modeling will help predict drug PK at targeted sites and support the BE recommendations for these drug products.

4.4. Physiologically based modeling-aided development of novel BE approaches

Developing appropriate BE metrics for locally acting drugs is always challenging because (1) it may not be possible to directly measure drug exposure at the site of action *in vivo*, and (2) the relationship between exposure at the site of action and plasma exposure is not clear for most cases. By definition, locally acting drugs reach the site of action before they enter the systemic circulation. Some examples of locally acting drugs include inhalation products that target the lung or nasal passages, topical products, and orally administered products targeting the GI tract. Physiologically based modeling may aid development of novel BE approaches in these areas.

GI locally acting drugs can be classified as non-absorbed and absorbed drugs. For non-absorbed drugs, *in vitro* methods are often used to document BE (FDA, 2010c). For locally acting drugs which are systemically absorbed, *in vivo* and/or *in vitro* methods have been recommended for demonstrating BE. *In vivo* methods include a BE study with PK endpoints, PD endpoints, or clinical endpoints. For example, FDA has recently recommended that both *in vitro* dissolution and *in vivo* PK studies be used to demonstrate BE for some mesalamine formulations (FDA, 2010d). Where PK metrics are considered most suitable for BE evaluation of locally acting GI drugs, modeling and simulation can be of great help in maximizing the utility of information obtained from different studies.

For inhalation drugs, the FDA currently limits PK studies to the assessment of systemic exposure and suggests pharmacodynamic studies for testing pulmonary equivalence (Lee et al., 2009). The flat dose-response profile of inhaled corticosteroids (ICS) represents a challenge to recruit a sufficient number of patients to show such a dose-response relationship.

At a 2009 workshop for bioequivalence of orally inhaled drug products, it was suggested that plasma PK may be valuable in assessing BE of ICS for local delivery to the lungs (Adams et al., 2010; FDA, 2004). Hochhaus et al. (Adams et al., 2010) used a "physiological" modeling approach to investigate whether local PK characteristics determining pulmonary efficacy (drug dissolution rate, central vs. peripheral deposition, the effects of mucociliary clearance, and other factors) will be reflected from plasma concentration profiles. The results of clinical trial simulations suggested that AUC and Cmax in healthy volunteers and asthmatics are likely to affect the pulmonary fate of ICS.

In 2010, FDA funded studies to (1) develop a mathematical model to evaluate the effect of physicochemical properties (e.g., aerodynamic particle size distribution) of an orally inhaled drug product and the effect of physiological parameters (e.g., breathing pattern and airway geometries) on total and regional lung deposition and (2) evaluate the effect of changes in critical drug product quality attributes (i.e. aerodynamic particle size and emitted dose) on pharmacokinetics for different orally inhaled drugs. These studies will help establish science-based regulatory requirements for approval of safe and effective generic orally inhaled drug products.

It may be of interest to determine whether transdermal drug delivery system (TDDS) products that utilize various approaches (e.g., penetration enhancers) to achieve bioequivalent systemic drug concentrations have equivalent interactions with skin (Sadrieh, 2009). In addition, BE demonstration of topical dermatological drug products are mostly limited to lengthy and resource-consuming clinical endpoint studies (Kanfer, 2010).

As in the case for inhalation products, PBPK modeling and simulation approaches should be explored to assess whether local concentrations can be predicted from systemic exposure. Dermal microdialysis (Chaurasia et al., 2007; Tettey-Amlalo et al., 2009), a semi-invasive technique that can directly sample drug concentrations within the dermis, can be employed to assess drug exposure profiles over time at the site of absorption under various skin conditions and validate the PBPK model. Research findings from this work will contribute to the estab-

lishment of novel BE approaches for local acting dermatological products.

4.5. Challenges in modeling and simulation

PBPK modeling requires comprehensive physiological, physicochemical and pharmacokinetic data. Some of the physiological processes may not be well characterized, which may lead to suboptimal description of drug pharmacokinetics behavior. For example, quantitative data on the distribution of transporters throughout the small intestine is lacking. Furthermore, some of these data are confidential and not accessible by the public. The underlying assumptions for some models or the use of adjustable parameters are not disclosed, resulting in difficulty of reproducing the modeling and simulation data.

No model is right but can be useful. To date, model utility is only demonstrated with a small set of drugs or formulations. For example, most compartmental and dispersion models have successfully predicted passive oral drugs, but have over- or underpredictions for drugs undergoing first-pass metabolism and transporter mediated influx/efflux (Huang et al., 2009). The validity and quality of the simulation depends not only on the established model and the input data, but also its purpose. Researchers should judge and interpret the simulation data in the right context and be aware of any prediction error and uncertainty. If possible, cross comparisons of various modeling software in predicting the same set of drugs and formulations should be performed. In addition, modeling should never be meant to replace experimental data from well conducted studies.

Within FDA, we noticed that modeling and simulation have been adapted by some companies (Zhao et al., 2010) in the drug development. Under the QbD initiative, we encourage generic applicants to utilize more of their rich formulation and bioequivalence data set to guide drug product development. To advance drug development science, it is essential that both industry and regulatory agencies encourage training opportunities to staff in modeling and simulation. Standardized study protocols and evaluation criteria should be established. Some efforts have been undertaken by the FDA to streamline the process of using PBPK during regulatory review, including criteria for conducting separate confirmatory PBPK modeling and simulations when reviewing PBPK data submitted by the applicant (Zhao et al., 2010).

5. Conclusion

In vivo performance prediction is a valuable tool in drug development and regulatory evaluation. As methods in modeling and simulation for predictions of bioavailability continue to expand and improve, the role of predictive tools in drug development and review will assume greater importance. In this article, we reviewed literature examples to illustrate how predictive mechanism-based models can be integrated in drug development. Example publications demonstrated how such models could help in time and cost savings, which are of great interests for pharmaceutical industries in a highly competitive environment. Modeling and simulation strategies are also gaining broader application in regulatory CMC review, as well as in bioequivalence recommendations. In particular, questions surrounding the most appropriate BE approaches for complex drug products present exciting opportunities for creative modeling and simulation approaches. Drug companies are encouraged to explore modeling and simulation methods to better implement QbD practices, and it is hoped that a collaborative effort among academia, government and industry will result in improved safe and effective new/generic drugs to the American public.

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