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Review Article

Theme: Towards Integrated ADME Prediction: Past, Present, and Future Directions
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Mechanistic Approaches to Predicting Oral Drug Absorption

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Abstract. Modeling and simulation of oral drug absorption have been widely used in drug discovery, development, and regulation. Predictive absorption models are used to determine the rate and extent of oral drug absorption, facilitate lead drug candidate selection, establish formulation development strategy, and support the development of regulatory policies. This review highlights the development of recent drug absorption models including dispersion and compartmental models. The compartmental models include the compartmental absorption and transit model; Grass model; gastrointestinal transit absorption model; advanced compartmental absorption and transit model; and advanced dissolution, absorption, and metabolism model. Compared to the early absorption models, the above models developed or extended since the mid-1990s have demonstrated greatly improved predictive performance by accounting for multiple factors such as drug degradation, gastric emptying, intestinal transit, first-pass metabolism, and intestinal transport. For future model development, more heterogeneous features of the gastrointestinal tract (villous blood flow, metabolizing enzymes, and transporters), food effects, and drug–drug interactions should be fully characterized and taken into consideration. Moreover, predicting population inter- and intravariability in oral drug absorption can be useful and important for the evaluation of clinical safety and efficacy of drugs. Establishing databases and libraries that contain accurate pharmaceutical and pharmacokinetic information for commercialized and uncommercialized drugs may also be helpful for model development and validation.

KEY WORDS: advanced compartmental absorption and transit (ACAT) model; advanced dissolution, absorption, and metabolism (ADAM) model; compartmental model; dispersion model; oral drug absorption.

INTRODUCTION

Oral drug absorption is a complex process. It consists of multiple steps that may include drug disintegration and dissolution, degradation, gastric emptying, intestinal transit, intestinal permeation and transport, intestinal metabolism, and hepatic metabolism. The factors that may have impact on the rate and extent of drug absorption are dosage form, physicochemical and biopharmaceutical properties of the active drug ingredient, and physiology of the gastrointestinal (GI) tract (1,2), as shown in Fig. 1. Knowledge of how these steps and factors influence absorption has fostered the development of predictive models for oral drug absorption. Currently, modeling and simulation of oral drug absorption have been widely used in drug discovery, development, and regulation. The predictive absorption models are used to determine the rate and extent of oral drug absorption, facilitate lead drug candidate selection, establish formulation development strategy, and support the development of regulatory policies.

Based on a previous review by Yu *et al.* (1), mechanistic approaches are classified into three categories: quasiequilibrium models, steady-state models, and dynamic models. The classification of these models is based upon their dependence on spatial and temporal variables. The quasiequilibrium models, which are independent of spatial and temporal variables, include the pH-partition hypothesis (3) and absorption potential concept (4,5). The steady-state models, which were independent of temporal variables, but dependent on spatial variables, include the film model (6), macroscopic mass balance approach (7,8), and microscopic balance approach (9,10). The steady-state models are limited to prediction of the extent but not the rate of oral drug absorption. The dynamic models consider spatial and temporal variables. As an improvement over the steady-state models, the dynamic models can predict both the rate and extent of oral drug absorption. The dynamic models include dispersion models (11) and compartmental models (12–14). Dispersion models portray the small intestine as a uniform tube with axial velocity, dispersion behavior, and concentration profile across the tube (11). Instead of treating the small intestine as one long cylindrical tube in a dispersion model, compartmental models assume the GI tract as one compartment or a series of compartments with linear transfer kinetics,

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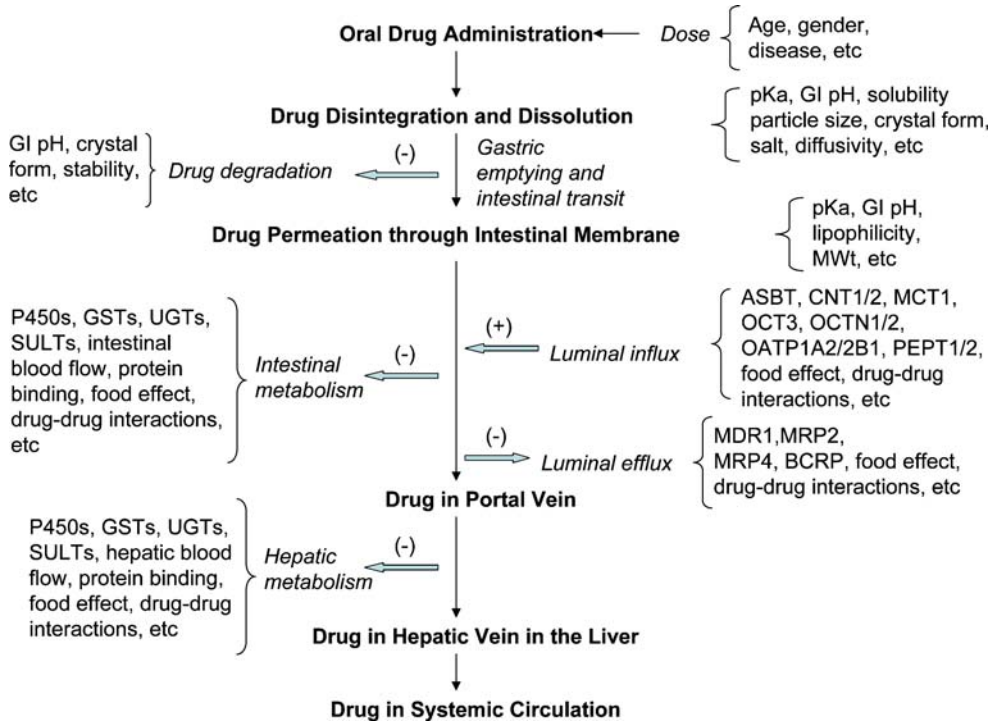

Fig. 1. Steps and related factors in oral drug absorption

and each compartment is well mixed with a uniform concentration (12–15). Both dispersion and compartmental models can be linked to pharmacokinetic models to predict plasma concentration-time profiles of drugs.

The article reviews and compares various mechanistic dynamic models developed and extended from the mid-1990s to the present, including the compartmental absorption and transit (CAT) model; Grass model; GI transit absorption (GITA) model; advanced compartmental absorption and transit (ACAT) model; and advanced dissolution, absorption, and metabolism (ADAM) model. In addition, this review explores future developments of oral drug absorption models with better predictability.

DISPERSION MODEL

The dispersion model defines the GI tract as a single tube with spatially varying properties (pH, surface area, etc.) along the tube. The dynamic drug absorption in the small intestine is based on the convection–dispersion equation, as shown below (1,11):

$$\frac{\partial C}{\partial t} = \alpha \frac{\partial^2 C}{\partial z^2} - \beta \frac{\partial C}{\partial z} - \gamma C \qquad (1)$$

where C is the concentration of a drug in the GI tract, z is the axial distance from the stomach, α is the dispersion coefficient that accounts for mixing by both molecular diffusion and physiologic effect, β is the velocity in the axial direction, and γ is the drug absorption rate constant.

Willmann *et al.* (16) employed an intestinal transit function T_{SI} (defined as the fraction of the drug dose in a certain GI segment at time t) in the dispersion model to describe the movement of the drugs though the intestine. By accounting for the effects of solubility and permeability on drug absorption, the dispersion model has successfully simulated fractions of dose absorbed for a variety of drugs that cover a wide range of absorption characteristics in rat (16), human (17), and monkey (18). For example, the model predicted the oral absorption of BCS Class I drugs (metoprolol, propranolol, levofloxacin, etc.), BCS Class II drugs (ciprofloxacin, diclofenac, carbamazepine, etc.), BCS Class III drugs (atenolol, nadolol, etc.), and BCS IV drugs (furosemide, etc.) (16–19). It was found that, for most passively absorbed drugs, the dispersion model predicted the extent of absorption very well, and the predicted values agreed with the literature (16–18).

However, due to the assumption of negligible first-pass, the original dispersion model may overestimate the absorptive fraction values for compounds such as benazepril, bromocriptine, and lovastatin, which undergo enzyme-mediated presystemic metabolism (18,20–22). In addition, the dispersion models only taking into account passive intestinal permeability may result in an overprediction of the fraction absorbed for P-gp substrates such as doxorubicin and ranitidine (23), and conversely, an underprediction for PEPT1 potential substrates such as valacyclovir (24,25), amoxicillin (26), cefalexin (27), and cefadroxil (27).

Therefore, additional inputs of Michaelis–Menten functions for metabolic enzymes and transporters are needed to overcome these limitations. Later, the dispersion model was used as a part of the PK-Sim® (http://www.pk-sim.com/) whole-body physiologically based pharmacokinetic model (28), which encompasses body and organ weight, blood flow, tissue composition, GI physiology, metabolism, active transport, and controlled release to simulate the GI transit and absorption process. Using *in vitro* dissolution data, PK-Sim® predicted the plasma concentration-time profiles of three

cimetidine tablets with different formulation and dissolution profiles (29). In addition, PK-Sim® also predicted the plasma concentration-time profile of nifedipine, a CYP3A substrate with significant first-pass metabolism (30).

COMPARTMENTAL MODELS

CAT Model

The basic equation for the CAT model is described as follows (Eq. 2):

$$dY_n/dt = K_t Y_{n-1} - K_t Y_n - K_a Y_n, n = 1, 2, \ldots, 7, \quad (2)$$

where Y_n is the percent of dose at the nth compartment, n is the number of total compartments, K_t is the transit rate constant, and K_a is the absorption rate constant.

The original assumptions for this model include passive absorption, instantaneous dissolution, linear transfer kinetics for each segment, and minor absorption from the stomach and colon (1). This model was originally developed to predict oral drug absorption for nondegradable and highly soluble drugs. Nevertheless, this model was shown to capture the dependence of the fraction of dose absorbed on the effective permeability for various drugs with different absorption characteristics (31). The CAT model could also be linked directly to pharmacokinetic models to predict plasma concentration-time profiles.

By incorporating Michaelis–Menten kinetics for carrier/transporter-mediated absorption, gastric emptying rate constant, and compartment-dependent degradation rate constant into the model, the CAT model was extended for predicting dose-dependent drug absorption with degradation in the small intestine, such as for cefatrizine (32). Moreover, the CAT model was extended to simulate the fraction of dose absorbed in controlled release dosage forms by including a compartment that represents the controlled-release dosage form (1). By taking gastric emptying and dissolution into consideration, the CAT model was also used to predict the fraction of dose absorbed for poorly absorptive drugs such as digoxin, griseofulvin, and panadiplon, and to determine the cause of poor oral absorption (dissolution-, solubility-, or permeability-limited absorption) (33).

Based on the CAT model, a very similar approach was developed by Kortejarvi *et al.* (34) by considering the process of gastric emptying, drug dissolution, and drug intestinal transit within the GI tract. This model was constructed using Stella software for investigating the effects of different factors including formulation types, physiology of the GI tract, dissolution, absorption, and elimination on biowaiver criteria evaluation (34). The investigators concluded that, based on the simulation, about half of BCS I drugs have a higher risk to fail a bioequivalence study than BCS III drugs do. The above statement can be valid for some BCS I drugs with rapid absorption and elimination *vs.* BCS III drugs when excipients have no impact on GI transit time and permeability.

ACAT Model

The ACAT model (35) was developed based on the CAT model to include first-pass metabolism and colon absorption (Fig. 2). This model includes linear transfer kinetics and nonlinear metabolism/transport kinetics, six states of drug component (unreleased, undissolved, dissolved, degraded, metabolized, and absorbed), nine compartments (stomach, seven segments of small intestine, and colon), and three states of excreted material (unreleased, undissolved, and dissolved). It takes into consideration physicochemical factors (pKa, solubility, particle size, particle density, and permeability), physiological factors (gastric emptying, intestinal transit rate, first-pass

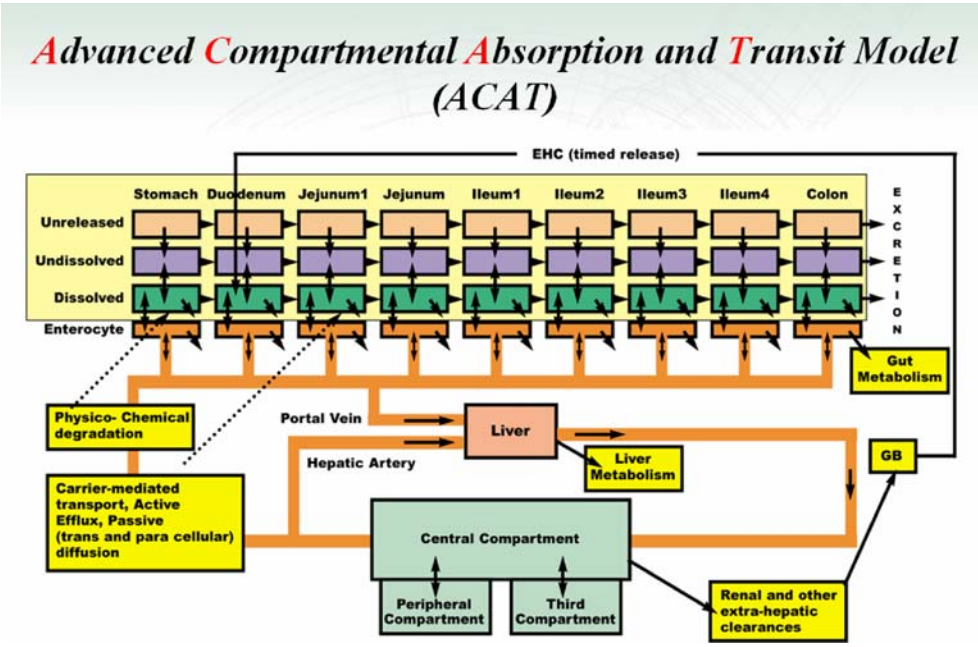

Fig. 2. The schematic diagram of the ACAT model developed by Agoram *et al.* (35). This recent version was provided by Dr. Michael Bolger

metabolism, and luminal transport), and dosage factors (dosage form and dose) in predicting oral drug absorption.

It should be noted that there are a variety of drug metabolizing enzymes and transporters localized in the intestinal epithelial cells (Fig. 3). The interaction of the metabolizing enzymes and transporters may have a complex impact on the oral absorption of their cosubstrates. The ACAT model was able to simulate nonlinear saturable Michaelis–Menten kinetics of metabolism and transport in oral drug absorption by using *in vitro* activity data (V_{max} and K_m) of enzymes and transporters (35).

For example, the ACAT model successfully predicted oral absorption for drugs undergoing first-pass hepatic metabolism (propranolol), first-pass intestinal and hepatic metabolism (midazolam), efflux transport (digoxin), and first-pass metabolism plus efflux transport (saquinavir, Fig. 4) (35). Furthermore, this model demonstrated the potential to predict food–drug interactions (e.g., grapefruit juice with CYP3A substrates) and drug–drug interactions (e.g., rifampin with P-gp substrate digoxin) during oral drug absorption. However, some features that have an impact on drug absorption, such as local structure of gut enterocytes, cytoplasmic protein binding, segregation of blood flow to the intestine, and the heterogeneous expression and activities of drug metabolizing enzymes and transporters along the GI tract were not included in the original ACAT model (35).

The commercially available software, GastroPlus™, was developed based on the ACAT mode. This software has undergone several improvements with respect to the capability in predicting oral absorption of a variety of drugs in comparison to the original ACAT model. Gastroplus™ has been used to simulate the *in vivo* absorption profile of drugs by using *in vitro* dissolution data, for establishing the *in vitro–in vivo* correlation (36,37). With an integration of drug physicochemical properties and physiological parameters, Gastroplus™ has been used to aid in justifying biowaivers for selected BCS II compounds (38). Moreover, the impact of different formulation factors such as solubility, particle size, and size distribution on oral drug absorption were also predicted by GastroPlus™ (39–41). Combined with biorelevant solubility, the magnitude of food effects and the oral pharmacokinetics of different drugs under fasted and fed

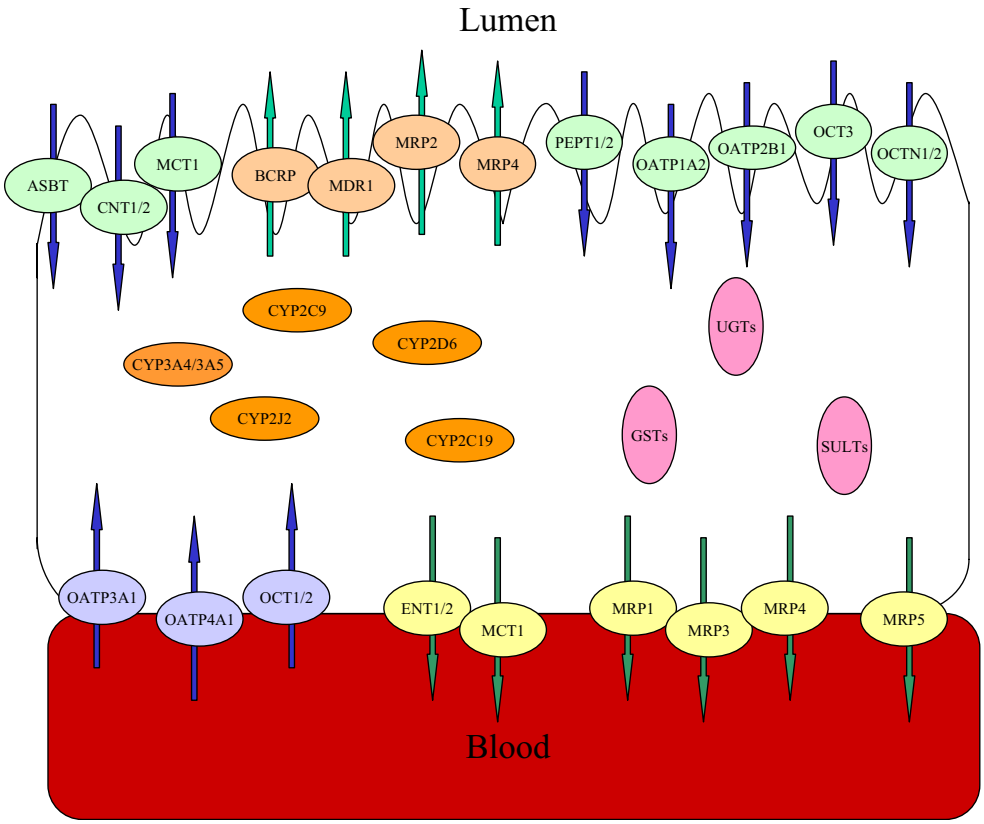

Fig. 3. The intestinal metabolizing enzymes and efflux/influx transporters. The metabolizing enzymes include phase I enzymes such as cytochrome P450s (*CYPs*) including CYP3A4/3A5, CYP2C9, CYP2C19, CYP2J2, CYP2D6, etc. (67), and phase II enzymes such as UDP-glucuronosyltransferases (*UGTs*), sulfotransferases (*SULTs*), and glutathione S-transferases (*GSTs*). The intestinal transporters are expressed in the intestinal basolateral membrane (MRP1, MRP3, MRP4, MRP5, MCT1, ENT1/2, OATP3A1/4A1, and OCT1/2. *MRP*, multidrug resistance-associated protein; *MCT*, monocarboxylic acid transporter; *ENT*, equilibrative nucleoside transporter; *OATP*, organic anion-transporting polypeptide transporter; *OCT*, organic cation transporter) and luminal membrane (MDR1, MRP2, BCRP, MRP4, PEPT1/2, MCT1, OATP1A2, OATP2B1, OCT3, ASBT, CNT1/2 and OCTN1/N2. *MDR*, multidrug resistance protein; *BCRP*, breast cancer resistance protein; *PEPT*, peptide transporter; *ASBT*, apical sodium-dependent bile acid transporter; *CNT*, concentrative nucleoside transporter; *OCTN*, carnitine/organic cation transporter) (19)

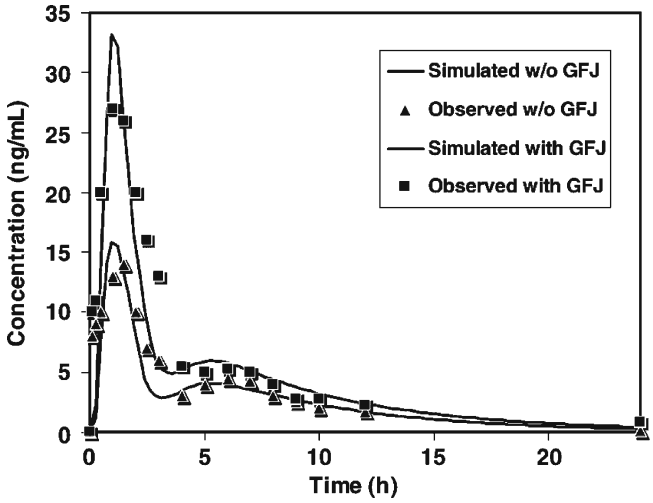

Fig. 4. Oral bioavailability of saquinavir with and without grape fruit juice simulated by using the ACAT model. Reprinted from Agoram *et al.* (35) with permission of Elsevier

conditions were also predicted by Gastroplus™ (42). In addition to its use for predicting oral drug absorption in the GI tract, whole-body physiologically based pharmacokinetic (43) and combined pharmacokinetic and pharmacodynamic (44) models have been constructed within Gastroplus™ for predicting whole-body pharmacokinetic and pharmacodynamic characteristics in humans.

For drugs that undergo intestinal efflux, such as talinolol (a P-gp substrate), an additional consideration of a heterogeneous expression of P-gp across the intestine was included to simulate the nonlinear pharmacokinetics (dose-dependent absorption) after administration of a series of doses of talinolol immediate-release tablets (44), based on the fact that the P-gp expression level increases from duodenum to jejunum, to ileum, to cecum, and to colon (45).

Grass Model

A physiologically based multiple-compartmental model was developed by Grass (46) for predicting oral drug absorption. This model describes fluid movement (emptying and transit) in the GI tract and calculates the drug absorption (flux) in each compartment (stomach, duodenum, jejunum, ileum, and colon) over time based primarily on three parameters—solubility, permeability, and tissue surface area.

This model was shown to predict plasma concentration-time profiles including the AUC, C_{max}, and T_{max} for ketorolac (BCS I) and ganciclovir (BCS III) well. The software IDEA™ (47) was developed based upon compartmental models (IDEA™ is not currently available). By using IDEA™, the fractions of dose absorbed for atenolol (BCS III), naproxen (BCS II), and ganciclovir (BCS III) in animals and humans were successfully predicted (47). Similar to GastroPlus™, factors including dose, solubility, and permeability are considered. However, IDEA™ does not take first-pass metabolism and drug transport into account.

The main difference between early versions of GastroPlus™ and IDEA™ is that, for pure *in silico* prediction, Gastroplus™ requires the aid of QMPRPlus™ to estimate solubility, permeability, and lipophilicity based on the chemical structure input, but IDEA™ only requires chemical structure as input. Another difference is that IDEA™ directly uses permeability data from Caco-2 cells or rabbit intestinal tissue, whereas GastroPlus™ uses human permeability data transformed from *in situ* intestinal permeability data of rat or dog or Caco-2 data (48,49). A set of 28 drugs was selected for predicting their absorption classes and fractions absorbed by using both early versions of GastroPlus™ and IDEA™; both approaches showed similar predictive abilities (48). In the early discovery phase, IDEA™ is easy and convenient to use for predicting characteristics of drug oral absorption based on chemical structure. For late discovery and development, as well as for formulation evaluation, however, GastroPlus™ is more powerful for integrating data and takes into consideration factors such as first-pass metabolism, transport process, and dosage form.

GITA Model

Intestinal transit time could be variable across different segments of intestine and could impact drug absorption. In addition, the extent of drug absorption in each segment could differ due to heterogeneity in physiology and structures, including heterogeneous expression patterns of metabolizing enzymes and transporters.

Based on the above considerations, the GITA model was proposed (50). This compartmental model divides the GI tract into eight segments (stomach, duodenum, upper jejunum, lower jejunum, upper ileum, lower ileum, cecum, and large intestine), and GI transit and absorption processes in each segment are incorporated. In this model, the absorption rate constant for each segment was determined by a conventional *in situ* closed-loop method, and the GI transit rate constant for each segment was determined based on *in vivo* studies using phenol red, a nonabsorbable marker. The following equations (Eqs. 3 and 4) describe drug movement from a segment (i) to the next segment (i+1) with segmental absorption (first-order absorption):

$$\text{Stomach: } dX_s/dt = -(k_s + k_{as})X_s \tag{3}$$

$$\text{Intestine: } dX_{i+1}/dt = X_i k_i - (k_{i+1} + k_{ai+1})X_{i+1}, \tag{4}$$

where at t=0, X_s is the dose of the orally administered drug and X, k, and k_a represent the amount, the transit rate constant, and the absorption rate constant, respectively. The subscripts s and i indicate stomach and each intestine site, respectively.

The GITA model was originally proposed to predict oral drug absorption in rats because it is possible and convenient to conduct the *in situ* closed-loop experiment in animals rather than in humans. Later, Kimura and Higaki (51) demonstrated an application of the GITA model to humans for prediction of oral absorption of theophylline. In this model, the transit rate constant in humans was measured via gamma scintigraphy, and the absorption rate constant in humans was estimated by normalizing the absorption rate constant in rats based on interspecies differences in surface area and luminal volume of the small intestine.

By accounting for the variations of drug absorption and GI transit among these segments, the GITA model was used to predict site-specific oral drug absorption (52). Moreover, this model was used to study the effects of food–drug interactions and drug–drug interactions on oral absorption (51). In the original GITA model, the plasma concentration-time profile was overpredicted for drugs undergoing first-pass metabolism, such as propranolol (50). Incorporating a first-pass effect into the GITA model successfully predicted the oral absorption profile of *N*-methyltyramine, a compound with first-pass metabolism (53). Furthermore, by incorporating the dissolution process, the GITA model predicted the plasma concentration-time profiles of theophylline (BCS I) and griseofulvin (BCS II) when administered as powders (54,55).

ADAM Model

Similar to the ACAT model, the ADAM model was recently developed based on the CAT mode, and it is a compartmental transit model consisting of seven compartments for the small intestine (56,57). The ADAM model considers the GI physiology including gastric emptying time, small intestinal transit time, and the radius and length of the small intestine, which were defined by the CAT model and literature values.

Similar to the ACAT model, the ADAM model accounts for the processes of dissolution, GI fluid transit, gut wall permeation, drug degradation, intestinal metabolism, and active transport (implicit consideration as stated by Jamei *et al.*) (56). In addition, the ADAM model also considers the heterogeneity of the GI tract such as heterogeneous distribution of enterocytic blood flow and enzymes in the gut wall. Food effects such as the impact of changes in gastric emptying, splanchnic blood flow, and luminal pH are also taken into consideration and simulated (56). Differing from other approaches using the Noyes–Whitney model (58), the ADAM model uses the generalized diffusion model developed by Wang and Flanagan (59) to describe dissolution under both sink and nonsink conditions.

The model is implemented in the simulation software Simcyp® (http://www.simCYP.com/). Simcyp® has successfully predicted the plasma concentration profiles for three modified release formulations (fast, moderate, and slow) of metoprolol (60). In addition, the midazolam first-pass intestinal extraction ratio and its interindividual variability were also predicted well by Simcyp®. The simulation also predicted the regional fractions of the dose absorbed and metabolized for midazolam, as well as the related interindividual variabilities in different segments of the small intestine (56).

CONCLUSIONS AND FUTURE DIRECTIONS

For the past decade, pharmaceutical scientists have developed and extended mechanistic absorption models to simulate the rate and extent of oral drug absorption. Compared to the early models, the recently developed or improved models have better predictability by accounting for multiple oral absorption factors such as dissolution, degradation, gastric emptying, intestinal transit, first-pass metabolism, and intestinal transport (Table I). In addition, recent models

Table I. Comparisons of Different Mechanistic Approaches for Predicting Oral Drug Absorption

Model	Classification	Rate-Limiting Step	Gastric Emptying and Intestinal Transit	Dissolution	Degradation	Passive Diffusion	First-Pass Metabolism	Active Transport	Reference
CAT	Dynamic/compartmental transit	Variable	√	√	√	√	×	√	(1,32,33)
Grass	Dynamic/compartmental transit	Variable	√	√[a]	×	√	x	x	(46,47)
GITA	Dynamic/compartmental transit	Variable	√	√	×	√	√	×	(50,53–55)
ACAT	Dynamic/compartmental transit	Variable	√	√	√	√	√	√	(35)
ADAM	Dynamic/compartmental transit	Variable	√	√	√	√	√	√[b]	(56)
Dispersion	Dynamic/dispersion	Variable	√	√[a]	×	√	×	×	(16–18)

All the models listed above are original models as shown in the references.
[a] Only solubility and dose are considered.
[b] Implicit consideration as stated by Jamei *et al.* (56).

have assessed food effect, explored *in vitro–in vivo* correlation, and estimated drug–drug interactions.

To date, there is no "perfect" model to completely capture the complexity of the oral drug absorption process. In addition, proof of model utility is based on illustration with a small set of drugs or formulations. There are very few cross comparisons of various methods in predicting the same set of drugs and formulations. In general, most compartmental and dispersion models successfully predicted passive oral drug absorption of selected drugs and drug formulations. However, for drugs undergoing first-pass metabolism and transporter-mediated influx/efflux uptake, over- or underpredictions may occur depending on the mechanisms involved. Scientists in the area of drug metabolism and transport have developed several novel approaches, such as the intestinal epithelial cell model (61), which can be used to predict the impact of intestinal CYP3A and P-gp interaction on oral drug absorption, the segregated-flow model (62) and segmental segregated-flow model (63), which can be used to explain "route-dependent" metabolism by assuming only a partial intravenous dose reaches the enterocyte region. These models may complement the oral drug absorption models to improve the predictability of oral drug bioavailability.

Although *in vitro* and *in vivo* animal data are often used to inform the models, we need to be cautious since there are significant interspecies differences in expression levels and patterns of metabolizing enzymes between human and rat that may influence the prediction of oral bioavailability in humans (64). In addition, Caco-2 permeability data are suitable to simulate the extent of passive oral dug absorption, but may not be valid for active transport-mediated oral drug absorption since the gene expression of transporters in Caco-2 cells differ qualitatively and quantitatively from those in human intestinal mucosa (65). Furthermore, in the early phase of drug development, different enzyme sources (microsomes, supersomes, and hepatocytes), cell line sources (Caco-2 and MDCK cells), and assay conditions (pH, coenzymes, and ionic strengths) may bring variability into the estimates of V_{max} and K_m that are used in the model.

For future model development, more heterogeneous features of the GI tract should be characterized and considered, such as heterogeneous distribution of villous blood flow, local structure of gut enterocytes, enterocyte protein binding, and different expression patterns of metabolizing enzymes and drug transporters in the intestine. Other factors, such as food effects and drug–drug interactions, including effects of inducers or inhibitors of enzymes/transporters, may increase inter- and intraindividual variations in oral drug absorption. These factors should also be fully characterized and taken into consideration. Moreover, predicting population inter- and intravariability in oral drug absorption can be useful and important to evaluate clinical safety and efficacy of drugs.

An important aspect in the development of new models will be the acquisition and collection of a large volume of absorption data. By establishing databases and libraries that contain accurate pharmaceutical and pharmacokinetic information for commercialized and uncommercialized drugs, the e-ADME concept that calls for reducing animal and human testing and enhancing computer prediction for drug development and regulation (66) may be implemented.

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