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Continuous Intestinal Absorption Model Based on the Convection–Diffusion Equation

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Abstract

Prediction of the rate and extent of drug absorption upon oral dosing needs models that capture the complexities of both the drug molecule and intestinal physiology. We report here the development of a continuous intestinal absorption model based on the convection–diffusion equation. The model includes explicit enterocyte apical membrane and intracellular lipid radial compartments along the length of the intestine. Physiologic functions along length x are built into the model and include velocity, diffusion, surface areas, and pH of the intestine. Also included are expression levels of the intestinal active uptake transporter OATP2B1 and efflux transporter P-gp. Oral dosing of solution as well as solid (with a dissolution function) was modeled for several drugs. The fraction absorbed (FA) and concentration–time (C – t) profiles were predicted and compared with clinical data. Overall, FA was well predicted upon oral ($n = 21$) or colonic dosing ($n = 11$), with four outliers. The overall accuracy (prediction of the correct bin) was 81% with outliers and 90% without outliers. Of the nine solution dosing data sets, six drugs were very well predicted with an exposure overlap coefficient (EOC) > 0.9 and predicted $C_{\max}$ and $T_{\max}$ values similar to those observed. Of the six solid dose formulations evaluated, the EOC values were > 0.9 for all drugs except budesonide. The observed precipitation of nifedipine at high doses was predicted by the model. Most of the poor predictions were for drugs that are known to be transporter substrates. As proof of concept, incorporating OATP2B1 and P-gp markedly improved the EOC and predicted $C_{\max}$ and $T_{\max}$ for fexofenadine. Finally, the continuous intestinal model accurately recapitulated the known relationships between drug absorption and permeability, solubility, and particle size. Together, these results indicate that this preliminary intestinal absorption model offers a simple and straightforward framework to build in complexities such as drug permeability, lipid partitioning, solubility, metabolism, and transport for improved prediction of the rate and extent of drug absorption.

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Notes

The authors declare no competing financial interest.

Supporting Information

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Equation details (PDF)

Graphical Abstract

Keywords

intestinal absorption; pharmacokinetics; modeling; transporter

INTRODUCTION

Use of models to predict pharmacokinetics (PK) is becoming an important part of the drug discovery and development process. These models range from classic compartmental models for which clearance and distribution terms are estimated from in vitro or preclinical data to full physiologically based pharmacokinetic models. Some of the most useful models today are hybrid models in which clearance or target organs (i.e., liver, kidney, brain) are modeled explicitly, and the rest of the body is modeled as central and peripheral compartments. However, PK prediction for oral drugs generally requires either an assumption of some combination of first- and zero-order absorption or inclusion of mechanistic absorption components. For a model to be useful in formulation efforts, an absorption model should be able to model permeability-, dissolution-, and solubility-limited absorption.

The most common intestinal absorption models in use today are based on a compartmental and transit approach.^{1–4} These models divide the intestine into several compartments and use transfer functions to move content from one compartment to the next. Compartments can also be provided for solid forms allowing for disintegration and dissolution. Dissolved drug can diffuse into the enterocytes, and saturable processes such as metabolism and transport can be included. Since all compartments are discrete, the system can be solved as ordinary differential equations (ODEs).

Another approach to modeling intestinal absorption is to treat the intestine as a continuous compartment with concentrations changing as a function of distance (x) and time (t). Several continuous models have been reported,^{5–9} but none appears to have seen wide use. Models by Ni⁵ and Stoll⁶ are based on the convection–diffusion equation, which describes velocity and diffusion in the lumen as the first and second derivatives of concentration, respectively. Although the resulting partial differential equations (PDEs) are computationally expensive to solve, the forms of these models are very simple. Since computational speeds have increased greatly and commercial software programs now provide robust numerical methods for the solution of PDEs, we revisited the use of the convection–diffusion equation to model

intestinal absorption. The foundation of this modeling effort is to use experimental data to parametrize velocity and diffusion and to incorporate simple functions that describe relevant physiological properties (surface area, pH, transporter expression, etc.) as a function of x . This foundation allows us to incorporate and test processes relevant to the rate and extent of drug absorption.

METHODS

The model described here is based on the convection–diffusion equation, similar to that described by Ni et al.⁵ and Stoll et al.⁶ The basic equation is

$$\frac{\partial}{\partial t}C(x, t) = D \frac{\partial^2}{\partial x^2}C(x, t) - \frac{Q}{\pi r^2} \frac{\partial}{\partial x}C(x, t) - \sum_{i=1}^n k_i C(x, t) \quad (1)$$

where drug concentration (C) varies as a function of distance (x) and time (t), D is the diffusion coefficient of the drug molecule, Q is the bulk fluid flow rate, r is the radius of the intestinal lumen, and k_i is the first-order rate constant for the i th radial transfer process such as diffusion or active transport. The first two terms, diffusion and convection, are associated with axial movement of drug (in the x direction) within the lumen, and the last term represents radial transfer of drug in and out of the lumen. For saturable processes, a hyperbolic function would be substituted for k_i .

The static structure of the model is a continuous cylinder (Figure 1A) with a radius $r_1 = 1.25$ cm for the small intestine and $r_2 = 2.5$ cm for the large intestine.¹⁰ The lengths of the various intestinal regions are set as 0.2 m for the duodenum, 1.3 m for the jejunum, 2.5 m for the ileum, and 3 m for the colon. The radial compartments are concentric tubes denoting lumen, apical enterocyte membrane, enterocyte cytosol, intracellular lipid, and basolateral blood (Figure 1B,C). The dynamic structure of the model consists of a pulse of drug that is introduced from a stomach model into the intestinal model. This pulse of drug moves with a predefined velocity profile with concurrent axial diffusion. Two of the complexities of intestinal absorption include a complex velocity profile and changes in water volume due to absorption and secretion. In this model, these two processes are directly related. Specifically, the experimentally observed absorption of water in the human proximal intestine¹¹ occurs concomitantly with a decrease in pulse velocity.¹² Also, secretion of water is observed in the terminal ileum,¹¹ and the velocity increases. This relationship allows us to construct a velocity-based model, where absorption and secretion of luminal water are modeled with a decrease and increase in velocity, respectively. Decreased/increased water content results in increased/decreased drug concentrations as well. The current approach models fasted drug absorption. Complexities such as food intake, physical activity, enterohepatic recirculation, etc. are not included here but could be incorporated into the model.

To derive the full PDEs for drug concentration as a function of x and t (distance and time), it is necessary to develop expressions for all processes that vary as a function of x . These processes include the following physiological parameters: velocity, effective diffusion,

cross-sectional areas for each radial compartment, surface areas, and pH. Functions for drug specific processes such as metabolism, transport, and degradation are also required. In general, we use a combination of logistic functions to construct the appropriate parameters as a function of x . Use of these functions allows for construction of continuous expressions with smooth transition between intestinal regions. These equations are easily differentiable and prevent mathematical discontinuities. The following equations were developed.

PHYSIOLOGIC FUNCTIONS

The units for all functions are distance, m; time, h; concentration, mg/m^3 ($\mu\text{g/L}$).

Velocity, $\text{vel}(x)$

Experimental position versus time data from Worsøe et al.¹² were used to calculate experimental velocities as a function of x . These data were used to build the following expression for $\text{vel}(x)$. Both the experimental velocities and equation show a decrease in velocity through the midileum and an increase from the midileum to the beginning of the colon. The increased radius of the colon also results in a decrease in velocity. Eq 2 was used, and the profile is shown in Figure 2A:

$$\text{vel}(x) = \frac{a_1}{a(x)} \left(6 - \frac{5.5}{1+e^{-3(x-1)}} + \frac{0.7}{1+e^{-6(x-3)}} - \frac{0.6}{1+e^{-3(x-4.75)}} - \frac{0.6}{1+e^{-6(x-6.8)}} \right) \quad (2)$$

where $a(x)$ is the cross-sectional area as a function of distance, and a_1 is the cross-sectional area at radius r_1 .

Effective Diffusion, $\text{dif}(x)$

For intestinal absorption, effective axial diffusion is likely due to the spreading of a drug pulse during peristalsis. The expression for $\text{dif}(x)$ was developed to match the experimentally observed position of intestinal contents at 6 h¹³ while maintaining a general relationship between effective diffusion and velocity. If the effective diffusion was too small for a given velocity, a numerical solution of the PDEs for convection–diffusion equations could not be obtained. The following expression was used for effective diffusion, and the profile is shown in Figure 2B:

$$\text{dif}(x) = 0.005 \left(6 - \frac{5.5}{1+e^{-3(x-1)}} + \frac{0.7}{1+e^{-6(x-3)}} - \frac{0.6}{1+e^{-3(x-4.75)}} - \frac{0.6}{1+e^{-6(x-6.8)}} \right) \quad (3)$$

Cross-Sectional Area, $a(x)$

The cross-sectional area is determined by the radii of the small and large intestines, r_1 and r_2 , as follows (Figure 2C):

$$a(x) = a_1 + \frac{a_2 - a_1}{1 + e^{-25(x - ile)}} \quad (4)$$

where $a_1 = \pi r_1^2$, $a_2 = \pi r_2^2$, and $ile = 4.0$ m was used for distance to the end of the ileum.

Surface Area, $sa(x)$

The expression for surface area per unit length (circumference) was based on reported physiological surface areas for each section of the intestine.¹⁰ These areas were determined by the radii and multiplication factors for villi and microvilli. The expressions to link the intestinal segments are as follows (Figure 2D,E).

Accounting for the increase in surface area due to villi, the surface area, $sa_{villi}(x)$ is

$$sa_{villi}(x) = 9.2 + \frac{4.9}{1 + e^{-25(x - (0.05 + duo))}} + \frac{1.6}{1 + e^{-50(x - jej)}} - \frac{9.1}{1 + e^{-25(x - ile)}} \quad (5)$$

where values (in meters) of $duo = 0.2$, $jej = 1.4$, and $ile = 4.0$ were used for distance to the end of the duodenum, jejunum, and ileum, respectively.

Further, accounting for the increase in surface area due to villi and microvilli, the net effective surface area, $sa_{lumen}(x)$ is

$$sa_{lumen}(x) = 3.9 + \frac{4}{1 + e^{-25(x - (0.05 + duo))}} - \frac{3.4}{1 + e^{-50(x - jej)}} - \frac{3.55}{1 + e^{-25(x - ile)}} \quad (6)$$

Cross-Sectional Area for the Enterocyte Apical Membrane, $a_{mem}(x)$

The cross-sectional area for the enterocyte apical membrane is determined by the surface area of the small and large intestines multiplied by the width of the plasma membrane (35 Å):

$$a_{mem}(x) = 35 \times 10^{-10} sa_{lumen}(x) \quad (7)$$

Cross-Sectional Area for the Enterocyte Cytosol, $a_{cell}(x)$

The cross-sectional area for the enterocyte cytosol is calculated as the surface area of the small and large intestines multiplied by an average diameter of an enterocyte (20 μm):

$$a_{cell}(x) = 20 \times 10^{-6} sa_{villi}(x) \quad (8)$$

Cross-Sectional Area for the Cytosolic Lipid, $a_{lip}(x)$

The cross-sectional area for the cytosolic lipid is calculated as 7% of the enterocyte volume:

$$a_{lip}(x) = 15 \times 10^{-7} sa_{villi}(x) \quad (9)$$

pH of the Intestines, pH(*x*)

The pH function was described by a combination of logistic functions to capture the varying pH across the length of the intestine¹⁴ (Figure 2F):

$$\text{pH}(x) = 6.1 + \frac{1.1}{1 + e^{-2(x-2)}} - \frac{0.8}{1 + e^{-50(x-4)}} + \frac{0.4}{1 + e^{-5(x-4.5)}} \quad (10)$$

DRUG-SPECIFIC FUNCTIONS

Apparent Permeability, $P_{\text{app}}(x)$

For the current model, apparent permeability (P_{app}) is based on Caco-2 cell permeability data conducted at a pH termed pH_{caco} . A scaling factor of 2.4 is used to convert this permeability to intestinal permeability ($P_{\text{app, scaled}}$). For neutral drugs, this value remains constant with x , but for acids and bases, permeability varies as a function of pH. A review of the literature^{15–21} shows that permeability versus pH profiles do not correspond to the neutral fraction, which would give a slope of 10 in the linear pH range. Instead, an average slope of 4.1 ± 2.1 was observed for acids (*ma*) and 3.9 ± 2.4 for bases (*mb*). Therefore, a slope of 4.0 is used for both acids and bases when the experimental slope for a specific drug is unavailable. The following expression was used for $P_{\text{app}}(x)$.

For acids,

$$P_{\text{app}}(x) = \frac{P_{\text{app, scaled}}}{1 + 10^{ma/10(\text{pH}_{\text{caco}} - \text{pKa})}} \times \frac{1}{1 + 10^{ma/10(\text{pH}(x) - \text{pKa})}} \quad (11)$$

A similar equation can be written for bases, and acids and bases were included into a single equation for $P_{\text{app}}(x)$.

Membrane Diffusional Clearances, $\text{CL}_i(x)$ and $\text{CL}_o(x)$

Diffusional clearance into the membrane ($\text{CL}_i(x)/2$,²² Figure 1C) is the product of the permeability and surface area:

$$\begin{aligned} \text{CL}_{i,1}(x) &= 2P_{\text{app}}(x)\text{sa}_{\text{lumen}}(x) \\ \text{and} \\ \text{CL}_{i,2}(x) &= 2P_{\text{app}2}(x)\text{sa}_{\text{lumen}}(x) \end{aligned} \quad (12)$$

$\text{CL}_{i,2}$ is the diffusional clearance from the lumen when radial diffusion is rate limiting (see below).

Further, $\text{CL}_o(x) = \text{CL}_i(x)/K_p$, where K_p is the membrane partition constant of the drug. The partition constant is calculated from the fraction unbound in microsomes f_{um} .²³

$$K_p = \frac{1 - f_{um}}{0.0007 f_{um}} \quad (13)$$

To model the slow radial diffusion in the lumen for the descending colon, the $P_{app}(x)$ was modified by a radial diffusion function:

$$f_{raddiff}(x) = 0.00025(1 - (1 - 0.014)\tanh[2(x-5)]) \times (1 - \tanh[5(x-6.5)]) \quad (14)$$

The following equation makes radial diffusion rate limiting in the terminal colon:

$$P_{app2}(x) = \frac{P_{app}(x)f_{raddiff}(x)}{P_{app}(x) + f_{raddiff}(x)} \quad (15)$$

SOLUTION DOSING INPUT AND DISPOSITION EQUATIONS

Input from the stomach was modeled with a unit pulse function with a lag time:

$$\text{upulse}(t) = 0.5(\tanh[100(t - \text{lag})] - \tanh[100(t - (0.3 + \text{lag}))]) \quad (16)$$

where $\text{lag} = 0.1$ h

This function was multiplied by the dose concentration and a volume correction factor to achieve the appropriate velocity in the duodenum:

$$\text{pulse}(t) = C_0 V_{\text{Corr}} \text{upulse}(t) \quad (17)$$

where $C_0 = \text{Dose} / V_{s,0}$ mg/mL, $V_{s,0}$ is the volume of water introduced into the stomach with the oral dose (usually 250 mL), and

$$V_{\text{Corr}} = \frac{V_{s,0}}{0.3\pi r_1^2 \text{Vel}_0}$$

$$\text{Vel}_0 = \text{Vel}(x) \text{ at } x=0$$

Although we use a simple pulse function with a lag, any output function from the stomach can be used to account for different formulations, food effects, etc.

Disposition of the drug solution in the intestine was modeled with the following PDEs (eqs 18–21) for drug concentrations in lumen, $C_1(x,t)$, enterocyte apical membrane, $C_2(x,t)$, enterocyte cytosol, $C_3(x,t)$, and a nonmandatory lipid compartment within the cytosol, $C_4(x,t)$. The path for drug absorption requires transfer from the lumen through the apical

membrane and cytosol. The drug molecule can but is not required to partition into the lipid compartment within the cytosol.²³

Eq 18 was derived from the basic convection–diffusion equation with differentiation by parts:

$$\begin{aligned} \frac{\partial}{\partial t} C_1(x, t) = & \text{dif}(x) \frac{\partial^2}{\partial x^2} C_1(x, t) + \left(-\text{vel}(x) + \frac{\partial}{\partial x} \text{dif}(x) + \frac{\text{dif}(x)}{a(x)} \frac{\partial}{\partial x} a(x) \right) \frac{\partial}{\partial x} C_1(x, t) \\ & + \left(-\frac{\partial}{\partial x} \text{vel}(x) - \frac{\text{vel}(x)}{a(x)} \frac{\partial}{\partial x} a(x) \right) C_1(x, t) \\ & - \frac{\text{CL}_{i2}(x)}{a(x)} C_1(x, t) + \frac{\text{CL}_{o2}(x)}{a(x)} C_2(x, t) \end{aligned} \quad (18)$$

$$\frac{\partial}{\partial t} C_2(x, t) = \frac{\text{CL}_{i2}(x)}{a_{\text{mem}}(x)} C_1(x, t) - \left(\frac{\text{CL}_{o1}(x) + \text{CL}_{o2}(x)}{a_{\text{mem}}(x)} \right) C_2(x, t) + \frac{\text{CL}_{i1}(x)}{a_{\text{mem}}(x)} C_3(x, t) \quad (19)$$

$$\begin{aligned} \frac{\partial}{\partial t} C_3(x, t) = & \left(\frac{\text{CL}_{o1}(x)}{a_{\text{cell}}(x)} \right) C_2(x, t) - \frac{\text{CL}_{i1}(x)}{a_{\text{cell}}(x)} C_3(x, t) - \frac{\text{CL}_{i1}(x)}{2a_{\text{cell}}(x)} C_3(x, t) + \frac{\text{CL}_{o1}(x)}{a_{\text{cell}}(x)} C_4(x, t) \end{aligned} \quad (20)$$

$$\frac{\partial}{\partial t} C_4(x, t) = \frac{\text{CL}_{i1}(x)}{a_{\text{lip}}(x)} C_3(x, t) - \frac{\text{CL}_{o1}(x)}{a_{\text{lip}}(x)} C_4(x, t) \quad (21)$$

Dirichlet boundary conditions for eqs 18–21 were:

$$C_1(t, 0) = \text{pulse}(t)$$

$$C_1(0, x) = C_{1,0}$$

Concentration at start of pulse defined as $C_{1,0} = \text{pulse}(t)$ at $t = 0$

$$C_1(t, 8) = 0$$

$$C_2(t, 0) = 0$$

$$C_2(0, x) = 0$$

$$C_2(t, 8) = 0$$

$$C_3(t, 0) = 0$$

$$C_3(0, x) = 0$$

$$C_3(t, 8) = 0$$

$$C_4(0,x) = 0$$

$$C_4(t,8) = 0$$

SOLID DOSING INPUT EQUATIONS

For dissolution of drug particles, the equation proposed by Wang and Flanagan^{3,24} was modified as follows:

$$f_{\text{diss}}(x, t) = \left(8C_{\text{part}}(x, t)\pi D_3 \sqrt{\frac{3C_{\text{solid}}(x, t)}{4\pi\rho C_{\text{part}}(x, t)}} \right) (S - C_1(x, t)) \quad (22)$$

where $f_{\text{diss}}(x, t)$ is the dissolution function, C_{part} is the concentration of drug particles, D is the drug diffusion coefficient, C_{solid} is the concentration of solid drug, ρ is the density of drug particles, and S is the solubility of drug in buffer at pH 7.4.

For the dissolution equation, the amount of drug in a particle was written as (concentration of solid drug)/(concentration of particles). Therefore, two additional concentrations were included in the input and disposition equations, the concentration of solid and concentration of particles (C_{solid} and C_{part}). Both C_{solid} and C_{part} move together along x as determined by the convection and diffusion components of the differential equations. Together, these terms define the particle radius as a function of x and t , which is necessary for the determination of rate of dissolution. In eqs 23–33, $C_{\text{solid},s}$ and $C_{\text{part},s}$ denote the respective concentrations in the stomach, while $C_{\text{solid},1}$ and $C_{\text{part},1}$ denote the respective concentrations in the intestinal lumen.

Further, although dissolution reduces the radius of particles, dissolution stops when C_{solid} reaches 0.001% of its initial value. This results in a constant number of particles in the intestine with $C_{\text{part},1}(x, t)$ determined by the convection and diffusion components of the differential equations. Although C_{solid} is essentially zero, particles remain and provide a scaffold for precipitation when necessary, that is, decrease in solubility or water content. The following function stops dissolution when C_{solid} in the intestinal lumen ($C_{\text{solid},1}$) reaches $C_{\text{solid},\text{lim}}$:

$$f_1(x, t) = 0.5(1 + \tanh[3(C_{\text{solid},1}(x, t) - C_{\text{solid},\text{lim}})]) \quad (23)$$

Precipitation is allowed to occur when C_1 exceeds the solubility of the drug by adding the following function:

$$f_2(x, t) = 0.5(1 + \tanh[-75(S - C_1(x, t))]) \quad (24)$$

Particle Dissolution in the Stomach

We used a one-compartment stomach model with the following ODEs to model particle dissolution and stomach emptying into the intestine:

$$\frac{d}{dt}C_{\text{part},s}=0 \quad (25)$$

$$\frac{d}{dt}V_s=-\frac{V_{s,0}\text{upulse}(t)}{0.3} \quad (26)$$

$$\frac{d}{dt}C_{\text{solid},s}=0.5(1+\tanh[50(C_{\text{solid},s}(t)-C_{\text{solid},\min})])\times\left(-8C_{\text{part},s}(t)\pi D\sqrt[3]{\frac{3C_{\text{solid},s}(t)}{4\pi\rho C_{\text{part},s}(t)}}\right)(S-C_{\text{diss},s}(t)) \quad (27)$$

$$\frac{d}{dt}C_{\text{diss},s}=0.5(1+\tanh[50(C_{\text{solid},s}(t)-C_{\text{solid},\min})])\times\left(8C_{\text{part},s}(t)\pi D\sqrt[3]{\frac{3C_{\text{solid},s}(t)}{4\pi\rho C_{\text{part},s}(t)}}\right)(S-C_{\text{diss},s}(t)) \quad (28)$$

where $C_{\text{solid},\min} = 0.001\%$ of C_0 .

The initial conditions for ODEs (eqs 25–28) are

$$\begin{aligned} C_{\text{part},s}(0) &= pt/V_{s,0} \\ V_s(0) &= V_{s,0} \\ C_{\text{solid},s}(0) &= \text{Dose}/V_{s,0} \\ C_{\text{diss},s}(0) &= 0 \end{aligned}$$

and the particle number pt for a particle with radius r_{part} was calculated as

$$pt = \frac{\text{volume of solid}}{\text{volume of particle}} = \frac{\text{Dose}/\rho}{4\pi r_{\text{part}}^3/3}$$

As modeled with the ODEs, the volume changes model stomach emptying, concentrations of $C_{\text{solid},s}$ and $C_{\text{diss},s}$ change as dissolution occurs, and particle concentration is constant.

This model provides the following input functions for particles, solid, and dissolved drug:

$$\text{pulse}_{\text{part}}(t) = \text{upulse}(t) V_{\text{corr}} C_{\text{part},s}(t) \quad (29)$$

$$\text{pulse}_{\text{solid}}(t) = \text{upulse}(t) V_{\text{corr}} C_{\text{solid},s}(t) \quad (30)$$

$$\text{pulse}_{\text{diss}}(t) = \text{upulse}(t) V_{\text{corr}} C_{\text{diss},s}(t) \quad (31)$$

SOLID DOSING DISPOSITION EQUATIONS

The input functions above (eqs 29–31) were used as Dirichlet boundary conditions for the intestinal absorption disposition equations for solid drugs (eqs 32–34 along with eqs 19–21) as follows:

$$\begin{aligned} \frac{\partial}{\partial t} C_{\text{part},1}(x, t) &= \text{dif}(x) \frac{\partial^2}{\partial x^2} C_{\text{part},1}(x, t) \\ &+ \left(-\text{vel}(x) + \frac{\partial}{\partial x} \text{dif}(x) + \frac{\text{dif}(x)}{a(x)} \frac{\partial}{\partial x} a(x) \right) \\ &\times \frac{\partial}{\partial x} C_{\text{part},1}(x, t) \\ &+ \left(-\frac{\partial}{\partial x} \text{vel}(x) - \frac{\text{vel}(x)}{a(x)} \frac{\partial}{\partial x} a(x) \right) C_{\text{part},1}(x, t) \end{aligned} \quad (32)$$

$$\begin{aligned} \frac{\partial}{\partial t} C_{\text{solid},1}(x, t) &= \text{dif}(x) \frac{\partial^2}{\partial x^2} C_{\text{solid},1}(x, t) \\ &+ \left(-\text{vel}(x) + \frac{\partial}{\partial x} \text{dif}(x) + \frac{\text{dif}(x)}{a(x)} \frac{\partial}{\partial x} a(x) \right) \\ &\times \frac{\partial}{\partial x} C_{\text{solid},1}(x, t) \\ &+ \left(-\frac{\partial}{\partial x} \text{vel}(x) - \frac{\text{vel}(x)}{a(x)} \frac{\partial}{\partial x} a(x) \right) C_{\text{solid},1}(x, t) \\ &- (f_1(x, t) + f_2(x, t))(f_{\text{diss}}(x, t)) \end{aligned} \quad (33)$$

$$\begin{aligned}
\frac{\partial}{\partial t} C_1(x, t) = & \text{dif}(x) \frac{\partial^2}{\partial x^2} C_1(x, t) + \left(-\text{vel}(x) + \frac{\partial}{\partial x} \text{dif}(x) + \frac{\text{dif}(x)}{a(x)} \frac{\partial}{\partial x} a(x) \right) \frac{\partial}{\partial x} C_1(x, t) \\
& + \left(-\frac{\partial}{\partial x} \text{vel}(x) - \frac{\text{vel}(x)}{a(x)} \frac{\partial}{\partial x} a(x) \right) C_1(x, t) \\
& + (f_1(x, t) + f_2(x, t))(f_{\text{diss}}(x, t)) \\
& - \frac{\text{CL}_{i2}(x)}{a(x)} C_1(x, t) + \frac{\text{CL}_{o2}(x)}{a(x)} C_2(x, t)
\end{aligned} \tag{34}$$

Dirichlet boundary conditions for eqs 32–34 along with 19–21 were:

$$C_{\text{part},1}(t,0) = \text{pulse}_{\text{part}}(t)$$

$$C_{\text{part},1}(0,x) = C_{p,0}$$

where $C_{p,0} = \text{pulse}_{\text{part}}(t)$ at $t = 0$

$$C_{\text{part},1}(t,8) = 0$$

$$C_{\text{solid},1}(t,0) = \text{pulse}_{\text{solid}}(t)$$

$$C_{\text{solid},1}(0,x) = 0$$

$$C_{\text{solid},1}(t,8) = 0$$

$$C_1(t,0) = \text{pulse}(t)$$

$$C_1(0,x) = C_{10}$$

$$C_1(t,8) = 0$$

$$C_2(t,0) = 0$$

$$C_2(0,x) = 0$$

$$C_2(t,8) = 0$$

$$C_3(t,0) = 0$$

$$C_3(0,x) = 0$$

$$C_3(t,8) = 0$$

$$C_4(0,x) = 0$$

$$C_4(t,8) = 0$$

FRACTION ABSORBED FOR ORAL AND COLONIC DOSING

Fraction absorbed (FA) was calculated by modeling solution dosing by oral or colonic administration. Oral dosing used the solution pulse (eq 17) with a pulse duration of 0.3 h. Colonic administration was modeled with a pulse duration of 0.5 h at $x = 4.0$ m. FA is obtained by integration of the cytosolic concentration times $\text{CL}_i/2$ (total dose absorbed) and dividing by the total dose.

These data were used to determine the scaling factor to convert Caco-2 permeability to intestinal permeability.

SYSTEMIC PK INPUT AND DISPOSITION FUNCTIONS

The transfer of drug from the enterocyte cytosol into the systemic PK model was achieved with an input function calculating amount of drug per unit time:

$$\text{Input } f(t) = \int_{x=0}^{x=10} \frac{CL_i(x)}{2} C_3(x, t) \quad (35)$$

The systemic disposition functions were generated from clinical IV data modeled with 2- or 3-compartmental PK models. The input function (eq 35) was combined with the systemic disposition functions to simulate oral PK profiles. Because of the unavailability of IV data for carbamazepine, the input functions were convolved with published integrated disposition equations.²⁵

METHODS FOR NUMERICAL SOLUTIONS

All models were developed using Mathematica 10.4.0. ODEs and PDEs were simulated using the NDSolve function. For the particle dissolution in the stomach, ODEs were solved with PrecisionGoal $\rightarrow$ 13. The PDEs were solved using the method of lines, with default step sizes, SpatialDiscretization $\rightarrow$ TensorProductGrid, DifferenceOrder $\rightarrow$ 2, and with grid x -coordinates defined as follows:

$$\begin{aligned} x_{\text{coord}} = & \text{Join}[0 + \text{Range}[0, 450]/300, 1.5 \\ & + \text{Range}[1, 250]/100, 4 + \text{Range}[1, 40]/20, 6 \\ & + \text{Range}[1, 150]/100, 7.5 + \text{Range}[1, 5]/10] \quad (36) \end{aligned}$$

For omeprazole, rapid absorption required a finer x -coordinate grid ($2x$ for the first 1.5m) along with a MaxStepSize $\rightarrow$ 0.005. The solutions of the PDEs and subsequent integration processes were checked for consistency and accuracy. This was done by integrating and summing the residual and transferred drug to check mass balance. In general, residual + mass out was within 0.05% of mass in. For IV data fitting, we used NonLinearModelFit with PrecisionGoal $\rightarrow$ Infinity and 1/Y weighting.

INPUT AND EXPERIMENTAL DATA

Permeability data from Caco-2 cells were obtained from the literature (Tables 1 and 2). Interlaboratory variability can be very high due to differences in experimental conditions. To compile a consistent data set, we preferentially selected data from experiments performed at pH 7.4 and with an orbital shaking rate of $\sim$ 100 rpm, when available.

Predicted FA values were calculated for 21 drugs and compared to literature values (Table 3). Colonic absorption data for 12 drugs are also listed in Table 3. For glyburide,

experimental bioavailability (F) and FA of 100% were used.²⁶ Experimental inputs for all predictions are given in Table 1. For the dissolution functions, drug diffusion coefficients were calculated with the Stokes–Einstein equation with molecular radii determined from the van der Waals volume calculated in MOE version 2015.1 (Chemical Computing Group, Quebec, Canada), and densities were calculated from van der Waals volume and molecular weight.

For the analysis of predicted values, outliers were identified by the BoxWhisker function in Mathematica with the upper and lower fences defined as 1.5-times the interquartile range. Since linear regression of FA data is not appropriate (due to the bounded nature of fractions), a confusion matrix was generated to evaluate FA predictability. Bins of >0.9, 0.3–0.9, and <0.3 were selected based on (1) the FDA Biopharmaceutical Classification System (BCS) Guidance (90% absorbed for high permeability) and (2) a cutoff of 30% for bioavailability per general industry standards.²⁷

To compare the simulated C – t profiles to the experimental oral PK profiles, the absolute average fold error values in $C_{\max}$, $T_{\max}$ were calculated. Root–mean–square errors are not always useful for comparing C – t profiles since rapidly changing concentrations can result in very large errors, even with small temporal differences in concentration profiles. Instead, an exposure overlap coefficient (EOC) was calculated to objectively compare the two continuous functions (experimental and predicted C – t profiles). First, an interpolation function was generated from the experimental C – t data (Interpolation function in Mathematica with Method $\rightarrow$ Spline and InterpolationOrder $\rightarrow$ 2). Next the simulated C – t profile was normalized to have the same AUC as the experimental profile. The minimum of the two C – t functions was integrated to obtain the overlap AUC. Finally, the EOC was calculated as the overlap AUC/experimental AUC. The EOC is similar to several similarity indices such as the Sorensen-Dice index.²⁸ The value of the EOC varies between zero and one for no, and perfect overlap, respectively. For the simulation of the oral absorption of solids, particle size is generally not reported in the clinical study reports. Therefore, particle size was optimized to provide the best EOC when experimental values were not available.

To simulate the impact of transporters ABCB1(P-gp) and OATP2B1 on fexofenadine absorption, reported transporter levels by Drozdziak et al.²⁹ were used. P-gp resides and transports from the apical membrane. Therefore, the concentration of transporter per mg mucosal tissue was assumed to be proportional to the transporter content per volume of apical membrane, and the reported expression levels were used directly. For OATP2B1, drug is transported from the lumen into the cytosol. Since the number of cells exposed to the lumen is greatly increased by villi, we multiplied quantitative OATP2B1 content data by the reported villi multiplication factors,¹⁰ normalized to the ileum. The P-gp and normalized OATP2B1 expression functions are shown in Figure 2G. This allowed development of Michaelis–Menten saturation functions:

$$\frac{\partial}{\partial t} C_1(x, t) = \frac{-V_{m,\text{OATP}}(x)C_1(x, t)}{((K_{m,\text{OATP}} + C_1(x, t))a(x))} + \frac{V_{m,\text{Pgp}}(x)C_2(x, t)}{((K_{m,\text{Pgp}} + C_2(x, t))a(x))} \quad (37)$$

$$\frac{\partial}{\partial t} C_2(x, t) = \frac{-V_{m, \text{Pgp}}(x) C_2(x, t)}{((K_{m, \text{Pgp}} + C_2(x, t)) a_{\text{mem}}(x))} \quad (38)$$

$$\frac{\partial}{\partial t} C_3(x, t) = \frac{V_{m, \text{OATP}}(x) C_1(x, t)}{((K_{m, \text{OATP}} + C_1(x, t)) a_{\text{cell}}(x))} \quad (39)$$

where

$$V_{m, \text{OATP}}(x) = \frac{10\,000 f_{\text{radiff}}(x) F_{\text{OATP}} \text{OATP2B1}(x)}{10\,000 f_{\text{radiff}}(x) + F_{\text{OATP}} \text{OATP2B1}(x)}$$

$$\text{OATP2B1}(x) = 0.6 + \frac{0.4}{1 + e^{-25(x-0.25)}} - \frac{0.5}{1 + e^{-15(x-1.5)}} + \frac{0.35}{1 + e^{-15(x-4.0)}}$$

$$V_{m, \text{Pgp}}(x) = F_{\text{Pgp}}(\text{Pgp}(x) - 0.2)$$

$$\text{Pgp}(x) = 0.1 + \frac{0.45}{1 + e^{-3(x-0.2)}} + \frac{0.55}{1 + e^{-5(x-2.5)}} - \frac{0.84}{1 + e^{-14(x-4.0)}}$$

F_{OATP} is the factor to convert pmol OATP2B1 per mg mucosal tissue into mg drug transported per hour per unit lumen volume, and F_{Pgp} is the factor to convert pmol P-gp per mg mucosal tissue into mg drug transported per hour per unit volume of apical membrane. As with P_{app} , a radial diffusion function ($f_{\text{radiff}}(x)$) is used to make radial diffusion rate limiting for luminal uptake in the descending colon.

RESULTS

For oral solution administration, solving the PDEs (eqs 18–21) results in concentration–distance–time profiles, $C(x, t)$, for the intestinal lumen (Figure 3A, $C_1(x, t)$), apical membrane (Figure 3B, $C_2(x, t)$), enterocyte cytosol (Figure 3C, $C_3(x, t)$), and cellular lipid (Figure 3D, $C_4(x, t)$). These profiles for atenolol are shown in Figure 3. Figure 3E shows the $C_1(x, 6)$ profile (position of drug at 6 h post dose). The observed position corresponds to the ascending colon, consistent with previous reports of gut transit.¹³ The increasing concentration in the lumen between $x = 0$ and $x = 2.5$ m is due to the absorption of water from the lumen. The poor permeability of atenolol results in incomplete absorption, seen as a persistent concentration of drug in the lumen over time and distance. The limiting radial diffusion function causes C_2 , C_3 , and C_4 concentrations to approach zero in the descending

colon ($x > 6$ m). As expected, the C_2 and C_4 concentrations are markedly higher than C_1 and C_3 , due to the membrane partition coefficient for atenolol ($K_p = 60$, eq 13).

The various compartmental $C(x,t)$ profiles for oral absorption with dissolution are shown in Figure 4. These figures were generated by solving the PDEs (eqs 32–34 and 19–21) for carbamazepine (400 mg, 70 μ m particle size). For the concentration in the lumen, (Figure 4A, $C_1(x,t)$), simulated profiles show an initial decrease in concentration as the drug solubilized in the stomach is absorbed, followed by an increase in concentration due to the absorption of water from the lumen. A second increase is observed due to absorption of water in the colon. Absorption is essentially complete by 10 h. Concentration of the solid, (Figure 4B, $C_{\text{solid},1}(x,t)$), shows the increase due to water absorption in the lumen, and dissolution is essentially complete by 5 h. Although the drug dissolves and the particle size decreases, the number of drug particles remains constant. Therefore, the increases in concentration of particles (Figure 4C, $C_{\text{part},1}(x,t)$) are due to water absorption in the small intestine and the colon. Again, the concentrations for C_2 and C_4 are much higher than C_1 and C_3 due to the high K_p for carbamazepine ($K_p = 213$).

Observed and predicted FA for solution-based drugs and drugs that are highly soluble are shown in Table 3 and Figure 5. Also shown are FA for colonic administration when experimental data are available. Four outliers were identified and shown in Figure 5A: ciprofloxacin (FA colonic), mannitol (FA), omeprazole (FA colonic), and terbutaline (FA). The confusion matrix for FA prediction is shown in Figure 5B. For the FA > 0.9 bin, the precision was 82% with outliers and 88% without outliers, and the sensitivity was 100%. For the $0.3 < \text{FA} < 0.9$ bin, the precision was 83% with outliers and 90% without outliers, and the sensitivity was 71% with outliers and 82% without outliers. For drugs with FA < 0.3 , precision was 83% with outliers and 100% without outliers, and the sensitivity was 71% with outliers and 83% without outliers. Overall accuracy (prediction of the correct bin) was 81% with outliers and 90% without outliers.

Figure 6 shows observed and predicted C – t profiles for nine drugs that were dosed as oral solutions. The predicted curves were normalized to the observed AUC from $t = 0$ to the last experimental data point. Although FA was predicted, first pass metabolism (FgFh) was chosen to obtain the experimental AUC. Therefore, these results should not be interpreted as a bioavailability prediction but as a prediction of the rate of absorption and the shape of the C – t profiles. The areas in green represent the overlap between observed and predicted profiles. The numerical values of the overlap (EOC), along with C_{max} and T_{max} , are listed in Table 3. Overall, six drugs were very well predicted with EOC > 0.9 , and predicted C_{max} and T_{max} values similar to those observed.

Figure 7 shows the predicted C – t profiles for six drugs dosed as solids. Again, the AUCs were normalized to the experimental AUCs by an appropriate FgFh. Also, particle sizes were not available for most drugs. Therefore, the particle size was chosen to match the observed C – t profile. The EOC, C_{max} , and T_{max} values are reported in Table 4. The EOC values were > 0.9 for all drugs except budesonide. Two preparations of glyburide were modeled, 419 and 420.³⁰ The 420 formulation (micronized) was modeled best with a 20 μ m particle size, whereas a 35 μ m particle size provided the best C – t profile for 419. Particle

sizes were available for two formulations of carbamazepine, a 5 μm preparation (200 mg dose) and a 75 μm preparation (400 mg dose). The predicted C - t profiles for the two formulations were very well predicted with EOC values of 0.99 and 0.96, respectively.

Precipitation of a solution dosage form of nifedipine is shown in Figure 8. It has been reported that 10 mg solution doses of nifedipine do not precipitate, but 20 mg and higher doses do precipitate.³¹ Figure 9 shows the $C_{\text{solid},1}(x,t)$ and $C_1(x,t)$ profiles at doses of 10, 20, and 40 mg. The model predicts no precipitation at the 10 mg dose and increasing precipitation with 20 and 40 mg doses.

The observed and predicted C - t profiles for fexofenadine at 60, 120, and 240 mg solution doses are shown in Figure 9. The shapes of the experimental profiles are not well predicted by a passive permeability model (Figure 9A–C). Addition of saturable OATP2B1 and P-gp functions (eqs 37–39) with K_m values of 10 μM and 800 μM , and scaling factors of 10 and 50 for OATP2B1 and P-gp, respectively, gave much more accurate simulated C - t profiles (Figure 9D–F). The average FA was 0.35 versus 0.42 (obs³² vs pred) for passive only simulations and 0.35 versus 0.35 for simulations with active transport. The average T_{max} was 1.6 versus 2.9 h (obs vs pred) for passive only simulations and 1.6 versus 1.5 h for simulations with active transport. The average EOC improved from 0.92 (passive) to 0.95 (active).

The impact of particle size and permeability on C - t profiles were evaluated in Figure 10. The parameters for atenolol were used as the base PK model. Figure 10A shows the impact of decreasing permeability for a set of hypothetical neutral compounds that move from BCS Class I to Class III. Profiles for acids and bases are simulated in the insets. As expected, the C_{max} decreases and T_{max} increases with decreasing permeability. Figure 10B shows the profile changes that occur when the absorption of a BCS Class I compound becomes dissolution limited due to increasing particle size. The profiles for a Class II and Class IV drug with increasing particle size are shown in Figure 10C and D, respectively.

DISCUSSION

This report describes a continuous absorption model based on the convection–diffusion equation. Other continuous models have been reported,^{5,6,8,9} but most absorption models are based on discrete compartments and ordinary differential equations.^{1–4} Compartmental absorption models result in a large number of ordinary differential equations, but the solution of these equations is computationally facile. The present continuous model is based on partial differential equations. While PDEs are computationally more difficult to solve, the resulting model structure is very simple. In contrast to previous models that use the convection–diffusion equation, we incorporate experimental velocities, physiological characteristics as a function of x , and explicit apical membrane, cytosol, and lipid compartments for the enterocyte. For our solution-based model, only four eqs (eqs 18–21) are required to model the lumen and enterocyte apical membrane, cytosol, and lipid, along the entire length of the intestine. The purpose of this modeling effort is two-fold: (1) to develop a high-resolution absorption model that incorporates explicit membranes and (2)

develop a modeling platform that can be easily modified to incorporate both physiologic and drug/formulation specific complexities.

The convection–diffusion equation requires that velocity and volume be directly linked. Thus, for the intestine, a decrease in velocity of the drug is accompanied by a decrease in intestinal water volume due to water absorption. The velocity function ($vel(x)$, Figure 2A) was parametrized with experimental velocities extracted from gastric transit data.¹² The rapid decrease in velocity correlates well with the rapid water absorption in the small intestine.³³ It has been shown that most of a 240 mL water dose was absorbed within an hour, corresponding to ~2m in our model. Since the primary transit parameter in this model is the experimentally derived velocity function, correct positioning of the dose over time can be expected. The diffusion term is an effective diffusion term that describes the spreading of a dose during transit. Since few data are available, the diffusion term was set proportional to velocity with a proportionality constant that shows an appropriate distribution when in the ascending colon¹³ (Figure 3E). Too little diffusion relative to velocity can hinder the numerical solution of the PDEs.

Although physiological values for small (r_1) and large (r_2) intestinal radii were used (1.25 and 2.5 cm, respectively), the effective radius for the small intestine may be smaller given the peristaltic nature of intestinal motility. To achieve the required velocity in the duodenum, the volume entering the small intestine must be increased. This is accomplished with the V_{Corr} term in eq 17. The result of this term is a more dilute drug solution at $x = 0$ than would be expected based on a 250 mL liquid stomach volume. A small intestine radius of 0.8 cm provides a more appropriate velocity and therefore drug concentrations that match those expected for 250 mL volumes. However, construction and parametrization of a model with $r_1 = 0.8$ did not reproduce C – t profiles as accurately as the $r_1 = 1.25$ model. One possibility is that the local effective water concentration is higher than that expected with a dose taken with 250 mL of water. This is consistent with a recent suggestion that solubility in 500 mL of water is a better parameter to describe the development of new drugs.³⁴ In addition, the precipitation of nifedipine is correctly predicted with the current model (see Figure 9 and discussion below). It is also possible that other missing (e.g., partitioning into micelles) or incorrectly parametrized characteristics of the model are canceling the effect of the larger effective radius of the small intestine. Since surface area need not be directly correlated with intestinal diameters, perhaps future models will incorporate more congruent physiological parameters.

The structure of this intestinal model with concentric tubes representing the lumen, apical membrane, cytosol, and lipid (Figure 1B) is an extension of our previously published explicit membrane compartment models.²³ The model shown in Figure 1C is similar to the six-compartment model with a physiological apical membrane volume. The inclusion of an apical membrane and intracellular lipid of the enterocyte has some specific advantages. First, experimental membrane partitioning can be used to model passive diffusion into and out of the cell and partitioning into intracellular lipids. Next, transport by P-gp and BCRP can be accurately modeled since these transporters remove drug directly from the apical membrane. We have shown previously that P-gp activity with apical membrane drug exposure (intestine and brain) cannot be correctly modeled without explicit membrane

compartments. If accurately parametrized, the model in Figure 1 allows us to predict the unbound intracellular concentrations necessary for metabolism and intracellular efflux, and apical membrane concentrations that drive active efflux out of the membrane (Pgp and BCRP).³⁵

The method used to include the effect of pH on permeability is based on the observation that in vitro permeability does not usually follow pH partition theory when aqueous pK_a values are used.^{15–21} The pH partition theory is consistent with the observed slopes of ~ 10 for pH-permeability profiles for partial artificial membrane permeability assays (PAMPA).^{36–38} In contrast, the average observed slopes for Caco-2 permeability are $\sim 4 \pm 2$ for both acids and bases, likely due to the impact of the polar headgroup region of a membrane. The pK_a of a molecule partitioned into the polar headgroup region will likely depend on the microenvironment, that is, proximity to phosphate, carboxylate, choline, etc. The resulting permeability profiles would show a broader and shallower relationship to pH. This shift in pK_a has been observed experimentally for sulfonylureas.³⁹ Unfortunately, the standard deviation of the average slope is high and generalizations may be difficult. Even related compounds such as beta blockers can show large differences in pH-permeability profiles.^{16,18,21} Therefore, experimental pH-permeability should be used when available. It should be noted that food intake, comedications, etc. can alter the pH profile of the intestine and could alter the rate and extent of absorption. To model fed-state absorption, an altered pH profile could be used.

The scaling factor for Caco-2 permeability was optimized to reproduce the FA and FAcronic data in Table 3 and Figure 5. The value of the scaling factor in this model is 2.4, similar to the scaling factor used by Ando et al., 2.23.⁹ A model with correct relative surface areas and an optimized scaling factor should result in good FA and FAcronic predictions, since Caco-2 permeability has been shown to correlate well with FA.^{40–42} In general, drugs that are not solubility or dissolution limited and do not undergo saturable transport or metabolism should show dose-independent values of FA. Poor predictions of FA could be due to one or more factors. First, the variability in in vitro Caco-2 P_{app} values or clinical FA values can be large for some compounds. Also, transporter activity, unexpected metabolic or degradation processes, or inadequate characterization of the pH dependence of absorption can result in poor predictions. FA and FAcronic are poorly predicted for two compounds each (outliers in Figure 5A). Inaccurate predictions for ciprofloxacin, omeprazole, and terbutaline could be due to transporter activity (see below). Mannitol FA is poorly predicted (0.21 observed, 0.49 predicted) but the range of clinically observed FA values is very large, 0.002–0.892.⁴³

In this work, dissolution was modeled using a simplified version of a function (eq 22) reported by Wang and Flanagan.²⁴ However, any dissolution function can be used instead. Maintaining particle count allows for the regrowth of particles upon precipitating conditions. If the precipitated drug has different dissolution characteristics than the original formulation, a separate population of particles can be easily defined and incorporated. Further, experimental solubility and dissolution profiles can be directly incorporated into the model. Finally, if a formulation includes rate-limiting disintegration, an additional luminal disintegration PDE can be added.

Figures 6 and 7 show the experimental and AUC-normalized oral absorption curves for 16 drugs. Predicted oral absorption input functions were used with experimental PK parameters for IV dosing to simulate the plasma C - t profiles. Since the areas are normalized to the experimental data (Fg/Fh is determined by the predicted FA and the experimental bioavailability), the data should be used only to compare experimental and predicted profile shapes. To quantitatively characterize the fit, we use $C_{\max}$, $T_{\max}$, and an exposure-overlap-coefficient (EOC) in Tables 3 and 4. For solution dosing, C - t profile shapes were very accurately predicted for atenolol, diltiazem, alprenolol, metoprolol, nisoldipine, and nifedipine (Figure 6). Terbutaline (EOC = 0.9), felodipine (EOC = 0.87) (Figure 5), and fexofenadine (Figure 6) are not predicted as accurately but they are likely complicated by transporter interactions (see below). Omeprazole (EOC = 0.8) has an experimental $T_{\max}$ of 0.2 h, and 20% of $C_{\max}$ is seen at 5 min. By default, we use a 0.1 h lag time and a stomach pulse length of 0.3 h, and very rapid absorption will result in a $T_{\max}$ of ~0.4 h. Sodium bicarbonate was given to protect omeprazole from stomach acid, and the short $T_{\max}$ for this study is likely due to very rapid stomach emptying (due to CO₂ generation). For the solids, profile shapes are reproduced well for tranexamic acid, glyburide, and carbamazepine. However, particle sizes were fit to provide the best EOC for all solids except carbamazepine. It is encouraging that good fits can be obtained with this model, but additional studies with clinical data for drugs with known particle sizes will be necessary to evaluate the accuracy of the dissolution/precipitation component of this model.

For several drugs with poor predictions of normalized C - t profiles, active transport processes may be implicated. Ciprofloxacin is primarily a substrate for jejunal BCRP.⁴⁴ Intestinal efflux transporter activity would delay absorption, increasing $T_{\max}$. Likewise, pindolol is an OCT2 substrate⁴⁵ on the basolateral membrane. OCT2 activity could cause a delay in absorption, consistent with the observation in Figure 8C. Although budesonide has not been shown to be a substrate for OATPs, it is a competitive inhibitor of OATPs.⁴⁶ It has also been shown to be a substrate for Pgp.⁴⁷ The data in Figure 8D are consistent with apical uptake to give a shorter $T_{\max}$. Terbutaline (Figure 6E) is reported to be an oct transporter substrate in mice,⁴⁸ and two OCTs are expressed in the human small intestine.²⁹ Also, half of the terbutaline uptake into human alveolar macrophages is mediated by active transport.⁴⁹ However, apical uptake transporter activity in the intestine has not been reported. The experimental profile in Figure 6E is consistent with the report that absorption occurs primarily in the jejunum⁵⁰ and not consistent with the low passive permeability of terbutaline ($P_{\text{app}} = 0.47 \times 10^{-6} \text{ cm s}^{-1}$).

Accurate incorporation of transporters into an absorption model will require detailed knowledge of accessible transporter content along the GI tract and knowledge of the expression level of transporters in the in vitro permeability model. In addition, prediction of the impact on drug transport will require accurate kinetic parameters for the drug. It is known that transporter expression alone may be insufficient to predict activity since some transporters can be found in intracellular reservoirs.^{51,52} Also, kinetic parameters for efflux transporters that remove drug from membranes or cytosol can deplete intracellular concentrations resulting in K_m values that depend on transporter content. Thus, different expression systems will give different kinetic parameters.

Although incorporation of transporters will require extensive effort, we have simulated absorption in the presence of transporters for fexofenadine as a proof-of-concept study. Fexofenadine has low permeability ($P_{app} = 0.31 \times 10^{-6} \text{ cm s}^{-1}$) but is a substrate for both OATP2B1 and P-gp.^{53–57} At this time, only two studies have been published that describe P-gp expression along the GI tract^{29,58} and one study for OATP2B1.²⁹ The two P-gp studies differ in sample preparation and method of quantitation. In the study by Bruyère et al.,⁵⁸ Western blots were used to quantitate P-gp levels in homogenized biopsies. Mass spectrometry was used to quantitate several transporters in mucosal tissue in the report by Drozdik et al.²⁹ Relative P-gp levels are not consistent between the two studies. Since both P-gp and OATP were characterized in the study by Drozdik et al., we used these data to simulate fexofenadine absorption.

As can be seen in Figure 9A–C, a passive permeability model overpredicts T_{max} for fexofenadine administered as a solution at three different doses. Incorporating Michaelis–Menten saturation kinetics provided good fits to the experimental data with improved FA, T_{max} , and EOC values. The $10 \mu\text{M}$ K_m value for OATP2B1 used in these simulations is similar to the values reported previously for various OATP transporters ($6\text{--}108 \mu\text{M}$).^{53,59,60} It is also encouraging that inclusion of the transporters results in a more accurate prediction of FA (passive, 0.42; active, 0.35; obs, 0.35). The interplay of uptake and efflux transporters and their effect on the $C\text{--}t$ profiles of fexofenadine is consistent with the reported spatial distribution of these transporters. In Figure 2G, the measured enzyme distribution of P-gp is overlaid with the normalized distribution of OATP2B1. The predominance of OATP2B1 in the jejunum and P-gp in the ileum results in more absorption in the first 2 h and less absorption in the next 2 h, converting the passive-only simulated $C\text{--}t$ profiles (Figure 9A–C) to profiles much closer to those observed clinically (Figure 9D–F). Although preliminary, these results provide support for the P-gp and normalized OATP2B1 intestinal content reported by Drozdik et al.²⁹

The relationships between permeability, solubility, and particle size are well-known. For high-permeability compounds, dissolved drug is rapidly absorbed, and decreasing particle size can increase absorption, even for low solubility drugs. Class IV drugs, on the other hand, are poorly absorbed, irrespective of particle size. These expected observations are reproduced by the current model, as shown in Figure 10. We anticipate that future improvements to this model will result in high resolution $C\text{--}t$ profile predictions. Improvements can include saturable metabolic processes (e.g., CYP3A4 and UGTs), additional transporters, enterohepatic recycling, etc. These models can be used to guide formulation design, predict drug interactions, and improve our overall efforts toward human PK prediction in normal and special populations.

In conclusion, we have developed a preliminary intestinal absorption model based on the convection–diffusion equation. This continuous model incorporates physiological processes relevant to drug absorption. Experimental velocity and diffusion data were used to describe time course for intestinal transit. The model accurately predicts both fraction absorbed values and $C\text{--}t$ profile shapes for a number of drugs dosed as solutions or solids. A dissolution function was successfully used to model the absorption and precipitation of solid dosage forms. As proof-of-concept, saturable transport by OATP2B1 and P-gp was used to

improve the prediction of fexofenadine $C-t$ profiles. This model should be considered preliminary. Building and validation of a comprehensive model that includes all relevant transport and metabolism processes as well as additional physiological complexities will require significant effort. It is hoped that the simplicity of this model will encourage use and improvement by other laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AUC	area-under-the-curve
BCRP	ABCG2
BCS	biopharmaceutical classification system
$C_{\max}$	maximum concentration
$C-t$ profile	concentration–time profile
EOC	exposure overlap coefficient
F	bioavailability
FA	fraction absorbed
FgFh	fraction escaping gut metabolism $\times$ fraction escaping hepatic metabolism
K_p	membrane partition constant
ODEs	ordinary differential equations
PAMPA	partial artificial membrane permeability assays
P_{app}	apparent permeability
PDEs	partial differential equations
P-gp	ABCB1
$T_{\max}$	time at maximum concentration

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Figure 1.

Continuous model for intestinal absorption. (A) Intestine is depicted as a continuous tube with radii r_1 and r_2 for the small intestine and colon, respectively. The length of each region of the intestinal tract used in the model is labeled. Duo: duodenum, Jej: jejunum, and Ile: ileum. (B) Cross-sectional view of the continuous intestine model, with concentric tubes depicting the lumen (drug concentration C1), apical membrane (C2), enterocyte cytosol (C3), and intracellular lipid (C4). (C) Two-dimensional depiction of the concentric tubes, modeled as a six-compartment model with drug concentrations C1–C4 as defined above, and portal blood concentration (C5). Diffusive clearances in and out of each compartment are as defined under Methods.

Figure 2.

Physiological functions describing the intestine. Functions along distance x are shown for (A) velocity, $vel(x)$, (B) effective diffusion, $dif(x)$, (C) cross-sectional area, $a(x)$, (D) surface area with villi, $sa_{villi}(x)$, (E) surface area with villi and microvilli, $sa_{lumen}(x)$, (F) intestinal pH, $pH(x)$, and (G) OATP2B1 normalized pmol/mg tissue, $OATP2B1(x)$, and P-gp pmol/mg tissue, $Pgp(x)$. Points are experimental data.²⁹ OATP2B1(x) was normalized with villi data.¹⁰

Figure 3.

Predicted concentrations with oral solution dose. Upon atenolol solution dosing, (A) $C_1(x,t)$, (B) $C_2(x,t)$, (C) $C_3(x,t)$, and (D) $C_4(x,t)$ are shown. (E) Position of atenolol at $t = 6$ h postdose is shown.

Figure 4.

Predicted concentrations with oral solid dose. Upon a 400 mg carbamazepine solid dose, (A) $C_1(x,t)$, (B) $C_s(x,t)$, (C) $C_p(x,t)$, (D) $C_2(x,t)$, (E) $C_3(x,t)$, and (F) $C_4(x,t)$ are shown.

Figure 5.

Prediction of FA and FA_{colonic}. (A) Observed versus predicted FA values are plotted, $n = 35$ data sets. See Table 3 for details of specific drugs used for FA and FA_{colonic} data. Blue, FA; red, FA_{colonic}. Outliers identified are ciprofloxacin, mannitol, omeprazole, and terbutaline. (B) Confusion matrix for prediction of FA and FA_{colonic} for a total of 35 data sets. True positives are labeled green. Results excluding outliers are listed in parentheses.

Figure 6.

Predicted C - t profiles with oral solution dose. Observed mean (blue points and line) and model-predicted (red) C - t profiles are overlaid upon normalization of AUC as described under Methods and Results. The green shaded region represents the overlapping area from time zero to last observed data collection time. Results are shown for (A) atenolol, (B) diltiazem, (C) alprenolol, (D) metoprolol, (E) terbutaline, (F) omeprazole, with inset showing data for $t = 0$ –5 h, (G) nisoldipine, (H) nifedipine, and (I) felodipine.

Figure 7.

Predicted C - t profiles with oral solid dose. Observed mean (blue points and line) and model-predicted (red) C - t profiles are overlaid upon normalization of AUC as described under Methods and Results. The green shaded region represents the overlapping area from time zero to last observed data collection time. Results are shown for (A) tranexamic acid, (B) ciprofloxacin, (C) pindolol, (D) budesonide, (E) glyburide 419 formulation, (F) glyburide 420 formulation, (G) furosemide, (H) 200 mg ($5\ \mu\text{m}$ particle size) carbamazepine, and (I) 400 mg ($75\ \mu\text{m}$ particle size) carbamazepine.

Figure 8. Prediction of precipitation of nifedipine. Model-predicted $C_{solid,1}(x,t)$ (top panel) and $C_1(x,t)$ (bottom panel) are shown for (A) 10 mg, (B) 20 mg, and (C) 40 mg doses of nifedipine solution.

Figure 9.

Impact of OATP2B1 and P-gp on $C-t$ profiles of fexofenadine. Upon solution dosing of fexofenadine, observed mean (blue points and line) and model-predicted (red) $C-t$ profiles are overlaid upon normalization of AUC as described under Methods and Results. The green shaded region represents the overlapping area from time zero to last observed data collection time. (A–C) Simulations conducted with passive diffusion only in the absence of active transporters. (D–F) Simulations conducted with active OATP2B1-mediated uptake and P-gp-mediated efflux. Oral doses of (A,D) 60 mg, (B,E) 120 mg, and (C,F) 240 mg were modeled. Observed and predicted FA and T_{max} (h) values are reported, along with EOC values for the simulations.

Figure 10.

Impact of permeability and particle size on absorption. Simulated $C-t$ profiles were generated with varying permeability or particle size, starting with atenolol drug parameters for a base PK profile. (A) For a set of hypothetical neutral compounds, simulations were run with $P_{\text{app}} = 25 \times 10^{-6} \text{ cm/sec}$ (blue), $5 \times 10^{-6} \text{ cm/sec}$ (red), $2 \times 10^{-6} \text{ cm/sec}$ (magenta), $1 \times 10^{-6} \text{ cm/sec}$ (black), and $0.2 \times 10^{-6} \text{ cm/sec}$ (green). Inset: the same simulations are shown for hypothetical acids (left inset) and bases (right inset). (B) For a hypothetical BCS Class I drug, $C-t$ profiles were simulated with particle size = 10 (blue), 25 (red), 30 (magenta), 50 (black), and 75 μm (green). (C) For a hypothetical BCS Class II drug, $C-t$ profiles were simulated with particle size = 2 (blue), 5 (magenta), 10 (red), and 25 μm (black). (D) For a hypothetical BCS Class IV drug, $C-t$ profiles were simulated with particle size = 2 (blue), 5 (magenta), 10 (red), and 25 μm (black).

Table 1

Physicochemical Properties, Microsomal Membrane Partitioning, and Caco-2 Permeability Data for Drugs Modeled with Solution Input

drug	nature (slope ^d)	acid pK _a	base pK _a	f _{0m} ^c	Caco-2 P _{app} (× 10 ⁻⁶ cm/s)
alprenolol	base	14	9.6	0.47	25.3 ⁶¹
atenolol	base (2) ⁶²	14	9.5	0.96	0.53 ⁶¹
budesonide ^b	neutral	14	1	0.73	12.9 ⁶³
cimetidine	neutral	14	1	0.99	1.37 ⁶¹
ciprofloxacin	zwitterion	5.8	8.7	0.99	1.7 ⁴²
diltiazem	base (5.6) ⁶⁴	14	8.2	0.69	29.4 ⁶³
felodipine	neutral	14	5.4	0.11	22.7 ⁴⁰
fexofenadine	zwitterion	4.04	9.01	0.95	0.31 ⁶³
glyburide ^b	acid	5.1	1	0.93	18.9 ⁶⁵
mannitol	neutral	14	1	0.99	0.38 ⁶¹
metolazone	neutral	9.7	1	0.97	6.2 ⁴²
metoprolol	base	14	9.6	0.84	23.7 ⁶¹
naproxen	acid	4.15	1	0.84	21.8 ⁶³
nifedipine	neutral	14	5.3	0.76	29.3 ⁶⁶
nisoldipine	neutral	14	5.3	0.068	24.4 ⁶⁷
omeprazole	neutral	9	4.8	0.92	56 ⁶⁸
pindolol ^b	base	14	9.6	0.74	16.7 ⁶¹
ranitidine	base (2.1) ²¹	14	8.2	0.92	0.49 ⁶¹
sulpiride	base	14	9.12	0.98	0.23 ⁴²
terbutaline	base (1.3) ¹⁸	14	9.8	0.87	0.47 ⁶¹
tranexamic acid ^b	zwitterion	4.6	10.2	0.99	0.53 ⁶³

^a A slope value of ma = 4 and mb = 4 was used unless noted within parentheses.

^b Drugs were dosed as solid dosage form.

^c All f_{0m} values were either calculated or experimental from.⁶⁹

^d Caco-2 data were collected at pH = 7.2 for diltiazem, and pH = 6.5 for nisoldipine.

Table 2
Physicochemical Properties, Microsomal Membrane Partitioning, and Caco-2 Permeability Data for Drugs Modeled with Solid Input

drug	nature ^a	acid p <i>K</i> _a	base p <i>K</i> _a	<i>f</i> _{um} ^b	particle size ^c (μm)	solubility (mg/mL)	density (mg/m ³)	diffusion coefficient (× 10 ⁻⁶ m ² /h)	Caco-2 <i>P</i> _{app} ^d (× 10 ⁻⁶ cm/s)
Budesonide	neutral	14	1	0.73	35.0	0.04	1.22	2.27	12.9 ⁶³
Carbamazepine 200	neutral	12	2.6	0.87	5.0	0.127	1.27	2.76	42.2 ⁶³
Carbamazepine 400	neutral	12	2.6	0.87	75.0	0.127	1.27	2.76	42.2 ⁶³
Ciprofloxacin	neutral	5.8	8.7	0.99	40.0	30	1.32	2.55	1.7 ⁴²
Glyburide 419	acid	5.1	1	0.93	30.0	0.025	1.33	2.24	18.9 ⁶⁵
Glyburide 420	acid	5.1	1	0.93	22.0	0.025	1.33	2.24	18.9 ⁶⁵
Pindolol	base	14	9.6	0.74	65.0	0.61	1.32	2.7	16.7 ⁶¹
Tranexamic acid	neutral	4.6	10.2	0.99	50.0	18.2	1.19	3.1	0.53 ⁶³

^a A slope value of *ma* = 4 and *mb* = 4 was used for all drugs.

^b All *f*_{um} values were either calculated or experimental from ref 69.

^c Particle size was optimized as detailed under Methods and Results, except for carbamazepine, for which particle size was reported.^{70,71}

^d Caco-2 data were collected at pH = 7.4.

Table 3
Pharmacokinetic Dose and Observed and Predicted Parameters/Metrics for Drugs Modeled with Solution Input

drug	dose (mg) ^a	FA		FA _{colonic}		C _{max} (μg/L)		T _{max} (h)		EOC
		obs	pred	obs	pred	obs	pred	obs	pred	
Alprenolol ⁷²	100	0.96	1			20.2	20.7	1.1	1.1	0.95
Atenolol ⁶²	25	0.57	0.53	0.28	0.13	121.0	130.2	3.2	3.2	0.96
Budesonide ^b	3	1	1	1	0.93	-- ^d	--	--	--	--
Cimetidine	200	0.84	0.8	0.18	0.24	--	--	--	--	--
Ciprofloxacin	120	0.84	0.95	0.06	0.39	--	--	--	--	--
Diltiazem ⁷³	120	1	1	0.82	0.87	243	334	0.7	0.6	0.92
Felodipine ⁷⁴	40	1	1	--	--	43.0	27.4	0.6	0.5	0.87
Fexofenadine	20	0.3	0.42	0.13	0.1	--	--	--	--	--
Glyburide ^b	2.5	1	1	1	1	--	--	--	--	--
Mannitol	1000	0.21	0.49	--	--	--	--	--	--	--
Metolazone	2.5	0.64	0.82 ^c	--	--	--	--	--	--	--
Metoprolol ⁷⁵	40 ^a	0.95	1	--	--	3.55	3.38	0.9	0.7	0.98
Naproxen	100	0.99	1	--	--	--	--	--	--	--
Nifedipine ⁷⁶	10	0.91	1	1	0.99	120	112	0.4	0.5	0.92
Nisoldipine ⁷⁷	20	0.88	1	1	0.97	8.1	7.7	0.4	0.4	0.92
Oneprazole ⁷⁸	40	0.97	1	0.66	1	1113	984	0.2	0.4	0.80
Pindolol ^b	5	0.92	1	--	--	--	--	--	--	--
Ranitidine	100	0.56	0.51	0.09	0.12	--	--	--	--	--
Sulpiride	200	0.36	0.21	--	--	--	--	--	--	--
Terbutaline ⁷⁹	5 ^a	0.73	0.51	--	--	5.7	4.9	1.4	3.1	0.90
Tranexamic Acid ^d	2000 ^a	0.53	0.61	--	--	--	--	--	--	--

^aDosing volume was 250 mL for all studies except metoprolol, terbutaline, and tranexamic acid studies, which had a dosing volume of 100 mL.

^bDrugs were dosed as solid dosage form.

^cOral dose administered as a suspension.

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p denotes not applicable.

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Table 4

Pharmacokinetic Dose and Observed and Predicted Parameters/Metrics for Drugs Modeled with Solid Input

drug	dose ^a (mg)	F	C _{max} (μg/L)		T _{max} (h)	
			obs	pred	obs	pred
Budesonide ⁸⁰	3	0.15	0.78	0.76	1.6	3.2
Carbamazepine ⁷¹	200	--	3090	3151	1.1	0.6
Carbamazepine ⁷⁰	400	--	3783	4153	14.5	7.2
Ciprofloxacin ⁸¹	100	0.53	0.46	0.39	1	0.6
Glyburide 419 ³⁰	2.5	0.85	85.7	68.4	2.7	2.8
Glyburide 420 ³⁰	2.5	0.92	125	118	2	1.9
Pindolol ⁸²	5	0.53	22.4	27.3	2	1.1
Tranexamic acid ⁸³	2000	0.29	13988	13804	2.7	2.7

^aDosing volume was 250 mL for all studies except tranexamic acid studies, which had a dosing volume of 100 mL.