A Physiologic Model for Simulating Gastrointestinal Flow and Drug Absorption in Rats

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Purpose. The development of a physiologically based absorption model for orally administered drugs in rats is described.
Methods. Unlike other models that use a multicompartmental approach, the GI tract is modeled as a continuous tube with spatially varying properties. The mass transport through the intestinal lumen is described via an intestinal transit function. The only substance-specific input parameters of the model are the intestinal permeability coefficient and the solubility in the intestinal fluid. With this physiologic and physicochemical information, the complete temporal and spatial absorption profile can be calculated.
Results. A first performance test using portal concentration data published in the literature yielded an excellent agreement between measured and simulated temporal absorption profiles in the portal vein. Furthermore, the dose dependence of a compound with solubility-limited fraction dose absorbed in rats (chlorothiazide) could be adequately described by the model.
Conclusions. The continuous absorption model is well suited to simulate drug flow and absorption in the GI tract of rats.

KEY WORDS: PB-PK modeling; simulation; intestinal absorption; fraction dose absorbed.

INTRODUCTION

Poor pharmacokinetic properties of potential drug candidates are known to be one of the major causes for failures in the development process. Between 20% and 50% of the failures of projects in late phases are caused by poor ADME properties (Absorption, Distribution, Metabolism, and Excretion) (1–3). Therefore, an early assessment of these properties should improve the efficiency of selecting suitable drug candidates. Physiologically based pharmacokinetic (PB-PK) (4–7) modeling can be used as a tool for an early *in silico* prediction of ADME properties of new compounds. Because the oral route is the preferred route of delivery for the majority of new drugs, models for the gastrointestinal (GI) transit and uptake via the epithelial membrane of the intestine are especially desirable. Drug absorption from the GI tract is a complex process that dependents on a variety of different factors. These factors include physicochemical parameters of the drug (e.g., the intestinal permeability coefficient, solubility in the intestinal fluid), physiologic properties of the GI tract (e.g., the effective surface area available for absorption, pH values in the various regions of the gut, and gastric emptying and intestinal transit times), and formulation aspects (e.g., tablet, capsule, liquid solution, etc.). Several physiologic models for intestinal absorption have been described in the literature (8–12), some of which have become commercially available, such as *iDEA*™ by Lion Bioscience (13) or *GastroPLUS*™ by Simulations Plus (14).

In this paper we describe the development of a physiologic, continuous model for absorption following oral drug administration in rats, focusing on the passive absorption of drugs delivered as liquid solutions in the fasted state. In contrast to other published multicompartmental models (10–12), the GI tract is modeled as a single tube with spatially varying properties. Drug transport through this tube is described as continuous plug flow with dispersion; i.e., the drug solution is initially confined to the stomach. Under the auspices of gastrointestinal transit, the solution moves in a concerted fashion along the gut, but with an ever-widening distribution about the median location. The intestinal physiology is simulated to change with the location in a way that corresponds appropriately to the passage of the drug-containing fluid through the gut lumen.

MODEL DEVELOPMENT

First, the physiologic parameters affecting oral absorption from the GI tract of male Wistar rats weighing approximately 250 to 300 g were collected from various literature sources (15–19). The small intestine is described in the model as a tube with varying diameter. In this model, the length of the duodenum is assumed to be 10 cm, its diameter increases from 1.5 mm at the pyloric junction to 2.0 mm at the proximal end of the jejunum. The jejunum has a total length of 87 cm and a constant diameter of 2.0 mm. The ileum is 3 cm long, and its diameter decreases from 2 mm at the proximal end to 1 mm at the ileocecal junction. Thus, the whole small intestine comprises to a total length of 100 cm and a volume of approximately 3 ml. The inner surface area of the tube is approximately 62 cm^2, but the effective surface area that is available for absorption is much larger because of the presence of villi. The effective surface area gradient as a function of the location within the rat intestine has been determined by Fischer and Parsons (16). The authors found that the effective surface area gradient decreases linearly from approximately 7.0 cm^2/cm in the duodenum to 3.8 cm^2/cm near the end of the ileum. In that study, the total surface area ranged from 470 to 516 cm^2 in rats of body weight 275 to 325 g and with intestinal lengths of 95.5 to 115 cm. Thus, the total surface area exceeds the cylindrical surface area of the tube approximately by a factor of 8.

Secondly, the emptying of the solution from the stomach into the duodenum and the movement of the compound through the intestine are described by an intestinal transit function T_{SI}. T_{SI} is defined as the fraction of the administered dose found within a certain segment of the GI tract at time t. To obtain a simple analytic expression for T_{SI}, a dimensionless coordinate $\tilde{z}$ was introduced as a measure of the position within the GI tract. $T_{SI}(\tilde{z},t)$ was then derived on the basis of an experimental data set presented by Sawamoto *et al.* (19), who measured the recovery of a nonabsorbable fluorescent

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marker (phenol red) as a function of time and position within the GI tract of male rats up to 6 h after administration. To obtain an empiric expression for the intestinal transit function, the measured distribution of the marker was approximated by a Gauss function with temporally varying center of mass $\tilde{z}_o(t)$ and width $\sigma(t)$:

$$T_{SI}(\tilde{z},t) = \frac{1 - \exp\{-t/\tau_{GE}\}}{\sqrt{2\pi}\sigma(t)} \exp\left\{-\frac{[\tilde{z} - \tilde{z}_o(t)]^2}{2\sigma^2(t)}\right\} \qquad (1)$$

Because the emptying of liquids from the stomach into the duodenum obeys a first-order kinetic under fasted conditions (time constant τ_{GE}, gastric emptying time) (17), the area under the T_{SI} curve is normalized to $1 - \exp\{-t/\tau_{GE}\}$; i.e., all material that is emptied from the stomach is added to the plug of material moving through the intestinal lumen. The mean gastric emptying time is reported to be approximately 30 min in rats (physiologic range 10–60 min) (17,18).

The dimensionless parameter functions $\tilde{z}_o(t)$ and $\sigma(t)$ have been fitted to obtain simple analytic expressions that empirically describe the experimental profile (19). $\tilde{z}_o(t)$ was fitted using a power function, and for $\sigma(t)$, a polynomial of the 9th order was chosen:

$$\tilde{z}_o(t) = \alpha + \beta(t - t_0)^n \quad \wedge \quad \sigma(t) = \sum_{k=0}^{9} \gamma_k t^k \qquad (2)$$

The model parameters α, β, t_0, n, and γ_0 to γ_9 obtained from the fit procedure are summarized in Table I.

The resulting calculated transit profile is graphically presented in Fig. 1 in comparison to the original transit profile obtained by Sawamoto *et al.* (19). As can be seen in this figure, the liquid is very rapidly transported through the duodenum into the jejunum. After approximately 1 h, the center of mass has already moved into the upper ileum. The small intestinal transit time (t_{SI}) is defined as the time at which 90% of the administered liquid has accumulated in the cecum, with 10% remaining in the lower ileum. This is the condition found experimentally after 6 h in the rat (19). After accumulation in the cecum, the substance is further transported to the colon, where stool formation starts. At that time, the compound is assumed to be unabsorbable. The comparison between the calculated and the original intestinal transit profile presented by Sawamoto *et al.* (19) indicates that the transport of a liquid through the GI tract in rats is very well described by the simple analytical expressions defined in Eqs. (1) and (2).

Table I. Model Parameters Used in Eq. (2) to Describe the Intestinal Transit Profile

Model parameter	Fitted value
α	–6.1
β	10.43
t_0	0.07
n	0.081
γ_0	0.32191
γ_1	2.86798
γ_2	–6.89234
γ_3	8.01795
γ_4	–5.19735
γ_5	2.04239
γ_6	–0.50334
γ_7	0.07631
γ_8	–0.0065
γ_9	0.000237493

On the basis of the above-defined transit function of the small intestine, the spatial and temporal dependence of the luminal concentration C_{lumen}, defined as the amount of drug in the lumen per volume element, dM_{lumen}/dV, can be calculated for a given dose [dose = administered mass (M) per body weight (BW)]. To this end, the dimensionless coordinate $\tilde{z}$ from Fig. 1 first has to be replaced by a true spatial coordinate z (in cm), which accounts for the actual lengths of the intestinal segments. For an absorbable substance, the total luminal concentration has to be reduced by the fraction of administered drug that has already reached the portal blood pool via the intestinal membrane [$f_{abs}(z,t)$]:

$$C_{lumen}(z,t) = \frac{\text{DOSE BW}[1 - f_{abs}(z,t)]}{\pi r^2(z) L_{SI}} T_{SI}(z,t) \qquad (3)$$

Here, r(z) denotes the radius of the small intestine at distance z from the pyloric sphincter, and L_{SI} is the total length of the small intestine.

For poorly soluble drugs, the intestinal solubility (S_{int}) can limit the concentration of the compound in the intestinal lumen. As a first approximation, it is assumed that dissolution/precipitation occurs instantaneously. Mathematically, this case can be treated by simply limiting the luminal concentration to the drug's intestinal solubility (12):

$$C_{lumen} = \begin{cases} C_{lumen} & , \text{ if } C_{lumen} \le S_{int} \\ S_{int} & , \text{ if } C_{lumen} > S_{int} \end{cases} \qquad (4)$$

The amount of the orally administered drug that is passively absorbed into the portal vein in the region [z, z+dz] in a time interval [t, t+dt] is then given by

$$\frac{d^2M_{pv}(z,t)}{dz\,dt} = P_{int} C_{lumen}(z,t) \frac{dA_{eff}(z)}{dz} \quad , \qquad (5)$$

where P_{int} is the apparent intestinal permeability coefficient of the drug for the gut wall, and $dA_{eff}(z)$ is the effective surface area element at intestinal position z. Integrating Eq. (5) with respect to time gives the amount of the dose absorbed as a function of the position within the small intestine, and integrating Eq. (5) over the length of the segments yields the temporal absorption profile of the intestine. The total fraction dose absorbed (F_{abs}) is consequently given by:

$$F_{abs} = \int_{t=0}^{\infty} \int_{z=0}^{L_{SI}} \frac{d^2M_{pv}(z,t)}{dz\,dt} dz\,dt/(\text{DOSE BW}) \qquad (6)$$

The physiologic parameters and model equations have been implemented in a software tool that numerically solves Eq. (6) using the fourth-order Runge-Kutta method (20) to obtain temporal and/or spatial absorption profiles.

RESULTS OF THE MODEL EVALUATION

To evaluate the model we compared simulated and experimentally determined absorption profiles in rats. Experimental absorption rates and cumulative fraction absorbed for ciprofloxacin (21), levofloxacin (22), diclofenac sodium (23), and oxacillin (24) were taken from the literature. These data were obtained by the portal–venous concentration difference

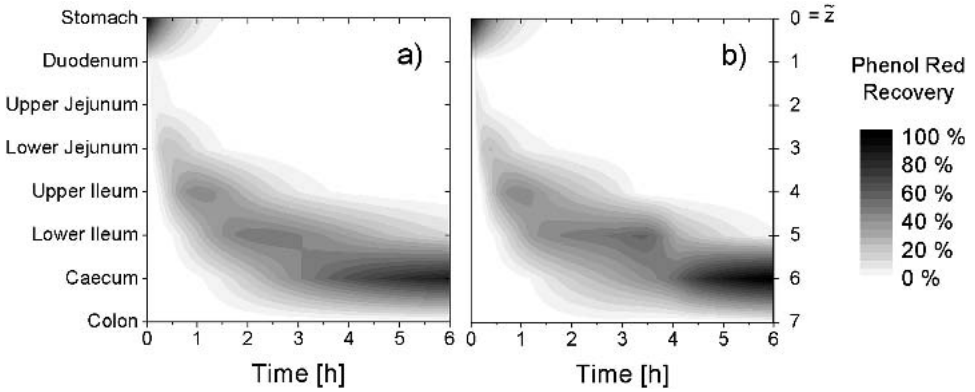

Fig. 1. (a) Intestinal transit profile of phenol red in rats presented by Sawamoto *et al.* (based on the calculated curve shown in Fig. 4 of Ref. 19). (b) Simulated intestinal transit profile using Eqs. (1) and (2) and the model parameters presented in Table I.

method, i.e., drug concentrations were determined simultaneously in portal and venous blood samples as a function of time after oral administration. In the calculations, the gastric emptying time τ_{GE} was set to 30 min except for ciprofloxacin, where τ_{GE} was set to 5 min. The intestinal transit time t_{SI} was assumed to be 6 h. The body weight of the rats and the dose were adjusted to the values reported in the respective references. The intestinal permeability coefficients were varied in order to achieve the best agreement between the measured and the calculated data for the temporal cumulative absorption curves. The results of the comparison between the measured and simulated data are shown in Fig. 2. As can be seen in this figure, the calculated time dependencies of the absorption rate and the cumulated fraction dose absorbed in the portal vein are in very good agreement with the experimental values. The fitted model parameters for P_{int} are listed in Table II.

Chlorothiazide was chosen as an example for solubility-limited absorption because this compound is known to exhibit a dose-dependent fraction dose absorbed in rats that has at least in part been attributed to a low solubility of the compound (25,28,29). For chlorothiazide, the intestinal permeability coefficient was first fitted to match the maximum fraction dose absorbed [57.3% (25) under permeability-limited conditions]. Then, the intestinal solubility was varied in order to match the reported decrease of F_{abs} with increasing dose. Figure 3 shows the experimentally determined and the simulated dose-dependent fraction dose absorbed for chlorothiazide. With a theoretical value of S_{int} = 30 mg/L for the intestinal solubility, the experimentally observed dose dependence of F_{abs} could be well described by the model.

In addition to temporally resolved absorption information, the model also provides quantitative information about different sites of absorption. In Table III, the fractions that were absorbed in different segments of the rat's intestine are shown. According to the model, the preferred site of absorption is the lower jejunum.

DISCUSSION

Predictive physiologically based absorption models are highly desirable for the drug development industry. Their utility at different stages of drug discovery has recently been reviewed (7). As input parameters, physiologic as well as substance-specific physicochemical properties are necessary. Our goal was to develop a model that provides a detailed description of the physiology of the GI tract with only a minimum amount of physicochemical information needed.

The physiology of the rat intestine relevant to drug absorption is available from the literature (15–18). Contrary to the published models that use a compartmental approach to model the GI tract (10–12), we modeled the intestine as a continuous tube with spatially varying properties such as diameter or effective surface area. The complete temporal and spatial distribution profile of a drug administered orally in solution is described by a simple transit function that assumes a Gaussian distribution of the drug mass within the tube. This Gaussian package is normalized to the amount of drug that has already been emptied from the stomach into the duodenum [Eq. (1)]. This simplification is justified only if the gastric emptying time is small compared to the intestinal transit time because any released amount of drug contributes equally to the concentration profile present in the gut lumen. If the time constants are similar, or if repeated drug doses are described, each "package" that is released from the stomach should be described by an individual transit function. However, for all simulations presented here, the assumption that τ_{GE} (5 to 30 min) is small compared to t_{SI} (6 h) is fulfilled. The parameters describing the Gauss function were obtained from a fit to reported experimental transit data of phenol red (19). The only substance-specific input parameters that are needed are the apparent intestinal permeability coefficient and the solubility within the intestinal lumen. Often, the intestinal permeability is thought of as a parameter that varies within different segments of the gut (30,31). In this model it is assumed that the apparent different uptake rates are entirely caused by differences in the effective surface area that is available for absorption (16) rather than by different permeability coefficients in the various intestinal segments.

For a first comparison of model calculations with experimental data, concentration–time curves in the rat portal vein of four different compounds published in the literature (21–24) were chosen. Temporally resolved absorption curves are advantageous because such curves contain more information than a single integrated fraction dose absorbed value. In the calculations, the gastric emptying time τ_{GE} was set to the mean value reported in rats [30 min (17)] for all compounds except for ciprofloxacin, where τ_{GE} was set to 5 min. For this

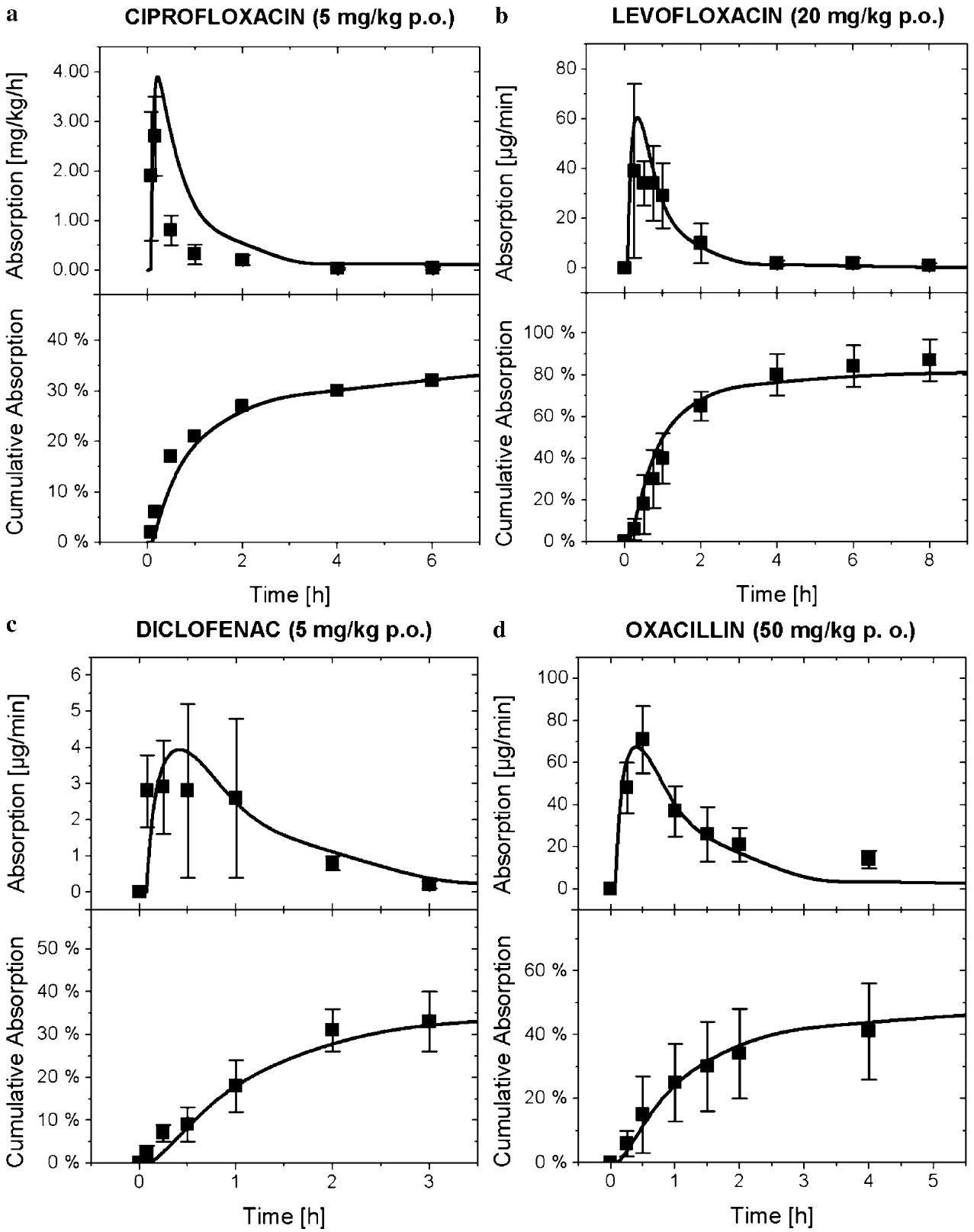

Fig. 2. Absorption rate and cumulative fraction absorbed for permeability-limited compounds. The *symbols* represent experimental data points (taken from Refs. 21–24); the *lines* represent the model simulations.

Table II. Compound Data Used for Model Evaluation

Compound	Dose	Ref.	Aqueous solubility	Ref.	Model parameters
Ciprofloxacin	5 mg/kg	21	11.5 g/L	26	$P_{int} = 6.3 \times 10^{-6}$ cm/s
Levofloxacin	20 mg/kg	22	>30 g/L	27	$P_{int} = 35 \times 10^{-6}$ cm/s
Diclofenac sodium	5 mg/kg	23	2.43 g/L	26	$P_{int} = 10 \times 10^{-6}$ cm/s
Oxacillin	50 mg/kg	24	>25 g/L	24	$P_{int} = 7.0 \times 10^{-6}$ cm/s
Chlorothiazide	variable	25	0.266 g/L	26	$P_{int} = 16 \times 10^{-6}$ cm/s $S_{int} = 30$ mg/L

The model parameters are the results of a fitting procedure.

compound, the rapid onset of absorption could not be explained otherwise. Besides natural interindividual differences, a possible explanation for the difference in the gastric emptying time is that a larger volume was administered in the ciprofloxacin study [1 ml by Moriwaki *et al.* (21) compared to 0.5 ml in the diclofenac and oxacillin studies; no information about the administered volume was available for levofloxacin]. This volume is comparable to the volume of a rat's stomach (15). Thus, rapid emptying into the duodenum could be caused by an overloading of the stomach with the test volume in this particular study. The reported aqueous solubilities of the compounds (see Table II) were greater than the maximum luminal concentrations observed in the calculations; i.e., no precipitation could occur in these simulations. The agreement of the simulated and the experimental concentration–time curves in the portal vein as well as the cumulated fraction absorbed is very good (Fig. 2). Thus, the model can reliably describe drug flow and uptake under permeability-limited conditions.

To evaluate the model performance under solubility-limited conditions, chlorothiazide was chosen as a model compound because chlorothiazide is known to have a nonlinear dose response in rats (as well as in humans) that has been attributed in the past to the low solubility of the compound (25,28,29). With this model, the experimentally observed dose dependence of the fraction dose absorbed in rats could be qualitatively well described (Fig. 3) on the basis of the simple solubility-limitation assumption in Eq. (4), but the fitted intestinal solubility of 30 mg/L is approximately a factor 10 lower than the reported aqueous solubility of chlorothiazide [266 mg/L at 30°C (26)]. However, the solubility of chlorothiazide decreases at acidic pH values (25). It is therefore possible that chlorothiazide rapidly precipitates in the rat stomach, where pH values around 4 to 5 are typically found (15), but does not dissolve within the time of intestinal transit again. In this case, the procedure to fit the intestinal solubility in the model yields the smallest pH value that is found in the stomach. This finding indicates that a more detailed description of the influence of the pH in the GI tract of rats on the absorption of acids and bases is needed, including a temporal term for the dissolution of poorly soluble drugs.

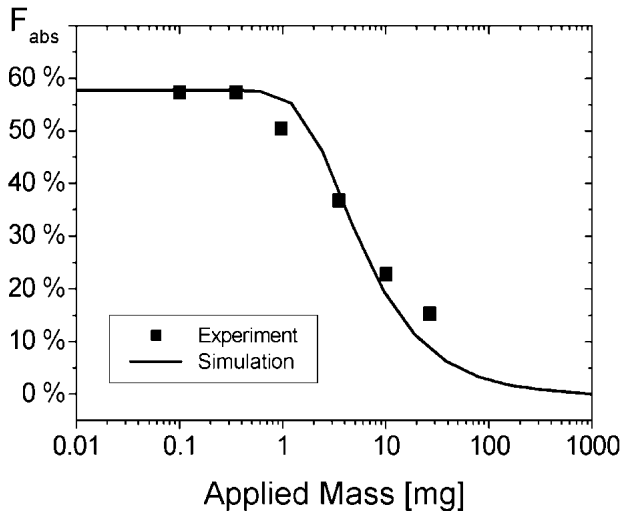

Fig. 3. Dose-dependent absorption of chlorothiazide in rats: The *symbols* represent experimental fraction dose absorbed (29); the *line* represents the model simulation.

In summary, the model provides detailed temporal and spatial information about drug uptake, such as the preferred site of absorption within the intestine, the influence of physiologic parameters such as the gastric emptying time on the absorption profile, and ultimately the overall fraction of the administered dose that is absorbed. Currently, the applicability of the model is limited to passively absorbed compounds undergoing negligible metabolism in the gut wall. A further limiting assumption is that the compound has to be administered in solution under fasted conditions. However, these limitations are, at least from the mathematical point of view, easy to overcome. For actively absorbed substances, for example, additional terms are necessary to describe the in- and efflux via the transporters using saturable Michaelis-Menton kinetics. Such terms can easily be implemented in Eq. (4). Similarly, metabolic processes in the gut lumen or gut wall can be described. All of the above-mentioned points will be addressed in future model versions.

CONCLUSIONS AND OUTLOOK

In conclusion, we have demonstrated that the continuous absorption model is well suited to simulate drug flow and absorption in the GI tract of rats under permeability-limited and solubility-limited conditions. Only two input parameters, the intestinal permeability coefficient and the solubility in the intestinal fluid, are necessary. The absorption model can be very useful to interpret experimental absorption curves in rats and to provide additional information, such as the preferred site of absorption, that is not easily accessible using common experimental techniques.

Currently we are working on an extension of the continuous absorption model to human physiology and on the establishment of reliable correlations between the model input parameters and simple physicochemical parameters (such as lipophilicity, solubility, and molecular size) in order to obtain a predictive absorption model that can be used in the drug discovery and lead optimization process.

Table III. Fraction of the Dose Absorbed in the Various Segments of the Rat GI Tract

Fraction absorbed	Ciprofloxacin	Levofloxacin	Oxacillin	Diclofenac	Chlorothiazide[a]
Duodenum	0.7%	1.3%	0.5%	0.4%	0.7%
Upper jejunum	8.6%	20.1%	9.7%	7.2%	11.7%
Lower jejunum	18.7%	48.8%	28.6%	22.1%	33.8%
Upper ileum	1.2%	2.9%	2.1%	1.7%	2.5%
Lower ileum	3.8%	8.3%	7.8%	6.6%	8.7%
Total	33.0%	81.4%	48.7%	38.0%	57.4%

[a] For Chlorothiazide, the data for the lowest reported dose in (29) is given.

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