A Physiological Model for the Estimation of the Fraction Dose Absorbed in Humans

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A physiologically based model for gastrointestinal transit and absorption in humans is presented. The model can be used to study the dependency of the fraction dose absorbed (F_{abs}) of both neutral and ionizable compounds on the two main physicochemical input parameters (the intestinal permeability coefficient (P_{int}) and the solubility in the intestinal fluids (S_{int})) as well as physiological parameters such as the gastric emptying time and the intestinal transit time. For permeability-limited compounds, the model produces the established sigmoidal dependence between F_{abs} and P_{int}. In case of solubility-limited absorption, the model enables calculation of the critical mass−solubility ratio, which defines the onset of nonlinearity in the response of fraction absorbed to dose. In addition, an analytical equation to calculate the intestinal permeability coefficient based on the compound's membrane affinity and molecular weight was used successfully in combination with the physiologically based pharmacokinetic (PB−PK) model to predict the human fraction dose absorbed of compounds with permeability-limited absorption. Cross-validation demonstrated a root-mean-square prediction error of 7% for passively absorbed compounds.

1. Introduction

Absorption of an orally administered drug from the GI tract is a complex process that is influenced by various factors. These factors include physiological properties such as the diameter, length, surface area,[1,2] and pH profile[3,4] of the intestine, the gastric emptying and intestinal transit times,[5−9] and physicochemical properties of the drug such as its solubility and effective permeability coefficient,[4,10,11] the latter of which has been correlated with the compounds lipophilicity and size.[12−14] The permeability and/or solubility can limit the fraction dose absorbed of a drug. In addition, degradation in the intestinal fluid and metabolism in the gut wall or the liver can also decrease the compound's bioavailability, which is usually defined as the fraction of the administered parent compound that reaches the systemic circulation. During the lead optimization process, identifying the causes of poor bioavailability is very important, because it can help to guide the synthesis program toward candidates with a more suitable pharmacokinetic profile and, thus, a higher chance for successful development. Ultimately, for real "drugs" the type of formulation (e.g. tablet, capsule, immediate or controlled release, etc.) and its composition also play an important role in determining the rate and extent of oral absorption.

Physiologically based pharmacokinetic (PB−PK) modeling has received a lot of attention in the recent past, because this technique can lead to a better understanding of how the various factors influence absorption and, therefore, can contribute to the challenge of identifying the causes of poor oral absorption in drug research and development projects.[15−19] In this paper we describe the development of a physiologically based model for gastrointestinal transit and absorption in humans. We have scaled up the continuous drug flow and absorption model developed previously for rats[20] to human physiology and implemented a more detailed description of the absorption of charged compounds. With the help of this new human model, the sensitivity of the fraction dose absorbed with respect to both physicochemical and physiological parameters can be demonstrated. In addition, we have developed an analytical equation for the intestinal permeability coefficient on the basis of the compound's membrane affinity and molecular weight, which, in combination with the PB−PK model, allows an accurate description of the human fraction dose absorbed for permeability limited compounds.

2. Development of the Absorption Model

Physiologically based absorption modeling consists of two essential steps: First, the physiological procedures relevant for GI-transit and uptake have to be identified, and, second, these must be translated into mathematical equations.

2.1 Human GI Physiology. Mean values for the dimensions,[21] pH-profile,[22,23] and transit patterns[24−27] of the GI tract of a healthy male person with a body weight of 70 kg were compiled from various literature sources. Because absorption from the stomach is neg-

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ligible for most drugs due to the small surface area and time that is available for absorption, the model focuses on a detailed description of the physiology of the intestine. The small intestine is described as a tube with a total length (L_{SI}) of 280 cm and a linearly decreasing radius (r_{SI}) ranging from 1.75 cm at the proximal to 1.00 cm at the distal end. Anatomically, the human small intestine can be divided into three segments: The duodenum (length 20 cm), the jejunum (length 104 cm), and the ileum (length 156 cm). The inner surface of the small intestine in contact with the luminal fluid is largely increased due to three structural elements: the folds, villi, and microvilli. The large folds are typically found from the lower half of the duodenum to about mid-ileum. With distance along the small intestine they become smaller and less numerous.[21] Thus, their amplification factor drops from 3 (in the mid duodenum to mid jejunum) to 1 (no amplification) at the distal end of the ileum in the model. Villi are present on the intestinal mucosa of the gut wall. Geometrically, a single villus can be regarded as a cylindrical tube with a spherical top. The average height of the villi decreases linearly with increasing distance from 800 μm (proximal end) to 500 μm (distal end of the small intestine). The radius of a single villus is nearly constant within the small intestine (approximately 50 μm), and their reported density is approximately 25 mm^{-2}.[21] For the amplification factor of the microvilli, a mean value of 25 was used (the reported interindividual variability is between 15 and 40). Using the physiological information given above, the effective intestinal surface area and its gradient $dA_{eff}(z)/dz$ (z denotes the distance from the pyloric junction) can be calculated. According to the model assumptions, the total effective area of the human small intestine is approximately 71 m^2 thus exceeding the lateral surface of a cut circular cone with the equivalent length and radius by a factor of ≈300.

The mean gastric pH determined in healthy volunteers is reported to vary between 1.5 and 2.5 (mean 2.0) under fasted conditions.[22] In the small intestine, there is a pH gradient, with pH values tending to rise as one moves further down the small intestine. In the fasted state, the mean pH value in the duodenum increases from 5.0 at the pyloric sphincter to 6.0 at the distal end of the duodenum. The jejunum is reported to exhibit a pH gradient ranging from 6.0 to 7.0. In the ileum, the pH rises further to a value of approximately 7.5.[23] For simplicity, a linear dependence of the pH as a function of the location within the intestinal segments is assumed in the model. Figure 1 summarizes the resulting physiological parameters of the human GI tract.

At one time it was thought that little or no drug absorption occurs from the colon. However, over the past decade or so, it has become increasingly evident that colonic absorption can contribute significantly to the overall absorption of many compounds.[28−30] Although folds and villi are absent in the colonic mucosa and, thus, the effective surface area is much smaller compared to the small intestine, the longer time of exposure can result in a high extent of absorption, comparable in some cases to absorption in the small intestine. In this model, we account for colonic absorption by describing the colon as a tube with a length of 1.5 m and a diameter of 7 cm. As a first approximation, the effective surface area is identical to the cylindrical area of this segment.

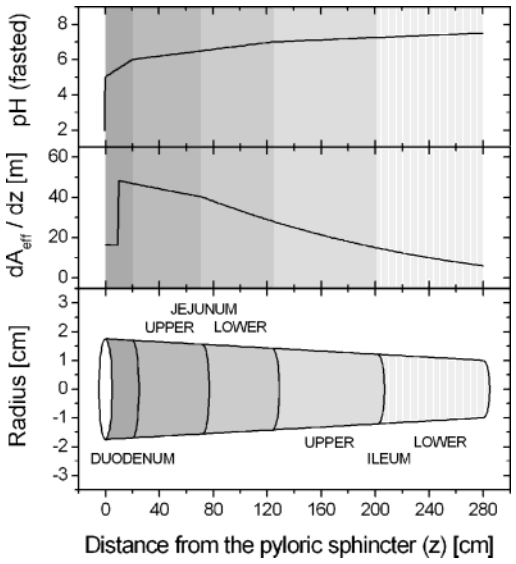

Figure 1. Radius, effective surface area gradient, and pH profiles for the fasted state in the human small intestine. The physiological data were collected from various literature sources (for details see text).

2.2 Drug Flow and Absorption. The human intestinal flow and absorption model is based on the continuous absorption model that has been previously developed for rats.[20] Contrary to other published absorption models that are based on a compartmental approach,[31,32] the luminal concentration $C_{lumen}(z,t)$ in this model is described with the help of an intestinal transit function $T_{SI}(z,t)$. This function represents the temporal and spatial distribution of the orally administered drug within the intestinal lumen.[20] As described in detail in ref 20, the function was originally derived on the basis of the published recovered fractions of an nonabsorbable marker (phenol red) within various intestinal segments as a function of time. These data were then used to generate the intestinal transit function, first using dimensionless scales for the spatial and temporal axes. The dimensionless axes are then scaled to the actual dimensions using literature values for the lengths of the intestinal segments and the first-order gastric emptying time τ_{GE} and the intestinal transit time t_{SI}. Gastric emptying of liquids in fasted humans appears to obey first-order kinetics with a mean τ_{GE} of approximately 30 min, the physiological range due to intra- and interindividual variations reported in the literature for τ_{GE} is approximately 10 to 60 min.[24−26] The mean small intestinal transit time (t_{SI}) of a solution administered in the fasted state is 4 h with a reported physiological range of approximately 2 and 6 h.[26,27] Because the stool starts to form in distal segments of the colon, the drug is considered absorbable for a maximum of seven more hours after reaching the caecum.

With the help of the intestinal transit function,[20] $C_{lumen}(z,t)$ is given by

$$C_{lumen}(z,t) = \frac{\text{DOSE BW}(1 - f_{abs}(t))}{\pi r_{SI}^2(z) L_{SI}} T_{SI}(z,t), \quad (1)$$

where "DOSE times BW" denotes the total drug mass

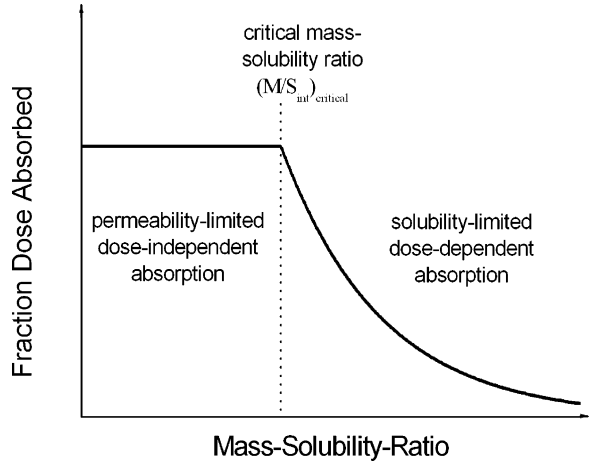

Figure 2. Schematic plot illustrating the theoretical dependence of the fraction dose absorbed on the administered mass: If the mass−solubility-ratio is smaller than a critical value, absorption is dose-independent and F_{abs} is constant. If the mass−solubility ratio exceeds the critical value, absorption becomes dose dependent and F_{abs} decreases with increasing administered mass.

that was orally administered, and $f_{abs}(t)$ denotes the fraction of the administered drug that has already reached the portal blood pool via the intestinal membrane.[20]

If the compound is an acid or base, the neutral and the ionized species have to be treated separately. In general, both species can permeate through the epithelial barrier, the ionized species usually at a much smaller rate. For the purposes of simplicity, we only consider monoprotonic acids and bases in the following derivation. For these acids and bases, the luminal concentrations of the neutral species (superscript "0") and the ionized species (superscript "i") can be written as

$$C^0_{lumen}(z,t) = f^0(z)C_{lumen}(z,t), \tag{2}$$

and

$$C^i_{lumen}(z,t) = [1 - f^0(z)]C_{lumen}(z,t). \tag{3}$$

$f^0(z)$ is the neutral fraction, dependent on the pK_a value of the compound and the pH at location z and can be obtained from the well-known Hendersson−Hasselbalch equation:

$$f^0(z) = \frac{1}{1 + 10^{\pm(pH(z) - pK_a)}} \text{ (+ for acids, − for bases)} \tag{4}$$

For poorly soluble drugs, the intestinal solubility (S_{int}) can limit the concentration of the compound in the intestinal lumen. A typical indication for solubility-limited absorption is that the fraction absorbed becomes dose dependent and starts to decrease with increasing administered mass, as indicated in Figure 2. If the drug concentration in the lumen is higher than the local intestinal solubility, the compound starts to precipitate and, hence, can no longer be absorbed. To account for the case of solubility-limited absorption in the model, it is assumed that the luminal concentration cannot exceed the value of the intestinal solubility.[20] Note that the solubility is a function of the pH in the intestine and, thus, varies with the position z (the superscripts "0" and "i" again denote the neutral and the ionized fraction, respectively):

$$C^{0/i}_{lumen}(z,t) = \begin{cases} C^{0/i}_{lumen}(z,t), \text{ if } C^{0/i}_{lumen}(z,t) \le S^{0/i}_{int}(z) \\ S^{0/i}_{int}(z), \text{ if } C^{0/i}_{lumen}(z,t) > S^{0/i}_{int}(z) \end{cases} \tag{5}$$

The limitation expressed in eq 5 is applied instantaneously, i.e., precipitation and dissolution are assumed to take place on a time scale that is short compared to the time scales of intestinal transit and absorption. As a consequence, this assumption is not suited for slowly dissolving/precipitating compounds or controlled release formulations. If such formulations are to be modeled, eq 5 needs to be modified appropriately.

Finally, 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 given by

$$\frac{d^2M_{pv}(z,t)}{dz\,dt} = P^0_{int}\left[C^0_{lumen}(z,t) - \frac{C_{pv}(t)}{K^0_{lumen}}\right]\frac{dA_{eff}(z)}{dz} + P^i_{int}\left[C^i_{lumen}(z,t) - \frac{C_{pv}(t)}{K^i_{lumen}}\right]\frac{dA_{eff}(z)}{dz}, \tag{6}$$

where $P^{0/i}_{int}$ and $K^{0/i}_{lumen}$ are the apparent permeability coefficients of the gut wall and the equilibrium partition coefficients between the portal blood and the gut content for the neutral and ionized species, C_{pv} is the concentration in the portal vein, and $dA_{eff}(z)$ is the effective surface area element at intestinal position z.[20] The simplest approach to describe the absorption of acids and bases is the pH-partition-hypothesis.[33] According to this hypothesis, only the neutral species of the compound is able to permeate across the intestinal epithelial membranes:

$$P^i_{int} \equiv 0 \text{ (pH-partition-hypothesis)} \tag{7}$$

A more realistic approach is to attribute a nonzero permeability to the ionized species. In this case, the ratio of the two permeability coefficients P^i_{int}/P^0_{int} is an additional input parameter of the model. The consequences of the two approaches to describe the permeability of the ionized species will be discussed in the results section. Similarly to P_{int}, the pH dependence of the intestinal solubility can be described with the fraction of the neutral species and the ratio of the solubility of the ionized and the neutral species S^i_{int}/S^0_{int} in eq 5.

Integration of eq 6 over the length of the segments yields the amount absorbed in the respective gut region at a designated time, while integration with respect to time gives the amount of the dose absorbed as a function of the position within the small intestine. The fraction dose absorbed (F_{abs}) for a passively absorbed compound undergoing negligible metabolism in the gut wall can be calculated from[20]

$$F_{abs} = \int_{t=0}^{\infty}\int_{z=0}^{L_{int}} \frac{d^2M_{pv}(z,t)}{dz\,dt} dz\,dt/(\text{DOSE BW}) \tag{8}$$

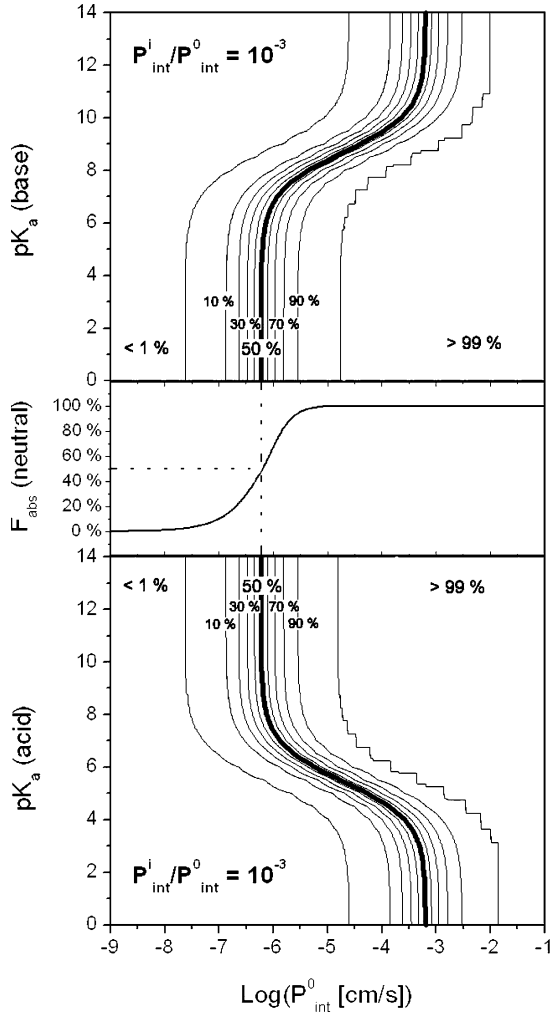

Figure 3. Contour plot of the human fraction dose absorbed as a function of the permeability coefficient of the neutral species and the pK_a for acids and bases (under permeability-limited conditions). The ratio of the permeability coefficients of the ionized and the neutral species is assumed to be 10^{-3}.

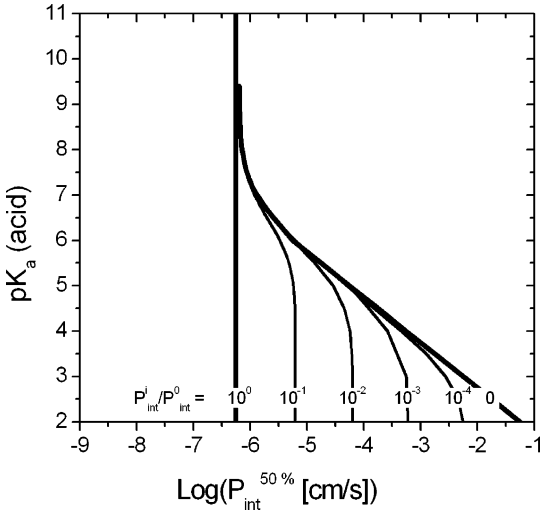

Figure 4. Shift of the apparent permeability coefficient that results in 50% absorption for various ratios of the permeability coefficients of the ionized and neutral species. The case $P^{i}_{int}/P^{0}_{int} = 0$ is equivalent to the pH-partition-hypothesis.

where L_{int} denotes the sum of the lengths of small and large intestine.

3. Results

Throughout the following calculations, the portal concentration C_{pv} was set to zero in eq 6, i.e., sink conditions were assumed in the following sections for simplicity. The variable physiological parameters were set to the mean values reported for healthy humans (e.g. $\tau_{GE} = 30$ min and $t_{SI} = 4$ h[26]) if not stated otherwise. If acids/bases were considered according to the pH-partition-hypothesis or if neutral substances were considered in the following, the superscript "0" was omitted in the permeability coefficient ($P^{0}_{int} \equiv P_{int}$).

3.1 Permeability-Limited Absorption. In Figure 3, the isoabsorption curves obtained with the model are shown for passively absorbed compounds under permeability-limited conditions. The figure describes the dependence of F_{abs} on the intestinal permeability coefficient for neutral substances, and additionally on the pK_a for acids, and bases. For neutral compounds, F_{abs} increases sigmoidally with log(P_{int}). An effective intestinal permeability coefficient of $P_{int} = 5.8 \times 10^{-7}$ cm/s results in 50% absorption. In case of acids or bases, this sigmoidal F_{abs}-vs-P_{int} curve is shifted more and more as the fraction of the ionized species increases. This shift reflects the fact that when the fraction of drug in the ionized form is greater at the pH of the intestinal tract, it will need a correspondingly higher intrinsic permeability in order to be absorbed to the same degree as a compound that is less extensively charged at the same pH. In Figure 3, the ratio of the permeability coefficients of the ionized and the neutral species P^{i}_{int}/P^{0}_{int} was assumed to be 10^{-3}. Figure 4 displays the influence of the value of P^{i}_{int}/P^{0}_{int} on the absorption curves. Here, the 50% iso-absorption lines are plotted for an acid as a function of log(P^{0}_{int}) and different ratios of P^{i}_{int}/P^{0}_{int}. The maximum shift of the iso-absorption curves is proportional to the ratio of the permeability coefficients of the ionized and the neutral species.

In addition to the dependence on the intestinal permeability coefficient, the fraction dose absorbed is also influenced by physiological parameters of the GI tract such as the gastric emptying and the intestinal transit times. In Figure 5, the logarithm of the intestinal permeability coefficient that results in 50% absorption, $P^{50\%}_{int}$ (in [cm/s]), is shown as a function of τ_{GE} and t_{SI}. The ranges of these parameters were chosen according to the typical range that has been reported for healthy humans.[24−27] As can be seen in Figure 5, the 50% isoabsorption curves are shifted by more than one log unit. As a consequence, the fraction dose absorbed for a given compound can change drastically, if the transit pattern in the GI tract varies. Thus, individual physiological variations can contribute significantly to variations in the fraction dose absorbed for a given compound, as is frequently reported in the literature.[34−38]

3.2 Solubility-Limited Absorption. If the fraction dose absorbed decreases with increasing administered mass, this is often an indication of solubility-limited absorption. This can result either from a lack of capacity on the part of the GI fluids to dissolve the drug or due to a precipitation of the compound as it moves through the gut (a typical case is the precipitation of a weak base upon passage out of the stomach into the higher pH fluids of the small intestine). Leaving all other param-

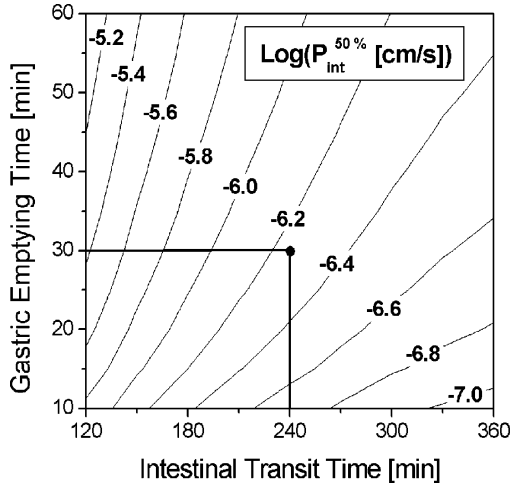

Figure 5. Variations of the logarithm of the apparent permeability coefficient that results in 50% absorption of the applied dose with varying gastric emptying and intestinal transit time. Slower gastric emptying as well as a more rapid intestinal transit shifts the sigmoidal absorption curve toward higher permeability coefficients and vice versa. The physiological "default" values in humans ($\tau_{GE} = 30$ min. and $t_{SI} = 4$ h) are indicated by the centered dot.

eters unchanged, this effect occurs at a certain ratio of the administered mass (or dose) to the (gastro)intestinal solubility. The value that marks the onset of the nonlinear dose response is defined as the "critical mass−solubility ratio" $(M/S_{int})_{critical}$ as shown in Figure 2. Note that in the model (as in reality) the transition between dose-independent and dose-dependent absorption is not as sharp as depicted in Figure 2. Hence, $(M/S_{int})_{critical}$ was defined as the mass−solubility ratio, at which the fraction dose absorbed was 1% smaller than under permeability-limited conditions, due to the compounds solubility.

In Figure 6a, the general dependence of F_{abs} on the permeability coefficient and the mass−solubility ratio is shown for neutral compounds. The dependencies observed with the model are as intuitively expected: If the mass−solubility ratio is smaller than the critical value, absorption is permeability-limited as described above, i.e., the fraction dose absorbed increases sigmoidally with the intestinal permeability coefficient. If, on the other hand, the mass−solubility ratio exceeds $(M/S_{int})_{critical}$, the fraction dose absorbed decreases with increasing administered mass. Four different regions can be distinguished in the (M/S_{int})-vs-P_{int}-space as indicated in Figure 6b. Region A represents the area in the (M/S_{int})-vs-P_{int}-plane where absorption is only limited by the permeability coefficient of the substance. Many orally applied marketed drugs can be found in this region (see Supporting Information for details). $(M/S_{int})_{critical}$ defines the transition from the dose-independent absorption regime (A) to the solubility-limited regime (B). C and D indicate regions where the fraction of the dose absorbed is smaller than 1%, either because of a low intestinal permeability (region D, $P_{int} < 5 \times 10^{-9}$ cm/s) or a low intestinal solubility (region C). Compounds in these regions are, of course, unattractive as prospective orally administered drugs. One important result that can be seen in Figure 6b is that the value of $(M/S_{int})_{critical}$ varies with the intestinal permeability coefficient. At higher permeabilities, the limiting effect of the solubility is shifted to higher doses. This finding is a consequence of the model assumption that dissolution of the compound occurs instantaneously up to its solubility limit. Under these circumstances, a decrease in the drug concentration in the lumen due to permeation results in immediate further dissolution. The higher the permeability coefficient of the compound is, the more dissolution can occur within the time frame of GI transit. Thus, the solubility-limitation condition in eq 5 can be overcome easier by rapidly permeating compounds.

In addition to our own model calculations, Figure 6b shows the FDA-definition[39] of a highly soluble substance and the empirical "minimum acceptable solubility" as defined by Curatolo[40] for compounds with "low" (L), "medium" (M), and "high" (H) permeability. According to the FDA definition, a drug substance is considered highly soluble when the mass−solubility ratio of a solution is less than or equal to 250 mL.[39] Thus, it is reasoned that solubility cannot be the overall absorption limiting factor if the applied mass can be completely dissolved in the glass of water that is usually taken with a drug. The values defined by Curatolo[40] are based on the experiences with several thousand research com-

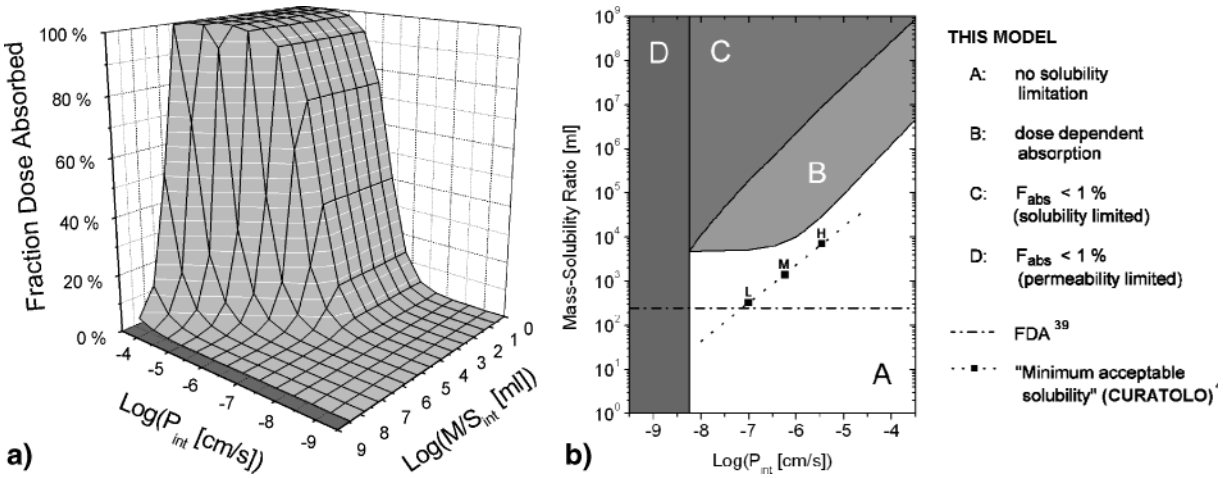

Figure 6. (a) Model simulation of the fraction dose absorbed in humans as a function of the intestinal permeability coefficient and the mass−solubility ratio. According to these simulation results, the (M/S_{int})-vs-LogP_{int}-space can be divided into four different regions (b); for details, see text.

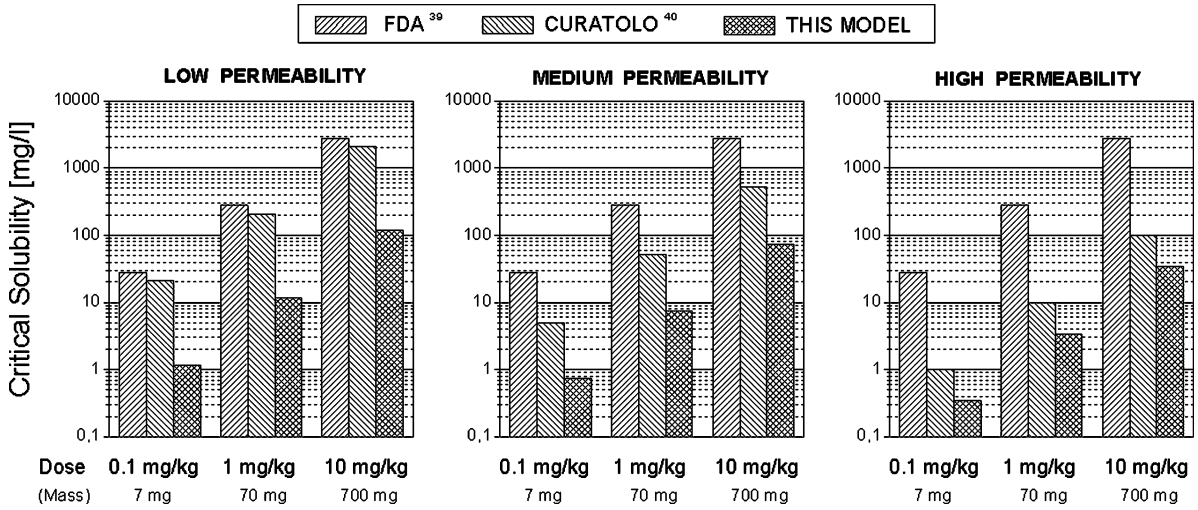

Figure 7. FDA definition of a "highly soluble" compound,[39] "Minimum acceptable solubility" according to Curatolo,[40] and critical solubility derived from this model as a function of the applied dose (assuming a body weight of 70 kg) for compounds with low, medium, and high permeability.

pounds obtained at the research facilities of Pfizer and indicate when to expect poor absorption due to a low solubility. For poorly permeating compounds, the resulting mass−solubility ratio is close to the FDA value of 250 mL but becomes much higher as we move to compounds with medium or high permeability coefficients. A different way to look at the results of Figure 6b is shown in Figure 7, where the critical mass−solubility ratio is converted to a critical solubility for three different doses (0.1, 1, and 10 mg/kg). In Figures 6b and 7, low, medium, and high permeability were chosen corresponding to F_{abs} values of 10, 50, and 90%, respectively.

3.3 Model Validation. To obtain a predictive model, reasonable and easily accessible input values for the intestinal permeability coefficient are necessary. A common way to derive this model input parameter experimentally makes use of the Caco-2 cell line, which is derived from human colon carcinoma cells.[11,13,41−44] Because the determination of a Caco-2 permeability is elaborate and prone to substantial inter-laboratory variability, we derived an analytical equation that allows computation of P_{int} from simpler physicochemical parameters. In our model, the intestinal permeability coefficient is calculated from the compounds membrane affinity (MA), which is defined as the equilibrium partition coefficient between water and immobilized lipid bilayers,[45,46] and a parameter called the effective molecular weight (MW_{eff}). (Physically, the diffusion coefficient is determined by the volume of a molecule rather than its weight. On the other hand, the molecular weight is more commonly available than the molecular volume and was therefore chosen as input parameter for the model. In-house data from Bayer suggest that the correlation between the molecular volume calculated from the 3D structure and the molecular weight of typical druglike molecules could be enhanced by the introduction of an *effective* molecular weight that uses different values for the masses of halogen atoms (unpublished results). In the calculation of the effective molecular weight, 17 mass units are subtracted for every F atom, 22 for every Cl atom, and 62 for every Br atom. The physical interpretation of this correction is that halogen atoms contribute less to the volume of a druglike molecule than their weight suggests.)

The calculation is based on a semiempirical formula first published by Leahy et al.:[12]

$$P_{int}(MW_{eff},MA) = A\frac{MW_{eff}^{-\alpha-\beta}\,MA}{MW_{eff}^{-\alpha} + B\,MW_{eff}^{-\beta}\,MA} + C\frac{MW_{eff}^{-\gamma}}{D^{-\gamma} + MW_{eff}^{-\gamma}}[cm/s] \quad (9)$$

The first term on the right-hand side of eq 9 accounts for transcellular and the second term for paracellular passive transport across the intestinal epithelium.[12] The term "$MW_{eff}^{-\alpha} + B\,MW_{eff}^{-\beta}MA$" accounts for the diffusion process in the unstirred water layer. The exponents α and β describe the mass-dependence of the diffusion coefficients in water (α) and in the membrane (β), respectively. The term "$MW_{eff}^{-\gamma}/(D^{-\gamma} + MW_{eff}^{-\gamma})$" describes a sigmoid function with values between 0 and 1 and slope γ. D can be interpreted as a threshold value for the molecular weight that allows for paracellular transport via the tight junctions. The value of C corresponds to the permeability coefficient of pure paracellular transport.

To determine an optimal set of coefficients for eq 9, a data set of 126 substances with reported human fraction dose absorbed obtained from five literature sources was used.[34−38] The complete list of compounds and data used for this study is available as Supporting Information (see below). According to the model, none of these compounds are likely to be solubility-limited (i.e. all compounds except Sulfasalacine are located in region A in Figure 6b at maximal single doses, for details see the Supporting Information).

The membrane affinities of these compounds were determined experimentally as described in detail in several references.[45,46] Seven compounds from the data set were known to be actively transported: amoxicillin, ampicillin, cefalexin, and cefadroxil are actively influxed,[47] whereas doxorubicin,[48] ranitidine,[49] and sulfasalazine[50] are actively effluxed. The model parameters in eq 9 were obtained by an iterative numerical opti-

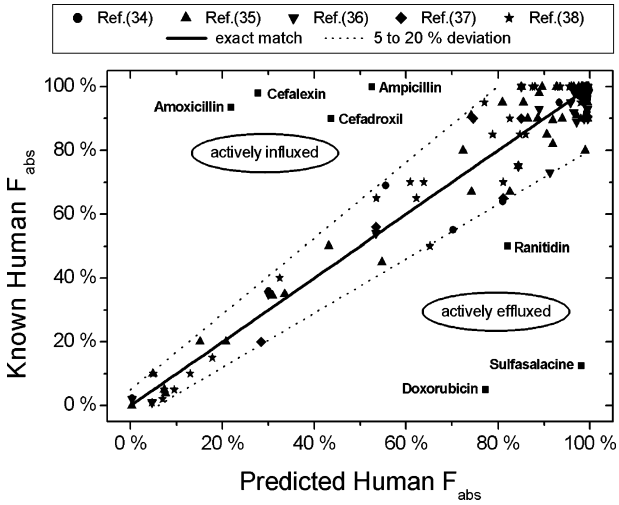

Figure 8. Correlation between known[34−38] and predicted human fraction dose absorbed (based on eq 9) for the set of permeability-limited compounds. Compounds that are known to be actively transported are marked by their name. The correlation coefficient for the passively absorbed compounds is $R = 0.97$.

Table 1. Resulting Fit-Parameters for Eq 9 According to the "Minimum Outlier" Rule

A	B	C	D	α	β	γ
7440	1.0×10^7	2.5×10^{-7}	202	0.60	4.395	16

mization according to a "minimum outlier" rule within an predefined uncertainty range. A linearly increasing absolute deviation between the predicted and the actual fraction dose absorbed ranging from ±5% for nonabsorbable compounds to ±20% for completely absorbed compounds was considered to be an acceptable uncertainty. The seven actively transported substances were excluded from the optimization procedure yielding $N =$ 119 data points for the parameter optimization. Figure 8 shows the resulting plot of the known data versus the predicted values for F_{abs} obtained using the optimized set of parameters listed in Table 1. As can be seen in this figure, an excellent agreement was obtained between the predicted and the actual fraction dose absorbed for this set of passively absorbed compounds (correlation coefficient $R = 0.97$).

To estimate the predictive power of our model, we performed a cross-validation procedure.[51] Therefore, the data set was randomly divided into 10 equally sized subsets. One of the subsets was defined as test set and the nine remaining subsets as training set ("Leave-10%-out method").[51] We consecutively performed our optimization procedure using the training data only. The resulting set of parameters was then used to predict the fraction dose absorbed for the compounds from the test set. The predictivity of our model was evaluated by calculating the cross-validation correlation coefficient (R_{CV}), the root-mean-square error of prediction (RMSE), and the percentage of compounds that was predicted outside our predefined uncertainty range. To get more robust values for the predictivity measures, the random subgroup selection was repeated 10 times, and the R_{CV} and RMSE values were averaged over the 10 runs. A mean correlation between measured and predicted F_{abs}-values of $R_{CV} = 0.93$ and a RMSE of 7% was obtained in this cross-validation procedure. The probability for a compound to be predicted outside our uncertainty range was 1%.

4. Discussion

The presented human absorption model is a "scaled up" version of the previously developed physiological absorption model for rats, which has been shown to accurately describe temporal absorption profiles in these laboratory animals.[20] The model simulates the gastrointestinal transit and passive absorption of a compound administered in solution in a fasted subject. The physiology of the GI tract is described based on literature data for a healthy male person with a body weight of approximately 70 kg. However, the physiological parameters within the model can be easily adjusted to account for individual variations or specific subpopulations (e.g. children, elderly people, etc.). As substance-specific input parameters, only the intestinal permeability coefficient and the solubility in the intestinal fluid are required for neutral compounds. Acids and bases can also be treated by the model. Their description requires the knowledge of the pK_a as well as the intestinal permeability coefficient and the solubility of the ionized species as additional input parameters.

The introduction of the term $C_{pv}/K^{0/i}_{lumen}$ in eq 6 allows, in principle, for a bidirectional transport across the gut wall, if the portal concentration exceeds the limit for the sink condition approximation (i.e. $C_{pv} < 0.1\ C_{lumen}$). This is usually the case after intravenous drug administration. After oral administration, however, the luminal concentration is usually larger than the concentration in the blood. For simplicity, $C_{pv} = 0$ was assumed in eq 6 throughout the calculations. In a general multicompartmental PB−PK model that describes the drug distribution in the whole mammalian body, K_{lumen} becomes an important parameter, because its value can strongly influence the rate and extent of intestinal absorption and the overall distribution of an orally administered compound.

In the current model version, eqs 6 and 9 only account for passive diffusion across the intestinal membrane via the trans- and paracellular route. If the substance is actively absorbed, additional terms are necessary to describe the influx and efflux via the transporter proteins using saturable Michaelis−Menton kinetics. Such terms can be easily implemented mathematically in the model.

The overall performance of the model was investigated by calculating the fraction dose absorbed for a broad range of the input parameters. The intestinal permeability coefficient was varied over 6 orders of magnitude, the mass−solubility ratio over 9 orders of magnitude. The resulting F_{abs}-vs-P_{int}-vs-(M/S_{int}) space shows the expected dependencies. It can be divided into four meaningful regions (Figure 6b). Under permeability-limited conditions (region A), the maximum absorbable fraction of the administered dose is only determined by the intestinal permeability coefficient in a sigmoidal manner. The critical mass−solubility defines the borderline between permeability-limited and solubility-limited absorption (region B). In this region, a nonlinear dose response with the administered mass is to be expected. The limiting effect of the solubility is shifted to higher doses if the permeability coefficient increases. This is the result of the model assumption

that dissolution and precipitation are fast compared to intestinal transit and absorption, as expressed in eq 5. This finding is qualitatively in agreement with the results of Curatolo,[40] who found that the "minimum acceptable solubility" depends on the compound's permeability. Quantitatively, however, the values obtained with this model differ from the values proposed in ref 40. In contrast to the empirical definition by Curatolo,[40] the critical mass−solubility ratio defined in our model is derived from physiological considerations. It denotes the ratio of M and S_{int}, where F_{abs} becomes dose-dependent. In absolute numbers, F_{abs} can still be high, but it will become smaller if the administered dose is further increased. Because of the different definitions, it is reasonable that the critical mass−solubility ratio defined in our model is always somewhat higher than the values presented by Curatolo[40] and more than 1 order of magnitude higher than the FDA cutoff for highly soluble compounds.[39] Finally, regions C and D are unfavorable for prospective oral drugs. They indicate the regions where F_{abs} is lower than 1%, either because of a low solubility (region C) or a low permeability (region D).

All the results were obtained on the basis of the assumption that dissolution and precipitation are fast compared to intestinal transit and absorption, as expressed in eq 5. The influence of the solubility on the rate and extent of absorption becomes more complex if dissolution is slow or release from the dosage form is the rate limiting step to absorption as, for example, for controlled release drug products. In principle, it is easily possible to account for the dissolution kinetic of a slowly dissolving drug by implementing a dissolution function, e.g. of the Weibull-type,[52] in the model.

To use the model as a predictive tool for F_{abs}, a correlation between the model input parameters and substance related descriptors, which can either be measured easily or directly obtained from the structure, has to be established. The available physiological absorption models often use experimental Caco-2 permeability coefficients as input parameters.[11,13,41−44] However, the experimental determination is rather elaborate and not easily adapted for the high throughput desirable at very early stages of research. Moreover, interlaboratory differences have been reported for many compounds, making an absolute scaling of the model input parameter difficult, if not impossible. In fact, individual scaling relations that are derived for a defined set of compounds are a prerequisite for the use of measured Caco-2 permeabilities as input parameters in existing commercial absorption models.[53−55] To overcome the need for Caco-2 measurements, we used an analytical equation derived by Leahy et al.[12] that relates the permeability input parameter required for our PB−PK model to the compound's lipophilicity and size. As a measure of lipophilicity, the membrane affinity, which is defined as the equilibrium partition coefficient between water and a biological membrane mimicking lipid bilayer,[45,46] is used. This quantity can be measured with acceptable throughput (approximately 8000 compounds per lab per year). The effective molecular weight serves as descriptor for the compound's size.

The model parameters were optimized using a dataset of 119 passively absorbed compounds with known permeability-limited absorption taken from five different literature sources.[34−38] All F_{abs} values of compounds that are predominately passively absorbed are found within a predefined uncertainty range that varies between 5% (F_{abs} = 0%) and 20% (F_{abs} = 100%), whereas the seven actively transported substances are either under- or overpredicted by the model, depending on the direction of their active transport. In case of Sulfasalazine, it is not possible to determine whether the low reported fraction absorbed of 12 to 13%[34,36] is only due to active efflux or also in part to the low solubility of this compound, because the doses that were administered in the human studies were not reported.

A "Leave-10%-out" cross-validation was performed to assess the predictivity of the model for compounds with predominate passive absorption (the seven known substrates for active transporters were excluded from the cross-validation). Only one percent of the compounds were predicted to fall outside the predefined uncertainty range. The expected correlation coefficient for F_{abs} values predicted for passively absorbed compounds, that are not in the training set, is 0.93, the corresponding root-mean-square error is only 7%. Thus, the cross-validation demonstrated that the model is very well suited for reliable, quantitative predictions of the fraction dose absorbed for passively absorbed compounds.

The general model results such as the F_{abs}-vs-P_{int}-vs-(M/S_{int}) plot (Figure 6) are especially useful in early drug research phases, when limited physicochemical information is available for a large number of compounds. This plot can then be used to rank the compounds in the order of F_{abs}, to judge whether good or poor absorption is to be expected at a given dose, and to determine whether the compound's solubility or permeability is more likely to result in absorption problems. In later R&D stages, when for example pharmacokinetic information in laboratory rats are available, the absorption model allows, in principle, for a physiological scaling of experimental rat data to predict the absorption behavior in humans. This concept is advantageous over the often-used allometrical scaling of pharmacokinetic parameters (i.e. using a power function of the body weight or body surface area with an allometric exponent α), because it accounts for the specific differences in the GI physiology of rats and humans that actually cause the differences in absorption, while the substance-specific properties such as the intestinal permeability and solubility remain unchanged. In clinical studies, the individual variability of the GI tract and transit pattern becomes an important factor. Here, the model can help to quantitatively determine the sensitivity of the fraction dose absorbed to physiological parameters, as shown in Figure 5.

The ultimate goal of PB−PK modeling, however, is the prediction of concentration time curves in plasma and body tissue. Experimental plasma concentration profiles after oral administration are available in-house and in the literature for a large number of compounds, but they cannot be compared to model calculations without further processing, because the plasma profile also depends on the distribution characteristics and metabolism of the compound. A PB−PK model with additional compartments simulating the whole mammalian body is necessary in order to calculate plasma

concentration profiles for orally administered drugs. This is the subject of further, current work.

5. Conclusions and Outlook

In conclusion, we have presented a physiologically based model for GI absorption in humans that reproduces the known dependencies of the fraction dose absorbed from the intestinal permeability coefficient and solubility. With this model, the sensitivity of the fraction dose absorbed with respect to physicochemical as well as physiological parameters can be described, and favorable regions for orally administered drugs within this multidimensional parameter space can be identified. In general, the model results can lead to a better understanding of the complex process of intestinal absorption and, therefore, can be usefully applied in the drug research and development process. The model cross-validation showed that the fraction dose absorbed can be predicted for passively absorbed compounds under permeability-limited conditions on the basis of simple physicochemical parameters with a root-mean-square error of only 7%. Soon, we will combine this GI absorption model with a "whole body" distribution model to obtain simulated concentration−time curves in plasma and various organs after oral administration.

Supporting Information Available: A table containing all relevant compound data and information about the chemical diversity of this data set are provided as supportive information. This material is available free of charge via the Internet at http://pubs.acs.org.

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