A Heterogeneous Tube Model of Intestinal Drug Absorption Based on Probabilistic Concepts

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Purpose. To develop an approach based on computer simulations for the study of intestinal drug absorption.

Methods. The drug flow in the gastrointestinal tract was simulated with a biased random walk model in the heterogeneous tube model (*Pharm. Res.* 16, 87–91, 1999), while probability concepts were used to describe the dissolution and absorption processes. An amount of drug was placed into the input end of the tube and allowed to flow, dissolve and absorb along the tube. Various drugs with a diversity in dissolution and permeability characteristics were considered. The fraction of dose absorbed (F_{abs}) was monitored as a function of time measured in Monte Carlo steps (*MCS*). The absorption number *An* was calculated from the mean intestinal transit time and the absorption rate constant adhering to each of the drugs examined.

Results. A correspondence between the probability factor used to simulate drug absorption and the conventional absorption rate constant derived from the analysis of data was established. For freely soluble drugs, the estimates for F_{abs} derived from simulations using as an intestinal transit time 24500 MCS (equivalent to 4.5 h) were in accord with the corresponding data obtained from literature. For sparingly soluble drugs, a comparison of the normalized concentration profiles in the tube derived from the heterogeneous tube model and the classical macroscopic mass balance approach enabled the estimation of the dissolution probability factor for five drugs examined. The prediction of F_{abs} can be accomplished using estimates for the absorption and the dissolution probability factors.

Conclusions. A fully computerized approach which describes the flow, dissolution and absorption of drug in the gastrointestinal tract in terms of probability concepts was developed. This approach can be used to predict F_{abs} for drugs with various solubility and permeability characteristics provided that probability factors for dissolution and absorption are available.

KEY WORDS: drug; tube model; heterogeneous; gastrointestinal absorption; fraction absorbed.

INTRODUCTION

Several oral drug absorption models have been developed in the past to study the factors affecting drug absorption from the gastrointestinal (GI) tract (1–7). However, the macroscopic mass balance approach (MMBA) (4,5) occupies a prominent position among the various models since it has been used successfully for the prediction of the fraction of dose absorbed and it has led to the development of the biopharmaceutics drug classification scheme (8). This scheme comprises the scientific basis for considering current bioequivalence and *in vitro-in vivo* correlation issues.

The MMBA utilizes mass transfer relationships for estimating the extent of absorption and relies on a tube model in which physiological characteristics, such as the volume of intestinal fluids and the volumetric flow rate have been incorporated (8). However, the tube model represents an oversimplification of the reality if one takes into account the enormous complexity of the structural and functional features of the GI tract (9). This realization prompted us to develop recently (10) a tube model in which heterogeneous geometrical and kinetic characteristics have been explicitly utilized. Thus, the interior of the cylinder wall bears a finite concentration of dendritic type villi attached to it, while the motion of the drug particles and molecules follows a diffusion model of biased (directional) random walk. These heterogeneous features have replaced the smooth internal wall of the cylinder and the ideal assumptions of the perfect mixing and homogeneous flow of the classical tube model. It was found (10) that the transit process of the oral dosage forms in the GI tract can be reproduced with the biased random walk of drug particles in the heterogeneous tube model. Probability concepts are now directly used to describe the time evolution of the dissolution and absorption processes. In this study, the heterogeneous tube model is further extended to study specifically dissolution and absorption phenomena in the GI tract. The aim is to develop a computer simulation based approach in order to predict the fraction of the dose absorbed for drugs exhibiting a diversity in the fundamental properties, solubility and permeability (8).

METHODS

Model and Dynamics

We use a Monte-Carlo simulation model based on first principles, as it was developed in our previous study (10). Briefly, a cylinder is built that incorporates all the random heterogeneities that make-up the GI tube. Drug particles are inserted in the input end of the cylinder and flow, following the rules of a biased random walk, towards the output end. During the flow they may further dissolve. Dissolved particles are tagged and continue the random walk and can be absorbed by the cylinder wall structure, or exit the tube if they reach its end. We monitor the quantities that are input and exiting through the tube, their transit time, and the fraction of the particles absorbed and dissolved during the flow. The optimal heterogeneous characteristics found previously (10) were assigned to the number of villi and the type of the biased random walk. Thus, the parameter number of villi N(villi) was set equal to 190 while the blind ant model for the biased random walk with forward probability $fp = 0.65$ was used to simulate the motion of the drug particles and the dissolved drug molecules. As the dissolved drug molecules flow through the cylinder, they may be absorbed by the villi. This happens when the position of a dissolved drug molecule is right next to the villi coordinates. For all details of the structures, and elucidating pictorials see (10).

The dynamics of the system is followed utilizing the Monte-Carlo technique (10). This includes motion of the particles through the tube, dissolution in the solvent flow, and absorption by the villi or the tube walls. Time is incremented

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by arbitrary time units, called Monte-Carlo steps (MCS). However, we have established in the past (10) the equivalence between MCS and real time, which is approximately 1.5 MCS = 1 sec.

Simulation of Dissolution and Absorption Processes

A pill can be inserted in one end of the tube (input end); the pill is modeled as an aggregate of drug particles of mass M. One pill can later be broken down successively to smaller units (particles) which represent the solid drug particles. All solid and dissolved drug particles flow through the cylinder from the input end towards the direction of the other end (output end). This is done by using the diffusion model of a biased random walk that simulates the fluid flow.

At each time step a portion of the mass of the pill can be dissolved. The rate of dissolution is considered to be dependent on three factors, which are all expressed in probability values.

The first factor, k_d, mimics the conventional dissolution rate constant, it is inherent for every drug, and takes values in the range $0 < k_d < 1$. A value close to unity denotes a drug with rapid dissolution characteristics. Thus, a specific k_d value is conceived for a given drug under certain experimental conditions. As a probability value, k_d, expresses the number of events occurring in a time unit. Consequently, k_d has units of time^{-1}.

The second factor, k_c, is related to the first-order concentration dependence of the dissolution rate. As dissolution proceeds the amount of drug in solution increases exponentially and therefore the value of k_c is reduced exponentially. This reduction is controlled by the relative amount dissolved, M_d/M_{dmax}, at each time point:

$$k_c = e^{-(M_d/M_{dmax})\ln(10)} \tag{1}$$

where M_d is the mass of the dissolved drug at any moment during the simulation and M_{dmax} is the dissolved mass at saturation. M_{dmax} is computed by multiplying the minimum physiologic solubility, $C_s^{\min}$ of the drug with the luminal volume, which is assumed to be 250 ml. The ln(10) factor was chosen so that the dissolution probability, k_c, when the dissolved mass was equal with the dissolved mass at saturation should arbitrarily be one tenth of the value of k_c when the dissolved mass is equal to zero. Figure 1a is a plot of k_c versus the ratio M_d/M_{dmax} and demonstrates the continuous exponential decrease of the factor, k_c, as dissolution proceeds. Of course, at saturation ($M_d/M_{dmax} = 1$) no more material is allowed to dissolve.

The third factor, k_s, depends on the surface area of the drug particles. It is known that the reduction of the surface area is related non-linearly with the reduction of mass as dissolution proceeds. Since the nonlinear relationship between the undissolved mass, M, and surface area is dependent on the geometrical characteristics of the drug particles, the value of k_s, is considered to decrease proportionally to the $\exp(M/M_0)$ in order to avoid any shape assumptions; M_0 is the initial mass of the pill. Therefore, k_s is calculated from the undissolved drug mass at any moment during the simulation. The exact equation that gives k_s is:

$$k_s = 0.01 \cdot e^{4.5(M/M_0)} \tag{2}$$

The constants in equation (2) are chosen so that k_s arbitrarily equals 0.9 when M equals M_0 and $k_s = 0.01$ when M is close to zero. Figure 1b is the plot of k_s versus the ratio M/M_0.

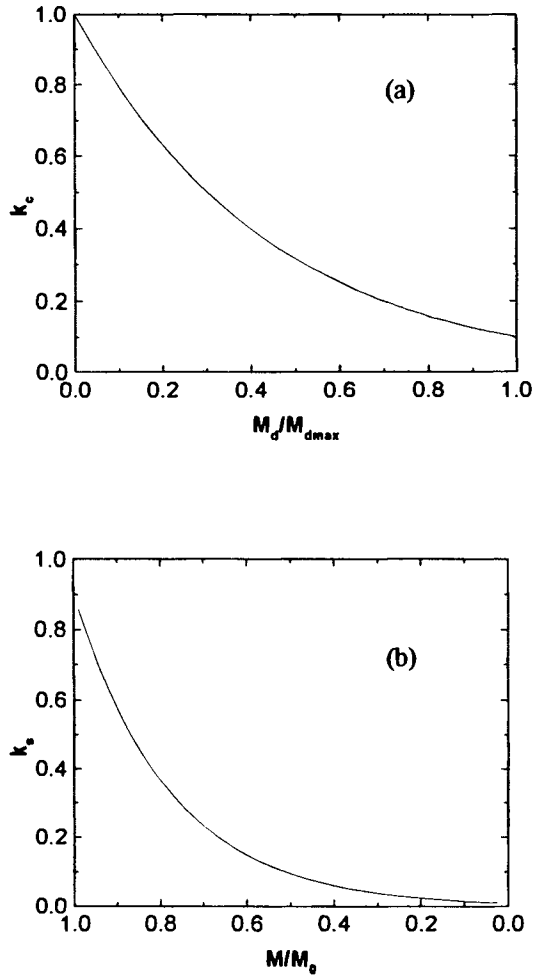

Fig. 1. a. Plot of the dissolution factor k_c versus the ratio M_d/M_{dmax}. b. Plot of the dissolution factor k_s versus the ratio M/M_0.

In essence, the probability factor k_s is related to the diminution of the surface area of drug particles during the dissolution process.

The quantities k_c and k_s, as seen from equations 1 and 2, result from a calculation of an exponential, and thus have no physical units. The effective dissolution probability rate "constant", k_{deff} is calculated by multiplying the above three factors, so that $k_{deff} = k_d \cdot k_c \cdot k_s$. Thus, k_{deff} has units of time^{-1} and denotes the fraction of the total number of drug particles which can be dissolved per MCS. The mass of the pill that will break off at any moment is given by multiplying the value of k_{deff} with the undissolved mass of the pill. If M_{diss} is this mass, then $M_{diss} = M \cdot k_{deff}$ and M_{diss}/m particles of the pill with mass m will break off, and get separated from the larger mass. The dissolved particles now flow on their own, with the same characteristics (forward probability) as the undissolved particles. The mass (M) of the undissolved drug is then reduced by M_{diss}.

Dissolved particles are tagged in the calculation at all times, so we know exactly their location relative to all other particles and the tube walls. When one of the dissolved particles comes "in touch" (when it is in a lattice site adjacent to villi or tube wall) with the tube walls or the villi there is a probability (k_a') that it will be absorbed. It is obvious that the higher the value of k_a' the higher the probability of a dissolved particle to

be absorbed. This proportionality implies that only passive mechanisms are considered in this work. If a dissolved particle is absorbed it is immediately removed from the system. If it is not absorbed it remains on its site and continues the diffusional flow. When a dissolved or undissolved particle reaches the end of the tube then it is discarded.

At the end of the simulation time we compute the mass that was absorbed and the mass that has exited from the end of the tube. Further, the dimensionless absorption number An can be computed (6) by the following scheme:

$$An = \frac{\langle T_{si} \rangle}{R/P_{eff}} \tag{3}$$

It is

$$k_a = \frac{2P_{eff}}{R} \tag{4}$$

and we get

$$An = \frac{\langle T_{si} \rangle k_a}{2} \tag{5}$$

where P_{eff} is the effective permeability, R is the radius of the tube and $\langle T_{si} \rangle$ = 24500 MCS, i.e. the mean intestinal transit time found previously (10). It must be noted that k_a as it appears in equation 5 is not identically the same as the one that we use as a parameter in our simulation. While they both describe probabilities, k_a in equation 5 is a first order macroscopic rate constant expressed in units of time^{-1}, while k_a' that we use in our simulations describes the microscopic probabilistic events of the simulation model.

The current work is divided in three parts. In the first part we focus on the relationship between the simulated k_a' values and the corresponding conventional k_a values which are computed from the simulation data assuming first order absorption. In this part of the simulations only freely soluble drugs were considered. To this end, the drug pill was inserted in the tube and instantly dissolved. In the second part of the work the fraction of dose absorbed was calculated for freely soluble drugs which exhibit a variety of permeability characteristics. The specific purpose of this part was to establish a relationship between F_{abs} and An using as intestinal transit time, $\langle T_{si} \rangle$ = 24500 MCS. In the third part, dissolution and absorption phenomena are considered concurrently. The simulation results, i.e., the amount of drug dissolved expressed in normalized concentration values as a function of the normalized tube length were compared with the data derived from the numerical solution of the following system of differential equations reported in literature (5), which describes the dissolution-absorption of drug particles of radius r_0 in a homogeneous tube of length L:

$$\frac{dr^*}{dz^*} = -\frac{Dn}{3} \cdot \frac{1 - C^*}{r^*} \tag{6}$$

$$\frac{dC^*}{dz^*} = -Dn \cdot Do \cdot r^*(1 - C^*) - 2An \cdot C^*$$

where $z^* = z/L$, $r^* = r_p/r_0$, $C^* = C_L/C_s$; Do is the dose number, Dn is the dissolution number, z is the elementary length, r_p is the radius of the drug particles as dissolution proceeds, C_L is the concentration of the compound at the end of the tube and C_s its solubility.

The fraction of the dose absorbed from the intestine can now be expressed as

$$F_{abs} = 1 - [r^*(z)]^3 - \frac{C^*(z)}{Do} \tag{7}$$

and can be computed from the solution of Eqs. (6).

RESULTS AND DISCUSSION

In the first set of simulations we studied the absorption of freely soluble drugs having various values of k_a'. Thus, an amount of instantly dissolved mass of 20000 was inserted in the input end of the tube. Both profiles of the fraction of the mass that was absorbed and exited the tube were recorded. To find out the relationship between k_a' and k_a Eq. 8 was used to fit the simulated data of the mass fraction absorbed (F_{abs}) versus time

$$F_{abs} = 1 - \exp(-k_a t) \tag{8}$$

where the fitting parameter is k_a in MCS^{-1} units, and time t is also expressed in MCS. The problem in this approach is that Eq. (8) does not take into account the drug mass that exits the tube, which causes a large deviation. A solution for this problem is to fit only the part of the curve for which no drug particles have yet exited the tube (i.e. the early time part). This procedure is shown in Fig. 2. In Fig. 2a we use a small value for k_a', and as a result only a small fraction of the drug mass is absorbed, while most of the mass exits the tube. This explains the large difference between the simulation curve and the fit for times longer than the time needed for the first drug particles to exit the tube. In Fig. 2b we use a larger value of k_a' and as expected the fraction of the drug mass absorbed is larger, while less drug mass exits the tube. In Fig. 2c we use such a value of k_a' that most of the drug is absorbed. In Fig. 3 we plot the values of k_a computed with the above procedure versus the simulated k_a' values. By fitting the resulting points with a linear equation we get the following relation between k_a' and k_a.

$$k_a = 0.885k_a' \tag{9}$$

Having established the relationship between k_a' and k we extended our simulations in order to predict the fraction of dose absorbed for freely soluble drugs exhibiting a diversity in An values. Again, an amount of drug of mass 20000 (arbitrary mass units) was inserted in the tube and was instantly dissolved. This means that there were 20000 drug particles instantly enter the tube entrance, and subsequently are travelling along the tube. This number is large enough to avoid any statistical errors and deviations. The procedure was repeated for various values of k_a' and the percentage (F_{abs}) of the drug dose that was absorbed at 24500 MCS was calculated. The k_a' values were then translated to MCS^{-1} values using equation (9) and the absorption number An was computed using Eq. (5). In Fig. 4 we plot the fraction of the dose that was absorbed versus the absorption number An. The solid points represent the experimental data of various drugs (6), while the line gives the simulation results derived from our model by adjusting the intestinal transit time to 24500 MCS. From the different intestinal transit times evaluated it was found that 24500 MCS gave the best description of the experimental data. If we use the correspondence between MCS and real time units from our previous work (10), the

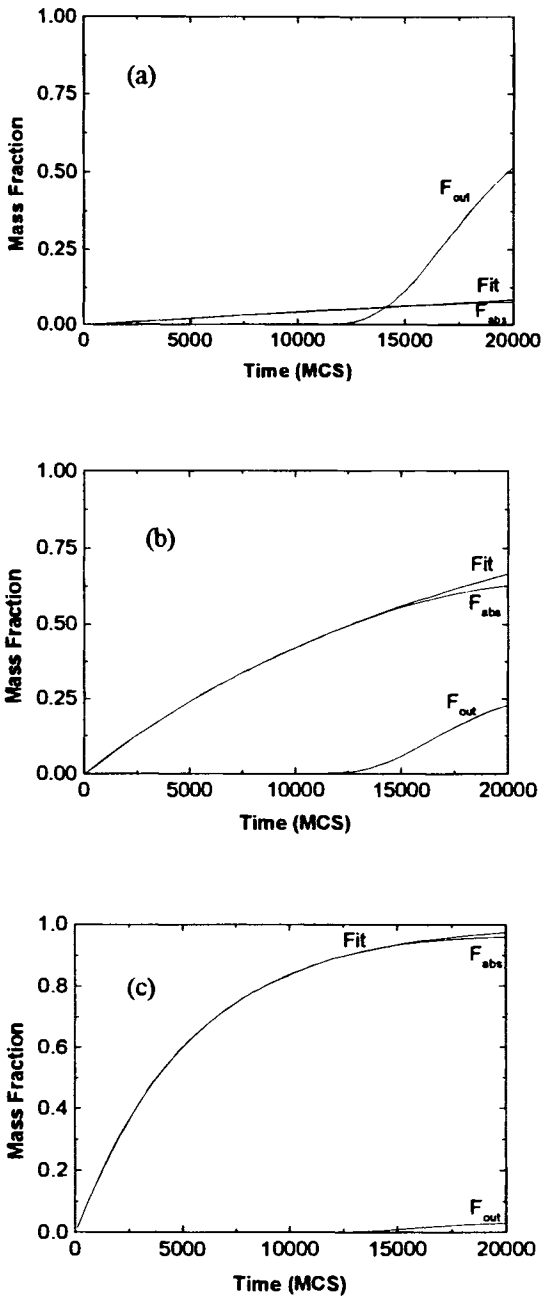

Fig. 2. The three curves depict the mass fraction that has exited (F_{out}) the tube versus time, the mass fraction that was absorbed (F_{abs}) versus time, and the fit, for three different values of k'_a. a. k'_a (*probability*) = $5 \cdot 10^{-6}$, k_a (MCS^{-1}) = $4.41 \cdot 10^{-6}$, b. k'_a (*probability*) = $6 \cdot 10^{-5}$, k_a (MCS^{-1}) = $5.5 \cdot 10^{-5}$, c. k'_a (*probability*) = $5 \cdot 10^{-4}$, k_a (MCS^{-1}) = $4.47 \cdot 10^{-4}$

24500 MCS are 16333 sec or 4.5 h. The duration of 4.5 h as an effective intestinal transit time to study GI drug absorption in our model is physiologically sound if one takes into account that i) the mean small intestinal transit time is 3.3 h (6) ii) the analysis based on the compartmental transit and dispersion models (11) showed that the small intestinal transit time distribution ranges from 1.5 to 10 h and iii) an average intestinal transit time of 30 h has been reported (5). It is also worthy to mention that both estimates for F_{abs} and An of the present

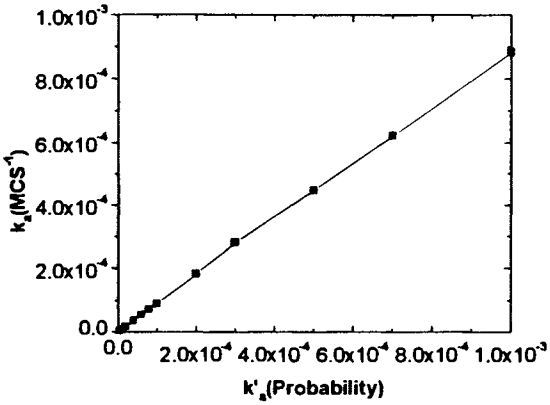

Fig. 3. Plot of k'_a (*probability*) versus k_a (MCS^{-1}).Solid points represent the fitting procedure results, while the solid line is a linear fitting to these points.

study are derived directly from the simulation experiments. This means that our system-approach is self-contained. Other models such as the single mixing tank model, the complete radial mixing model and the compartmental absorption transit model (6) utilize equations to predict F_{abs} from An values which are derived from permeability studies in rats. Recent studies, relying on perfusion experiments in humans, attempt to correlate permeability coefficients in rats and humans (12).

In the last part of the work we study drugs of low solubility. Numerical results of the system of differential Eq. (6) are compared to the simulations. In the simulations the z* variable is computed using the mean transit time of the particles, $\langle T_{si} \rangle$ = 24500 MCS, and $z^* = t/\langle Tsi \rangle$ expressing both t and $\langle Tsi \rangle$ in MCS. We used the data for *Do*, *Dn*, *Dose* and C_s^{min}, listed in Table I, that corresponded to representative drugs (8) while An was set equal to zero in order to concentrate on the dissolution process. Similarly, we used $k'_a = 0$ in our simulations. In the present case the drug is inserted in the tube entrance as a bolus, of a given weight (e.g., 200 or 500 mg). We arbitrarily set that the bolus may break up eventually to a large number of particles, each weighting 0.01 mg. Thus, each drug pill of mass M can be finally broken down to *M/0.01* particles. The values of k_c and k_s were continuously computed during the simulation-fitting procedure from Eqs. 1 and 2. Various values of the parameter

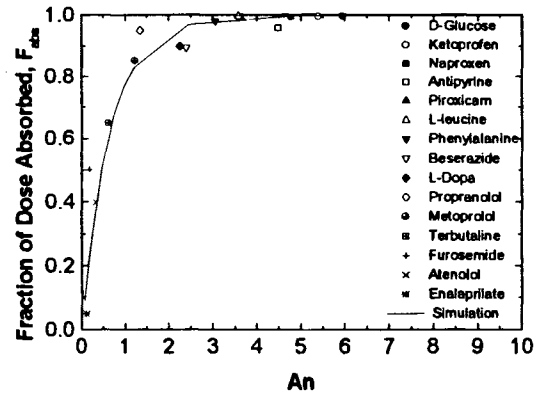

Fig. 4. Fraction of dose absorbed versus An. The solid line represents the simulation results for 24500 MCS and the points the experimental data.

Table I. Values of Dose, C_s^{min}, *Do* and *Dn* that Were Used in the Equations and in the Simulation, and Estimates of k_d for Representatives Drugs

Drug	Dose (mg)	C_s^{min} (mg/ml)	Do	Dn	k_d (MCS^{-1})
Piroxicam	20	0.007	11.4	0.15	0.001
Chlorthiazide	500	0.786	2.54	17.0	0.36
Digoxin	0.5	0.024	0.08	0.52	0.001
Griseofulvin	500	0.015	133	0.32	0.002
Carbamazepine	200	0.26	3.08	5.61	0.08

k_d were used to get a good matching of the simulation and the theoretical curves derived from the solution of Eqs. 6 for the normalized concentration profile in the tube, Fig. 5. The estimates for k_d of five drugs studied are shown in Table I. We can easily see in Fig. 5 that there is a good agreement between the theoretical curves and the simulations for our model except for high z^* values. In high z^* values (which in turn means long time values) some drug mass is starting to exit the tube. This causes the fall in the concentration profile. Since the theoretical Eqs. 6 are based on a fixed volumetric flow rate (5) they do not include the fact that dissolved drug particles exit the tube as a result of the distribution of transit times of our approach (10). This causes the difference between the two curves at long time values, Fig. 5. However, this difference is due to technical reasons only. This is not observed for the dimensionless *(C*)* profile of digoxin in the tube due to its low dose number (8).

Using the estimates for k_d of the five drugs studied, Table I, we also constructed the plot of the fraction of dose dissolved in the tube as a function of t^* (reduced time), Fig. 6. The increase of the fraction dissolved for chlorthiazide and carbamazepine at long time values, beyond the plateau level, is apparently due to the exit of a significant portion of dissolved drug which in turn induces further drug dissolution. As expected, the other three less water soluble drugs exhibit a lower, but continuous, increase of the fraction dose dissolved in the tube, Fig. 6. Finally, a three dimensional plot of the fraction of dose absorbed

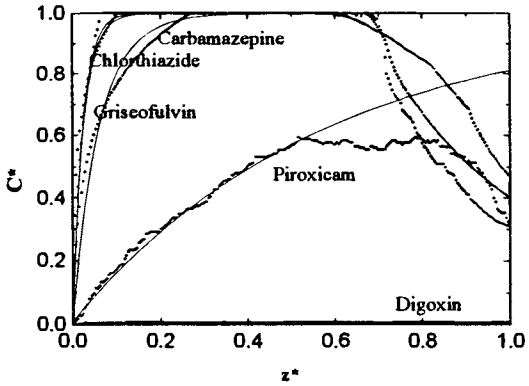

Fig. 5. Normalized concentration of the dissolved drug (C^*) versus the normalized distance from the input end of the tube (z^*). The solid line represents the theoretical curve derived from the solutions of equation 6 and the points the simulation. The values of Dose (mg), C_s^{min} (mg/ml), *Do* and *Dn* that were used in the equations and in the simulation are listed in Table I.

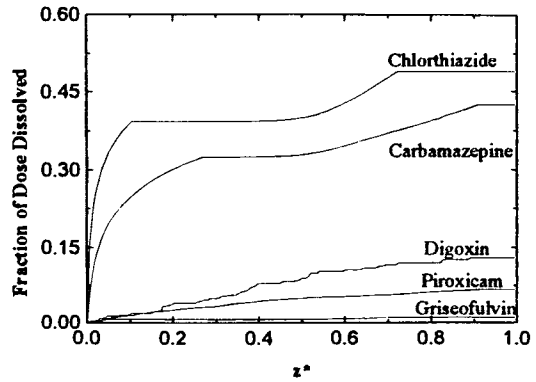

Fig. 6. Fraction of dose dissolved versus t^* for the five drugs using the k_d values reported in Table I.

(F_{abs}) at 24500 MCS for various values of the parameters k_a' and k_d, is shown in Fig. 7 using values for dose and C_s^{min} corresponding to those of digoxin and griseofulvin. The plots of Fig. 7 are indicative of the effect of dose on the fraction of dose absorbed for sparingly soluble drugs. For example, a highly permeable drug ($k_a' \approx 0.5$) given in a large dose (500 mg) and having the dissolution characteristics of griseofulvin (log $k_a \approx$

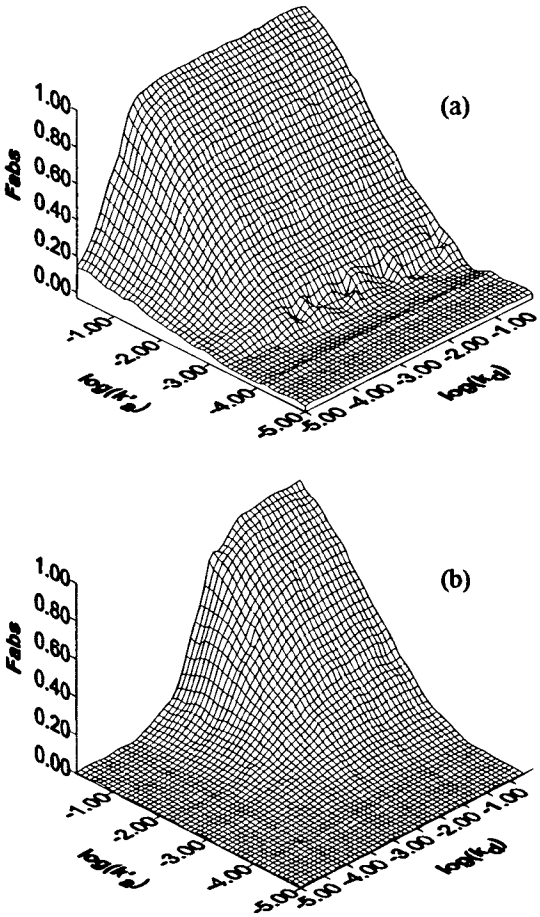

Fig. 7. Three dimensional graph of fraction dose absorbed (F_{abs}) versus k_a' and k_d. Dose and C_s^{min} values correspond to those of (a) Digoxin and (b) Griseofulvin reported in Table I.

-3, Table I), ~25% of the administered dose will be absorbed according to Fig. 7b. On the contrary, a drug given in a low dose (0.5 mg) like digoxin which exhibits the same permeability and dissolution characteristics ($k'_a \approx 0.5$, $\log k_d \approx -3$) as the previous one will be almost completely absorbed, Fig. 7a. These results are in agreement with previous observations (6).

CONCLUSIONS

We presented a self-contained simulation model based on the heterogeneous tube model in which all processes, such as flow, dissolution and absorption are described with probability concepts. It was demonstrated that the absorption of freely soluble drugs exhibiting diversity in *An* values was well characterized using as intestinal transit time 24500 MCS which corresponds to 4.5 h. Moreover, estimates for the probability dissolution factor were derived for five drugs by comparing their dissolution profiles in the heterogeneous tube with the profiles generated from equations describing the dissolution process in the tube. The fraction of dose absorbed of not freely soluble drugs can be estimated using the values for the probability factors of dissolution and absorption. Experimental studies are required to establish relationships between the probability factors k'_a and k_d and the conventional parameters used to characterize permeability and dissolution, respectively. This will certainly facilitate the application of the present approach.

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