An Integrated Model for Determining Causes of Poor Oral Drug Absorption

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Purpose. To develop an integrated absorption model for estimating the fraction of dose absorbed and determining the causes of poor oral drug absorption.

Methods. Both analytical and numerical methods were used to estimate the fraction of dose absorbed.

Results. An integrated absorption model was developed by considering transit flow, dissolution, and permeation processes, simultaneously. A framework was proposed to determine permeability-, dissolution-, and solubility-limited absorption. Digoxin, griseofulvin, and panadiplon were employed to illustrate the applications of the integrated model in identifying the causes of poor absorption and guiding formulation development.

Conclusions. The integrated absorption model was successfully applied to digoxin, griseofulvin, and panadiplon to estimate the fraction dose absorbed and to roughly determine the causes of poor oral drug absorption.

KEY WORDS: small intestinal transit; dissolution; permeation; absorption; modeling.

INTRODUCTION

Despite recent progress in the use of combinatorial chemistry and high throughput screening techniques to identify orally active medicines, the fact that poorly absorbable compounds make their way into development will probably not change in the foreseeable future. We have been relying heavily on formulation approaches to resolve issues relating to poor absorption. Rational formulation design based on pharmaceutical properties of compounds is far from a reality, however. Among many factors, our lack of understanding of the causes of poor oral drug absorption often contributes to long and costly formulation development processes.

Based on our previous work (1–3), the report aims at developing an integrated absorption model for determining the causes of poor absorption. We propose a framework to determine dissolution-, solubility-, and permeability-limited absorption. The utilities and limitations of the model are illustrated using model drugs: digoxin, griseofulvin, and panadiplon.

THEORETICAL

Integrated Absorption Model

If a drug is not in solution when administered, its absorption from the GI tract can be described by a four step process: first, delivering the drug into its absorption site (gastric emptying and small intestinal transit flow); second, getting the drug into solution (dissolution); third, permeating the dissolved drug through the intestinal membrane (permeation/absorption); and finally, moving the drug away from the site of absorption into the general circulation. Step 1 and 2 are not necessary sequential and lymphatic absorption is not considered. The impact of the final process is expected to be very small for poorly soluble drugs because the gastrointestinal tract is well perfused by the bloodstream, which permits the efficient delivery of the absorbed drug into the body (4).

Figure 1a illustrates the integrated absorption model, accounting for gastric emptying, and transit flow, dissolution and passive absorption in the duodenum, jejunum, and ileum The gastrointestinal tract is divided into three segments; stomach, small intestine, and colon. The assumptions for the model include:

(1) Absorption from the stomach and colon is insignificant compared with that from the small intestine;

(2) Transport across the small intestinal membrane is passive and the amount of drug transported is equal to its uptake;

(3) Liquid and solid drug moving through the small intestine can be viewed as a moving process flowing through a series of segments, each described by a single compartment with linear transfer kinetics from one to next, and all compartments having different volumes and flow rates, but having the same residence times (2).

Therefore, for a non-degradable drug dosed in an immediate release dosage form, the transit, dissolution and permeation in the n-th compartment of the small intestine can be depicted for both solid and liquid drug as follows:

$$\frac{dM_{ns}}{dt} = R_{ns,in} - R_{ns,out} - R_{nd},\ n = 1, 2, \ldots, 7 \quad (1)$$

$$\frac{dM_{nl}}{dt} = R_{nl,in} - R_{nl,out} + R_{nd} - R_{na},\ n = 1, 2, \ldots, 7 \quad (2)$$

where M is the amount of drug in the compartment, t is time, R_{in} is the rate of the amount of drug influx, R_{out} is the rate of drug outflow, R_d is the rate of drug dissolution and R_a is the rate of drug permeation across the membrane. The subscripts "ns" and "nl" refer to solid and liquid forms of drug in the nth compartment.

Substitution of the rates of drug flux, dissolution, and permeation (Fig. 1b) gives detailed mass balance equations in the small intestine:

$$\frac{dM_{ns}}{dt} = K_t M_{(n-1)s} - K_t M_{ns} - \frac{3DM_{ns}}{\rho hr}\left(C_s - \frac{M_{nl}}{V_n}\right),$$

$$n = 1, 2, \ldots, 7 \quad (3)$$

$$\frac{dM_{nl}}{dt} = K_t M_{(n-1)l} - K_t M_{nl} + \frac{3DM_{ns}}{\rho hr}\left(C_s - \frac{M_{nl}}{V_n}\right) - \frac{2P_{eff}M_{nl}}{R},$$

$$n = 1, 2, \ldots, 7 \quad (4)$$

where K_t is the transit rate constant (2), P_{eff} is the effective human permeability, R is the radius of the small intestine, D is the diffusion coefficient, h is the diffusion layer thickness,

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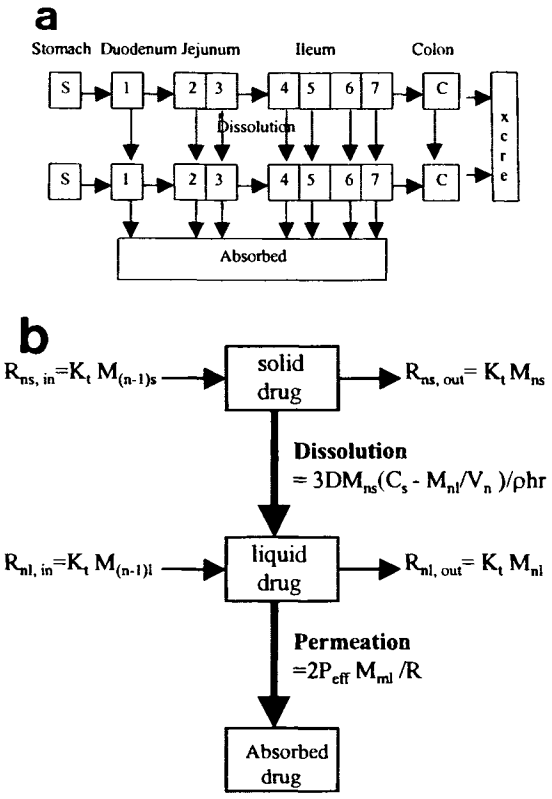

Fig. 1. (A) A schematic diagram of an integrated absorption model for determining the causes of poor oral drug absorption. The model accounts for gastric emptying, and transit flow, dissolution and passive absorption in the duodenum, jejunum, and ileum. The gastrointestinal tract is divided into three segments: stomach, small intestine, and colon. (B) Schematic of transit flow, dissolution and permeation processes in a compartment.

ρ is the density of solid drug, r is the drug particle radius, C_s is the solubility, and V is the volume. The thickness of the film is assumed to be 30 μm regardless of drug particle size and the effect of particle size distribution is not considered (5). The volumes of the compartment are from our previous publication (3).

Gastric emptying is included in this absorption model. Drug particles of 1000 μm or less are small enough to pass through the closed pylorus and can behave more as a solution than a solid when administered (6). Therefore, for both liquid and solid drug particles of 1000 μm or less, the gastric emptying can be described by first order kinetics:

$$\frac{dM}{dt} = -K_s M \tag{5}$$

where M can be the amount of solid or liquid drug and K_s is the gastric emptying rate constant. The initial amount of solid and liquid drug in the stomach has to be determined. In general, the initial amount of solid drug is equal to the dose.

The overall rate of drug absorption can be calculated by

$$\frac{dM_a}{dt} = \frac{2P_{eff}}{R} M_L \tag{6}$$

where M_a is the amount of drug absorbed at time t and $M_L = \Sigma M_{nl}$, n = 1, 2, . . . , 7. The fraction of dose absorbed can then be estimated by

$$F_a = \underset{t\to\infty}{M_a/M_0} = \frac{1}{M_0}\int_0^\infty \frac{2P_{eff}}{R} M_L\, dt \tag{7}$$

Eqs. (6) and (7) can be used to estimate the fraction dose absorbed and the rate of drug absorption which in turn can be related to conventional compartment pharmacokinetic models.

Absorption Limiting Steps

Figure 1b shows the schematic of absorption processes. Without considering the transit flow, the absorption can be limited by dissolution rate and permeation rate, where permeation rate refers to the flux of drug across the intestinal membrane. The supply rate of dissolution and the uptake rate of permeation determine the concentration of drug in the GI tract. However, the concentration in the GI tract is also limited by the solubility of drug. When the supply rate is far more than the uptake rate, the drug concentration in the gastrointestinal fluid approaches its solubility limit. Mathematically, the dissolution rate is expressed by

$$R_d = \frac{3DM_s}{\rho hr}\left(C_s - \frac{M_l}{V}\right) \tag{8}$$

Thus, poor dissolution can be caused either by particle size (r) or solubility (C_s). To emphasize the importance of solubility, we refer to the dissolution/solubility-limited case as solubility-limited absorption. The dissolution/particle size-limited case is still called dissolution-limited absorption. Thus, the absorption of poorly absorbable drugs can be limited by permeability, solubility, and/or dissolution.

To determine dissolution-, solubility-, and permeability-limited absorption, we will define three characteristic parameters, dissolution time (T_{diss}), effective permeability (P_{eff}), and absorbable dose (D_{abs}) (The definitions of these parameters is given in Table 1). Dissolution time is an estimate of the minimum time to dissolve a single particle under sink conditions (7). Effective permeability can be measured directly using the human perfusion technique (8). Absorbable dose is the amount of drug that can be absorbed during the period of transit time when the solution contacting the effective intestinal surface area for absorption is saturated with the drug.

The absorption limiting steps may be roughly determined based on relative values of the dissolution time, permeability and absorbable dose. Table 2 summarizes the framework for determining the corresponding absorption limiting processes. The mean small intestinal transit time was found to be 199 minutes with a standard deviation of 78 minutes (2). This means that as a worst case scenario, the small intestinal transit in some individuals may be only 43 minutes (mean small intestinal transit time $-2 \times$ standard deviation). We used 50 minutes as a reference time of dissolution to determine if the dissolution is fast enough to permit complete dissolution in the small intestine. The effective human permeability is set at 2×10^{-4} cm/sec which corresponds to over 90% of dose absorbed (1). Table 2 provides distinguishing conditions under which each limiting case occurs.

Table 1. Calculation of Dissolution Time and Absorbable Dose

$$T_{diss} = \frac{\rho h r_0}{3DC_s} \quad D_{abs} = P_{eff}C_sA\langle T_{si}\rangle$$

A—Effective intestinal surface area for absorption. If the small intestine is assumed to be a cylindrical tube with a radius of 1.5 cm and length of 350 cm, the available surface area and volume are 3297 cm^2 and 2473 mL, respectively. In reality, the actual volume is around 600 mL and the effective intestinal surface area is then estimated to be about 800 cm^2 assuming the same ratio. On the other hand, if the drug is given as a bolus, it will spread and form a spectrum when it travels down the tube. The spectrum width determines the effective surface area for absorption. Based on the variance of the liquid transit time (5), the effective surface area was calculated to be 732 cm^2. Thus, we used the surface area of 800 cm^2 for future evaluation.

C_s—Aqueous solubility; it is recognized that the actual solubility *in vivo* is affected by many factors such as bile acids. Aqueous solubility provides a conservative estimate.

D—Diffusion coefficient. For simplicity, the diffusion coefficient of 5×10^{-6} cm^2/sec may be used.

h—Diffusion layer thickness was set to be 30 μm.

M_0—Dose

P_{eff}—Effective human intestinal permeability.

r_0—Initial radius of particles

$\langle T_{si}\rangle$—Mean small intestinal transit time, 199 minutes (2).

ρ—Density of drug, generally, 1200 mg/cm^3.

METHODS

Computer Simulation

Model Eqs. (1–7) are a typical initial value problem of an ordinary differential equation system. This system was numerically solved by the ADAPT pharmacokinetic and pharmacodynamic modeling package to estimate the fraction of dose absorbed (9). A subroutine was written to accommodate the model equations.

Table 3. Summary of Parameters Used to Estimate the Absorption of Digoxin, Griseofulvin, and Panadiplon

Parameters	Digoxin	Griseofulvin	Panadiplon
Dose (mg)	0.50	500	10
Solubility (μg/mL)	24	15	77
Diffusion coefficient (cm^2/sec)	4.5×10^{-6}	8.2×10^{-6}	6.1×10^{-6}
Permeability (cm/sec)	1×10^{-3}	1.6×10^{-3}	1.85×10^{-4}
Dissolution Time[1]			
5 μm particle (min)	46	41	11
100 μm particle (min)	926	488	213
Absorbable Dose[1] (mg)	229	229	136
References	7	7, 16	19

[1] Calculated from equations in Table 1.

Drugs

Digoxin, griseofulvin, and panadiplon were employed to show the applications of the integrated absorption model. The fundamental pharmaceutical parameters are shown in Table 3. The dissolution time and absorbable dose are calculated based on equations in Table 1 and are given in Table 3.

RESULTS AND DISCUSSION

Absorption Limiting Steps

Permeability-limited absorption has been widely discussed in the literature (1). In this paper we focus on solubility and dissolution-limited absorption. Figure 2 shows a plot of the fraction of dose absorbed versus dissolution number (the ratio of the small intestinal transit time to the dissolution time, as defined in the literature (7)), and the permeation number (the ratio of the absorbable dose to the actual dose, as defined here). For highly permeable drugs, P_{eff} is greater than 2.0×10^{-4} cm/sec. Thus, with the permeability defined, Fig. 2 actually shows the fraction of dose absorbed as a function of particle size

Table 2. Absorption Limiting Steps and their Corresponding Conditions

Absorption limiting steps	Conditions	Comments
Dissolution limiting	$T_{diss} > 199$ min[a] $P_{eff} > 2 \times 10^{-4}$ cm/sec $D_{abs} >>$ Dose	Solubility also contributes to poor dissolution. But, the dissolution here mainly refers to particle size. The absolute amount of drug absorbed increases with increasing dose.
Permeability limiting	$T_{diss} < 50$ min[b] $P_{eff} < 2 \times 10^{-4}$ cm/sec $D_{abs} >>$ Dose	Permeability-limited absorption occurs for highly soluble drugs or drugs dosed in solutions; assume no precipitation occurs. The absolute amount of drug absorbed increases with increasing dose.
Solubility limiting	$T_{diss} < 50$ min[b] $P_{eff} > 2 \times 10^{-4}$ cm/sec $D_{abs} <$ Dose	Solubility-limited absorption occurs mainly when a high dose saturates part of the gut. The absolute amount of drug absorbed does not increase with increasing dose.

[a] For un-micronized drugs.
[b] For micronized drugs.

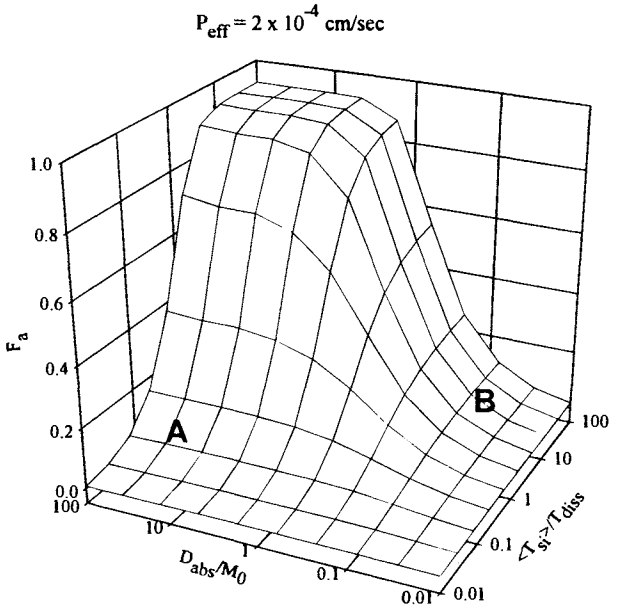

Fig. 2. Fraction of dose absorbed versus the ratios of the small intestinal transit time to the dissolution time and the absorbable dose to the actual dose. Region A: dissolution limiting absorption; Region B: solubility limiting absorption

(dissolution number) and dose (permeation number). Two regions, solubility- and dissolution-limited absorption, are clearly marked. In the solubility-limited absorption region, the reduction of particle size has the minimum effect on the fraction of dose absorbed while in the dissolution-limited absorption region, dose has the minimum effect. Thus, the particle size has its most significant effect in the dissolution-limited absorption region and the dose has its maximum effect in the solubility-limited absorption region.

Figure 2 can be employed to determine the feasibility of improving absorption by reducing particle size. For example, if a drug dosed at 1 mg has a dissolution time of 1000 min, and an absorbable dose of 10 mg, we would expect that the fraction of dose absorbed can be improved from 15% to 85% by decreasing the dissolution time to 50 min with micronization. However, if we dose the same drug at 100 mg, we would not expect much improvement by reducing particle size.

Digoxin

Considering the values for dissolution time, permeability and absorbable dose in Table 3, we would expect that the absorption of digoxin is dissolution-limited. Figure 3 shows the theoretical fraction of dose absorbed as a function of particle size. The experimental bioavailability is also shown for the dose range from 0.25 to 0.75 mg (10–13). There is agreement between the experimental data and the predicted results. The model predicts that digoxin particles of 8 μm or less will be completely absorbed (>90%), suggesting that micronization suffices to improve digoxin absorption. Discrepancy at large particle sizes is likely caused by the model assumption of uniform particle size.

It is evident from equations in Table 1 that prolonging small intestinal transit will allow more time for dissolution, enhancing absorption. This agrees with findings by Manninen

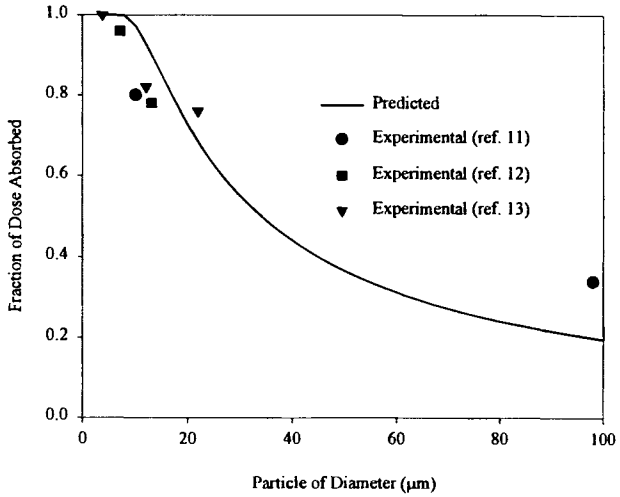

Fig. 3. Experimental and predicted fraction of digoxin absorbed as a function of particle size.

et al. (14), in studies of a slowly dissolving digoxin tablet, that the administration of metoclopramide, which increases intestinal motility, decreased the absorption of digoxin while the anticholinergic drug propantheline, which slows intestinal motility, increased the absorption of digoxin. Propantheline, however, does not alter the absorption of digoxin administered in solution, because the digoxin administered in liquid form is completely absorbed (14). The slower intestinal motility or longer small intestinal transit time, certainly, would not provide any further help.

Griseofulvin

Griseofulvin is an antibiotic, antifungal agent used in the treatment of mycotic diseases of the skin, hair, and nails. Based on dissolution time, permeability and absorbable dose in Table 3, we concluded that the absorption of griseofulvin is limited by both dissolution and solubility. Figure 4 shows the predicted fraction of dose absorbed as a function of particle size for 250, 500, and 1000 mg doses. At the high dose, absorption is largely

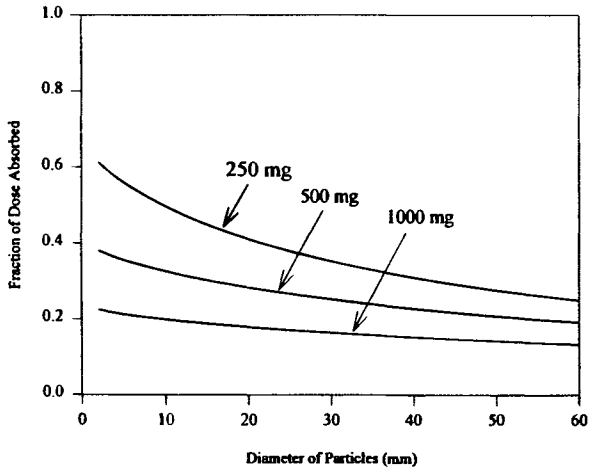

Fig. 4. Predicted fraction of griseofulvin absorbed as a function of particle size.

limited by solubility, while at the low dose, dissolution also limits the absorption. Therefore, particle size reduction has a much stronger effect on the low dose than the high dose. However, unlike the case with digoxin absorption (Figure 3), micronization only provides limited improvement of griseofulvin absorption.

Chiou and Riegelman *et al.* (17) studied absorption kinetics of micronized griseofulvin in man at a dose of 500 mg and found that the absolute bioavailability was about 45%. That is very close to the predicted fraction of dose absorbed, 38%. The model predicts that when the particle is reduced from 30 μm to 4 μm, the fraction of dose absorbed is improved by a factor of 1.7 (from 35% to 58%) at a dose of 250 mg, in agreement with the findings of Kabasakalian *et al.* (18) that about twice as much micronized griseofulvin is absorbed as regular size griseofulvin.

Panadiplon

Panadiplon is an anxiolytic agent for the treatment of generalized anxiety disorders. Based on the dissolution time, permeability and absorbable dose in Table 3, we conclude that the absorption of panadiplon is dissolution limited although the absorption is also very weakly limited by permeability. For small particles; the dissolution is fast enough, with the corresponding fraction of dose absorbed around 90%. The model predicts that about 71% of the dose is absorbed at a particle size of 39 μm, which is in agreement with the experimental bioavailability, 73%, obtained by Nichols *et al.* (personal communication). It is estimated that 89%, 79%, and 45% of dose is absorbed at particle sizes of 8.8, 25, and 100 μm, respectively. These predicted results are in line with the absolute bioavailability in dogs: 81%, 74%, and 24% at the respective particle sizes (19).

CONCLUSIONS

An integrated absorption model was developed to estimate the fraction of dose absorbed and to determine the causes of poor oral drug absorption by defining conditions for dissolution-, solubility- and permeability-limited absorption to occur. The model assumptions are: a drug is dosed in a suspension or in an immediate release dosage form; drug particles are spheres with the same size; there are no reactions (metabolism) in the intestine; solubility is independent of particle size and intestinal environment (pH); and no aggregation occurs. These assumptions must be kept in mind when applying the proposed model to actual cases.

The integrated absorption model considers three major processes of absorption: transit flow, dissolution, and permeation. The defined mode can be used in lead candidate selection and formulation design. The usefulness of the model was demonstrated using digoxin, griseofulvin, and panadiplon.

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