

Estimating the Fraction Dose Absorbed from Suspensions of Poorly Soluble Compounds in Humans: A Mathematical Model

Doo-Man Oh,^{1,2} Rane L. Curl,³ and Gordon L. Amidon^{1,4}

Received January 16, 1992; accepted August 13, 1992

A microscopic mass balance approach has been developed to predict the fraction dose absorbed of suspensions of poorly soluble compounds. The mathematical model includes four fundamental dimensionless parameters to estimate the fraction dose absorbed: initial saturation (I_s), absorption number (An), dose number (Do), and dissolution number (Dn). The fraction dose absorbed (F) increases with increasing I_s , An , and Dn and with decreasing Do . At higher Dn and lower Do , the fraction dose absorbed reaches the maximal F , which depends only on An . The dissolution number limit on F can appear at both lower Do and lower Dn . Likewise, at higher Do and Dn , the fraction dose absorbed reaches a Do limit. Initial saturation makes a significant difference in F at lower Do and Dn . It is shown that the extent of drug absorption is expected to be highly variable when Dn and Do are approximately one. Furthermore, by calculating these dimensionless groups for a given compound, a formulation scientist can estimate not only the extent of drug absorption but also the effect, if any, of particle size reduction on the extent of drug absorption.

KEY WORDS: absorption; dose; particle size; permeability; solubility; suspensions.

INTRODUCTION

Several mathematical models for absorption from the intestine have been presented in the literature (1–7). Goodacre and Murray (1) introduced three resistances for the absorption process: the dissolution resistance, the wall boundary layer resistance, and the membrane resistance. However, they assigned the dissolution resistance an average time-independent value so that the changing surface area of particles down the intestine was not considered. Dressman and Fleisher (5) used a mixing tank model to predict the fraction dose absorbed of dissolution rate-controlled compounds.

Recently a macroscopic mass balance approach with respect to absorption and solubility considerations has been developed (6,7). Three cases were considered with regard to inlet and outlet concentrations of a compound in the intestinal lumen. In those papers Case III described the situation

where the drug concentration is always above its solubility. For the dissolution rate-controlled absorption of a poorly soluble compound, Case III is a useful limit (6). The constant luminal concentration, assumed equal to the solubility, is restrictive for suspensions because it does not include the dissolution resistance but, rather, gives the limit of no dissolution resistance. Recently, the absorption number (An) and the dose number (Do) were introduced to predict oral drug absorption in humans for passive and carrier-mediated compounds (7). It has been shown that the extent of drug absorption in Case III can be estimated from An and Do .

The factors that can influence oral absorption are physicochemical properties, physiological parameters, and formulation factors (8). The physicochemical properties of a compound include lipophilicity, chemical or enzymic stability, solubility, particle size, density, diffusivity, pK_a , and crystal form. Physiological factors include permeability, membrane transport mechanism, gastrointestinal pH, motility, and stomach emptying.

The objective of this report is to estimate the fraction dose absorbed from suspensions of poorly soluble compounds by including a variable dissolution resistance as a function of particle size. Four underlying dimensionless parameters are developed to estimate the fraction dose absorbed of suspensions using a microscopic mass balance approach: initial saturation (I_s), absorption number (An), dose number (Do), and dissolution number (Dn).

THEORETICAL

The following assumptions are made to simplify the mathematical model: the intestine is a cylindrical tube where absorption occurs; particles are spheres with the same size; there are no reactions (metabolism) in the intestine; solubility is independent of the particle size and the intestinal pH gradient; and no aggregation occurs.

Plug (complete radial mixing) flow is employed for a long tube and small particles: the intestinal length (L) is much longer than its radius (R), so that length Peclet number⁵ (Pe_L) is very large compared to radial Peclet number (Pe_R). Steady state is assumed.

Derivation of Differential Equations

A physical model for the fraction dose absorbed with plug flow (complete radial mixing flow) containing particles is shown in Fig. 1. Mass balances in both solid phase and solution phase are used to derive a set of differential equations. For the mass balance of the solid phase, the rate of mass dissolved is assumed to be equal to the difference between the rate of solid mass into and that out of a differential element of volume,

$$(\text{rate of mass in}) - (\text{rate of mass out}) - (\text{rate of mass dissolved}) = 0 \quad (1)$$

or

⁵ Peclet number is defined to be $v_z \cdot L/\mathcal{D}_L$ for Pe_L and $v_z \cdot R/\mathcal{D}_R$ for Pe_R , where v_z is the axial flow velocity, and \mathcal{D}_L and \mathcal{D}_R are diffusivities to the axial and radial directions, respectively.

¹ College of Pharmacy, The University of Michigan, Ann Arbor, Michigan 48109-1065.

² Present address: School of Pharmacy, University of California, San Francisco, California 94143-0446.

³ Department of Chemical Engineering, The University of Michigan, Ann Arbor, Michigan 48109.

⁴ To whom correspondence should be addressed.

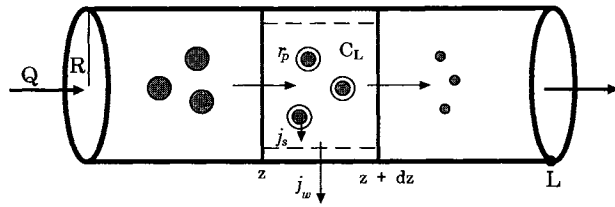


Fig. 1. Schematic absorption model of suspensions. A microscopic mass balance approach is applied for both solid and solution phases in a volume element of the intestine.

$$\dot{M}_s|_z - \dot{M}_s|_{z+dz} - j_s \cdot S_p \cdot \pi R^2 \cdot dz = 0 \quad (2)$$

Dividing Eq. (2) by dz and then taking the limit gives

$$\frac{d}{dz}(\dot{M}_s) + j_s \cdot S_p \cdot \pi R^2 = 0 \quad (3)$$

where

$$\dot{M}_s = Q \cdot (N_0/V_0) \cdot \frac{4\pi r_p^3}{3} \cdot \rho$$

$$j_s = k_s(C_s - C_L) = \frac{\mathcal{D}}{r_p} (C_s - C_L)$$

$$S_p = (N_0/V_0) \cdot 4\pi r_p^2$$

The assumption of $k_s = \mathcal{D}/r_p$ is based on the limiting Sherwood number ($Sh = k_s \cdot r_p/\mathcal{D} = 1$) in pseudo-steady-state transfer at low Reynolds numbers (9). This gives a lower limit on the maximum rate of dissolution possible for a particle of radius of r_p . This is preferred to the constant-film thickness assumption for small spherical particles (10). Simplifying Eq. (3), one obtains the rate of change for the particle radius:

$$\frac{dr_p}{dz} = -\frac{\mathcal{D} \cdot \pi R^2}{Q \cdot \rho} \cdot \frac{C_s - C_L}{r_p} \quad (4)$$

Similarly for the mass balance of the solution phase, the sum of the rate of mass dissolved and the rate of mass absorbed is assumed to be equal to the difference between the rate of mass into and that out of a differential element of volume,

$$\begin{aligned} &(\text{rate of mass in}) - (\text{rate of mass out}) \\ &+ (\text{rate of mass dissolved}) \\ &- (\text{rate of mass absorbed}) = 0 \end{aligned} \quad (5)$$

or

$$\dot{M}_1|_z - \dot{M}_1|_{z+dz} + j_s \cdot S_p \cdot \pi R^2 \cdot dz - j_w \cdot (2\pi R) \cdot dz = 0 \quad (6)$$

Taking the limit after dividing Eq. (5) by dz gives

$$-\frac{d}{dz}(\dot{M}_1) + j_s \cdot S_p \cdot \pi R^2 - j_w \cdot (2\pi R) = 0 \quad (7)$$

where

$$\dot{M}_1 = Q \cdot C_L$$

$$j_w = k_w(C_L - 0) = P_{\text{eff}} C_L$$

$$P_{\text{eff}} = \left(\frac{1}{P_w} + \frac{1}{P_{\text{aq}}} \right)^{-1}$$

Assuming sink conditions at the blood side, Eq. (7) is simplified to

$$\frac{dC_L}{dz} = \frac{\mathcal{D} \cdot (N_0/V_0) \cdot 4\pi^2 R^2}{Q} \cdot r_p (C_s - C_L) - \frac{P_{\text{eff}} \cdot 2\pi R}{Q} \cdot C_L \quad (8)$$

To make the variables dimensionless, let $z^* = z/L$, $r^* = r_p/r_0$, and $C^* = C_L/C_s$, where C_s is the solubility of a compound. Equations (4) and (8) become

$$\frac{dr^*}{dz^*} = -\frac{Dn}{3} \cdot \frac{1 - C^*}{r^*} \quad (9)$$

$$\frac{dC^*}{dz^*} = Dn \cdot Do \cdot r^* (1 - C^*) - 2An \cdot C^* \quad (10)$$

where

$$An = \frac{P_{\text{eff}}\pi RL}{Q} = \frac{\text{radial absorption rate}}{\text{axial convection rate}} \quad (11)$$

$$Do = \frac{M_0/V_0}{C_s} = \frac{\text{dose concentration}}{\text{solubility}} \quad (12)$$

$$Dn = \frac{(\mathcal{D}/r_0) C_s (4\pi r_0^2)/(\rho/3\pi r_0^3)}{Q/(\pi R^2 L)} = \frac{\text{residence time}}{\text{dissolution time}} \quad (13)$$

An is the absorption number, which is the ratio of the radial absorption rate to the axial convection rate. An consists of the effective permeability of a compound and volumetric flow rate in the intestine. Do is the dose number, which is the ratio of dose concentration to solubility. Do is a function of solubility, dose, and water volume taken with a compound. Dn is the dissolution number, which is the ratio of residence time in the intestine to dissolution time from particles of initial radius of r_0 . Dn includes solubility, diffusivity, density, and initial particle radius of a compound and volumetric flow rate in the intestine. Equations (9) and (10) are solved simultaneously by a numerical method (11).

Initial Saturation

To estimate the extent of drug absorption, it is assumed that the dose taken is the sum of the initially dissolved amount in solution and the remaining amount in the solid phase at the beginning of the intestine. It can be assumed that there is a precompartment before the intestine, but some of the drug must be in suspension form at the beginning of the intestine regardless of the dosage form taken, as assumed in the model. The initial saturation, Is , is defined as

$$Is = \frac{C_L(0)}{C_s} \quad (14)$$

where $C_L(0)$ is the luminal concentration at the beginning of the intestine. I_s is the dimensionless inlet concentration in solution. The boundary condition at the beginning of the intestine ($z^* = 0$) is that $C^* = I_s$ and $r^* = (1 - I_s/Do)^{(1/3)}$, where Do is the dose number.

Fraction Dose Absorbed

It is assumed that the difference between the mass into and that out of the intestine is equal to be the mass absorbed at steady state. From the mass balance in the intestine, the fraction dose absorbed (F) is

$$F = 1 - \frac{(\text{mass out})_{\text{solid} + \text{solution}}}{(\text{mass in})_{\text{solid} + \text{solution}}} \quad (15)$$

where

$$(\text{mass in})_{\text{solid} + \text{solution}} = M_0 = (4/3) \pi r_0^3 \rho N_0$$

$$(\text{mass out})_{\text{solid} + \text{solution}} = (4/3) \pi r_p^3 \rho N_0 + V_0 C_L / M_0$$

The fraction dose absorbed from the intestine becomes

$$F = 1 - \{r^*(1)\}^3 - \frac{C^*(1)}{Do} \quad (16)$$

where $r^*(1)$ and $C^*(1)$ are the dimensionless radius of particles and the dimensionless concentration at the end of the intestine. The values of $r^*(1)$ and $C^*(1)$ can be calculated from the solutions to Eqs. (9) and (10).

If there is no dissolution limitation ($Dn \rightarrow \infty$) from particles and some particles remain undissolved at the end of the intestine, the drug concentration in the elemental volume of the tube approaches its solubility ($C^* \rightarrow 1$). From Eqs. (9) and (10) the rate of change of particle size with respect to the tube length becomes

$$\frac{dr^*}{dz^*} = -\frac{2An}{3(r^*)^2 \cdot Do} \quad (17)$$

From Eqs. (16) and (17) the fraction dose absorbed of suspensions with no dissolution limitation becomes

$$F = \frac{2An}{Do} \quad (18)$$

the same as case III derived previously (6).

If the particles are dissolved at or before the end of the intestine (when $An > \frac{1}{2}(Do - 1)$ and $Do > 1$), the fraction dose absorbed of suspensions with no dissolution limitation is

$$F = 1 - \frac{C^*(1)}{Do} = 1 - \frac{1}{Do} e^{-2An+Do-1} \quad (19)$$

For the case of a solution, the dissolution terms of Eqs. (9) and (10) are dropped out and the concentration gradient along the tube becomes

$$\frac{dC^*}{dz^*} = -2AnC^* \quad (20)$$

The fraction dose absorbed of the solution is

$$F = 1 - e^{-2An} \quad (21)$$

as derived previously (6).

RESULTS AND DISCUSSION

Figure 1 illustrates three processes involved in drug absorption of suspensions: dissolution from particles, absorption through the intestinal wall, and convection along the intestine. Particle size decreases down the tube so that the dissolution rate from the particles increases. A microscopic mass balance approach was applied for both solid and solution phases in a volume element of the tube. Four dimensionless parameters are fundamental variables for estimating the fraction dose absorbed from the intestine: initial saturation (I_s), absorption number (An), dose number (Do), and dissolution number (Dn). Physicochemical properties of a drug and physiological factors in the intestine are incorporated into these four parameters.

Figure 2 shows the fraction dose absorbed (F), the dimensionless concentration (C^*), and the dimensionless radius of particles (r^*) profiles in the tube. It can occur that all particles are dissolved before the end of the intestine, as shown in Fig. 2(B), and that the concentration decreases exponentially after all particles have dissolved. The dimensionless concentration and particle radius at the end of the intestine are calculated from Eqs. (9) and (10), so that F can be estimated using Eq. (16), or from analytical solutions for specific cases in Eqs. (18), (19), and (21).

Figure 3 shows a three-dimensional graph with a contour plot of the fraction dose absorbed as a function of dose number and dissolution number for $An = 1$ and $I_s = 0$. It shows the limits of the fraction dose absorbed as they depend upon An , Do , and Dn . At higher Dn and lower Do , the fraction dose absorbed reaches the maximal F , which depends only on An . The dissolution number limit on F can appear at both lower Do and lower Dn . Likewise, at higher Do and Dn the fraction dose absorbed reaches a Do limit.

Initial Saturation

Initial saturation (I_s), the initial conditions, should be known in order to estimating the fraction dose absorbed. An estimation of I_s is difficult due to dosage form and other formulation factors that may affect the disintegration and/or dissolution of the compound in the stomach. In addition, the physicochemical properties and physiological factors such as solubility, stability, particle size, food, and gastric emptying rate may also affect I_s . Consequently, the dimensionless concentration profiles along the intestine are shown in Fig. 4 for two extreme values of I_s ($I_s = 0$ and $I_s = 1$). The case of $I_s = 0$ is when no mass is dissolved at the beginning of the intestine and the luminal concentration is zero, while $I_s = 1$ is the case where the luminal concentration at the beginning of the intestine is the same as its solubility. For a poorly soluble compound, dissolution is usually small so that Dn is low, while its An and Do are usually high. There is no difference in the luminal concentration profiles as shown in Fig. 4B for higher Do with the same Dn and An as compared to Fig. 4A. In general, at higher Dn and Do , there is no difference between F at $I_s = 0$ and F at $I_s = 1$. At lower Do and Dn the difference in F becomes significant (11).

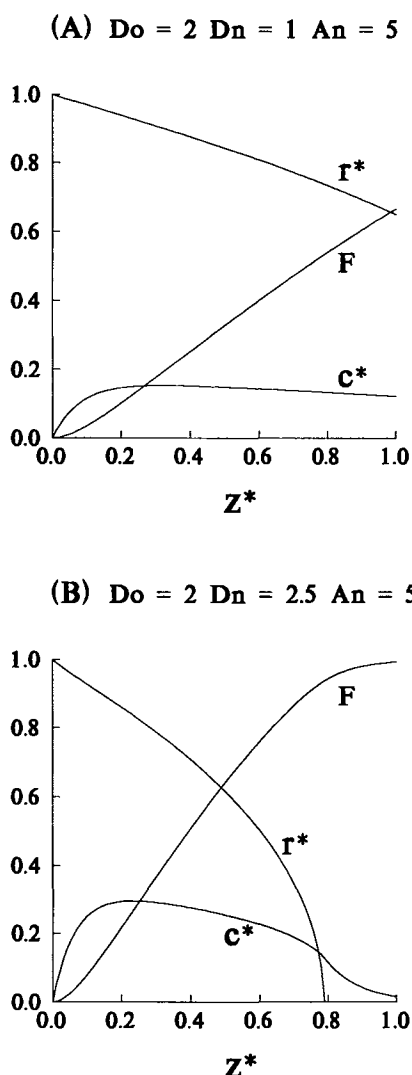


Fig. 2. Fraction dose absorbed (F), dimensionless concentration (C^*), and dimensionless radius of particles (r^*) profiles along the intestine. All particles are dissolved before the end of the intestine in B. Values of parameters used for calculations: $Do = 2$, $Dn = 1$ (for A) or 2.5 (for B), $An = 5$, and $Is = 0$.

Absorption Number

It has been shown that the absorption number is a primary variable for predicting oral absorption (6,12). The fraction dose absorbed is an exponential function of An as in Eq. (21), assuming that dissolution and dose do not limit oral absorption. The maximal fraction dose absorbed of a compound with $An = 1$ is about 86% (Fig. 3). Complete absorption can be expected for a compound if An is larger than 1. The correlation between F and An has been reported previously (6,7,12).

Dose Number

The dose number is a variable of particular importance for estimating oral absorption of water-insoluble compounds. The solubility of a compound is used as a reference concentration because it is a fundamental thermodynamic property with regard to the actual luminal concentration in

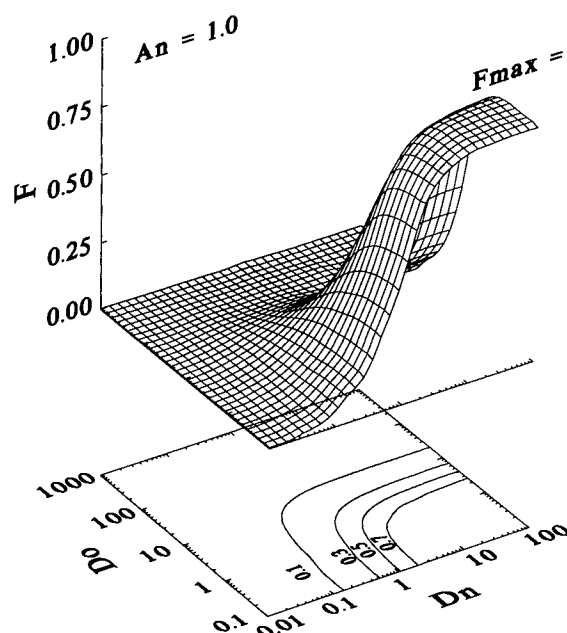


Fig. 3. Three-dimensional graph and contour of fraction dose absorbed (F) in the plot of dose number (Do) against dissolution number (Dn) at $An = 1.0$ and $Is = 0$.

the intestine. If a compound is highly soluble and administered at a low dose, Do is not important. Figure 5 shows a plot of the fraction dose absorbed versus dose number at three absorption numbers, 0.5, 1, and 5. As Do becomes smaller, F increases, but it does not reach the maximal F because of the parameter, dissolution number (see below). A smaller Do will always improve F , but the dose of a drug is determined from the pharmacokinetic and pharmacodynamic considerations outside of pharmaceutical control. In general, taking more water with the same dose gives a better fraction dose absorbed.

Dissolution Number

The main focus in this report is a dissolution consideration on the estimation of the fraction dose absorbed from suspensions of poorly soluble compounds. The dissolution number, Dn , represents the relative rate of the dissolution to axial convection and is the principal variable under pharmaceutical control. Figure 3 shows the strong dependency of F on Dn .

Most poorly water-soluble compounds will have a high absorption number because of their nonpolar characteristic (2). The fraction dose absorbed of suspensions of poorly soluble compounds may be low, because of Do and/or Dn limitations. Several contours of the fraction dose absorbed at $An = 0.5$, 1, and 10 in the plot of Do against Dn are shown in Fig. 6. The results show that F increases with increasing Dn and An and with decreasing Do . At higher Dn , the fraction dose absorbed decreases rapidly with increasing Do . Similarly, F decreases sharply with a decrease in Dn . Higher permeability, smaller particle size, higher solubility, and lower dose increase F . Figure 6 gives some reference values of F at various An , Do , and Dn .

If there is no dissolution resistance during absorption,

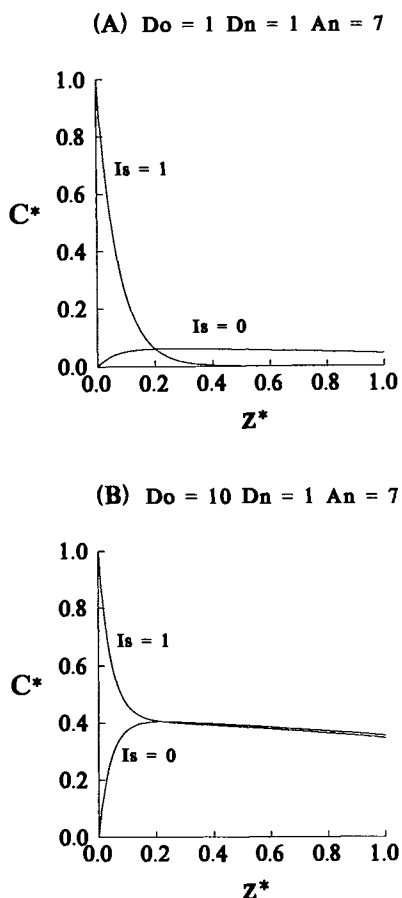


Fig. 4. Dimensionless concentration (C^*) profiles along the intestine at $Is = 0$ or $Is = 1$. Values of parameters used for calculations: (A) $Do = 2$, $Dn = 1$, and $An = 7$; (B) $Do = 10$, $Dn = 1$, and $An = 7$.

the fraction dose absorbed can be calculated by Eqs. (18), (20), and (21). A contour plot of the fraction dose absorbed as a function of An and Do with no dissolution limitation is shown in Fig. 7. The dashed line represents the boundary for

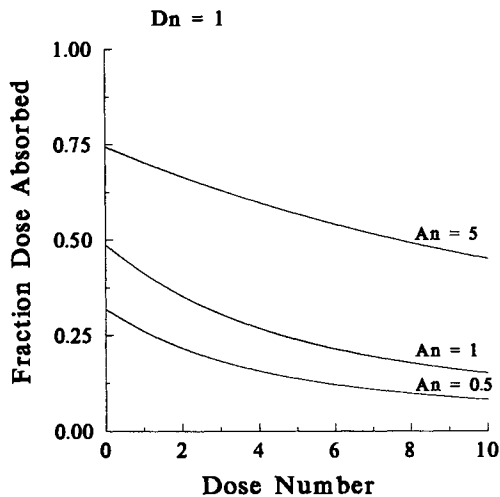


Fig. 5. Plot of fraction dose absorbed (F) versus dose number (Do) at three absorption numbers (An), 0.5, 1, and 5. Values of parameters used for calculations: $Dn = 1$ and $Is = 0$.

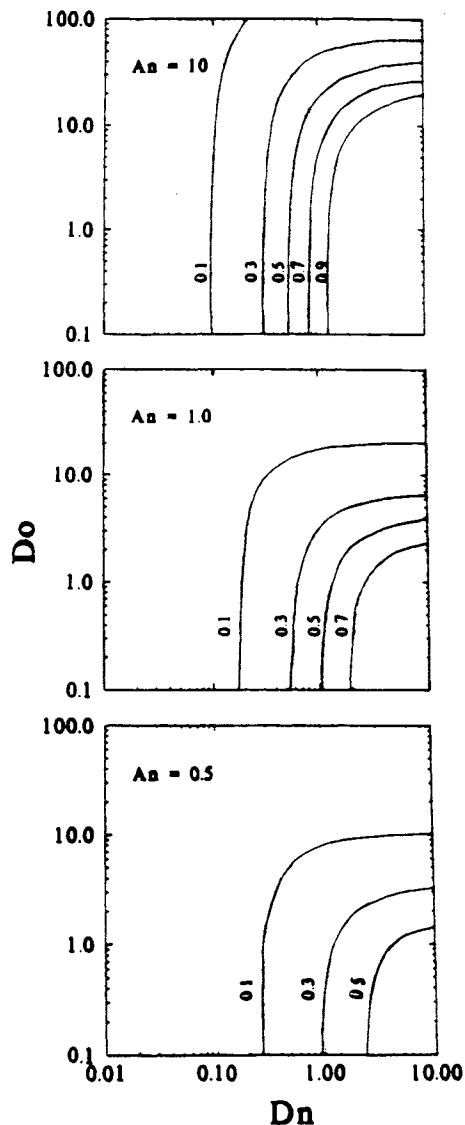


Fig. 6. Contours of fraction dose absorbed (F) at $An = 0.5, 1, \text{ or } 10$ in the plot of dose number (Do) versus dissolution number (Dn). $Is = 0$.

the existence of particles at the end of the intestine. At lower Do and higher An , no particles are found at the end of the intestine. If Do is above one, some particles may remain undissolved, depending on An .

One of the most significant results of this analysis is that the fraction dose absorbed has a very steep dependence on Do and Dn when they have values around 1. This can also be observed in Fig. 3. The simplicity of this result is one of the advantages of making the model dimensionless. If a drug is dosed in this range, it can be expected to have highly variable bioavailability. To illustrate this, Dn can be rewritten from Eq. (13) as

$$Dn = \left(\frac{3\phi}{r_0^2} \right) \left(\frac{C_s}{\rho} \right) \langle t \rangle \quad (22)$$

where $\langle t \rangle$ is the average intestinal transit time and the other terms are as defined previously. For $\langle t \rangle = 1800 \text{ min } (\approx 30 \text{ hr})$,

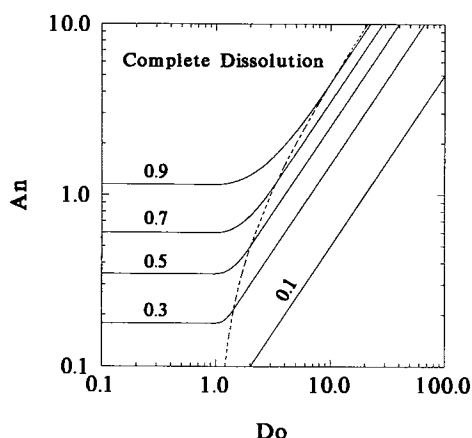


Fig. 7. Contour of fraction dose absorbed (F) in the plot of An and Do at no dissolution limitation. The dashed line represents the boundary for existence of particles at the end of the intestine.

$\rho = 1000$ mg/mL, $C_s = 0.01$ mg/mL, and $\mathcal{D} = 1 \times 10^{-4}$ cm²/min, Dn is equal to 0.01, 0.1, and 1.0 for a particle size of 23.2, 7.3, and 2.3 μ m, respectively. For a drug with a high membrane permeability, typical of nonpolar water-insoluble drugs ($An = 10$, $Do = 10$), it can be estimated that less than 0.1, 10, and 60% of drug absorption might occur, respectively. For a particle size of 1.6 μ m ($Dn = 2$), 90% absorption could occur.

Table I shows values of An , Do , and Dn to get 90% fraction dose absorbed for suspensions. To get the same F at the fixed An , a higher value for Dn allows higher Do . However, above a certain Do , the fraction dose absorbed will not

Table I. Values of Absorption Number (An), Dose Number (Do), and Dissolution Number (Dn) for a Fraction Dose Absorbed of 90% ($IS = 0$)

An	Do	Dn
1.15	— ^a	— ^b
2.0	0.1	1.87
2.0	0.5	2.06
2.0	1.0	2.38
2.0	4.4	— ^b
3.0	0.1	1.49
3.0	0.5	1.59
3.0	1.0	1.73
3.0	5.0	6.29
3.0	6.7	— ^b
5.0	0.1	1.33
5.0	0.5	1.39
5.0	1.0	1.46
5.0	5.0	2.44
5.0	10.0	13.94
5.0	11.1	— ^b
7.0	0.1	1.28
7.0	0.5	1.32
7.0	1.0	1.36
7.0	5.0	1.89
7.0	10.0	3.64
7.0	15.6	— ^b

^a No Do limit is assumed.

^b No Dn limit is assumed.

reach 90% due to the solubility limitation even if Dn is increased further. For example, Dn is infinitely large for $F = 90\%$ at $Do = 11.1$ and $An = 5$. Thus F cannot be improved by reducing the particle size of a drug in this limit. This, then, represents solubility-limited absorption. Further consideration of the effects of micronization and solubility on the fraction dose absorbed of suspensions will be discussed in a subsequent report (13).

The situation in the intestine is, of course, complex in that several considerations are needed for a refinement of this physical model. One of the assumptions in this model is that the fluid flow in the intestinal tract is plug flow with complete radial mixing. Further refinements on the fluid flow and mixing and longitudinal spreading in the intestinal tract are needed. In addition, surfactant solubilization and particle size distributions will be considered.

In summary, a model for dissolution and drug absorption has been developed that highlights the critically important variables of dissolution number, Dn , and dose number, Do . It is shown that the extent of drug absorption can be highly variable when these dimensionless groups approximate one. In addition, by calculating the dimensionless numbers for a new drug and by referencing Fig. 6, an estimate of the extent of drug absorption and the effect of micronization can be made. This can provide considerable guidance to the formulation scientist in the development of water-insoluble compounds.

ACKNOWLEDGMENT

This work was supported in part by NIGMS Grant GM37188.

NOMENCLATURE

An	Absorption number
C^*	Dimensionless concentration = C_L/C_s
C_L	Luminal concentration of the compound (mg/mL)
C_s	Solubility (mg/mL)
\mathcal{D}	Diffusivity of the compound (cm ² /min)
Dn	Dissolution number
Do	Dose number
F	Fraction dose absorbed
Is	Initial saturation
j_s	Mass flux from particles to lumen (mg/cm ² /min)
j_w	Mass flux from lumen to blood (mg/cm ² /min)
k_s	Mass transfer coefficient from particles to lumen (cm/min)
k_w	Overall mass transfer coefficient from lumen to blood (cm/min)
L	Length of the intestine (cm)
M_0	Dose (mg)
\dot{M}_l	Longitudinal mass flux in the liquid phase (mg/min)
\dot{M}_s	Longitudinal mass flux in the solid phase (mg/min)
N_0	Number of particles in a dose
P_{aq}	Aqueous permeability across the wall boundary layer (cm/min)
P_{eff}	Effective wall permeability of the compound (cm/min)
P_w	Wall permeability of the compound (cm/min)
Q	Volumetric flow rate (ml/min)
R	Radius of the intestine (cm)
r^*	Dimensionless radius of particles = r_p/r_0

r_0	Initial radius of particles (<i>cm</i>)
r_p	Radius of particles at z (<i>cm</i>)
S_p	Surface area of particles per unit volume of lumen (cm^2/mL)
V_0	Volume taken with dose or luminal volume (<i>mL</i>)
z	Axial coordinate along the intestine (<i>cm</i>)
z^*	Dimensionless axial coordinate = z/L
ρ	Density of the compound (mg/mL)

REFERENCES

1. B. C. Goodacre and R. J. Murray. A mathematical model of drug absorption. *J. Clin. Hosp. Pharm.* 6:117-133 (1981).
2. N. F. H. Ho, H. P. Merkle, and W. I. Higuchi. Quantitative, mechanistic and physiologically realistic approach to the biopharmaceutical design of oral drug delivery systems. *Drug Dev. Ind. Pharm.* 9:1111-1184 (1983).
3. J. B. Dressman, D. Fleisher, and G. L. Amidon. Physicochemical model for dose-dependent drug absorption. *J. Pharm. Sci.* 73:1274-1279 (1984).
4. J. B. Dressman, G. L. Amidon, and D. Fleisher. Absorption potential: Estimating the fraction absorbed for orally administered compounds. *J. Pharm. Sci.* 74:588-589 (1985).
5. J. B. Dressman and D. Fleisher. Mixing-tank model for predicting dissolution rate control of oral absorption. *J. Pharm. Sci.* 75:109-116 (1986).
6. P. J. Sinko, G. D. Leesman, and G. L. Amidon. Predicting fraction dose absorbed in humans using a macroscopic mass balance approach. *Pharm. Res.* 8:979-988 (1991).
7. D.-M. Oh, P. J. Sinko, and G. L. Amidon. Predicting oral drug absorption in humans: A macroscopic mass balance approach for passive and carrier-mediated compounds. In D. Z. D'Argenio (ed.), *Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis*, Plenum Press, New York, 1991, pp. 3-11.
8. N. F. H. Ho, J. Y. Park, P. F. Ni, and W. I. Higuchi. Advancing quantitative and mechanistic approaches in interfacing gastrointestinal drug absorption studies in animals and humans. In W. Crouthanel and A. C. Sarapu (eds.), *Animal Models for Oral Drug Delivery in Man: In Situ and In Vivo Approaches*. American Pharmaceutical Association, Washington, DC, 1983, pp. 27-106.
9. R. B. Bird, W. E. Stewart, and E. N. Lightfoot. *Transport Phenomena*, John Wiley & Sons, New York, 1960, p. 647.
10. W. I. Higuchi and E. N. Hiestand. Dissolution rates of finely divided drug powders. I. Effect of a distribution of particle size in a diffusion-controlled process. *J. Pharm. Sci.* 52:67-71 (1963).
11. D.-M. Oh. *Estimating Oral Drug Absorption in Humans*, Ph.D. thesis, University of Michigan, Ann Arbor, 1991.
12. G. L. Amidon, P. J. Sinko, and D. Fleisher. Estimating human oral fraction dose absorbed: A correlation using rat intestinal membrane permeability for passive and carrier-mediated compounds. *Pharm. Res.* 5:651-654 (1988).
13. D.-M. Oh, R. L. Curl, and G. L. Amidon. Effect of micronization on the extent of drug absorption from suspensions in humans (submitted for publication).