Arch. Pharm. Res. Vol.18, No.6, pp. 427-433, 1995

Effect of Micronization on the Extent of Drug Absorption from Suspensions in Humans

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(Received August 11, 1995)

A microscopic mass balance approach has shown that the initial saturation (*Is*), absorption number (*An*), dose number (*Do*), and dissolution number (*Dn*) are four fundamental dimensionless parameters that can be used to estimate the fraction dose absorbed (*F*) of suspensions of poorly soluble drugs in humans. The dissolution number of a drug increases with decreasing its particle size. The effect of micronization on *F* for suspensions was investigated in terms of *Dn*. About 90% of maximal *F* can be achieved at $Dn \approx 2$. Increasing the solubility of a drug results in better oral absorption through increasing *Dn* and decreasing *Do*. The fractions dose absorbed of digoxin, griseofulvin, and benoxaprofen agree with predicted *F* values using estimated parameters. Drugs with low *Do* and low *Dn* can be more completely absorbed by reducing particle size, while absorption of drugs with high *Do* and low *Dn* is limited by solubility and requires higher solubility to enhance the fraction dose absorbed in addition to micronization. Solubility at the physiological pH should be used for the estimation of the fraction dose absorbed.

Key Words : Absorption, Dose Particle size, Permeability, Solubility

INTRODUCTION

It has been shown that the absorption of several poorly soluble drugs administered in suspension formulations is dissolution-rate limited (Abdou, 1989). According to the dissolution equation derived from the film theory, dissolution rate is directly proportional to the surface area, the solubility of a compound, and its concentration gradient across the diffusion layer. In general, micronization of a compound enhances the dissolution rate due to the increase in surface area available to the dissolving medium. The dissolution rate can also be increased by increasing the solubility, which is usually accomplished by pH effect, salt formulation, solubilization by surface active agents, change in crystal form, complexation, or by a sufficient reduction in particle size (Leeson and Carstensen, 1974). Increasing the dissolution rate usually results in more rapid and complete absorption. Poor aqueous solubility may cause a slow dissolution rate. Recently the importance of the dose to solubility ratio on the extent of absorption has been discussed (Dressman, 1989; Sinko *et al.*, 1991).

There are instances in which particle size reduction fails to increase the absorption rate of a drug (Gibaldi, 1984). For drugs with aqueous solubilities below 0.1 mg/ml, micronization may not be enough to get complete oral absorption depending on the dose. Micronization sometimes dramatically increases the tendency of a drug powder to aggregate, which may lead to a decrease in effective surface area. The effective surface area of hydrophobic drug particles may be increased by the addition of a wetting agent to the formulation.

A microscopic mass balance approach has been employed for prediction the bioavailability of suspensions (Oh *et al.*, 1993) and the drug-drug interaction (Oh and Amidon, 1995). It was shown by Oh *et al.* (1993) that the fraction dose absorbed (*F*) from suspensions of poorly soluble compounds is governed by four fundamental dimensionless parameters: initial saturation (*Is*), absorption number (*An*), dose number (*Do*), and dissolution number (*Dn*). The effects of particle size and solubility on *F* from suspensions can be explained by *Dn* and *Do*. The ob-

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jectives of this report are to demonstrate the effects of micronization and solubilization on the fraction dose absorbed from suspensions of poorly soluble drugs and to determine when micronization can significantly increase *F*. Furthermore the pH effect on solubility for weak electrolytes will be discussed in order to estimate *F*.

Fraction dose absorbed of suspensions

To predict the fraction dose absorbed from suspensions of poorly soluble compounds, a microscopic mass balance approach has been developed (Oh *et al.*, 1993). A physical tube model with a plug flow containing particles is employed. The length of the intestine is *L* with radius *R* and initial radius of particles is r_0. Mass balances in both solid phase and solution phase were considered to get the set of differential equations:

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

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

where,

$$An = \frac{P_{eff}}{Q/(\pi R L)} \quad (3)$$

$$Do = \frac{M_0/V_0}{C_s} \quad (4)$$

$$Dn = \frac{(D/r_0)\, C_s\, (4 \pi r_0^2)/(\frac{4}{3} \pi r_0^3 \rho)}{Q/(\pi R^2 L)}$$

P_{eff} is the effective wall permeabilty, Q is the volumetric flow rate in the intestine, and M_0 is the dose taken with water volume of V_0. For dimensionless parameters, $z^* = z/L$, $r^* = r_p/r_0$, and $C^* = C_L/C_s$, where z is the axial coordinate down the intestine and r_p and C_L are the radius of particles and the luminal concentration at z, respectively. C_s, D, and ρ are the solubility, diffusivity, and density of the compound, respectively. *An* is the absorption number, which is the ratio of radial absorption rate to axial convection rate, *Do* is the dose number, which is the ratio of dose concentration to solubility of a compound, and *Dn* is the dissolution number, which is the ratio of residence time in the intestine to dissolution time from initial particles.

To estimate the extent of drug absorption, it is assumed that the dose taken is the sum of the initially dissolved amount is solution and the remaining amount in solid at the beginning of the intestine. The initial saturatiion, *Is*, is defined to be:

$$Is = C_L(0)/C_s \quad (6)$$

where $C_L(0)$ is the luminal concentration at the beginning of the intestine. *Is* is the dimensionless inlet concentration in solution. For poorly soluble drugs, *Is* is close to zero so that $C^* = 0$ and $r^* = 1$ at the beginning of the intestine ($z^* = 0$).

It is assumed that the difference between mass in and mass 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:

$$F = 1 - \{r^*(1)\}^3 - \frac{C^*(1)}{Do} \quad (7)$$

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 Eqs. (1) and (2) by a numerical method (Oh *et al.*, 1993).

Simulation

Differential equations were solved by the Runge-Kutta-Merson method. Simulation was performed with a personal computer using a NDP Fortran-386 compiler (Microway, Inc., Kingston, MA). The absorption number (*An*) of griseofulvin is about 7 and was calculated from single-pass perfusion data in rats (Poelma, 1989). The value of *An* for other drugs in assumed to be 7, based on the fact that they are nonpolar of moderate moleular weight (Sinko *et al.*, 1991). The conclusion would be essentially the same for any *An* greater than about 1 (Oh *et al.*, 1993). The initial saturation was assumed to be 0 ($r^* = 1$ and $C^* = 0$ at $z^* = 0$) because most poorly soluble drugs have very slow dissolution rates. The volume flow rate was assumed to be 1 ml/min, and the luminal volume was taken to be 250 ml if it was not given in the literature. Dose number and dissolution number were calculated by Eqs. (4) and (5), respectively.

RESULTS AND DISCUSSION

It has been shown in the previous paper (Oh *et al.*, 1993) that there are four fundamental dimensionless parameters to estimate the fraction dose absorbed (*F*) of suspensions: initial saturation (*Is*), absorption number (*An*), dose number (*Do*), and dissolution number (*Dn*). Fig. 1 shows a three dimensional graph and contour for the fraction dose absorbed in the plot of dose number versus dissolution number at $An = 5$ and $Is = 0$. It is clearly demonstrated that *F* is dependent on both *Do* and *Dn* at a fixed *An*. In addition to *Do* and *Dn*, *An* can vary *F* (Oh *et al.*, 1993). In general, the fraction dose absorbed may be limited by low *An*, low *Dn*, or high *Do*, or by any combination thereof. For example, a drug with high *An*, low *Do* and high *Dn* is well absorbed. As shown in Fig. 2, an increase

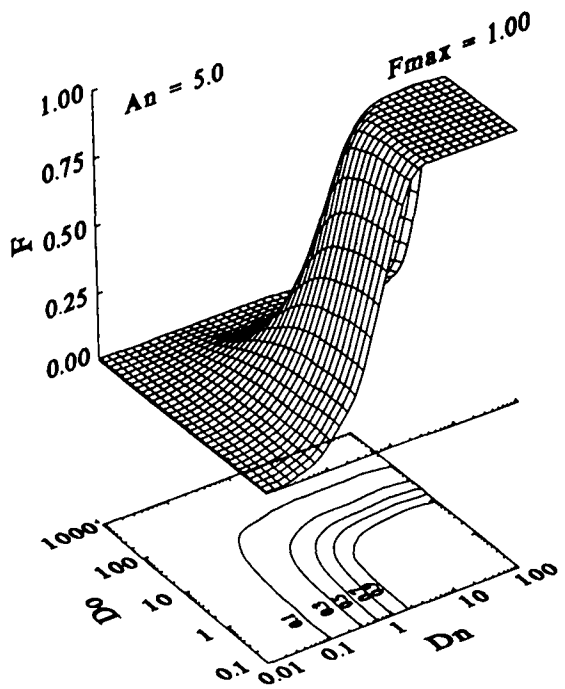

Fig. 1. Three dimensional graph and contour of the fraction dose absorbed (F) in the polt of dose number (Do) versus dissolution number (Dn) at An=5 and Is=0.

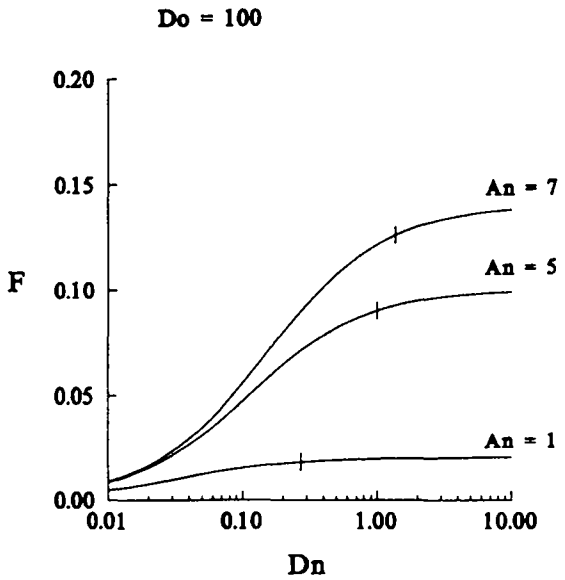

Fig. 2. Plot of fraction dose absorbed (F) versus dissolution number (Dn) at several different absorption numbers (An=1, 5,7). Bar(I) indicates 90% of maximal F which can be obtained at no dissolution limitation. Values of parameters used for calculations: Do=100, Is=0.

in An results in higher F. However, absorption cannot be complete only by increasing An and Dn if Do is too high. Fig. 2 shows that F is about 0.15 at Do=100 even when An is 7. Fig. 3 shows a plot of the fraction dose absorbed versus dissolution number at several dose numbers. At higher Dn, the reduction in F is significant with increasing Do. If a drug has a low An and/or high Do, its chemical structure needs to be

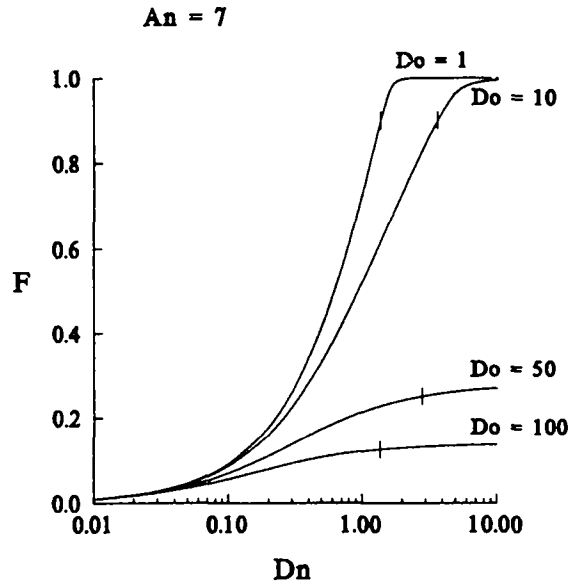

Fig. 3. Plot of fraction dose absorbed (F) versus dissolution number (Dn) at several different dose numbers (Do=1, 10, 50, 100). Bar(I) indicates 90% of maximal F which can be obtained at no dissolution limitation. Values of parameters used for calculations: An=7, Is=0.

modified to obtain a better wall permeability, higher solubility and higher potency. Taking more water is also favorable to F through decreasing Do.

Another way to increase the fraction dose absorbed of a drug is to increase Dn. The dissolution number is the ratio of residence time in the intestine to the dissolution time of the particles, and is a function of solubility, diffusivity, density, initial particle radius of a drug, and volumetric flow rate in the intestine. A typical way to increase Dn in pharmaceutics is to reduce the particle size, since Dn is inversely proportional to the square of the initial radius of the particles. However F reaches a plateau as Dn increases (Fig. 2).

Ten percent ($0.1 \cdot F_{max}$) and 90% ($0.9 \cdot F_{max}$) of maximal F (obtained at no dissolution limitation; $Dn \rightarrow \infty$) are shown in Fig. 4, illustrating that $0.9 \cdot F_{max}$ can be achieved in the range of 1 to 3 of Dn. Bars in Fig. 2 and Fig. 3 also indicate 90% of maximal F. This points out that the micronization does not increase F significantly if Dn is larger than about 2. In this case F is limited by other variables such as Do and we refer to this as solubility (or dose number) limited absorption. A compound that falls in the region between $0.1 \cdot F_{max}$ and $0.9 \cdot F_{max}$ is most sensitive to micronization.

Digoxin and griseofulvin were chosen because they have similar solubilities but quite different doses. Solubilities of digoxin and griseofulvin are 0.024 mg/ml and 0.015 mg/ml, respectively. The dose number of digoxin ranges from 0.1 to 0.5 (dose of 0.25 to 0.5 mg), while that of griseofulvin ranges 67 to 267 (dose

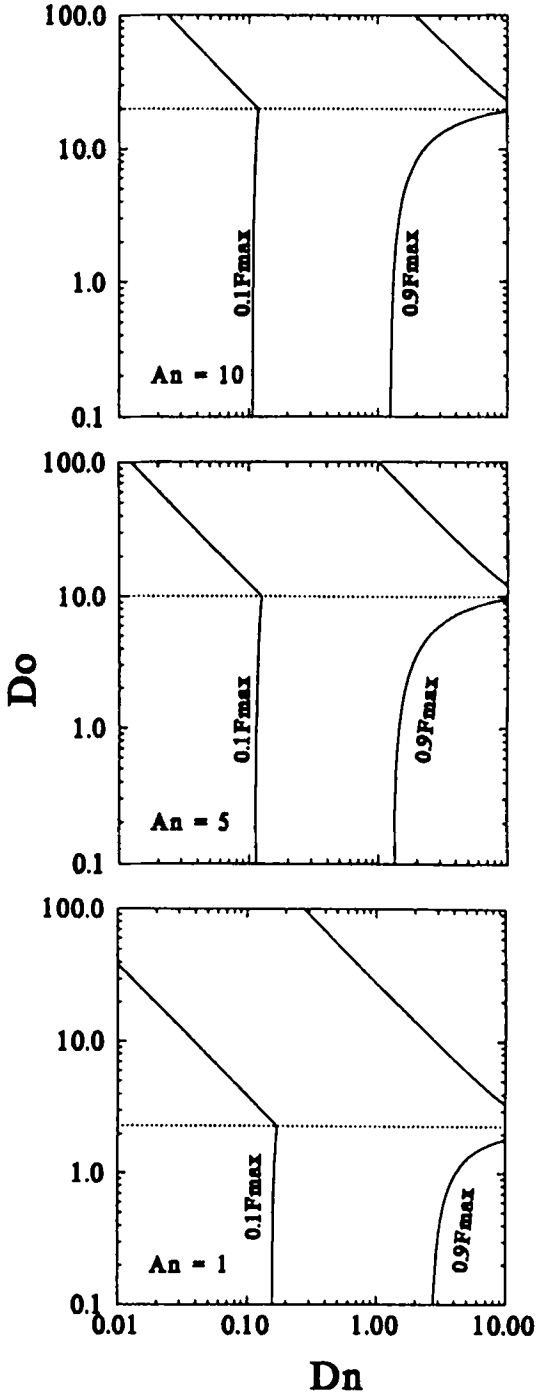

Fig. 4. Ten percent ($0.1 \cdot F_{max}$) and 90% ($0.9 \cdot F_{max}$) of maximal F (at no dissolution limitation; Dn $\rightarrow \infty$) in the plot of *Do* versus *Dn* for *An* of 1,5, and 10. Dotted lines represent the dose numbers at Dn $\rightarrow \infty$.

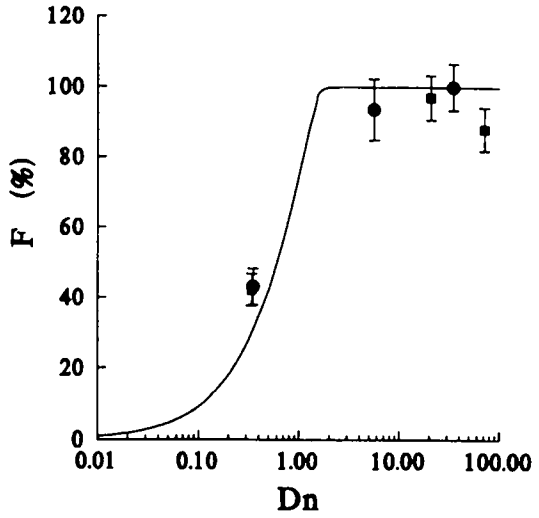

Fig. 5. Fraction dose absorbed (F) of digoxin. Predicted values are shown by a solid line. Values of parameters used for calculations: Do=0.1, An=7, Is=0. Human dat were taken from Jounela *et al.* (1975) and Johnson *et al.* (1978).
●: Johnson *et al.* (1978), ■: Jounela *et al.* (1978)

of 250 to 1000 mg). Fig. 5 shows the fraction dose absorbed of digoxin at various *Dn*. Predicted values are calculated using Do=0.1, An=7, and Is=0, and reported data were taken from the literature (Jounela *et al.*, 1975; Johnson *et al.*, 1978). Good agreement between reported and predicted fractions dose absorbed is observed. A *Dn* of 1.3 (particle radius of 26 μm) results in 90% absorption. Jounela *et al.* (1975) reported that the bioavailability of digoxin with mean particle radii of 3.5 or 6.5 μm was 78 to 97%, while that with larger particle size (51 μm) was only 39%. It was also demonstrated that absorption from a formulation of particle radius of 45 to 53 μm was reduced about 43% of that of micronized digoxin (5 μm of radius) (Johnson *et al.*, 1978). The present analysis suggests that complete oral absorption of digoxin may be expected if particle radius is smaller than 26 μm. There are however some conflicting reports in the literature. Shaw and Carless (1974) found in human patients that the bioavailability of digoxin with a particle radius of 11 μm was about 46% compared to that when given in solution, and that reduction of mean particle radius from 11 μm to 1.85 μm resulted in 31% increase in mean digoxin plasma level. There is a significant shift to the right on the plot of F versus *Dn*, indicating that more micronization is required to get the same F in patients. The reason for this discrepancy is not known. It may be from shifts on *Dn* and *An*. However the comparison of bioavailability data from patients with those of healthy volunteers cannot be possible without any attempt to normalize the human data.

In the case of griseofulvin, *Do* is very high so that the *Do* limitation of F may be expected even if *Dn* is large. Fig. 6 shows the fraction dose absorbed of griseofulvin with predicted lines for Do=67 and Do=267. Reported F values were scattered over the range estimated, partly due to its absorption variability (Atkinson *et al.*, 1962; Khalafalla *et al.*, 1980; Terhaag *et al.*, 1985). Each point in Fig. 6 has various *Do* ranging 67 to 267, even if they are from the same report. Micronization may play a role to increase F, but particle size in most formulations of griseofulvin is already small enough so that *Dn* is much larger

than 2. Therefore reducing the particle size does not increase F very much, without reducing Do. This may be a reason that a meaningful correlation between dissolution rate and extent of griseofulvin absorption was not observed (Khalafalla *et al.*, 1980). It was suggested from Fig. 6 that the variability in bioavailability might result primarily from high Do. To increase F of griseofulvin, Do must be reduced by enhancing its solubility. It may, in part, expain the better absorption of griseofulvin in the fed state. Physiolgical surface active agents, like bile salts and lysolecithin, probably facilitate the dissolution and absorption of poorly water-soluble drugs in the small intestin (Miyazaki *et al.*, 1980).

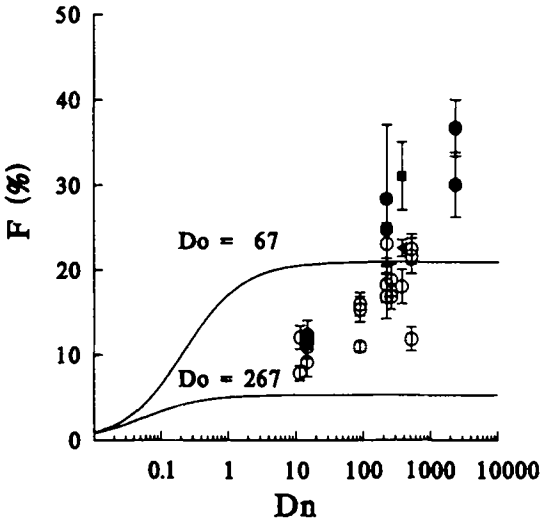

Fig. 6. Fraction dose absorbed (F) of griseofulvin. Predicted values are shown by solid lines. Values of parametrers used for calcuations: Do=67 and 267, An=7, Is=0, Human data were taken from Atkinson *et al.* (1962), Khalafalla *et al.* (1980), and Terhaag *et al.* (1985).
○: Atkinson *et al.* (1962)-tablets, ●: Atkinson *et al.* (1962)-capsules, ◀: Khalaflla *et al.* (1980), ■: Terhasg *et al.* (1985)

To improve bioavailability of suspensions in practical situations, the physicochemical properties of interest are the radius of particles and solubility, in addition to the dose taken. Contours of the fraction dose absorbed in the plot of solubility and the radius of particles for two different initial dose concentrations (2 mg/ml or 0.1 mg/ml) are shown in Fig. 7. It shows the dependency of F on the dose concentration, the solubility, and the radius of the particles. For drugs with a high dose concentration and low solubility (as with griseofulvin), the effect of micronization may not be significant (Fig. 7(A)). On the other hand, drugs with low dose concentration and low solubility (such as digoxin) may be completely absorbed by reducing their particle size (Fig. 7(B)).

Ridolfo *et al.* (1979) reported that solubilities of benoxaprofen, an antiinflammatory drug, were dramatically changed with increasing pH. Higher solubility at higher pH decreases Do and increases Dn, resulting in a greater fraction dose absorbed. The simulations in Figs. 1 to 4 don't apply to benoxaprofen, since Is value is expected to vary as a function of pH. Changing solubility makes Is to increase at higher pH values. Fig. 8 shows the fraction dose absorbed of benoxaprofen at various pH values with two different Is values (Is=0 and 1). It shows estimated data of F at two different particle sizes (9.25 μm and 305 μm) of benoxaprofen and the reported values of F in the literature (Wolen *et al.*, 1979). As expected, estimated F increases with increasing pH, pointing out that the physiological pH should be used to estimate F for weak electrolytes. In case of benoxaprofen the proper pH is 6 to 7 to estimate F in humans (Fig. 8). Several estimated F values of benoxaprofen at pH 7.0 were shown in Table I, which is in good agreement with reported F values (Ridolfo *et al.*, 1979; Wolen et al., 1979; Nash *et al.*, 1980). It should be pointed out that Is=1 rather than Is=0 may be appropriate at the

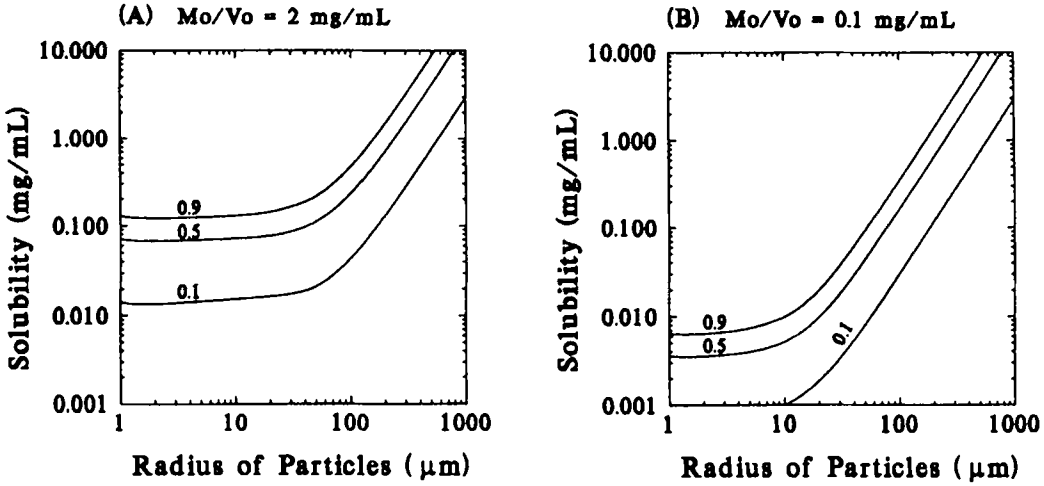

Fig. 7. Contours of fraction dose absorbed (F) in the plot of solubility and radius of particles for M_0/V_0=2 mg/mL (A) or 0.1 mg/mL (B). Values of parameters used for calculations: An=7, Is=0.

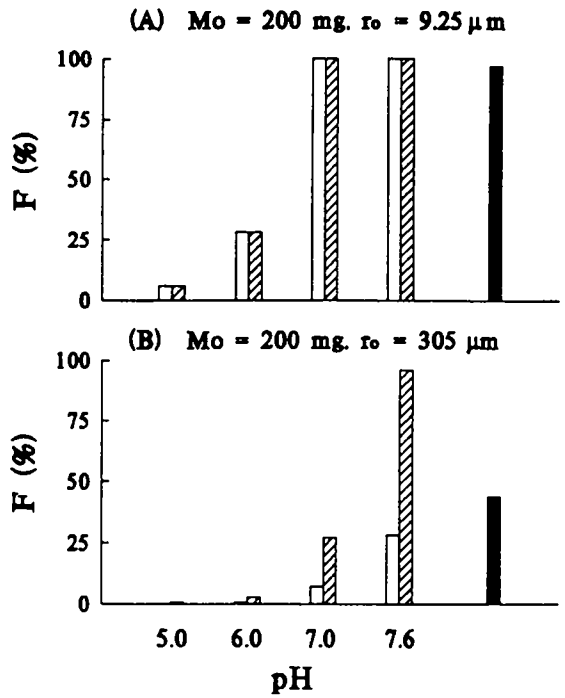

Fig. 8. Fraction dose absorbed (*F*) of benoxaprofen at various pH values. Dose is 200 mg and radii of particles are 9.25 μm (A) or 305 μm (B). The fractions dose absorbed are estimated using *Is*=0 or 1 and *An*=7. The closed bars represent the reported values in the literature (Wolen *et al.*, 1979).
■ : Wolen *et al.* (1979), ■: Estimated F (Is=1), □ : Estimated F (Is=0)

Table I. Estimated and reported fractions dose absorbed (*F*) of benoxaprofen[a]

Do	Dn	An	Estimated *F* (%)		Reported	Reference
			Is=0	*Is*=1	F (%)	
2.7	0.07	7.0	6.7	42.3	60	[b]
2.7	6.72	7.0	100.0	100.0	100	[b]
7.7	52.40	7.0	100.0	100.0	98	[c]
11.6	52.40	7.0	99.6	99.6	95	[c]
4.8	88.18	7.0	100.0	100.0	96	[d]
4.8	0.08	7.0	7.2	27.0	41	[d]
19.3	0.08	7.0	6.7	11.3	22	[d]

[a]density=1000 mg/ml, solubility=0.207 mg/ml (at pH=7.0)
[b]from Ridolfo *et al.* (1979)
[c]from Nash *et al.* (1980)
[d]from Wolen *et al.* (1979).

pH where a drug has higher solubility. The calculated *F* was somewhat underestimated compared to the reported *F*, suggesting a partial role of the intrinsic bile salts. In addition to the effect of bile salts, pH variation down the intestine may change the wall permeability of the compound. The physical model may be refined by introducting the effect of surfactants and ionization on *Dn* and *Do*.

In summary, the fraction dose absorbed of suspensions can be estimated from a dissolution model with parameters; *Is*, *An*, *Do*, and *Dn*. The dose, the radius of particles, and the solubility at the physiological pH are needed for estimation of *F*. About 90% of maximal *F* can be achieved at $Dn \approx 2$. Drugs with low *Do* and low *Dn* can be completely absorbed by reducing their particle sizes, while the absorption of drugs with high *Do* and low *Dn* is solubility (dose number) limited and requires a higher solubility, in addition to micronization, to enhance the fraction dose absorbed.

ACKNOWLEDGEMENT

This work supported in part by NIGMS Grant GM 37188.

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