Guidance in the Setting of Drug Particle Size Specifications to Minimize Variability in Absorption

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Purpose. To provide guidance in setting particle size specifications for poorly soluble drugs to minimize variability in absorption.
Methods. A previously reported computer method was used to simulate the percent of dose absorbed as a function of solubility, absorption rate constant, dose, and particle size.
Results. The simulated percent of dose absorbed was tabulated over a realistic range of solubilities, absorption rate constants, and doses using drug particle sizes that might be typically found in a dosage form.
Conclusions. The greatest effect of particle size on absorption was simulated for low dose- low solubility drugs. In general, the sensitivity of absorption to particle size decreased with increasing dose or solubility. At a solubility of 1 mg/mL, particle size had practically no effect on the percent of dose absorbed over the range of doses simulated (1–250 mg).

KEY WORDS: particle size; solubility; absorption rate constant; absorption; dose; simulation.

INTRODUCTION

The particle size of a drug can affect its dissolution rate, and subsequently, the rate of absorption. In certain cases, the effect can lead to significant variability in drug disposition if particle size is not adequately controlled. Although computer methods for simulating the effect of particle size on absorption for nonionized drugs have been reported (1–3), a comprehensive series of simulations covering the range of important parameters has not. The objective of the current work is to map out the effect of particle size on absorption over a range of important variables that would likely be encountered for new drugs entering development. These variables are dose, solubility, and absorption rate constant. The intent is to provide guidance in setting particle size specifications to minimize variability in absorption.

METHODS

The process of drug dissolution and absorption was simulated using a previously reported computer method (2,3). This method handles the polydisperse nature of real drug powders by treating them as collections of monodisperse particle groups of different diameters, indicated by the subscript i in the following equations. In particular, a Noyes-Whitney type equation was derived for spherical particle geometry and a time-dependent diffusion layer thickness (2,3) to simulate the rate of dissolution as shown in Equation 1:

$$\frac{dX_{s_i}}{dt} = -\frac{3DX_{0_i}^{2/3}X_{s_i}^{1/3}}{\rho h_i r_{0_i}}\left[C_s - \frac{X_{d_T}}{V}\right] \quad (1)$$

where X_{s_i} is the amount of solid drug in the i^{th} particle size group at any time, D is the drug diffusion coefficient, X_{0_i} is the initial amount of solid drug in the i^{th} particle size group, ρ is the drug density, h_i is the diffusion layer thickness of the i^{th} particle size group, r_{0_i} is the initial particle radius of the i^{th} particle size group, C_s is the drug solubility, X_{d_T} is the total amount of dissolved drug at any time, and V is the estimated volume of fluid present in the gastrointestinal tract.

The rate of change of dissolved drug shown in Equation 2 is equal but opposite in sign to Equation 1 minus the rate of absorption as shown in Equation 3:

$$\frac{dX_{d_i}}{dt} = +\frac{3DX_{0_i}^{2/3}X_{s_i}^{1/3}}{\rho h_i r_{0_i}}\left[C_s - \frac{X_{d_T}}{V}\right] - k_a X_{d_i} \quad (2)$$

$$\frac{dX_{a_i}}{dt} = k_a X_{d_i} \quad (3)$$

where X_{d_i} is the amount of dissolved drug in the i^{th} particle size group at any time, k_a is a first-order absorption rate constant, and X_{a_i} is the amount of absorbed drug in the i^{th} particle size group at any time.

The initial amount of drug in each group X_{0_i} was calculated based on the log-normal function with geometric means of 10, 25, 50, or 100 μm and geometric standard deviations of 2. Table 1 shows the distributions used. High and low particle size limits were calculated as described previously (3).

The Runge-Kutta numerical method with a step size of 0.001 minutes was used for iterative solutions of Equations 1–3. After each step, the total amount of solid, dissolved, and absorbed drug was calculated by summing up the contributions

Table I. Particle Size Distributions Used for Simulations in Table II

Particle Size Distributions (μm)				
10 μm mean	25 μm mean	50 μm mean	100 μm mean	Percent Mass
1.2	3.1	6.3	12.5	0.2
1.6	4.1	8.2	16.5	0.5
2.2	5.4	10.9	21.8	1.4
2.9	7.2	14.4	28.7	3.2
3.8	9.5	18.9	37.9	6.0
5.0	12.5	25.0	50.0	9.7
6.6	16.5	33.0	66.0	13.3
8.7	21.8	43.5	87.1	15.7
11.5	28.7	57.4	114.9	15.7
15.2	37.9	75.8	151.6	13.3
20.0	50.0	100.0	200.0	9.7
26.4	66.0	132.0	263.9	6.0
34.8	87.1	174.1	348.2	3.2
45.9	114.9	229.7	459.5	1.4
60.6	151.6	303.1	606.3	0.5
80.0	200.0	400.0	800.0	0.2

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from each monodisperse particle group as shown in Equations 4–6 respectively:

$$X_{s_T} = \sum X_{s_i} \quad (4)$$

$$X_{d_T} = \sum X_{d_i} \quad (5)$$

$$X_{a_T} = \sum X_{a_i} \quad (6)$$

All simulations were done assuming a drug diffusion coefficient of 5×10^{-6} cm^2/sec, a density of 1.3 gm/cm^3, and a dissolution volume of 250 mL. Minor alterations of these nominal values, within the range likely to be encountered, do not materially affect any of the results. The diffusion layer thickness h_i was set equal to radius r_{0_i} for all particle size groups with r_{0_i} less than 30 μm and equal to 30 μm for all larger groups based on earlier work (2,3). Simulations were run over a range of doses, solubilities, and absorption rate constants that were judged to be typical, with emphasis on the solubility region where particle size had an effect on absorption. Only the cumulative total amount of drug absorbed X_{a_T} at 6 hours, expressed as a percent of dose, is reported in Table 2.

Taking the general form of Equation 3, the cumulative amount of drug absorbed can be obtained by integrating that equation:

$$\int dX_a = k_a \int X_d \, dt \quad (7)$$

By allowing the dose to increase indefinitely, the amount of dissolved drug X_d can be hypothetically maintained at a constant saturation value given by:

$$X_d = C_s V \quad (8)$$

Since $C_s V$ is a constant, its value can be moved outside the integral when substituting Equation 8 into 7 to yield the maximum absorbable dose (MAD):

$$\text{MAD} = k_a C_s V \int dt \quad (9)$$

or:

$$\text{MAD} = k_a C_s V t \quad (10)$$

at any time t. Table 2 lists MAD values at 6 hours.

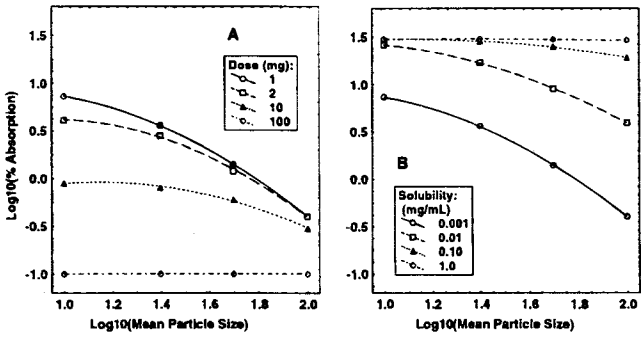

Fig. 1. Computed percent of dose absorbed at 6 hours versus mean particle size, with an absorption rate constant of 0.001 min^{-1}: (A) at doses from 1 to 100 mg, with a solubility of 0.001 mg/mL; and (B) at solubilities from 0.001 to 1.0 mg/mL, with a dose of 1 mg.

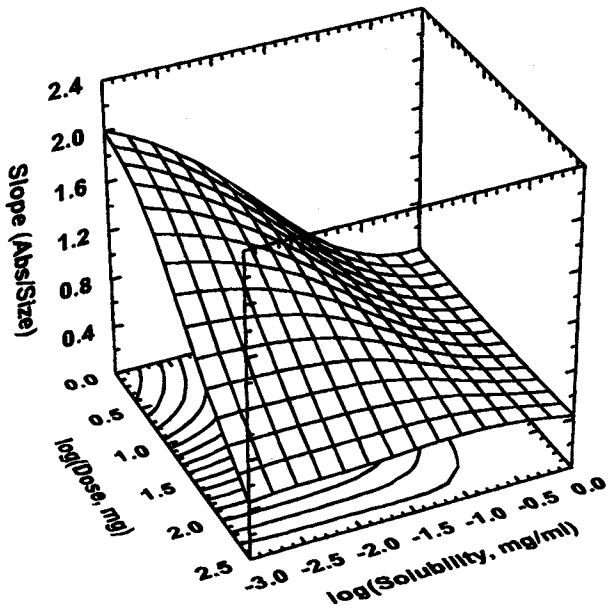

Fig. 2. The dependence of absorption on particle size, expressed as the slope of $\log_{10}$(% of dose absorbed at 6 hours) versus $\log_{10}$(mean particle size) plotted against solubility and dose, with an absorption rate constant of 0.01 min^{-1}. The vertical axis reflects the degree of sensitivity of absorption to drug particle size.

RESULTS AND DISCUSSION

Table 2 shows the simulated percent of dose absorbed at 6 hours as a function of absorption rate constant, solubility, dose, and particle size. Reporting values at 6 hours reveals the kinetic effect of particle size on absorption within a time frame where one of the model assumptions is more physiologically reasonable compared to later times; that is, that the gastrointestinal tract can be treated as a well stirred tank. Thus colonic absorption is ignored in the present analysis.

The patterns of effects of particle size on percent dose absorbed at less than 6 hours post-dose are qualitatively the same as patterns computed for 6 hours, although quantitative differences obviously exist. The simulated data are intended to provide guidance in setting particle size specifications, and cannot take the place of experiments designed to establish appropriate specifications. Moreover, concerns about the effect of particle size on content uniformity may override concerns related to absorption, particularly for low dose drugs (4).

The effects of particle size on absorption are illustrated for various doses of a low-solubility drug (Figure 1A), and for various solubilities of a low-dose drug (Figure 1B). The greatest effect of particle size is for low-solubility, low-dose drugs. There is little effect of particle size on a low-solubility drug at high dose (uniformly low absorption), or on a high-solubility drug at low dose (uniformly high absorption). Lines in Figure 1 represent least-squares fit of quadratic functions although equations 1–6 describe the actual relationships. Slopes were calculated for each setting in the simulation as the first derivatives of the fitted functions. For purposes of illustration, the points at which log(particle size) = 2.0 are used in Figure 2, although results are equivalent regardless of the point chosen for slope calculations. Slopes are plotted in 3 dimensions vs. dose and solubility for drugs that have the intermediate absorp-

Table II. Simulated Percent of Dose Absorbed at 6 Hours as a Function of Absorption Rate Constant k_a, Solubility, Dose, and Particle Size Distribution as Shown in Table I

			Percent of Dose Absorbed				
k_a (min-1)	Solubility (mg/mL)	Dose (mg)	10 μm	25 μm	50 μm	100 μm	MAD (mg)
0.001	0.001	1	7.3	3.6	1.4	0.4	0.09
0.001	0.001	10	0.9	0.8	0.6	0.3	0.09
0.001	0.001	100	0.1	0.1	0.1	0.1	0.09
0.001	0.001	250	0.0	0.0	0.0	0.0	0.09
0.001	0.01	1	25.8	16.9	9.0	3.9	0.9
0.001	0.01	10	8.8	7.9	5.7	3.1	0.9
0.001	0.01	100	0.9	0.9	0.9	0.8	0.9
0.001	0.01	250	0.4	0.4	0.4	0.3	0.9
0.001	0.1	1	29.8	28.2	24.7	19.2	9
0.001	0.1	10	29.7	27.5	23.6	18.0	9
0.001	0.1	100	9.0	8.9	8.5	7.7	9
0.001	0.1	250	3.6	3.6	3.5	3.4	9
0.001	1	1	30.2	30.0	29.7	29.1	90
0.001	1	10	30.2	30.0	29.7	29.1	90
0.001	1	100	30.2	30.0	29.5	28.7	90
0.001	1	250	30.0	29.3	28.5	27.0	90
0.01	0.001	1	43.2	18.1	6.5	2.1	0.9
0.01	0.001	10	8.6	6.8	4.1	1.7	0.9
0.01	0.001	100	0.9	0.9	0.8	0.6	0.9
0.01	0.001	250	0.4	0.4	0.3	0.3	0.9
0.01	0.01	1	91.3	66.9	38.5	17.5	9
0.01	0.01	10	70.0	50.0	30.7	15.4	9
0.01	0.01	100	9.0	8.7	8.0	6.3	9
0.01	0.01	250	3.6	3.6	3.4	3.1	9
0.01	0.1	1	97.1	95.6	90.4	76.7	90
0.01	0.1	10	97.0	95.1	89.0	74.5	90
a,b 0.01	0.1	100	82.0	73.8	63.4	51.0	90
0.01	0.1	250	35.9	35.2	33.2	29.3	90
0.01	1	1	97.3	97.2	97.0	96.7	900
0.01	1	10	97.3	97.2	97.0	96.7	900
0.01	1	100	97.3	97.2	97.0	96.6	900
0.01	1	250	97.2	97.0	96.7	96.1	900
0.1	0.001	1	65.8	26.1	9.0	2.8	9
0.1	0.001	10	48.9	21.9	8.3	2.7	9
0.1	0.001	100	8.6	7.2	4.6	2.1	9
0.1	0.001	250	3.5	3.3	2.6	1.6	9
c 0.1	0.01	1	97.4	77.5	47.8	22.8	90
d 0.1	0.01	10	96.9	75.9	46.7	22.4	90
0.1	0.01	100	75.9	55.9	35.7	18.9	90
e 0.1	0.01	250	35.1	31.4	24.0	14.8	90
0.1	0.1	1	100.0	99.8	97.8	88.5	900
0.1	0.1	10	100.0	99.8	97.8	88.3	900
0.1	0.1	100	100.0	99.7	97.0	86.1	900
0.1	0.1	250	100.0	99.3	95.0	81.9	900
0.1	1	1	100.0	100.0	100.0	100.0	9000
0.1	1	10	100.0	100.0	100.0	100.0	9000
0.1	1	100	100.0	100.0	100.0	100.0	9000
0.1	1	250	100.0	100.0	100.0	100.0	9000

Note: The maximum absorbable dose (MAD) is shown in the last column. A crude classification of drugs known to have particle size-dependent absorption is indicated as follows: nitrofurantoin-a, benoxaprofen-b, digoxin-c, nifedipine-d, and griseofulvin-e. The error in k_a values from the literature could be one order of magnitude.

tion rate constant of 0.01 min^{-1}. The intention is to provide a perspective on the global relationships among all the variables in these composite plots (Figures 1 and 2). Inferred relationships should not be extrapolated outside the range of simulated data.

In general, the relative effect of particle size on the percent of dose absorbed decreases with increasing solubility, with particle size becoming practically irrelevant for drugs at a solubility of 1 mg/mL. There is also an increased sensitivity of absorption on particle size with increasing absorption rate constant for drugs in the solubility range of roughly 0.001–0.01 mg/mL with doses in range of 10–100 mg. Other trends are more subtle. It should be kept in mind that large relative changes in percent of dose absorbed due to particle size do not necessarily represent large absolute changes.

Also shown in Table 2 is the maximum absorbable dose (MAD) which is the maximum amount of drug that could be absorbed in 6 hours if the concentration of drug in solution could be hypothetically maintained at its solubility. Its value is unique for any combination of solubility and absorption rate constant and is approached if the dose is allowed to increase without constraints. It serves as a useful reference point. If the absolute amount of drug absorbed is similar to MAD, further reduction of particle size or increase in dose will yield little improvement in absorption. This can be seen in row 3 of Table 2. The MAD can also be used to rank order drugs in terms of how much drug can be absorbed.

The effect of drug particle size on absorption has been clinically demonstrated in humans for nifedipine (5), nitrofurantoin (6), benoxaprofen (7), digoxin (8), and griseofulvin (9). A crude classification of these compounds is indicated in Table 2. This was done by finding the closest match of absorption rate constant, solubility, and dose in Table 2 to corresponding literature values for the respective drugs. The values for digoxin and griseofulvin were taken from references 1 and 9. Values for the dose, solubility, and absorption rate constant for nifedipine were taken from references 5, 10, and 11 respectively. Values for the solubilities and doses for nitrofurantoin and benoxaprofen were taken from references 6 and 7 respectively. References for the absorption rate constants for nitrofurantoin and benoxaprofen were taken from references 12 and 13 respectively. In general, Table 2 is in agreement with known cases of particle size-dependent absorption. Moreover, the authors are unaware of any studies showing particle size-dependent absorption for drugs with solubilities greater than 1 mg/mL. This is consistent with the simulated lack of sensitivity to particle size in Table 2 at 1 mg/mL.

The dissolution model used to generate the values in Table 2 has only been validated with relatively small, neutral organic drug molecules. Any attempt to draw conclusions for acids and bases should be done with caution. In particular, it is very difficult to predict the effect of particle size on absorption for bases whose solubilities change over the pH range of the gastrointestinal tract. This is due to the uncertainty of knowing whether drug dissolved in the stomach at low pH will precipitate as it exits the stomach or remain supersaturated relative to its equilibrium solubility at the pH of the intestine. The same concern applies to the maximum absorbable dose calculation.

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