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Research Paper

A Modified Approach to Predict Dissolution and Absorption of Polydisperse Powders

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Purpose. Particle size of a drug is an important factor that affects thermodynamic solubility and oral absorption of drug molecules. Weight fraction of different particle sizes in a polydisperse powder together with Noyes Whitney parameters (diffusion coefficient, solubility, density of the drug, boundary layer thickness and dissolution volume) can be used to predict dissolution and absorption of drug molecules. Such a simulation can be a valuable tool in setting up guidance with regards to dependence of dissolution and absorption on particle size.
Materials and methods. In this note a modified method is reported to predict dissolution of polydisperse drug powder. These use simplified equations developed from a set of differential equations described previously. The idea was to convert all the terms in one single equation which can then be solved by a Matlab program.
Conclusion. Discrepancies not reported earlier have been discussed to get the same results as reported previously.

KEY WORDS: absorption; dissolution rate prediction; particle size; polydisperse powders; solubility.

INTRODUCTION

Evolution of the "Rule of five" in the late 1990s established the significance of two major physicochemical properties of a drug molecule in the success of a drug discovery and development process; solubility and permeability (1). It has been estimated that 30% to 40% of the new chemical entities, developed through a high throughput drug discovery programme, have severe physicochemical (solubility) or biopharmaceutical (permeability) problems, because of which, the drop out rate is quite high (2). These poorly soluble drugs pose severe bioavailability problems. This may be attributed mainly to two reasons; first low dissolution velocity and second poor permeability of the drug to the gut wall. Even if the drug has high gut permeability and fast uptake from the gut lumen, the drug levels in the blood would be low, as the drug may not dissolve sufficiently fast due to poor solubility. Moreover, the low concentration gradient between lumen and blood further contributes to relatively slow drug diffusion from the gut to the blood. The particle size of a drug is an important factor which affects its dissolution rate in GI tract. Several attempts have been made to predict *in vivo* dissolution and plasma concentration based on the particle size and size distribution of polydisperse powders (3,4,5,6, and 7). Incorporation of standard pharmacokinetic parameters (volume of distribution and clearance) in the derived equations even leads to prediction of *in vivo* plasma concentrations. A further improvement in this integrated approach was its extension to predict dissolution of immediate—and modified—release dosage forms (4).

The Noyes–Whitney equation describes that the dissolution velocity dc/dt is proportional to the concentration gradient$A(C_s - C_x)/h$, where A is the surface area of the solid, C_s is the concentration of the solid in the diffusion layer surrounding the solid, C_x is the bulk concentration of the drug in the surrounding liquid and h is the diffusional distance above the drug particle surface (8). This equation has been customized to a set of differential equations to discuss the dissolution behaviour of polydisperse powder by dividing a mass of polydisperse powder into different fractions of particle size groups. Following set of equations has been derived previously (5).

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

$$\frac{dX_{d_i}}{dt} = -K_a X_{d_i} + \frac{3DX_{0_i}^{2/3}X_{S_i}^{1/3}}{\rho h_i r_{0_i}}\left(C_s - \frac{X_{d_T}}{V}\right),$$

$$\frac{dX_{a_i}}{dt} = K_a X_{d_i},$$

$$X_{s_T} = \sum_{i=1}^{n} X_{s_i},$$

$$X_{d_T} = \sum_{i=1}^{n} X_{d_i},$$

$$X_{a_T} = \sum_{i=1}^{n} X_{a_i},$$

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Table I. Standard and Modified Notation

Standard notation	Notation in this note
$\frac{2DX_{0i}^{2/3}}{\rho h_i r_{0i}}$	a_i
K_a	K
X_{si}	X_I
$\sum_{i=1}^{n} X_{di}$	Y
$\sum_{i=1}^{n} X_{ai}$	Z
C_s	C

where X_s is the mass of solid drug, X_d is the mass of dissolved drug, X_a is the mass of absorbed drug, t is time, D is the drug diffusivity, X_0 is the initial mass of the drug, C_s is the aqueous solubility of the drug, V is the dissolution volume, ρ is the drug density, h is the diffusion layer thickness, r_0 is the initial drug particle size radius, K_a is the absorption rate constant, X_{s_T} is the summation of solid drug mass at any time from all particle size groups, X_{d_T} is the summation of dissolved drug mass at any time from all particle size groups, X_{a_T} is the summation of absorbed drug mass at any time from all particle size groups. Subscript i refers to various particle size groups in a polydisperse powder mass. Particles in a particular size group have same size. Their size and mass will change as a result of dissolution or precipitation.

In the simulations used, with time, the size of the particles in a size group becomes small due to dissolution but their number remains constant. As a result, when the particles are completely dissolved (size going below molecular size of the drug), an error occurs in the simulation (adding negative results in the summation). To deal with this error in the simulation software, the authors have included internal error handling routine (4). However, the error handling routine and software used to carry out the simulations were not discussed. The purpose of this note is to convert the above mentioned equations into a single equation using one variable. The modified equation can be used by a Matlab program and also include the error handling system with in the equations. Further, to verify the accuracy, the results reported earlier (5) have been reproduced using the equations reported in the present paper.

Table II. Parameters for Eq. 5

Parameter	Value
Solubility (C)	0.01 mg/mL
Drug diffusion coefficient (D)	5×10^{-6} cm^2/s
Density (ρ)	1.3 g/cm^3
Dissolution volume (V)	250 mL
Diffusion layer thickness (h^i)	10 μm
Integration step	0.001 min
Time interval (t)	6 h
Particle size distribution[a] (μm) with mean particle size 10 μm	1.2 (0.2), 1.6 (0.5), 2.2 (1.4), 2.9 (3.2), 3.8 (6.0), 5.0 (9.7), 6.6 (13.3), 9.7 (15.7), 11.5 (15.7), 15.2 (13.3), 20.0 (9.7), 26.4 (6.0), 34.8 (3.2), 45.9 (1.4), 60.6 (0.5), 80.0 (0.2)

[a] Percent mass of each hypothetical particle size is shown in brackets.

Table III. Comparison of Results from (5) (A) and Our Matlab Program (B)

K (min^{-1})	Solubility (mg/mL)	Dose (mg)	Percent of dose absorbed (A)	Percent of dose absorbed (B)
0.001	0.01	1	25.8	25.78
0.001	0.01	10	8.8	8.80
0.001	0.01	100	0.9	0.89
0.001	0.01	250	0.4	0.36
0.01	0.01	1	91.3	91.33
0.01	0.01	10	70.0	70.03
0.01	0.01	100	9.0	8.95
0.01	0.01	250	3.6	3.59
0.1	0.01	1	97.4	97.46
0.1	0.01	10	96.9	96.92
0.1	0.01	100	75.9	75.90
0.1	0.01	250	35.1	35.09

METHODS

For convenience a modified notation has been used. This is shown in Table I. From this table, we see that $C - y/V$, which is standard notation equals $C_s - X_{d_T}/V$, is of crucial significance because it appears as a factor in the rate at which material in each particle group is dissolved. It is convenient, not to use $C - y/V$ directly, but rather to use its integral from 0 to t. Denote this integral by u so that u represents the accumulated ability for dissolving to have taken place, up to the present time. Furthermore, u satisfies the differential equation

$$\frac{du}{dt} = C - \frac{y}{V}, \quad u(0) = 0 \tag{1}$$

We can interpret this as saying that the rate at which material is being dissolved is proportional to the rate at which u is increasing.

The aim is to write y as a sum of various quantities which can all be written in terms of u. This means that there will be a single differential equation to solve instead of a large system. For generality, it is assumed that there is an initial amount of dissolved material y_0. To find the value of y at a later time, it is necessary to add the amount of newly dissolved material and subtract the amount of absorbed material. That is

$$y = y_0 + \sum_{i=1}^{n} (X_0 - X_i) - z. \tag{2}$$

To see how X_i behaves, its equation is written in the form

$$\frac{dX_i}{dt} = -\frac{3}{2} a_i X_i^{1/3} \left(C - \frac{y}{V}\right), \qquad X_i(0) = X_{0i},$$

which can be rewritten as

$$\frac{d}{dt} X_i^{2/3} = -a_i \left(C - \frac{y}{V}\right), \qquad X_i^{2/3}(0) = X_{0i}^{2/3}.$$

Compare this equation with Eq. 1 and it is seen that $X_i^{2/3} - a_i u$ is constant and its value is the same as when t=0. That is, $X_i^{2/3} - a_i u = X_{0i}^{2/3}$. Thus,

$$X_{0i} - X_i = X_{0i} - \left(X_{0i}^{2/3} - a_i u\right)^{3/2}. \tag{3}$$

The next step is to find z in terms of u. Start with the equation

$$\frac{dz}{dt} = Ky$$

and add KV times (Eq. 1). This gives

$$\frac{d}{dt}(z + KVu) = KVC,$$

with solution $z + KVu = KVCt$. Hence,

$$z = KV(Ct - u). \tag{4}$$

Substitute from Eqs. 3 and 4 into Eq. 2 and it is found that

$$\begin{aligned} \tfrac{du}{dt} = C - \tfrac{1}{V}\left(y_0 + \textstyle\sum_{i=1}^{n}(X_{0i} - (X_{0i}^{2/3} - a_i u)^{3/2})\right) \\ -KV(Ct - u). \end{aligned} \tag{5}$$

Account needs to be taken of the possibility that some of the terms $X_{0i}^{2/3} - a_i u$ become zero. This corresponds to one of the particle size groups being completely dissolved. In this case this term has to be interpreted as being set to zero for all later times.

EXPERIMENTAL RESULTS

A Matlab program has been written to solve Eq. 5 and trial data was used to investigate the consistency of the results. The trial data was taken from a previous work (5). We have selected a hypothetical particle size, 10 μm, and the same parameters (Table II) as reported in the previous work (5). The ultimate aim of developing these equations is to predict dissolution and absorption of a drug of certain particle size, solubility, absorption rate constant and dose.

In Table III, we have reported the percent dose absorbed for 10 μm particle size with a solubility of 0.01 mg/ml at four doses (X_{0i}=1, 10, 100 and 250 mg). For each of the doses, three values of K (0.001, 0.01 and 0.1 min^{-1} are used. It is clear that by using a single equation developed in this paper (Eq. 5) similar results were obtained, which proves the application of developed equation in predicting dissolution (and absorption) of polydisperse powder.

In conclusion, the above mentioned equations can be used on a Matlab program for prediction of dissolution, and also of absorption, of polydisperse powder.

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