The Mean Dissolution Time Depends on the Dose/Solubility Ratio

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Purpose. To investigate the relationship between mean dissolution time (*MDT*) and dose/solubility ratio (q) using the diffusion layer model.

Methods. Using the classic Noyes–Whitney equation and considering a finite dose, we derived an expression for *MDT* as a function of q under various conditions. q was expressed as a dimensionless quantity by taking into account the volume of the dissolution medium. Our results were applied to *in vitro* and *in vivo* data taken from literature.

Results. We found that *MDT* depends on q when $q < 1$ and is infinite when $q > 1$ and that the classic expression of $MDT = 1/k$, where k is the dissolution rate constant, holds only in the special case of $q = 1$. For the case of perfect sink conditions, *MDT* was found to be proportional to dose. Using dissolution data from literature with $q < 1$, we found better estimates of *MDT* when dependency on dose/solubility ratio was considered than with the classic approach. Prediction of dissolution limited absorption was achieved for some of the *in vivo* drug examples examined.

Conclusion. The mean dissolution time of a drug depends on dose/solubility ratio, even when the model considered is the simplest possible. This fact plays an important role in drug absorption when absorption is dissolution limited.

KEY WORDS: dissolution; mean dissolution time; solubility; dose/solubility ratio.

The concept of mean time of the various drug processes is linked with their stochastic consideration and is widely used in biopharmaceutics and pharmacokinetics (1,2). In the field of dissolution studies, the mean dissolution time (*MDT*) corresponds to the first moment (3) and can be calculated arithmetically from the experimental data by the following equation:

$$MDT = \frac{\int_0^{W_\infty} t \cdot dW(t)}{\int_0^{W_\infty} dW(t)} \tag{1}$$

where $W(t)$ is the cumulative amount of drug dissolved at time t. Equation (1) is very useful, especially in cases where a correlation of *in vitro* and *in vivo MDT* values is attempted (3). In actual practice, an equivalent form of Eq. (1) is used to derive an estimate of *MDT* from experimental dissolution data (3):

$$MDT = \frac{ABC}{W_\infty} \tag{2}$$

where W_∞ is the asymptote of the dissolved amount of drug and ABC is the area between the cumulative dissolution curve and W_∞. Equations (1) and (2) apply only when the entire available amount of drug is dissolved. Otherwise, the mean dissolution time of the entire amount is not defined, and the term mean saturation time (MDT_s) (4) refers only to the portion of the drug dose that is actually dissolved.

Theoretically, the rate of dissolution for the diffusion layer model, expressed in terms of the change of drug concentration, C, as a function of time, t, is described by the Noyes–Whitney equation (5):

$$\frac{dC}{dt} = k(C_s - C) \tag{3}$$

where C_s is the saturation solubility and k is the dissolution rate constant. Because Eq. (3) has the classic form of a first-order rate process, the mean dissolution time, MDT_{cl}, is considered equal to the reciprocal of the rate constant, k (4,6–8):

$$MDT_{cl} = \frac{1}{k} \tag{4}$$

As a matter of fact, all dissolution studies that invariably rely on Eq. (3) and do not make dose considerations use Eq. (4) for the calculation of the MDT_{cl}.

However, Lansky and Weiss (4) proved that for a dissolution model with a time-dependent fractional dissolution rate, which in essence adheres to a reaction-limited dissolution case (see Appendix of Ref. 4), the *MDT* is a function of the dose/solubility ratio. It is the purpose of the present work to show that for the classic dissolution model of Eq. (3), *MDT* is also dependent on dose/solubility ratio if one takes into account the dose used. Also, it will be shown that the widely used Eq. (4) applies only to a special limiting case.

Multiplying both parts of Eq. (3) by V/M_0 (volume of the dissolution medium/dose), one gets the same equation in terms of the fraction of drug dose dissolved, Φ:

$$\frac{d\Phi}{dt} = k\left(\frac{1}{q} - \Phi\right) \tag{5}$$

where $q = M_0/VC_s$ is the dose/solubility ratio expressed as a dimensionless quantity because the volume of the dissolution medium is taken into account. Equation (5) has two solutions:

(i) When $q \leq 1$, which means that the entire dose is eventually dissolved,

$$\Phi = \begin{cases} \dfrac{1}{q}(1 - e^{-kt}) & \text{for } t < -\dfrac{\ln(1-q)}{k} \quad (\Phi < 1) \\ 1 & \text{for } t \geq -\dfrac{\ln(1-q)}{k} \quad (\Phi = 1) \end{cases} \tag{6}$$

where

$$t = -\frac{\ln(1-q)}{k}$$

is the time when dissolution terminates.

(ii) When $q > 1$, which means that only a portion of the dose is dissolved and the drug reaches the saturation level $1/q$,

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$$\Phi = \frac{1}{q}(1 - e^{-kt}) \tag{7}$$

The mean dissolution time when $q \leq 1$ is

$$MDT = \frac{ABC}{W_\infty} = \int_0^\infty (1 - \Phi)dt = \int_0^{-\frac{\ln(1-q)}{k}} \left(1 - \frac{1}{q}(1 - e^{-kt})\right) dt = \frac{q - (q-1)\ln(1-q)}{kq} \tag{8}$$

Equation (8) reveals that the *MDT* depends on both k and q. Figure 1 shows a plot of *MDT* as a function of q for three different values of the rate constant, k. Note that Eq. (4) is derived from Eq. (8) for $q = 1$ (the dose is equal to the amount needed to saturate the volume of the dissolution medium). In other words, the classically used Eq. (4) is a special case of the general Eq. (8).

When $q > 1$, the *MDT* is infinite because the entire dose is not dissolved. In this case, one may calculate the MDT_s in order to get a meaningful time scale for the portion of the dissolved drug particles:

$$MDT_s = \frac{ABC}{W_\infty} = \frac{\int_0^\infty \left(\frac{1}{q} - \Phi\right)dt}{1/q} = \frac{\int_0^\infty (e^{-kt}/q)dt}{1/q} = \frac{1}{k} \tag{9}$$

which is independent of q.

In the special case of perfect sink conditions, Eq. (3) is written for $C_s >> C$:

$$\frac{dC}{dt} = k \cdot C_s = k_0 \tag{10}$$

where k_0 is the zero-order rate constant. Equation (10) can be expressed in terms of fraction of drug dose dissolved, Φ:

$$\frac{d\Phi}{dt} = \frac{k_0 \cdot V}{M_0} \tag{11}$$

This has the solution:

$$\Phi = \begin{cases} \frac{k_0 \cdot V}{M_0} t & \text{for } t < \frac{M_0}{k_0 \cdot V} \quad (\Phi < 1) \\ 1 & \text{for } t \geq \frac{M_0}{k_0 \cdot V} \quad (\Phi = 1) \end{cases} \tag{12}$$

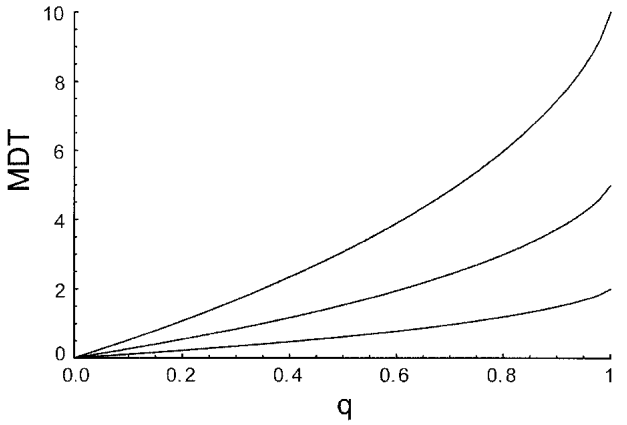

Fig. 1. Plot of *MDT* vs. q using Eq. (8) for three different values of k (top to bottom: 0.1, 0.2, 0.5).

In this case,

$$MDT = \frac{M_0}{2k_0 \cdot V} = \frac{\tau}{2}, \tag{13}$$

where τ is the duration of the dissolution process. Equation (13) reveals that under perfect sink conditions, *MDT* is proportional to dose.

Apart from the theoretical significance of the results, two important applications can be considered. First, when the entire dose is dissolved ($q \leq 1$), the estimates for *MDT* derived from Eq. (8) are superior to those of the classic approach, MDT_{cl}, using Eq. (4). This is demonstrated in Table I by comparing the mean dissolution time estimates derived from the analysis of *in vitro* dissolution literature data with the graphically determined value MDT_{gr} using Eq. (2). In all cases examined, the estimates for *MDT* derived from Eq. (8) were found to be closer to the graphic estimates, MDT_{gr}, than the corresponding values of $MDT_{cl.}$

Second, Eq. (8) can be used to calculate the mean dissolution time for drugs of different dose/solubility ratios to determine whether or not gastrointestinal absorption is likely to be dissolution limited. This can be accomplished by comparing the *MDT* estimates derived from Eq. (8) with the mean small intestinal transit time (*MITT*), 199 min (10). The three drug examples considered by Yu (11), namely, digoxin, griseofulvin, and panadiplon, were also analyzed in the present study. An estimate for the dissolution rate constant, k, was derived from the following equation (12):

$$k = \frac{D \cdot A}{h \cdot V} \tag{14}$$

where D is the diffusion coefficient, h is the diffusion layer thickness, and A is the surface area of the drug particles. The volume of liquids in the intestinal lumen, V, was assigned to 250 or 500 ml (13,14), while the values of all other drug parameters (dose, solubility, diffusion coefficient, diffusion layer thickness, density, initial radius of the spherical drug particles) were obtained from Yu (11). Figure 2 shows a plot of the *MDT* derived from Eq. (8) or MDT_s derived from Eq. (9) for the three drugs of either 5- or 100-μm particle size, as a function of the dose/solubility ratio, assigning either 250 or 500 ml to the volume of the intestinal fluids. The predicted results for digoxin and panadiplon at the 5-μm particle size indicate that both drugs are completely absorbed because their *MDT* values are well below the *MITT* limit. In contrast, incomplete dissolution and therefore absorption is anticipated at the large particle size (100 μm) for digoxin. The *MDT* value for panadiplon of 100-μm particle size lies very

Table I. Mean Dissolution Time Estimates for Fast Extended-Release Tablets of Metoprolol Tartrate (9)

Experimental conditions	MDT[a](h)	MDT_{cl}[b](h)	MDT_{gr}(h)
Apparatus II, pH 1.2, 50 rpm	1.94	2.19	2.02
Apparatus I, pH 6.8, 100 rpm	1.08	1.21	1.08
Apparatus I, pH 6.8, 150 rpm	0.93	1.08	0.95

[a] Calculated from Eq. (8); the estimate for k was derived from the fitting of Eq. (6) to experimental data.

[b] Calculated from Eq. 4; the estimate for k was derived from the fitting of Eq. (7) to experimental data.

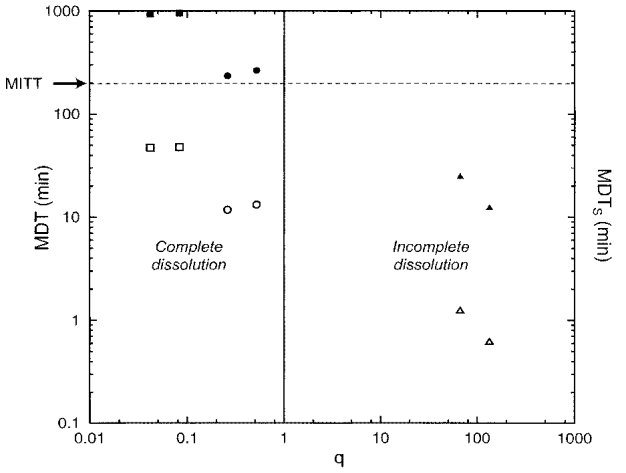

Fig. 2. Predicted *in vivo MDT* and MDT_s as a function of dose/solubility ratio, *q,* for digoxin, panadiplon, and griseofulvin. *MDT* values are correlated with *q* values ≤1. MDT_s values are correlated with *q* values >1. Two estimates for *q* were derived for each drug using either 250 or 500 ml as the volume of intestinal fluids. The *dashed line* indicates the mean intestinal transit time, *MITT*. *Filled symbols* refer to 100-μm and *outline symbols* to 5-μm particle size. Key: (■,□) digoxin; (●,○) panadiplon; (▲,△) griseofulvin.

close to the boundary of *MITT,* and therefore, its absorption will be partially dissolution limited. For griseofulvin, incomplete dissolution of the entire dose is anticipated on the basis of the *q* values under all experimental conditions simulated (particle size and volume of intestinal fluids). It should be emphasized that the values of MDT_s refer only to the dissolved portion of griseofulvin dose, 500 mg. Therefore, griseofulvin exhibits dissolution-limited absorption regardless the particle size or the volume considered. Overall, the results for all drugs analyzed are in full agreement with the previously published findings (11,13,15).

The results of the present study reveal that when $q < 1$, dose/solubility considerations should be taken into account in accord with Eq. (8) for the calculation of *MDT*; the *MDT* is infinite when $q > 1$. Equation (4) can be used to derive an estimate for *MDT* only in the special case $q = 1$. Also, Eq. (9) describes the MDT_s of the fraction of dose dissolved when $q > 1$. Finally, in the case of perfect sink conditions, the *MDT* is proportional to dose [Eq. (13)]. The practical relevance of the theoretical analysis was discussed in terms of the proper estimation of *MDT* or MDT_s and its application in predicting dissolution limited absorption.

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