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RESEARCH PAPER

In Vivo Dissolution Rates: An Error Analysis

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ABSTRACT

The uncertainty associated with the determination of in vivo dissolution rates was determined by Monte Carlo simulation. Error was imposed upon sets of artificially generated data that simulated plasma drug levels after tablet and solution dosage from ingestion. Deconvolutions were performed on the data sets to determine how error in the plasma levels propagated into the in vivo dissolution determinations. Two approaches were taken in the performance of the deconvolution step of the simulation. In the first, a model was explicitly assumed for dissolution. In the second, deconvolution was accomplished by a mass balance approach in which no explicit model for dissolution was assumed.

INTRODUCTION

The in vivo dissolution rate of solid dosage forms is of intrinsic interest to the pharmaceutical scientist because such knowledge permits the scientist to correlate the release rate of a drug with formulation parameters. In addition, the determination of in vivo release rates has taken on added importance for regulatory reasons: those companies that can show a linear correlation between in vitro and in vivo dissolution may be able to make small formulation changes or may be able to change manufacturing sites without performing additional human trials (1).

Methods used for the determination of in vivo dissolution rates rely on data gathered in two experiments. In the first, a patient is given the drug in solution form orally, and the plasma levels are then monitored. In the second, the patient is given the drug in a solid dosage form and the plasma levels are again monitored. The two plasma level curves are related to each other in a way that depends upon the in vivo dissolution rate of the solid dosage form. If the kinetics of drug disposition are linear, the most general statement of this relationship is given by the convolution integral (2):

$$O(t) = \int_0^t I(u)R(t-u)du \qquad (1)$$

Here O is the plasma level time course obtained after tablet dosing and I is the in vivo dissolution rate. R is the plasma level time course measured after dosing the

drug in solution and then dividing the result by the dose size. A derivation of the equation has been outlined by Cutler (3).

A number of numerical techniques have been suggested for solving the convolution integral for I when O and R are known (3–8). However, for the purposes outlined in the first paragraph, we would not only like to know the dissolution rate, but we would like to know how *well* we know the dissolution rate. Because the measurement of plasma levels contain significant uncertainty, calculated dissolution rates are also uncertain. Just how uncertain these calculated results are has not been described in the pharmaceutical literature, and this paper represents a first attempt at such an analysis.

Normally, when one must estimate the uncertainty in a quantity, f, that has been calculated from measured quantities x and y with uncertainties σ_x and σ_y, one uses the propagation of errors formula (9):

$$\sigma_f^2 = \left[\left(\frac{\delta f}{\delta x}\right)_y^2 \cdot \sigma_x^2 + \left(\frac{\delta f}{\delta y}\right)_x^2 \cdot \sigma_y^2\right] \tag{2}$$

We believe the use of this approach for the current case to be flawed. The derivation of Eq. (2) is predicated on a Taylor's series expansion of f. This is a local expansion about a point, and for this reason should not be applied to the convolution integral. It is evident by an examination of Eq. (1) that the value of O at a particular time does not depend on local values of I and R. Instead, it depends on all values of I and R prior in time. This fact is inconsistent with the derivation of Eq. (2). The point may be moot because the application of Eq. (2) to Eq. (1) yields complicated derivatives with unobvious solutions.

Because of the complexity of the problem, a general solution to the problem using the model independent convolution integral was not performed. Instead, an experimental approach to the problem was taken in the form of a Monte Carlo experiment.

METHODS

Experimental Overview

Two error-loaded data sets (O and R) were constructed as described below. The in vivo dissolution rate was then inferred from the two data sets by deconvolution. The results were then stored and the process repeated at least 5000 times. After the process was completed, the results were sorted, a histogram constructed, and the distribution determined. In cases for which the distribution proved to be normal, the standard deviation of the distribution served as an uncertainty estimate.

Programming for the Monte Carlo experiments described above was written using the student edition of MATLAB (10). Sorting of the final results was performed using a program written in BASIC. Plotting and fitting of the results were accomplished using the program Scientist (11).

Data Generation

Data for the Monte Carlo experiment were simulated. The simulated data were based on the open one-compartment model of drug absorption and disposition. This model assumes that absorption from the GI tract into the body is first order:

$$\frac{dG(t)}{dt} = -k_a G(t) \tag{3}$$

Here G is the amount of drug in the GI tract, t is time, and k_a is a constant. The model also assumes that elimination of drug from the body is first order. When the two assumptions are combined, the amount of drug in the body after solution dosing, R, is given by the differential equation

$$\frac{dR(t)}{dt} = k_a G(t) - k_e R(t) \tag{4}$$

where k_e is a constant. The two equations can be integrated to give

$$R(t) = \frac{k_a G_0}{k_a - k_e} \cdot (e^{-k_e t} - e^{-k_a t}) \tag{5}$$

where G_0 is the dose given, and which will be assumed to be of unit size in what follows.

In order to simulate data for tablet dosing, a model had to be assumed for the dissolution rate. Dissolution from tablets can approximately be described by

$$M = M_0 \cdot e^{-q \cdot t} \tag{6}$$

where M is the mass of drug remaining undissolved, M_0 is the initial drug dose, and q is a constant. This model suggests a dissolution rate given by

$$I = M_0 \cdot q \cdot e^{-q \cdot t} \tag{7}$$

The result can be combined with Eq. (5) by the use of the convolution integral to give the following descrip-

tion of drug in the body after dosing with a tablet having unit drug content:

$$O(t) = e^{-qt}\left(\frac{\alpha}{k_e - q} - \frac{\alpha}{k_a - q}\right) + \frac{\alpha \cdot e^{-k_a t}}{k_a - q} - \frac{\alpha \cdot e^{-k_e t}}{k_e - q} \tag{8}$$

where

$$\alpha \frac{k_a \cdot q}{k_a - k_e} \tag{9}$$

Eqs. (5) and (8) were used to simulate plasma data at times 0, 1, 2, 4, 8, 12, 18, and 24 time units. Values for k_a, k_e, and k_q were 1, 0.15, and 0.5 respectively. Normally distributed random error was added to each of the simulated points from distributions that were constructed so that the standard deviation of each distribution was a percentage of the plasma level value. For example, assume the unit impulse response function, R, is to be constructed with 2% error. A time point with a plasma level equal to four would have error selected from a distribution with standard deviation of $0.02 \times 4 = 0.08$. A time point with a plasma level equal to two would have error selected from a distribution with standard deviation of $0.02 \times 2 = 0.04$.

The previously described error-loading process made use of a function call contained within the MATLAB language that is based on the algorithm by Park et al. and Forsythe et al. (12,13). To guard against the unlikely generation of a nonrandom sequence of numbers by the algorithm, the algorithm's output was reshuffled using a procedure suggested by Press (14).

Deconvolution

Two approaches were taken for the deconvolution step of the Monte Carlo experiment. In the first, the model used to simulate the data was assumed to be correct and the parameters were optimized for the error-loaded case in the following manner. The error-loaded solution data were first fit according to Eq. (5). The absorption and elimination constants obtained were then substituted into Eq. (8) and the error-loaded tablet data were fit by optimizing only the dissolution parameter q.

The second approach also relied on fitting error-loaded solution data using Eq. (5). However, tablet dissolution was inferred without assuming a model for dissolution by use of the following mass balance approach. The amount of drug that has been dissolved in vivo, A_d, is equal to the amount dissolved in the gastrointestinal tract, A_g, plus the amount in the rest of the body, A_b, plus the amount eliminated, A_{el}:

$$A_d = A_g + A_b + A_{el} \tag{10}$$

All of the terms on the right can be expressed in terms of the amount of drug in the body. The rate of drug elimination is proportional to the amount of drug in the body:

$$\frac{dA_{el}}{dt} = k_{el} A_b \tag{11}$$

The amount of drug dissolved in the gastrointestinal tract can be obtained from the equation describing the time course of drug in the body:

$$\frac{dA_b}{dt} = k_a A_g - k_{el} A_b \tag{12}$$

With the integrated form of these relationships, the amount of drug dissolved in vivo can be expressed in terms of the amount in the body:

$$A_d = k_{el}\int_0^t A_b du + \frac{1}{k_a}\int_0^t A_b(u) \cdot e^{-k_{el}(t-u)} du + A_b \tag{13}$$

Eq. (13) provides the second means of deconvolution used in this study. The approach is similar to one that was derived in the context of electronic circuit models of drug release, absorption, and disposition (15).

It is evident upon examination of Eq. (13) that in order to use the equation, the amount of drug in the body must be known. Normally one does not experimentally measure this directly, but instead one measures the concentration of drug in the plasma. If the drug distribution volume were known, the amount of drug in the body could be obtained from the plasma concentration measurements and Eq. (13) could be used. In practice, determination of the distribution volume is made by doing an additional experiment in which the patient is given the drug in the form of an IV bolus dose. We show in the Appendix that this additional experiment is not needed, and that the distribution volume can be inferred from the tablet and oral solution dose data.

Deconvolution using Eq. (13) is quite inaccurate unless some sort of interpolation between the data points is made. This was accomplished by use of a cubic spline fitting routine resident in the MATLAB programming language. Cubic splines fit data by drawing a curve between successive data points such that the data points are intersected and the derivatives are continuous. In addition, a boundary condition must be supplied in that

the slope of the curve at the first data point must be specified. The MATLAB program does not permit the user to specify this initial slope. To get the program to draw a spline that approximated the desired curvature, it was necessary to include error-free data at time equal to 0.02 time units.

RESULTS

Because the first deconvolution method assumes a one-parameter model for dissolution, the results of Monte Carlo experiments using the model can be characterized in terms of this one parameter. An example is shown in Fig. 1 for the case in which O and R were loaded with error levels of 2% and 3%, respectively. It is apparent from the fit to the results of the Monte Carlo experiments that the dissolution parameter, q, is normally distributed. However, the dissolution parameter is not linearly related to dissolution rates [Eq. (7)]. This means that the uncertainty in dissolution rate is a function of time, and it also means that the uncertainty in the dissolution rate at a particular time may not be normally distributed. An example is shown for the present case in Fig. 2. At time $t = 2$, the distribution is completely one sided. This result can be traced to a quirk in the model. Values of q other than the error-free value of 0.5 all produce smaller values of the dissolution rate at this particular time point than is produced by the error-free value. This situation is nonphysical and brings up an important point: assumed models of dissolution may not be able to conform to propagated error.

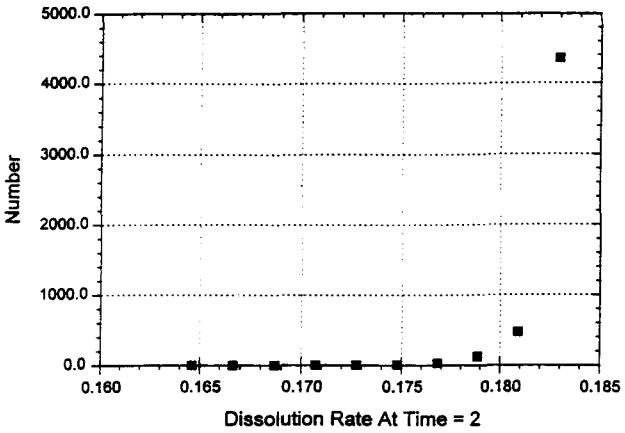

Figure 2. Distribution of dissolution rates at time $t = 2$ obtained from a Monte Carlo experiment in which tablet data, O, and solution data, R, were loaded with 2% and 3% error, respectively. The boxes are midpoints of the steps of the histogram constructed by sorting the results.

The second approach to deconvolution avoids this problem because the dissolution step is model-free. However, this means the uncertainty results obtained from a Monte Carlo experiment cannot be expressed in terms of a single parameter. Instead, the result at each time point must be examined in turn and the uncertainty determined. An example of this is provided in Fig. 3 in

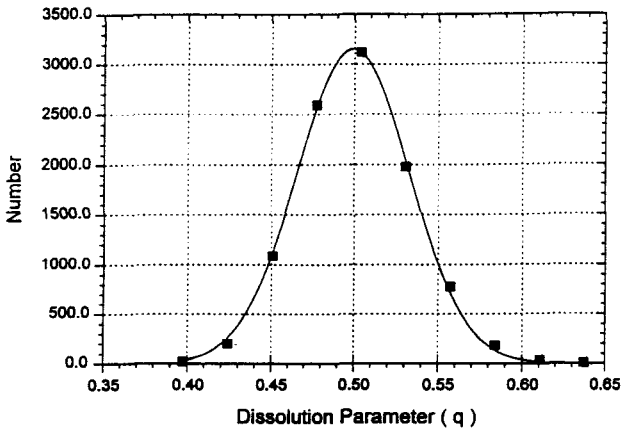

Figure 1. Distribution of dissolution parameters, q, obtained from a Monte Carlo experiment in which tablet data, O, and solution data, R, were loaded with 2% and 3% error, respectively. The boxes are midpoints of the steps of the histogram constructed by sorting the Monte Carlo results. The solid curve is a fit to these data assuming a normal distribution.

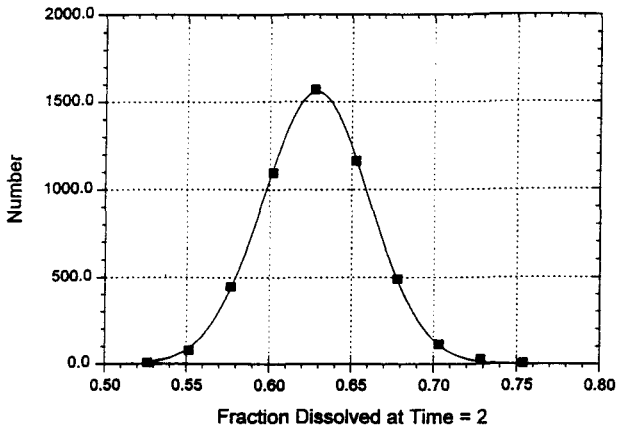

Figure 3. Distribution of amount dissolved at time $t = 2$ obtained using the mass balance model. Error levels in the tablet data, O, and solution data, R, were both 4%. The boxes are midpoints of the steps of the histogram constructed by sorting the Monte Carlo results. The solid curve is a fit to these data assuming a normal distribution.

which results for the time $t = 2$ are presented. The assumed error levels in this example were 4% for O and 4% for R. It is apparent from the fit that the results are normally distributed. Normally distributed results were also observed for all other time points examined.

The parameters obtained for these normal distributions are listed in Table 1. The values obtained for the midpoint of the distributions agree quite well with the analytical solution of the error-free case, as might be expected. The standard deviations of the distributions are first seen to increase with time and then to decrease.

This behavior might be expected by examining Eq. (13). The third term of the equation suggests that the amount of drug that has dissolved up to a particular time can never be known to a precision greater than the amount of drug in the body at that time. The first two terms involve integrals, and the process of integration would tend to cancel out random errors at longer times. The result is an initially increasing and then decreasing uncertainty in the amount of drug that has dissolved.

In summary, two methods have been outlined for estimating the uncertainty associated with the determination of in vivo dissolution rates. It was shown that a method that explicitly assumes a model for dissolution may not be accurate, because the assumed model may not be able to conform to propagated error. A second approach was outlined in which no explicit model for dissolution was assumed. Monte Carlo experiments using this approach gave normally distributed values for the amount dissolved at all time points examined, and the widths of these distributions varied with time.

APPENDIX

For a drug obeying the one-compartment model, the amount of drug in the body and the plasma concentration are simply related to each other through the distribution volume, V, by

$$A_b = CV \tag{14}$$

If Eq. (13) is multiplied and divided by the distribution volume, the amount dissolved can be expressed in terms of the plasma levels, C_b:

$$A_d = V\left(k_{el}\int_0^t C_b du + \frac{1}{k_a}\int_0^t C_b(u)\cdot e^{-k_{el}(t-u)}du + C_b\right) \tag{15}$$

It is now useful to note the following theorem (16). For the functions, f, f_1, and f_2 related to each other by the convolution integral,

$$f = \int_0^t f_1(u)f_2(t-u)du \tag{16}$$

the following holds true for the derivative of f:

$$f' = \int_0^t f_1'(u)f_2(t-u)du + \lim_{t\to 0} f_1(t)f_2(t) \tag{17}$$

If f_1 is the amount of drug dissolved, A_d, and f_2 is the unit impulse response function expressed in terms of plasma concentration, R_s, then f is given by

$$f = \int_0^t A_d(u)R_S(t-u)du \tag{18}$$

The derivative of f is simply

$$f' = \int_0^t A_d'(u)R_S(t-u)du \tag{19}$$

because the limit term prescribed in the above theorem is zero on physical grounds for a solid dosage form. The result for f' is just the plasma concentration, C_b, and

Table 1

Normal Distribution Parameters for the Uncertainty in the Amount Dissolved

Time	Amount Dissolved (Error-Free Value)	Distribution Midpoint	Distribution Standard Deviation
1	0.393	0.394	0.020
2	0.632	0.628	0.032
4	0.864	0.869	0.040
6	0.950	0.961	0.033
8	0.982	0.980	0.033
12	0.998	1.000	0.031

this in turn implies that f is the area under the plasma level curve, AUC.

We can now use Eq. (15) to determine the distribution volume by normalizing the result to unit volume:

$$\frac{A_d}{V} = k_{el}\int_0^t C_b du + \frac{1}{k_a}\int_0^t C_b(u)\cdot e^{-k_{el}(t-u)}du + C_b \quad (20)$$

Upon substitution into the convolution integral, Eq. (18), we get:

$$AUC = V\int_0^t \frac{A_d(u)}{V} R_S(t-u)du \quad (21)$$

The distribution volume can then be found by substituting the results obtained using Eq. (20) into Eq. (21) and performing a linear least-squares fit on Eq. (21) with the volume factor outside the integral viewed as the adjustable parameter.

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