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Short Communication

Kinetics of drug dissolution and dialysis from suspension dosage forms

M. BARZEGAR-JALALI and JOHN H. RICHARDS

School of Pharmacy, Leicester Polytechnic, P.O. Box 143, Leicester (England)

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Dialysis methods have been used in the determination of drug release from suspension dosage forms by Shah and Sheth (1976) and Barzegar-Jalali and Richards (1979). In order to detect the effects of formulation factors on the dissolution of the drug it is essential that the dissolution of the drug inside the dialysis sac should be the rate-determining stage in the release process. Swarbrick (1970) and Shah and Sheth (1976) have pointed out that attention should be paid to the area of the dialysing membrane in order to avoid a rate determining dialysis stage.

The equation used initially by Shah and Sheth (1976) and subsequently by us (1979) to calculate an apparent release rate constant from the data obtained with suspension dosage forms was derived originally by Davis et al. (1971) to describe the dialysis of drugs from solutions. Theoretical justification of the application of this equation to suspensions is presented in this communication.

The relationship, given by Davis et al. (1971) to describe the rate of appearance of a drug in the outer solution of a dialysis apparatus (dA_0/dt), may be expressed by Eqn. 1,

$$\frac{dA_0}{dt} = k\left(\frac{A_i}{V_i} - \frac{A_0}{V_0}\right) \tag{1}$$

where k is the dialysis rate constant, V_i and V_0 are the volumes of liquid inside and outside the dialysis sac, respectively, and A_i and A_0 are the amounts of drug in these corresponding volumes at time t. Equation 1 may be rewritten as Eqn. 2.

$$\frac{dA_0}{dt} = k\,\frac{(A_iV_0 - A_0V_i)}{V_iV_0} \tag{2}$$

The dimensions of k are volume/time and in order to obtain a rate constant having first-order dimensions the numerator and denominator of the right hand side of Eqn. 2 are multiplied by $(V_i + V_0)$ and after rearrangement Eqn. 3 is obtained

$$\frac{dA_0}{dt} = \frac{k(V_i + V_0)}{V_iV_0}\left[\frac{A_iV_0 - A_0V_i}{V_i + V_0}\right] \tag{3}$$

Since k, V_i and V_0 are constants for a given drug in an experiment the term $k(V_i + V_0)/V_iV_0$ can be denoted by k_D, which may be defined as the first-order dialysis rate constant. Thus, Eqn. 3 may be rewritten as Eqn. 4.

$$\frac{dA_0}{dt} = k_D \frac{(A_iV_0 - A_0V_i)}{V_i + V_0} \tag{4}$$

The conversion of k to k_D is necessary in relation to the equation used by us (1979) and in order to allow comparison of the dialysis rate constant with a first-order dissolution rate constant.

In the case of a suspension A_i, the amount of drug in solution inside the dialysis sac at any time t is given by Eqn. 5,

$$A_i = A_T - A - A_0 \tag{5}$$

where A_T is the total amount of drug in the system, A is the amount remaining undissolved inside the dialysis sac at time t and A_0 is the amount of drug in solution outside the dialysis sac at the same time. If it is assumed that the dissolution rate (dA/dt) of the undissolved drug inside the sac follows first-order kinetics then

$$\frac{dA}{dt} = -k_FA \tag{6}$$

where k_F is the first-order dissolution rate constant.

The Laplace transform of Eqn. 6 is

$$s\bar{A} - (A_T - a) = -k_F\bar{A} \tag{7}$$

and

$$\bar{A} = \frac{A_T - a}{s + k_F} \tag{8}$$

where a is the product of the solubility of the drug in the suspension medium and the volume of the sample of suspension that is placed inside the dialysis sac. Since usually $A_T \gg a$, Eqn. 8 may be simplified to

$$\bar{A} = \frac{A_T}{s + k_F} \tag{9}$$

Eqn. 4 may be written in the form,

$$\frac{dA_0}{dt} = PA_i - QA_0 \tag{10}$$

where

$$P = \frac{k_DV_0}{V_i + V_0} \tag{11}$$

and

$$Q = \frac{k_DV_i}{V_i + V_0} \tag{12}$$

Substitution for A_i from Eqn. 5 into Eqn. 10 gives

$$\frac{dA_0}{dt} = PA_T - PA - A_0(P + Q) \tag{13}$$

The Laplace transform of Eqn. 13 is

$$s\bar{A}_0 = \frac{PA_T}{s} - P\bar{A} - \bar{A}_0(P + Q) \tag{14}$$

Substitution for $\bar{A}$ from Eqn. 9 into Eqn. 14 and solving for $\bar{A}_0$ gives

$$\bar{A}_0 = \frac{k_F PA_T}{s(s + P + Q)(s + k_F)} \tag{15}$$

Eqn. 15 has the standard form of

$$\bar{y} = \frac{B}{s(s + b)(s + c)}$$

(Resigno and Segre, 1966) and the anti-Laplace form is

$$y = B\left[\frac{1}{bc} + \frac{e^{-bt}}{b(b - c)} - \frac{e^{-ct}}{c(b - c)}\right]$$

Therefore, the anti-Laplace form of Eqn. 15 is

$$A_0 = k_F PA_T\left[\frac{1}{(P + Q)\,k_F} + \frac{e^{-(P+Q)t}}{(P + Q)(P + Q - k_F)} - \frac{e^{-k_F t}}{k_F(P + Q - k_F)}\right] \tag{16}$$

Substitution for P and Q from Eqn. 11 and 12, respectively, into Eqn. 16 gives

$$A_0 = \frac{k_F k_D V_0 A_T}{V_i + V_0}\left[\frac{1}{k_D k_F} + \frac{e^{-k_D t}}{k_D(k_D - k_F)} - \frac{e^{-k_F t}}{k_F(k_D - k_F)}\right] \tag{17}$$

Simplification of Eqn. 17 results in

$$A_0 = \frac{V_0 A_T}{V_i + V_0}\left[1 + \frac{k_F e^{-k_D t}}{k_D - k_F} - \frac{k_D e^{-k_F t}}{k_D - k_F}\right] \tag{18}$$

Study on an aspirin solution using the method described in a previous report (Barzegar-Jalali and Richards, 1979) showed that the first-order dialysis rate constant was 0.074 min^{-1}. Comparison of this value with the release rate constant of a dispersion of aspirin powder in water (0.0141 min^{-1}) obtained from data presented in that report indicates that the dissolution rate must be the slowest step in the overall release process, i.e. $k_F < k_D$. Therefore, the term $k_F e^{-k_D t}/k_D - k_F$ is very small in comparison with the term $k_D e^{-k_F t}/k_D - k_F$ and, for the same reason, $k_D - k_F \approx k_D$. Eqn. 18 may therefore be simplified further to give

$$A_0 = \frac{V_0 A_T}{V_i + V_0}(1 - e^{-k_F t}) \tag{19}$$

Rearrangement of Eqn. 19 results in

$$V_0A_T - (V_i + V_0)\,A_0 = V_0A_Te^{-k_Ft} \tag{20}$$

Taking common logarithms of both sides of Eqn. 20 gives

$$\log[V_0A_T - (V_i + V_0)\,A_0] = \frac{-k_Ft}{2.303} + \log(V_0A_T) \tag{21}$$

Eqn. 21 is identical to the one that we used in our previous report (Barzegar-Jalali and Richards, 1979). In that report we defined k_F as the apparent first-order rate constant for the release of aspirin into the liquid on the outside of the dialysis sac. As can be seen from the above derivation it can be defined more precisely in the present situation, i.e., where $k_F < k_D$, as the first-order dissolution rate constant.

It should be borne in mind that the above derivation of Eqn. 21 assumes that release of drug from a suspension dosage form in a dialysis apparatus is a two-stage process, i.e. dissolution followed by dialysis. In systems where the liquid inside the dialysis sac is not agitated adequately, particularly if this liquid is viscous, or where a suspending agent forms clumps of gel on contact with the dissolution medium (e.g. sodium alginate in an acidic medium), then a diffusion stage may need to be taken into account .

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