Drug Permeation through Membranes II: Simultaneous Dissolution and Permeation of Drug from Solid Dosage Forms

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Abstract □ The simultaneous dissolution and permeation of a drug from solid oral dosage forms were analyzed by a treatment based on Fick's second law of diffusion. The analysis shows that dissolution rate constants can be obtained from the permeation lag time, while the coefficients of permeability are estimated, as usual, from the rate of drug transfer across the membrane under steady-state conditions. Drug–excipient interactions, if any, would be expected to affect the rate of drug transfer across the membrane. Therefore, from a single experiment, the dissolution rate and the extent of drug–excipient interaction can be obtained. The equation was tested by dissolution–permeation measurements on two amobarbital formulations.

Keyphrases □ Drug permeation—membranes, amobarbital, analysis of dissolution and permeation from solid oral dosage forms, application of Fick's second law of diffusion, relevance to drug–excipient interactions, equations □ Drug–excipient interactions—application of Fick's second law of diffusion to determine both dissolution and membrane permeation, amobarbital from a solid oral dosage form, equations □ Dissolution–membrane permeability data—generated by application of Fick's second law of diffusion, relevance to drug–excipient interactions, amobarbital from solid oral dosage form, equations □ Permeation, membrane—used to evaluate drug–excipient interactions and drug dissolution by application of Fick's second law of diffusion, amobarbital from a solid oral dosage form □ Membrane permeation–dissolution data—generated by application of Fick's second law of diffusion, relevance to drug–excipient interactions, amobarbital from a solid oral dosage form, equations

It is now well recognized that the *in vivo* dissolution characteristics of drug formulations may have a pronounced effect on their bioavailability. Because *in vivo* dissolution rates are difficult to measure directly, attempts to assess this aspect of drug quality are commonly made from *in vitro* dissolution rate data. Dissolution specifications *in vitro* have been promulgated for a number of drugs (1, 2), and attempts to correlate these with bioavailability have met with varying degrees of success (3–5).

In addition to *in vivo* dissolution, bioavailability depends upon transfer of the drug across the GI membrane. For typical oil-soluble drugs, the transfer rate depends upon the concentration of free, unionized drug in the GI tract. The concentration may be adversely affected by adsorption, absorption, reprecipitation, partitioning into bile micelles or fat particles, or any other factor that reduces the concentration of free drug (6). Substances having an adverse effect on absorption rates may be endogenous to the GI tract or may be introduced as nutrients or tablet excipients. *In vitro* assessment of the latter can be made by comparing the permeation rate of unformulated drug to that of drug released from formulations dissolved, or dispersed, in an appropriate buffer. Drug–excipient interactions may account for the low bioavailabilities observed in some formulations.

This paper describes a method for the simultaneous determination of the dissolution rate constant of drug in a formulation and the permeability coefficient of the drug in that formulation.

THEORETICAL

The experiment involves dissolution of drug from a solid dosage form, followed by drug transfer across the membrane of a permeation cell mounted in the dissolution vessel. The term permeation refers to transfer of drug from the aqueous solution in which it dissolves, across the membrane, and into the aqueous solution within the permeation cell, while diffusion refers to movement of drug molecules within the cell membrane.

Movement of drug within a homogeneous membrane can be described by Fick's second law of diffusion:

$$\frac{\partial C^*}{\partial t} = D\frac{\partial^2 C^*}{\partial x^2} \qquad \text{(Eq. 1)}$$

where C^* is concentration of drug within the membrane, t is time, D is the diffusion coefficient, and x is the space coordinate normal to the surface of the membrane (7). For a membrane of thickness l, x lies between zero and l. On the absorbing side of the membrane, where $x = 0$, the concentration of drug is time dependent and given by:

$$C^* = C_0^* G(t) \qquad \text{(Eq. 2)}$$

where C_0^* is the drug concentration in the membrane at $x = 0$ when the dosage form has completely dissolved, and $G(t)$ is a particular driving function with range [0, 1]. The drug concentration is zero when time is zero. On the desorbing side, where $x = l$, the drug concentration is maintained at zero by buffering the desorbing solution at an appropriate pH. These considerations lead to the following boundary conditions:

$$C^*(l,t) = 0 \qquad \text{(Eq. 3)}$$

$$C^*(x,0) = 0 \qquad \text{(Eq. 4)}$$

$$C^*(0,t) = C_0^* G(t) \qquad \text{(Eq. 5)}$$

Solution of Eq. 1 for C^* as a function of x and t is given in *Appendix I*. The rate at which drug diffuses across the plane of the membrane at $x = l$ is given by:

$$-D\left.\frac{\partial C^*}{\partial x}\right|_{x=l} \qquad \text{(Eq. 6)}$$

so that, for a membrane of unit area, the quantity of drug crossing the plane during the time interval from 0 to t is:

$$q = -D\int_0^t \left(\frac{\partial C^*}{\partial x}\right)_{x=l} dt \qquad \text{(Eq. 7)}$$

The particular driving function, $G(t) = (1 - e^{-\alpha t})$, was chosen to represent the rate of drug dissolution from a solid dosage form. It probably represents actual dissolution behavior as well as any other function and it is convenient to handle mathematically. The

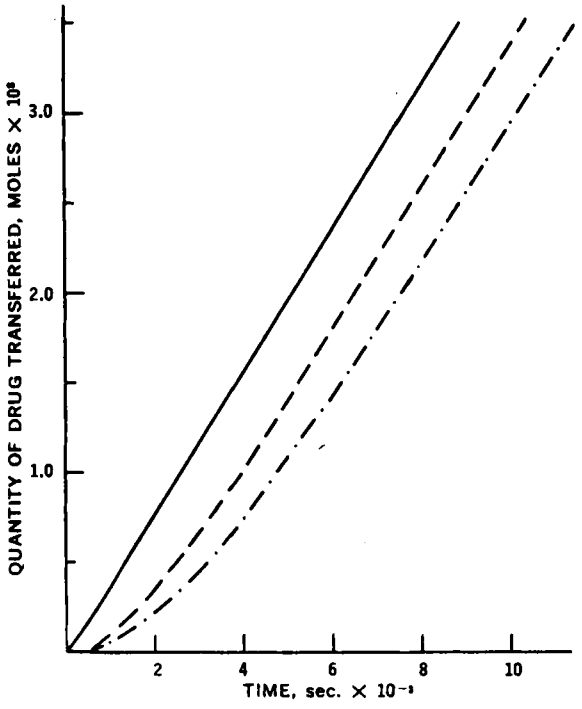

Figure 1—*Plots of theoretical* q versus t *for various half-times of dissolution. Key:* ——, $t_{1/2}$ = *0 min.;* - - -, $t_{1/2}$ = *16.6 min.;* -.-., $t_{1/2}$ = *30 min.;* P = 10^{-6} *cm.*^{2} *sec.*$^{-1}$, C* = 10^{-6} *mole cm.*$^{-3}$, *and* l = 2.54×10^{-3} *cm.*

constant κ is characteristic of a given dosage form and is a measure of the rate at which it dissolves. Solution of Eq. 1 for this particular case is given in *Appendix II*. Differentiation with respect to x at $x = l$ and integration over time lead to:

$$q = C_0^* \left\{ \frac{Dt}{l} - \frac{l}{6} - \frac{D}{\kappa l} + \frac{e^{-\kappa t}}{\sqrt{\kappa/D}\sin\{l\sqrt{\kappa/D}\}} + \frac{2\kappa l}{\pi^2 D}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\frac{e^{-(n\pi/l)^2 Dt}}{(n\pi/l)^2 - \kappa/D}\right\} \quad \text{(Eq. 8)}$$

provided that $(l/\pi)\sqrt{\kappa/D} \neq n = 1, 2, 3 \ldots$.

If the limit of q in Eq. 8 is taken as t becomes large, then:

$$q = \frac{C_0^* AD}{l}t - C_0^* A\left(\frac{l}{6} + \frac{D}{\kappa l}\right) \quad \text{(Eq. 9)}$$

where A is the surface area of the membrane. To apply Eq. 9 to permeation, it is necessary to replace DC_0^* by PC_0, where P is the permeation coefficient and C_0 is the concentration of drug in solution when dissolution is complete. Thus, the partition coefficient,

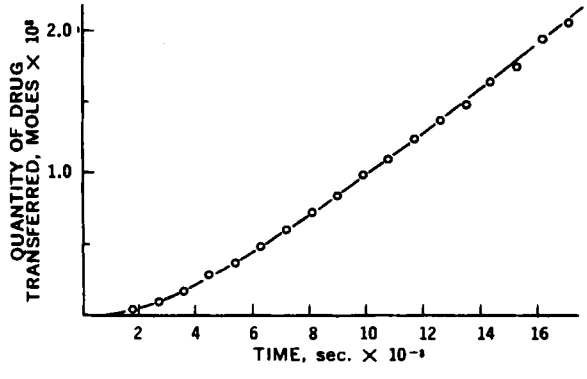

Figure 2—*Experimental points and fitted theoretical curve of* q versus t *for amobarbital Formulation B. The curve was calculated for* C* = 2.90×10^{-7} *mole cm.*$^{-3}$, P = 8.2×10^{-6} *cm.*^{2}*/sec.*$^{-1}$, l = *0.014 cm., and* $\kappa = 3.11 \times 10^{-4}$ *sec.*$^{-1}$. P *and* κ *were calculated from the steady-state portion of the curve.*

Table I—Experimentally Determined Dissolution and Permeability Coefficients of Amobarbital Formulations

Tablet Number	Lag Time, t^*, sec.	Permeability Coefficient, P, cm.^{2} sec.$^{-1}$ × 10^6	Dissolution Constant, κ, sec.$^{-1}$ × 10^4	Dissolution Half-Time, $t_{1/2}$, min.
		Formulation A		
1	1450	8.99	9.2	12
2	1180	8.42	12.7	9
3	990	7.84	17.4	7
4	1080	7.84	15.1	8
5	—	—	—	9[a]
6	—	—	—	9[a]
		Formulation B		
1	4608	7.42	2.40	48
2	4480	7.74	2.46	47
3	5280	8.35	2.04	56
4	3610	8.23	3.11	37
5	—	—	—	20[a]
6	—	—	—	65[a]
7	—	—	—	82[a]

[a] Dissolution half-times determined by direct measurement.

K_p, is C_0^*/C_0. This substitution assumes that the concentration of drug in the membrane at $x = 0$ is proportional to the concentration of drug in solution. The term P includes diffusion of the drug across the aqueous boundary layer in contact with the membrane. Thus:

$$q = \frac{C_0 AP}{l}t - C_0 A\left(\frac{l}{6} + \frac{P}{\kappa l}\right) \quad \text{(Eq. 10)}$$

Equation 10 is applicable to dissolution–permeation experiments of sufficient duration to reach the steady state, where the plot of q *versus* t is linear. Under these conditions:

$$P = \frac{(dq/dt)l}{C_0 A} \quad \text{(Eq. 11)}$$

and:

$$\kappa = \left(t^* - \frac{l^2}{6D}\right)^{-1} \quad \text{(Eq. 12)}$$

where t^*, the lag time, is the value of t when q is zero.

Before attempting to use Eqs. 8–12 to determine κ and P from experimental measurements of q and t, it is important to know whether κ and P vary significantly with changes in the experimental parameters. Figure 1 gives curves of q *versus* t for various κ's between 10^3 and 3.851×10^{-4} sec.$^{-1}$, corresponding to a range in half-times of dissolution from 0 to 30 min. Clearly, the curves and lag times are well separated with the lag time increasing from 2 to 45 min. It is, therefore, feasible to determine κ by this technique. Plots of Eq. 8 for various values of P (not shown) demonstrate that while t^* depends on P, the change in t^* is less than a factor of 2 when P is varied over an order of magnitude. However, highly permeable membranes are preferred since the time required to carry out an experiment increases as P decreases.

The significance of changes in lag time can be visualized by recasting Eq. 12:

$$t^* = \frac{l^2}{6D} + \frac{1}{\kappa} \quad \text{(Eq. 13)}$$

showing t^* to be made up of a diffusion term and a dissolution term. As l becomes smaller, the contribution of the first term to t^* decreases, enhancing the relative importance of κ^{-1} and facilitating its determination. In addition, small values of l reduce the time required to reach the steady state and, hence, the overall time of the experiment. The effect of an increase in l on q is to decrease the drug transfer rate, increase the lag time, and prolong the period required to reach a steady state.

EXPERIMENTAL

Dissolution–permeation experiments were carried out in a 1-l. resin kettle at 37 ± 1°. The kettle contained a wire basket of the

type used in the USP dissolution procedure (1) placed near the rim of the kettle, about halfway down, and rotated at 150 r.p.m. A diffusion cell of the type described by Garrett and Chemburkar (8), equipped with 0.014-cm. membranes of polydimethylsiloxane, was placed opposite the rotating basket.

Dissolution–permeation experiments were carried out on two tablet formulations of amobarbital, A and B. The experiment was started by placing 900 ml. of acetate buffer, pH 5, in the kettle and 15 ml. of borate buffer in the diffusion cell. A tablet was put into the wire basket at time zero; at appropriate time intervals, the concentration of amobarbital in the diffusion cell was measured by UV spectroscopy at 240.5 nm., following the procedure already described (6). Tablet dissolution rates were measured directly by sampling the resin kettle at appropriate time intervals. These samples were diluted with borate buffer, and the amobarbital concentration was read spectrophotometrically.

RESULTS AND DISCUSSION

To measure the dissolution constant κ and the permeability coefficient P by the method described, it is necessary for the transfer rate of drug across the membrane to reach the steady state. The steady state cannot be achieved before the tablet has completely dissolved. The time taken to reach the steady state also increases as the membrane thickness increases.

The dissolution constant κ for two brands of amobarbital, A and B, was determined in the dissolution–permeation apparatus by two methods: (*a*) from the lag time as described in this paper, and (*b*) by measurement of the drug concentration in the dissolving medium.

The results (Table I) show $t_{1/2}$ as determined by the two methods to be in agreement, remembering that large intralot variations in tablet dissolution times are commonly observed. The permeability coefficients are, within experimental error, the same as those reported previously for amobarbital (6). The component of the lag time due to the nature of the drug and the membrane thickness, $l^2/6D$, in Eq. 13 is about 425 sec. for this experiment. The difference between this quantity and t^*, the experimentally observed lag time, is a reflection of the time required for the tablet to dissolve.

Equation 8 was tested by calculating the theoretical curve of q *versus* t for an amobarbital tablet with a dissolution half-time of 37 min. and plotting the experimental points of Tablet 4, Formulation B, on the same graph (Fig. 2). It is evident that the experimental results are adequately described by Eq. 8.

In conclusion, it was possible to determine the dissolution constant and the permeability coefficient of a drug in a solid dosage form by a single experiment. The time required to determine κ by this method is greater than in a single dissolution experiment, but additional information is gained. Comparison of P as determined from tablet dissolution, with P for the pure drug in question, indicates whether or not a portion of the drug is unavailable for membrane transfer. Drug availability could be reduced by interaction with tablet excipients. Further studies are planned to determine if dissolution–permeation experiments are of value in monitoring drug quality and whether the results can be correlated with human bioavailability data.

APPENDIX I

Suppose $C^*(x,t)$ is well defined for $0 < x < l$, $t > 0$, so that for fixed x, $C^*(x,t)$ is sectionally continuous in every finite interval $0 < t < N$ and of exponential order γ for $t > N$, where N and γ are finite numbers. Then by the method of Laplace transformations (9), the partial differential Eq. 1 can be transformed into the ordinary differential equation:

$$sc^*(x,s) - C^*(x,0) = D\frac{d^2c^*}{dx^2} \qquad \text{(Eq. A1)}$$

where the Laplace transformation of $C^*(x,t)$ is denoted by the lower case function $c^*(x,s) \overset{\text{defn}}{\equiv} \int_0^\infty e^{-st}\, C^*(x,t)\, dt$.

The Laplace transforms of boundary conditions (Eqs. 3–5) are, respectively:

$$c^*(l,s) = 0 \qquad \text{(Eq. A2)}$$

$$c^*(x,0) = 0 \qquad \text{(Eq. A3)}$$

$$c^*(0,s) = C_0^* g(s) \qquad \text{(Eq. A4)}$$

The general solution of Eq. A1 after the substitution of Eq. 4 is given by:

$$c^*(x,s) = \kappa_1 \cosh \sqrt{s/D}x + \kappa_2 \sinh \sqrt{s/D}x \qquad \text{(Eq. A5)}$$

Using boundary condition A2, one finds:

$$\kappa_2 = \kappa_1 \cosh\{\sqrt{s/D}l\}/\sinh\{\sqrt{s/D}l\} \qquad \text{(Eq. A6)}$$

and:

$$c^*(x,s) = \kappa_1 \sinh\{\sqrt{s/D}(l-x)\}/\sinh\sqrt{s/D}l \qquad \text{(Eq. A7)}$$

After imposing boundary condition A4, one has:

$$c^*(x,s) = C_0^* g(s) \sinh\{(l-x)\sqrt{s/D}\}/\sinh\sqrt{s/D}l \qquad \text{(Eq. A8)}$$

The solution to the partial differential equation is given by the inverse Laplace transformation of Eq. A8 and can be found by use of the convolution theorem. That is:

$$C^*(x,t) = L^{-1}\left\{C_0^* g(s)\frac{\sinh(l-x)\sqrt{s/D}}{\sinh l\sqrt{s/D}}\right\} = \int_0^t \left(L^{-1}\frac{\sinh(l-x)\sqrt{s/D}}{\sinh l\sqrt{s/D}}\bigg|_{x=u}\right) C_0^* G(t-u)\,du = \frac{2\pi D}{l^2} C_0^* \sum_{n=1}^{\infty}(-1)^{n-1} n \int_0^t e^{-(n\pi/l)^2 Du} G(t-u)du \times \sin n\pi(l-x)/l \qquad \text{(Eq. A9)}$$

The rate of transfer at $x = l$ at time t is given by:

$$-D\frac{\partial C^*}{\partial x}\bigg|_{x=l}$$

so that the quantity of diffusing substance during the interval $[0,t]$ is:

$$q = -D\int_0^t \left(\frac{\partial C^*}{\partial x}\right)_{x=l} d\tau \qquad \text{(Eq. A10)}$$

APPENDIX II

For the particular driving function $G(t) = (1 - e^{-\kappa t})$, it is necessary to evaluate:

$$\int_0^t e^{-(n\pi/l)^2 Du}\{1 - e^{-\kappa(t-u)}\}\,du = \int_0^t e^{-(n\pi/l)^2 Du}\,du - e^{-\kappa t}\int_0^t e^{-\{(n\pi/l)^2 D-\kappa\}u}du = [(1-e^{-\kappa t})/\{(n\pi/l)^2 D - \kappa\}] - [\kappa\{1 - e^{-(n\pi/l)^2 Dt}\}/(n\pi/l)^2 D\,\{(n\pi/l)^2 D - \kappa\}] \qquad \text{(Eq. A11)}$$

provided $(n\pi/l)^2 D \neq \kappa$. Substituting into Eq. A9, one has:

$$C^*(x,t) = \frac{2C_0^*\pi D}{l^2}\left[(1-e^{-\kappa t})\sum_{n=1}^{\infty}\frac{(-1)^{n-1}n}{(n\pi/l)^2 D - \kappa}\times \sin\frac{n\pi(l-x)}{l} + \kappa\sum_{n=1}^{\infty}\frac{(-1)^n n}{\{(n\pi/l)^2 D - \kappa\}(n\pi/l)^2 D}\times \{1 - e^{-(n\pi/l)^2 Dt}\}\sin n\pi(l-x)/l\right] = C_0^*(1-e^{-\kappa t})\times \frac{\sin(l-x)\sqrt{\kappa/D}}{\sin l\sqrt{\kappa/D}} + \frac{2\kappa C_0^*}{\pi D}\sum_{n=1}^{\infty}\frac{(-1)^n}{\{(n\pi/l)^2 - \kappa/D\}n}\times \{1 - e^{-(n\pi/l)^2 Dt}\}\sin\frac{n\pi(l-x)}{l} \qquad \text{(Eq. A12)}$$

where the first summation was executed by series 557 in Jolley (10).

After differentiating Eq. A12 with respect to x and using summation formula 558 in Jolley (10), one obtains:

$$\left(\frac{\partial C^*}{\partial x}\right)_{x=l} = C_0^* \left\{\sqrt{\frac{\kappa}{D}}\frac{e^{-\kappa t}}{\sin l\sqrt{\kappa/D}} - \frac{1}{l} + \frac{2\kappa}{Dl}\sum_{n=1}^{\infty}\frac{(-1)^n e^{-(n\pi/l)^2 Dt}}{(n\pi/l)^2 - \kappa/D}\right\} \quad \text{(Eq. A13)}$$

Consequently, upon integration and simplifying by means of series 337 and 558 in Jolley (10), one obtains Eq. 8. Under experimental conditions, l, D, and κ will be rational numbers while π^2 is irrational so that $l^2\kappa/\pi^2 D \neq 1, 4, 9, 16, \ldots$. However, it may be sufficiently close to an integer to cause "round off" difficulties in computing the infinite sum.

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Acute Effects of Narcotic Analgesics on Behavioral Arousal in the Rat

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Abstract □ Locomotor activity measured by photocell actometers was taken as an index of behavioral arousal in rats following acute administration of pentazocine, morphine, methadone, levorphanol, and meperidine. The intraperitoneal doses tested were 1.25, 2.5, 5.0, 10, and 20 mg./kg. The low doses of morphine and methadone and an intermediate dose of pentazocine produced an early (1st hr.) increase in motility. Higher doses of these three drugs and the lowest dose of levorphanol caused a delayed excitation (2nd–3rd hr.). An early inhibition of activity was seen for the higher doses of morphine, methadone, meperidine, and levorphanol but not for pentazocine. Meperidine did not elicit significant locomotor excitation in these doses. The enhanced motility after pentazocine and the narcotic analgesics was blocked by pretreatment with α-methyltyrosine.

Keyphrases □ Locomotor activity—effect of pentazocine and narcotic analgesics, compared to morphine, pretreatment with α-methyltyrosine, rats □ Pentazocine and narcotic analgesics—effect on locomotor activity, compared to morphine, pretreatment with α-methyltyrosine, rats □ Analgesics, narcotic (methadone, meperidine, levorphanol)—effect on locomotor activity, compared to morphine, pretreatment with α-methyltyrosine, rats □ Methadone—effect on locomotor activity, rats □ Meperidine—effect on locomotor activity, rats □ Levorphanol—effect on locomotor activity, rats □ α-Methyltyrosine pretreatment—effect of pentazocine and narcotic analgesics on locomotor activity, rats

Previous reports from this laboratory have analyzed the occurrence of locomotor stimulation following low doses of morphine in nontolerant rats (1–4). This effect had been little emphasized and had not been systematically evaluated in earlier works, which did, however, describe repeatedly an enhancement of motility by morphine occurring after an interval of repeated dosing in the study of tolerance and/or physical dependence (5–9). Certain studies have cited gross observations or limited data concerning such an effect in nontolerant rats (9–12). Locomotor excitation provides evidence for behavioral arousal in response to morphine in the nontolerant rat despite the classification of this species among those showing predominantly a response of depression and behavioral inhibition (13, 14).

Interest in this excitatory component of the CNS pharmacology of the opiates led to a consideration of the generality of the motility response seen with low doses of morphine. Specifically, it was of interest whether similar effects might be found not only after the synthetic narcotic analgesics but also after an agent of the narcotic antagonist–analgesic class. Therefore, methadone, meperidine, levorphanol, and penta-