Two-Phase Method for the Investigation of Interphase Transport: I: Theoretical Aspects

S. A. HOWARD*, M. A. FARVAR, AKIRA SUZUKI†, and W. I. HIGUCHI

Abstract □ As part of a program aimed at the quantitation of factors involved in the oil–water interphase transport of drugs, a two-phase model was theoretically investigated. The model essentially consists of the transport of the drug from an aqueous phase of a given volume across an aqueous diffusion layer of defined thickness, the water–oil interface, and into a lipid sink. Three methods for treating this problem were developed for the one-dimensional case. With the assistance of a digital computer the resulting equations were used to compute the effects of a number of variables over a wide range of conditions. The calculations showed that when the oil–water partition coefficient is large, the transport is aqueous diffusion controlled and first-order behavior is followed in the aqueous phase with time. Deviation from first-order behavior occurs when the partition coefficient is low, when the diffusion coefficient in the oil is low, when the diffusion coefficient in the aqueous phase is large, or when the thickness of the aqueous diffusion layer is small. These results are expected to be useful in the design and interpretation of both *in vitro* and *in vivo* data on drug transport.

Keyphrases □ Interphase transport—theoretical aspects □ Partition coefficient effect—oil–water diffusion system □ Equations—solute transport, oil–water system □ Model—interphase transport

In recent years there has been much in the literature concerning the three-phase model for drug and chemical transport especially for drug absorption. Brodie, *et al.* (1–4) have demonstrated that the gastrointestinal absorption of drugs is often dependent upon their ability to penetrate a lipoidal barrier, and that for some compounds absorption is accomplished by passive diffusion. Several others have shown that drug partitioning that occurs between tissues in the brain and fluids is influenced by the drug's partition coefficient (5, 6). In addition, metabolism in the liver is influenced by the pKa and partition coefficient of the drug (7).

Liquid "oil" membranes have been studied for many years. Nernst and Riesenfeld (8) as early as 1902 worked with such a system using phenol saturated with water as a membrane in order to study electromotive behavior. In fact, nonaqueous liquid membranes are used often as models to study the selective flux of salts and ions, and the influence of amphoteric surface-active agents (phospholipids) on diffusion and carrier transport (9–11). The liquid membrane is formed by placing the nonaqueous liquid on top of aqueous solutions placed in the two compartments of a polystyrene box, partitioned in such a way that the two aqueous solutions do not mix.

Davies and Rideal (12) have pointed out the hazards of using a simple oil–water interface with stirring as a diffusion controlled model. Stirring creates eddies and a turbulent interface. Even in the completely unstirred system, which they have recommended, complications arise from spontaneous interfacial turbulence and spontaneous emulsification. Rosano (9) stated that slight oscillations of the interface were always visible. Changing the interface by adding surfactants or changing the oil could change this constant movement and therefore change the diffusion layer thickness. Using a completely unstirred system would force the system to be diffusion controlled in the aqueous phase and not sensitive to any other factors such as interfacial changes or changes in diffusion characteristics such as micelle breakup near the interface. Swintosky and Doluisio (13, 14) in order to avoid the problems of rapid stirring used a rocking apparatus. In this model, however, the interface is constantly moving and changing size. Since surface changes occur in both cases, it would be difficult to quantitatively determine to what extent aqueous diffusion and interfacial barriers may influence the rate of transport.

Several successful attempts have been made at incorporating a lipid in an inert matrix and thus possibly avoid some of the interfacial movement found in the liquid membrane model. Lakshminarayanaiah (15) was able to incorporate up to 20% lipids (all solids, steric acid, or phosphatidyl-L-serine or cholesterol) into a membrane made of parlodion. Banaszak and McDonald (16) were able to incorporate up to 5% paraffin oil into a collodion membrane. This membrane was soaked with water overnight and proved permeable to cholesterols in partially aqueous dialysis systems. Tobias (17, 18) was able to add phospholipid or cholesterol to a filter disk.[1] At one laboratory[2] (19, 20), filters saturated with liquid and solid lipids were used in water permeation studies as an *in vitro* model of the skin. Even

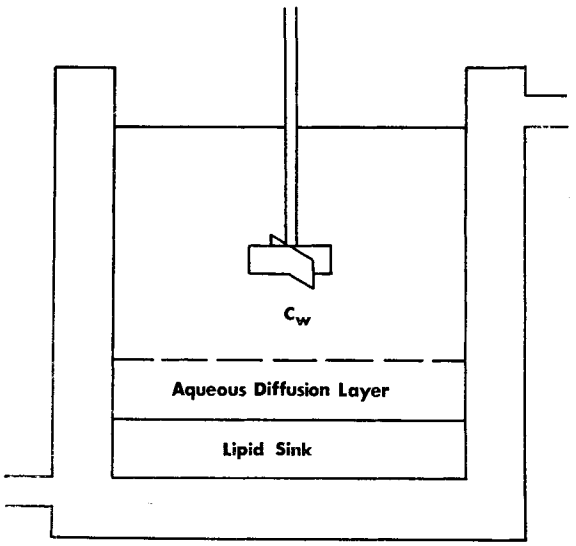

Figure 1—*A schematic illustration of the experimental system for studying the transport of a solute from an aqueous phase to a lipid sink.*

[1] Millipore Filter Corp., Bedford, Mass.
[2] Lever Brothers.

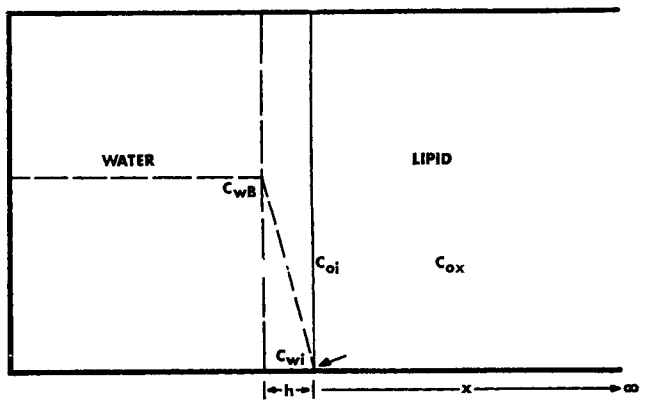

Figure 2—*Method I. Diagram showing solute transport across an aqueous diffusion layer with a thickness* h *into an infinite lipid sink. Key:* C_{wB} = *bulk aqueous concn.;* C_{wi} = *interfacial aqueous concn.;* C_{ox} = *lipid conn. at* x; C_{oi} = *lipid interfacial concn.; the dotted line and the arrow represent condition at time equals zero.*

more recently Levy and Mroszczak (21) used a filter saturated with olive oil or linoleic acid as a membrane in a three-phase model.

In this study a two-phase, rather than a three-phase model is presented. This model has the following uses: (*a*) To provide quantitative information regarding systems in which diffusion in the aqueous phase is an important rate step in interphase transport. It is difficult in a three-phase model to isolate and quantitate this factor and, therefore, a two-phase model becomes useful. (*b*) To find the apparent diffusion coefficient of a substance in an oil-saturated membrane. As will be shown later, when the partition coefficient is low the diffusion in the oil is an important factor in two-phase diffusion controlled drug transport. Through a method of curve fitting the apparent diffusion coefficient of a relatively low partitioning solute can be obtained. (*c*) To provide a system for studying transport and deposition into tissues. Deposition of cholesterol from blood to tissue walls or the passage of water insoluble drugs from the aqueous lumen of the intestine to the lipid wall are just two of the many problems in which a two-phase model might provide very important quantitative data. (*d*) To study interfacial barriers. Because of the presence of a thin aqueous diffusion layer the system should be relatively sensitive to surface barrier effects when the oil–water partition coefficient is high. The comparable situation may be achieved only with difficulty in many of the three-phase systems. (*e*) To study micellar transport. Using this model it might be possible to obtain quantitative information regarding micellar two-phase transport and inter-barrier effects on such transport.

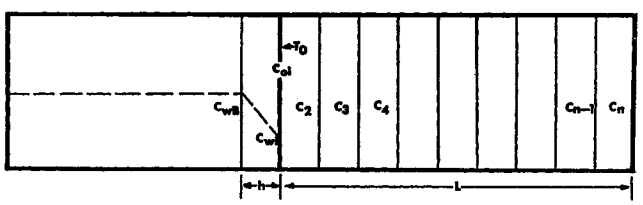

Figure 3—*Method II. Diagram showing solute transport across an aqueous diffusion layer with a thickness* h *into a finite lipid sink, with a thickness of* L. *For computational purposes the sink thickness has been divided into* n − 1 *units. The dotted line and the* T_0 *point show conditions when time is equal to zero. See text.*

This is very important in the understanding of the absorption of water insoluble drugs and fats, which are solubilized by and transported in the form of micelles.

A working experimental model has been developed and is illustrated schematically in Fig. 1. The apparatus employs a filter membrane, saturated with lipid or a gelled lipid as the nonaqueous sink. This sink material is placed at the bottom of a constant-temperature water-jacketed beaker with provisions for controlled stirring of the aqueous phase. This system provides a constant oil–water interface even under stirring conditions in which a relatively thin diffusion layer is obtained. The mass transfer for such an arrangement is one dimensional and the appropriate equations may be conveniently formulated.

The experiment involves the transport of the solute from the aqueous phase through an effective aqueous diffusion layer to the lipid sink. The rate of transport, which is the quantity of prime interest in this work, should depend upon a number of factors: (*a*) the rate of agitation, since this affects the thickness of the aqueous diffusion layer, (*b*) the diffusion coefficient of the solute in the aqueous phase, (*c*) the lipid–water partition coefficient for the solute, since this may determine both the sink "capacity" and the concentration gradient across the aqueous diffusion layer, and finally (*d*) the effective diffusion coefficient of the solute in the lipid-sink phase. In addition to the above factors, when an interfacial barrier is important its effect must also be considered.

DERIVATION OF EQUATIONS

Three methods have been considered for solving this problem of single-solute transport from a stirred aqueous compartment to a lipid sink. Method I is based on an analytic solution of the infinite lipid sink in series with the aqueous diffusion barrier. The second method (II) utilizes the finite difference method and is for the finite sink case. The former has the advantage of being rigorous and straightforward but is applicable to initial rate data only. The latter has the advantage of being applicable for later time periods and easy to computerize but is an approximation and is subject to error if values are not wisely chosen for the time and *n* parameters. Method III is an analytic solution for a finite sink.

Method I—Figure 2 describes the semi-infinite sink problem. It is assumed that the aqueous phase is well stirred except in the diffusion layer region which is assumed to be effectively stagnant and through which a quasi-steady-state diffusion condition is assumed to exist. At the lipid–water interface instantaneous partitioning is assumed which is governed by a concentration independent lipid-water partition coefficient, *K*. The diffusion coefficient of the solute is given by D_w and D_0 in the aqueous and lipid phases, respectively. The problem is described by the following three equations:

$$V_w\,(dC_{wB}/dt) = -(D_wA/h)\,(C_{wB} - C_{wi}) \qquad \text{(Eq. 1)}$$

$$AD_0\,(\partial C_0/\partial x)_{x=0} = -(D_wA/h)\,(C_{wB} - C_{wi}) \qquad \text{(Eq. 2)}$$

$$dC_0/dt = D_0\,(d^2C_0/dx^2) \qquad \text{(Eq. 3)}$$

where V_w is the volume of the aqueous phase, x is the position coordinate in the lipid, A is the area of the interface, h is the thickness of the aqueous diffusion layer, C_0 is the concentration of solute in the lipid at any given x, and C_{wB} is the aqueous concentration of solute in the bulk aqueous solution. C_{wi} is the aqueous concentration at the interface which is assumed to be equal to C_{0i}/K where C_{0i} is the concentration in the lipid at the interface.

Equation 1 relates the concentration change in the stirred aqueous phase to the rate of solute transport across the aqueous diffusion layer. Equation 2 is the continuity relationship which states that the transport rate in the lipid phase immediate to the aqueous–lipid boundary is equal to the transport rate in the aqueous diffusion

layer. Finally, Eq. 3 is Fick's second law for diffusion in the lipid phase.

Carslaw and Jaeger (22) give the solution to the analogous problem for heat conduction. When this solution is converted to the mass transfer case one obtains the following equations, making the further assumption that the activity of the solute in water is equal to the concentration in the water:

$$C_0 = \frac{D_w C_{w0}}{hD_0(\beta - \alpha)}\left[\exp(\alpha x + D_0 t\alpha^2)\,\mathrm{erfc}\left(\frac{x}{2\sqrt{D_0 t}} + \alpha\sqrt{D_0 t}\right) - \exp(\beta x + D_0 t\beta^2)\,\mathrm{erfc}\left(\frac{x}{2\sqrt{D_0 t}} + \beta\sqrt{D_0 t}\right)\right] \quad \text{(Eq. 4)}$$

$$C_{wB} = \frac{C_{w0}}{\beta - \alpha}\left[\left(\frac{D_w}{hD_0K} - \alpha\right)\exp(D_0 t\alpha^2)\,\mathrm{erfc}(\alpha\sqrt{D_0 t}) - \left(\frac{D_w}{hD_0K} - \beta\right)\exp(D_0 t\beta^2)\,\mathrm{erfc}(\beta\sqrt{D_0 t})\right] \quad \text{(Eq. 5)}$$

where C_{w0} is equal to the initial concentration of solute in the aqueous phase, t is time, and

$$\alpha = {}^1/_2\left[D_w/hD_0K + \sqrt{(D_w/hD_0K)^2 - 4AD_w/V_w hD_0}\right]$$
$$\beta = {}^1/_2\left[D_w/hD_0K - \sqrt{(D_w/hD_0K)^2 - 4AD_w/V_w hD_0}\right]$$

These equations yield imaginary numbers for most of the situations mentioned in this work. These equations were therefore rearranged by expanding the erfc term and thereby the $\sqrt{-1}$ was eliminated in the final solution (Eqs. 6 and 7):

$$C_0 = 2D_w C_{w0}/hD_0K\,[\exp -(x^2/4D_0 t)\,V(q,r)] \quad \text{(Eq. 6)}$$

$$C_{wB} = C_{w0}\left[\frac{D_w\,V(q,r)}{hD_0K\sqrt{|(D_w/hD_0K)^2 - 4AD_w/V_w hD_0|}} + U(q,r)\right] \quad \text{(Eq. 7)}$$

where V and U are functions with the variables q, r, and s:

$$q = \frac{\sqrt{D_0 t}}{2}\sqrt{\left|\left(\frac{D_w}{hD_0K}\right)^2 - \frac{4AD_w}{V_w hD_0}\right|}$$

$$r = \frac{x + D_w t/hK}{2\sqrt{D_0 t}}$$

$$s = \frac{D_w\sqrt{D_0 t}}{2hD_0K}$$

The values for the U and V functions have been compiled by Faddeev and Terentev (23).

The concentration in the water was confirmed by plotting C_0 *versus* x and graphically integrating, obtaining a value called $C_{0\text{Total}}$ for any given time. The concentration at any given time is therefore given by Eq. 8.

$$C_{wB} = C_{w0}(V_w - AC_{0\text{Total}})/V_w \quad \text{(Eq. 8)}$$

Method II—In this method for solving the problem, the lipid sink is given a finite thickness and is divided into $n - 1$ elements, as shown in Fig. 3. At time zero the interfacial concentrations in the oil and water are given initial values. Otherwise the basic assumptions and boundary conditions are the same as those made in the first method.

The following equations apply in Method II:

$$V_w\frac{dC_{wB}}{dt} = -\frac{D_w A}{h}(C_{wB} - C_{0i}/K) \quad \text{(Eq. 9)}$$

$$\frac{D_w}{h}(C_{wB} - C_{0i}/K) = \frac{D_0}{L/2\,(n-1)}(C_{0i} - C_2) \quad \text{(Eq. 10)}$$

$$\frac{dC_{0i}}{dt} = \frac{1}{[D_0/L/2\,(n-1)] + (D_w/hK)} \times \left(\frac{D_w}{h}\frac{dC_{wB}}{dt} + \frac{D_0}{L/2\,(n-1)}\frac{dC_2}{dt}\right) \quad \text{(Eq. 11)}$$

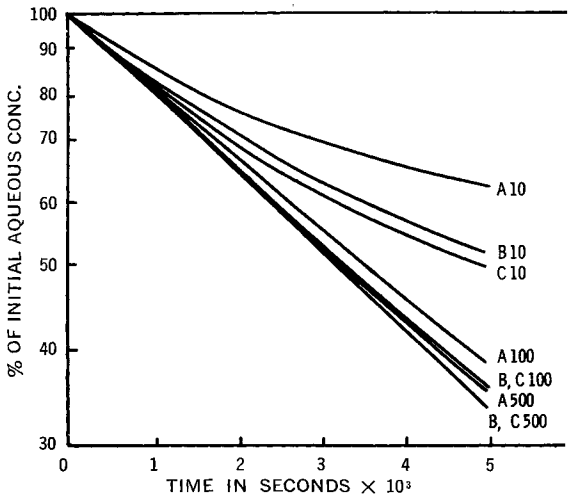

Figure 4—*Theoretical computation demonstrating the effect of the partition coefficient and of the effective diffusion coefficient in the lipid phase, on the concentration changes in the aqueous compartment as a function of time. The numbers adjacent to each curve are the o/w partition coefficients* (K). *The letters adjacent to each curve are the effective diffusion coefficient in the oil phase* (D). *Key:* A = 10^{-6} *cm.²/sec.;* B = 5 × 10^{-6} *cm.²/sec.;* C = 10^{-5} *cm.²/sec.;* V_w = *10 ml.;* h = *0.05 ml.;* L = *0.15 cm.*

$$V_0\frac{dC_2}{dt} = \frac{D_0 A}{L/2\,(n-1)}(C_{0i} - C_2) - \frac{D_0 A}{L/(n-1)}(C_2 - C_3) \quad \text{(Eq. 12)}$$

$$V_0\frac{dC_j}{dt} = \frac{D_0 A}{L/(n-1)}(C_{j-1} - 2C_j + C_{j+1})\; j = 3\ldots n-1 \quad \text{(Eq. 13)}$$

$$V_0\frac{dC_n}{dt} = \frac{D_0 A}{L/(n-1)}(C_{n-1} - C_n) \quad \text{(Eq. 14)}$$

C_2, C_3, ... C_{n-1}, or C_n are the mean concentrations in any of the segments of the oil sink. The thickness of the lipid sink is denoted by L and therefore the thickness of each segment is $L/(n-1)$. All other notations are the same as in Method I.

Equation 9 has the same meaning as that used in Method I. In Eq. 10 the right side denotes the interface transport rate which is equal to the transport rate through the aqueous diffusion layer (left side of the equation). Solving for C_{0i} and differentiating this equation with respect to time gives the rate of change of the interfacial

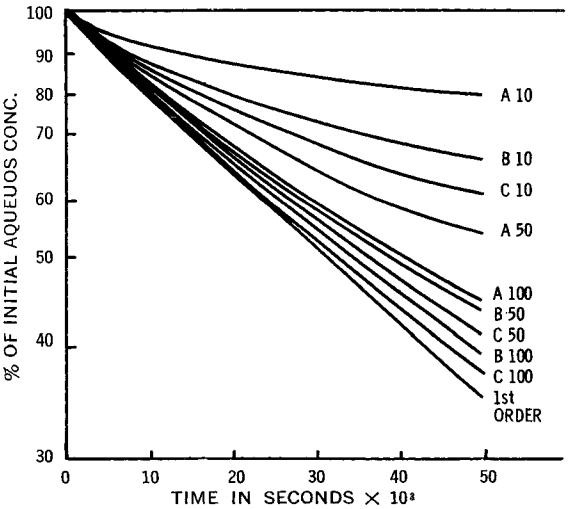

Figure 5—*Theoretical computation demonstrating the effect of the partition coefficient and the effective diffusion coefficient in the lipid phase, on the concentration changes in the aqueous compartment as a function of time. Key:* V_w = *100 ml.,* h = *0.05 cm.,* L = *0.15 cm.*

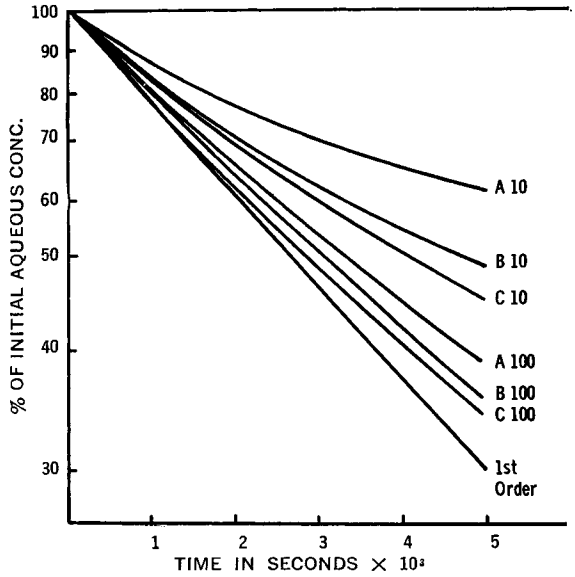

Figure 6—*Theoretical computation demonstrating the effect of the partition coefficient and the effective diffusion coefficient in the lipid phase, on the concentration changes in the aqueous compartment as a function of time. Key:* V_w = *10 ml.;* h = *0.05 cm.;* L = *10 cm.*

lipid concentration (Eq. 11). Equation 12 equates the rate of accumulation of solute in the first lipid element to the difference in the transport rate into and out of this element. Equation 13 is the corresponding relation for the jth element, and Eq. 14 is that for the last element for which the rate out is always zero (a boundary condition). The value given to the interfacial oil concentration C_{0i} at time zero (T_0) is obtained by solving Eq. 10 for C_{0i}. C_2 is equal to zero at this time, and C_{wi} at time zero is equal to C_{0i}/K. The dotted line shows these conditions at time zero.

These equations were solved with the digital computer (IBM 360) by numerical methods involving the Hamming method (24). This was done by first converting these equations to corresponding difference equations (*i.e.*, $(dC_i/dt) \simeq (\Delta C_i/\Delta t)$. Sufficiently small Δt's were taken so that the limiting values were approached.

Method III—This solution is the same as that of Method I except that instead of the infinite oil layer of Method I, the lipid layer now has a finite thickness, L. The problem is described by the same three equations (Eqs. 1, 2, and 3) of Method I, with the addition of the boundary condition that $(\delta C_0/\delta_x)_{X=L} = 0$. Carslaw and Jaeger (22) give the solution to the analogous problem for

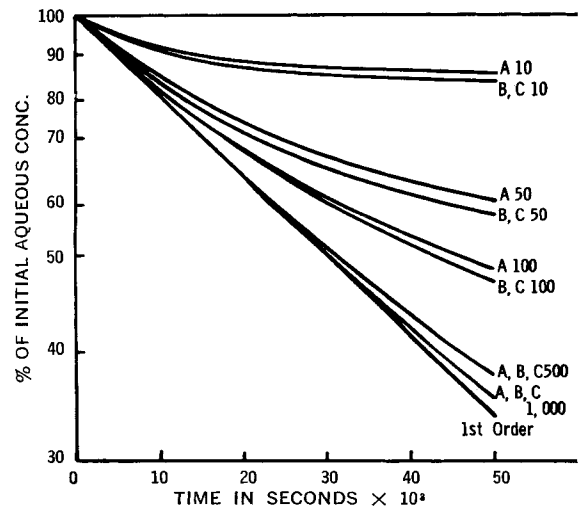

Figure 7—*Theoretical computation demonstrating the effect of the partition coefficient and the diffusion coefficient in the lipid phase, on the concentration changes in the aqueous compartment as a function of time. Key:* V_w = *100 ml.;* h = *0.05 cm.;* L = *10 cm.*

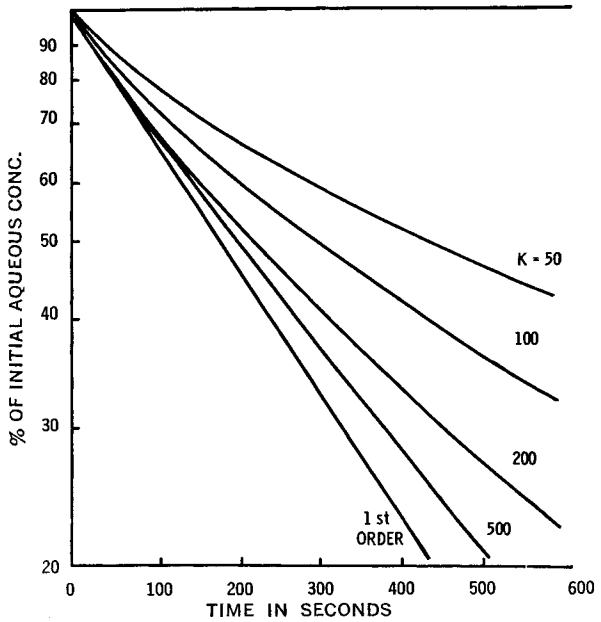

Figure 8—*Theoretical computation demonstrating the effect of the partition coefficient on the concentration changes in the aqueous compartment as a function of time. Key:* V_w = *30 ml.;* h = *0.001 cm.;* L = *1 cm. or 0.1 cm. or* ∞.

heat conduction. When this solution is converted to the mass transfer case, one obtains the following equations:

$$C_0 = \frac{KC_{w0}}{1+W} - 2JC_{w0}K\sum_{s=1}^{\infty}\frac{\alpha_s^2 - WJ}{F_s\cos\alpha_s}\exp(-\alpha_s^2T)\cos\alpha_s(1-x/L) \quad \text{(Eq. 15)}$$

$$C_{wB} = \frac{C_{w0}}{1+W} + 2WJ^2C_{w0}\sum_{s=1}^{\infty}\frac{1}{F_s}\exp(-\alpha_s^2T) \quad \text{(Eq. 16)}$$

where $J = LD_w/hD_0K$, $W = LAK/V_w$, $T = D_0t/L^2$, the α_s are the positive roots of $\tan\alpha = (J\alpha/\alpha^2 - WJ)$, and $F_2 = \alpha_s^4 + (J^2 + J + 2WJ)\alpha_s^2 + WJ^2(1+W)$.

Computation of the numerical solution was obtained using a computer (IBM 360 digital).

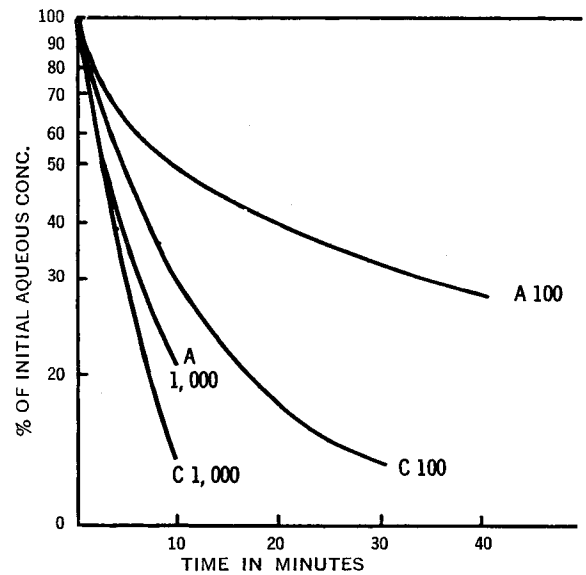

Figure 9—*Theoretical computation demonstrating the effect of the diffusion coefficient of the solute in the lipid phase, on the concentration changes in the aqueous compartment as a function of time. Key:* V_w = *30 ml.;* h = *0.001 cm.;* L = ∞.

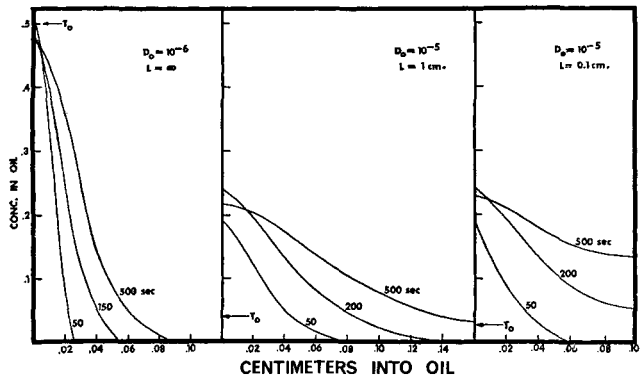

Figure 10—*Theoretical computation of the concentration profile of the solute in the oil phase. The profiles on the left show the effect of a low diffusion coefficient in the oil. The diagram at the far right shows the backup in the oil phase when the total thickness* (L) *in that phase is very small.* T_0 *is the interfacial concentration in the oil at time = 0. The o/w partition coefficient* (K) *is 100 in all cases.*

Results of Computation—The three methods have been employed to compute theoretical solute uptake rates under a variety of conditions for use both in the design of experiments and in the interpretation of experimental results. Figs. 4–10 represent some of these computations under physically realistic conditions. In all of these computations $C_{w0} = 0.01$, $A = 11$ cm.^{2}, $D_w = 10^{-5}$ cm.^{2}/sec. The letters A, B, and C in the figures refer to D_0 values of 1×10^{-6}, 5×10^{-6}, and 1×10^{-5} cm.^{2}/sec., respectively.

Let us consider some properties of the lipid governing the transport behavior. The influence of the lipid-water partition coefficient on the uptake of solute by the lipid sink is shown in Figs. 4–8. Figure 8 shows this effect most dramatically. When K (the numbers next to each curve) is high, the loss of solute from the aqueous compartment is essentially first order. Such behavior is true only when the lipid acts as an essentially perfect sink. It can be seen that as K decreases there is increasing deviation from linearity particularly for the larger t values. Figures 4–7 as well as Fig. 9 similarly show that as the diffusion coefficient in the lipid sink decreases, deviations from linear first-order pickup also occur. Figure 10 helps to explain this deviation from first order. These concentration profiles in the lipid phase show the build-up of solute in the lipid with time. A decrease in the lipid phase diffusion coefficient from 10^{-5} to 10^{-6} increases the interfacial solute concentration in the lipid. This then corresponds to a reduction in the concentration gradient across the aqueous diffusion layer.

Changing the thickness of the oil phase markedly alters the oil profiles. In this case, however, the effect on the interfacial concentration is relatively small and thus the rate of pickup from the water is not greatly affected. When the thickness of the lipid sink is varied from infinity to 0.1 cm., with all else remaining constant, the corresponding water transport profiles (Fig. 8) are essentially unaffected. When Figs. 4 and 5, which have an oil thickness (L) of 0.15 cm., are compared with Figs. 6 and 7, which have an oil thickness (L) of 10 cm., it should be noted that for the larger aqueous volume (V_w), backup (Fig. 10) in the oil sink becomes a major factor especially when the D_0 is large.

The factors associated with the aqueous phase influencing the transport behavior may be grouped in the function $[(D_w A)/h]$. Increasing the thickness of the aqueous diffusion layer (h) lowers this function and thereby reduces the rate of aqueous pickup. Since aqueous diffusion becomes slower, the solute has more time to be removed from the surface. This is so, especially when the partition coefficient and the diffusion coefficient in the oil are fairly high and thus less deviation from first order occurs. However, when the lipid sink is not thick enough, backup occurs regardless of the thickness of the aqueous diffusion layer. When the volume of the aqueous phase is increased the rate of percentage loss of solute from that phase is decreased but the amount of solute leaving is not. Build-up at the interface due to a low diffusion coefficient in the oil or a thin oil layer becomes an important cause for deviation from first-order pickup.

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*Present address: Wyeth Laboratories, Inc., P. O. Box 8299, Phila., PA 19101

†Present address: Tanabe Seiyaku Co., Osaka, Japan.