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COMMUNICATIONS

Total Mathematical Resolution of Diffusion Layer Control of Barrier Flux

Keyphrases ☐ Diffusion layer control -mathematical derivation ☐ Membrane permeability -equations describing diffusion layer control ☐ Derivation- resolution of diffusion layer control, barrier flux

Sir:

Equations describing the flux of a penetrant through a membrane sandwiched between two liquid phases under the conditions where the chemical potential gradient is *virtually* entirely in the diffusion layers (diffusion layer control) were derived. With like solvent on each side of the membrane, these equations confirm that the steady-state flux is only dependent on the applied phase concentration, the diffusivity within the diffusion layers, and the reciprocal of the sum of the diffusion layer thicknesses.

Furthermore, a lag time expression was derived which relates the duration of the nonstationary state to the thicknesses of both the membrane and the diffusion layers, the membrane/solvent partition coefficient, and the reciprocal of the diffusivity within the solvent. This equation is of major theoretical significance because it, along with the relationship of partition coefficient to homolog chain length, indicates that at some point in a homologous series the lag time will begin to grow exponentially. This effect extrapolated to biological systems, *i.e.*, drug absorption and biodistribution, indicates that the activity of a long chain congener may not only be limited by the plateauing of steady-state transport but also by inability to break through the biological barrier(s) in sufficient time to exert an effect. The saliency of this point is heightened when it is realized that metabolism and elimination by filtration may not be similarly affected. Relative potency from biological assays with fixed, timed end-points, *i.e.*, vasoconstriction at 6-hr. postapplication, could be misleading if the time chosen is not relevant to actual drug usage. In short, the lag time dependency alone can suffice as the limiting factor in the structure–activity profile for a series of organic homologs.

Figure 1 describes the physical situation to be treated. It is a concentration profile of a membrane (III) positioned between two homogeneous solvent phases (I and V). Phase I is of relatively high concentration, C_0. C_0 is assumed to remain constant. Phase V is assumed to be a solute sink and thus is maintained at zero concentration. Regions II and IV represent solvent diffusion layers (Nernst layers) contiguous to the membrane surfaces (1–3). The thickness of the diffusion layers (II and IV) are h_{AQII} and h_{AQIV}, respectively, and the membrane is of thickness h_M.

By assuming the concentration curves C_0 to C_1 and C_3 to C_4 to be linear, the flow into (V_1) and out of (V_2) Compartment III, the membrane, may be represented, respectively, by:

$$V_1 = \frac{(C_0 - C_1)}{h_{AQII}} D_{AQ}A \qquad \text{(Eq. 1)}$$

$$V_2 = \frac{(C_3 - C_4)}{h_{AQIV}} D_{AQ}A \qquad \text{(Eq. 2)}$$

where D_{AQ} is the aqueous (solvent) diffusion coefficient, and A is the cross-sectional area available for diffusion. The rate of change of concentration in III is:

$$\frac{dC_{III}}{dt} = \frac{dC_2}{dt} = \frac{1}{h_M A}(V_1 - V_2) \qquad \text{(Eq. 3)}$$

As diffusion layer control is approached, the membrane concentration at each membrane interface becomes imperceptibly different and, thus, $C_2 = (PC)C_1 = (PC)C_3$, where (PC) is the membrane/solvent partition coefficient. The identical assumption is made for the concentration across the diffusion layers under membrane control of flux. For convenience at this point, assume that $h_{AQII} = h_{AQIV}$; then:

$$V_1 - V_2 = \frac{2D_{AQ}A}{h_{AQII} + h_{AQIV}}\left\{C_0 - \frac{2C_2}{(PC)}\right\} = \frac{D_{AQ}A}{h_{AQ}}\left\{C_0 - \frac{2C_2}{(PC)}\right\} \qquad \text{(Eq. 4)}$$

and:

$$\frac{dC_2}{dt} = \frac{D_{AQ}}{h_M h_{AQ}}\left\{C_0 - \frac{2C_2}{(PC)}\right\} \qquad \text{(Eq. 5)}$$

where the term h_{AQ} is the thickness of the individual diffusion layer. With the boundary conditions $C_2 = 0$

at $t = 0$ and $C_0 =$ constant, the solution of this equation is:

$$C_2 = \frac{(PC)C_0}{2}\{1 - e^{-2D_{AQ}t/(PC)h_M h_{AQ}}\} \quad \text{(Eq. 6)}$$

and $C_2 \rightarrow (PC)C_0/2$ as $t \rightarrow \infty$.

The cumulative amount through to Compartment V is given by:

$$M_V = \int_0^t V_2\, dt \quad \text{(Eq. 7)}$$

and since:

$$V_2 = \frac{D_{AQ}C_3A}{h_{AQ}} = \frac{D_{AQ}C_2A}{(PC)h_{AQ}} \quad \text{(Eq. 8)}$$

then, by replacing C_2 by the previous equation and integrating, one gets:

$$M_V = \frac{D_{AQ}AC_0}{2h_{AQ}}\left\{t - \frac{(PC)h_M h_{AQ}}{2D_{AQ}}(1 - e^{-2D_{AQ}t/(PC)h_M h_{AQ})}\right\} \quad \text{(Eq. 9)}$$

As t increases, M_V approaches the straight line:

$$\lim_{t\rightarrow\infty} M_V = \frac{D_{AQ}AC_0}{2h_{AQ}}\left\{t - \frac{(PC)h_M h_{AQ}}{2D_{AQ}}\right\} \quad \text{(Eq. 10)}$$

which extrapolates back to a time axis intercept or lag time of:

$$t_L = \frac{(PC)h_M h_{AQ}}{2D_{AQ}} \quad \text{(Eq. 11)}$$

The slope of the steady-state line (the steady-state flux) is:

$$\text{slope} = F_{ss} = \frac{D_{AQ}AC_0}{2h_{AQ}} \quad \text{(Eq. 12)}$$

Diffusion layer control has been treated so far by assuming diffusion layer thicknesses and diffusivities equal as well as equivalent partitioning into and out of the membrane. This situation could only be expected for identical solvent on each membrane side using a totally symmetrical diffusion cell. A more general solution to the diffusion layer control of flux situation where $h_{II} \neq h_{IV}$, $D_{II} \neq D_{IV}$, and $(PC)_{II} \neq (PC)_{IV}$ may be obtained using the same stepwise procedure. Because of the number of terms, the equations become cumbersome. However, the final expression for M_V is:

$$M_V = \frac{D_{IV}A}{h_{IV}(PC)_{IV}} \cdot \frac{1}{B_1}\left\{t - \frac{1}{B_1B_0}[1 - e^{-B_1B_0t}]\right\} \quad \text{(Eq. 13)}$$

where:

$$B_1 = \left(\frac{D_{II}}{h_{II}(PC)_{II}} + \frac{D_{IV}}{h_{IV}(PC)_{IV}}\right)\Big/\frac{D_{II}}{h_{II}C_0} \quad \text{(Eq. 14)}$$

and:

$$B_0 = \frac{D_{II}C_0}{h_M h_{II}} \quad \text{(Eq. 15)}$$

The general expression for the steady-state slope is thus:

$$F_{ss} = (PC)_{II}AC_0\left\{1\Big/\left[\frac{h_{II}(PC)_{II}}{D_{II}} + \frac{h_{IV}(PC)_{IV}}{D_{IV}}\right]\right\} \quad \text{(Eq. 16)}$$

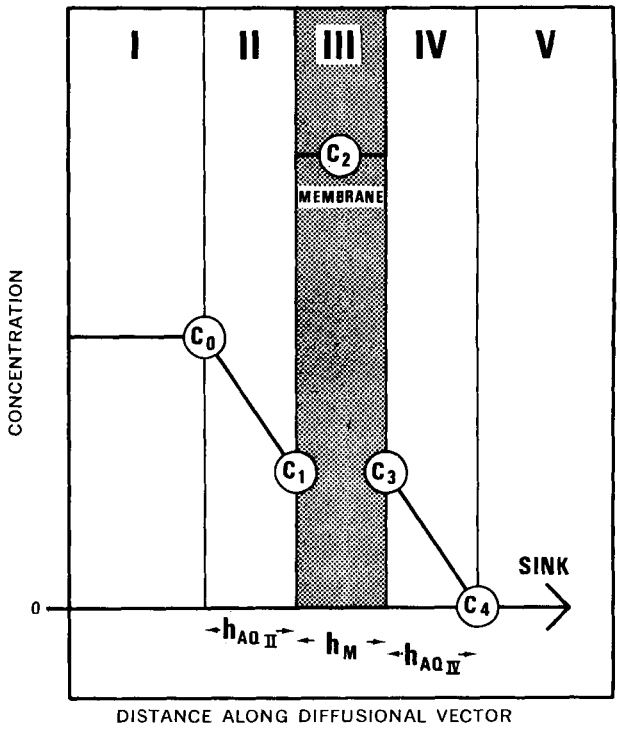

Figure 1—*Concentration profile through a membrane–diffusion layer barrier operating under diffusion layer flux control.*

and the lag time expression is:

$$t_L = h_M\Big/\left[\frac{D_{II}}{h_{II}(PC)_{II}} + \frac{D_{IV}}{h_{IV}(PC)_{IV}}\right] \quad \text{(Eq. 17)}$$

These equations reduce to the previous case when the appropriate terms are made equal.

Under what conditions are the equations actually applicable? Without the membrane interposed (except as a plane about which the diffusion layers are generated, *i.e.*, for an infinitely thin membrane), the lag time based on Daynes' (4) and Barrer's (5) equations would be:

$$t_L = \frac{(\Sigma h_{AQ})^2}{6D_{AQ}} \quad \text{(Eq. 18)}$$

where Σh_{AQ} indicates the sum thickness of the diffusion layers on each side of the membrane.

The first condition of applicability, therefore, is that the lag time, as expressed in Eq. 17, must be much greater than that expressed in Eq. 18, a condition which is certain for virtually all thick membranes. A second condition is that the overall process is in diffusion layer control. By independent derivation, it can be shown that steady-state flux across such a barrier can be expressed mathematically by (6, 7):

$$F_{ss} = PAC_0 \quad \text{(Eq. 19)}$$

where P is the permeability coefficient:

$$P = \frac{(PC)D_M D_{AQ}}{D_{AQ}h_M + (PC)D_M\Sigma h_{AQ}} \quad \text{(Eq. 20)}$$

Diffusion layer control occurs when $(PC)D_M\Sigma h_{AQ} \gg h_M D_{AQ}$, and the flux equation reduces to:

$$F_{ss} = \frac{D_{AQ}AC_0}{\Sigma h_{AQ}} \quad \text{(Eq. 21)}$$

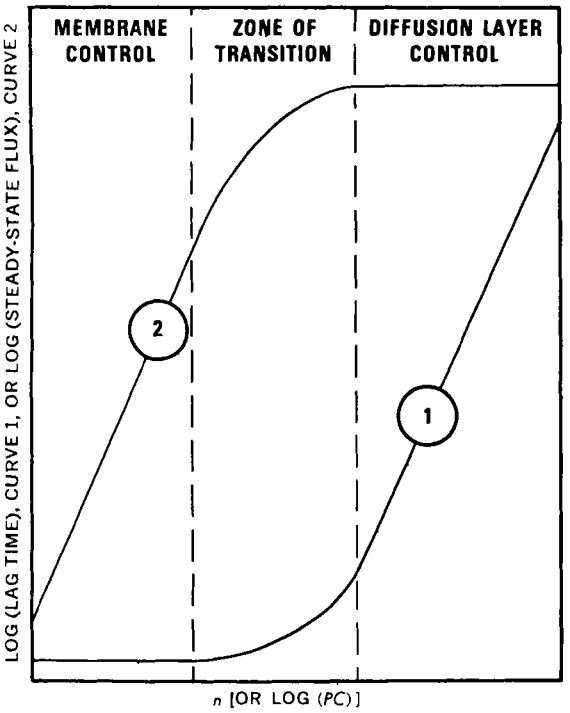

Figure 2—*Plot of the log (lag time), curve 1, or log (equimolar steady-state flux) against carbon number or its equivalent on the dimensionless axis, log* (PC). *If the two* Y*-axis variables are in compatible units, the limiting slope of 1 and the initial slope of 2 will be equal because the partition coefficient dependencies are the same in these regions.*

which will be recognized as being identical to Eq. 12. Thus, the principal condition is that $(PC)D_M\Sigma h_{AQ}$ must dominate the permeability expression. This will occur at some point in a homologous series because the partition coefficient will grow exponentially with chain length (8). Experimental verification will be presented in a subsequent report. For the present, it suffices to say that not only can one expect steady-state flux from equimolar solutions to level off within the series (3, 6), but one can also expect the time of barrier breakthrough to grow exponentially as chain length is increased once diffusion layer control has been attained. This dependency of lag time on chain length, n [or log (PC) which is directly related], is illustrated in Fig. 2. Also included in Fig. 2 for comparison is the relationship for concentration normalized steady-state flux which was previously derived (3). Both curves exhibit a marked change in slope at the crossover to diffusion layer control. The regions of total membrane control and total diffusion layer control are indicated, as is the transition zone between.

In 1963, Barrie *et al.* (9) derived steady-state and lag time equations for gaseous permeation of three-layer composite rubber membranes. The transient-state equation found in this paper can be converted so that it is applicable to the diffusion layer–membrane situation. This may be accomplished by multiplying each term in the equation (numerator and denominator) by S_2, the solubility in the middle layer of the laminate. The S_2/S_1 and S_2/S_3 ratios obtained are equivalent to $(PC)_{II}$ and $(PC)_{IV}$ as defined here. A careful examination of this equation in this form indicates that it reduces to Eq. 18 when $h_M \rightarrow 0$ and to Eq. 11 or 17 if the partition coefficient(s) is(are) large. Thus, when appropriate boundary conditions are placed on the Barrie *et al.* (9) expression, it is in total harmony with the equations derived independently in this report.

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Identification of *o,p'*-Dichlorodiphenyl Acetic Acid as a Urinary Metabolite of 1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane

Keyphrases ☐ 1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane—metabolism, metabolite identification ☐ *o,p'*-Dichlorodiphenyldichloroethane—metabolism, metabolite identification ☐ Mitotane—metabolism, metabolite identification ☐ *o,p'*-Dichlorodiphenyl acetic acid—mitotane metabolite, isolation, characterization, GLC, TLC ☐ GLC—isolation, identification ☐ TLC—isolation, identification

Sir:

The recent FDA approval of mitotane, 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane (*o-p'*-dichlorodiphenyldichloroethane) (I), for treatment of adrenocortical carcinoma and adrenocortical hyperfunction (Cushing's syndrome) prompted this report of the isolation and characterization of *o,p'*-dichlorodiphenyl acetic acid (II) as a urinary metabolite of *o,p'*-dichlorodiphenyldichloroethane in rabbit and man. This result confirms Moy's (1) anticipation of *o,p'*-dichlorodiphenyl acetic acid as the principal metabolite based upon literature reports of the metabolism of the related compound, the insecticide *p,p'*-dichlorodiphenyltrichloroethane (III).

In initial experiments, four rabbits ingested over 11–18 days a total of 1.18–2.13 g. of Compound I, coated with the aid of hexane on food pellets. Results were