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Membrane Diffusion II: Influence of Physical Adsorption on Molecular Flux through Heterogeneous Dimethylpolysiloxane Barriers

G. L. FLYNN and T. J. ROSEMAN

Abstract □ Dimethylpolysiloxane is an isotropic polymer which provides an excellent nonpolar barrier for diffusional studies. Commercial polymer contains appreciable siliceous filler to enhance mechanical properties. Diffusion through pure polymer may be characterized as Fickian, but diffusion through heterogeneous polymer is complex due to adsorption on the active filler. Two solutions integrating Fick's second law with special cases of the Langmuir adsorption isotherm are known. The first solution, Case I, is for the region where adsorption is directly proportional to the local concentration of permeant; Case II applies when the mass of penetrant adsorbed per unit of filler is fixed. The effect of filler in the dimethylpolysiloxane membrane is particularized with respect to these equations. Specifically, lag time relationships indicated that adsorption was linear over the greatest part of the concentration range employed for the specific penetrants, *p*-aminoacetophenone and ethyl *p*-aminobenzoate. These and literature data afforded a complete characterization of the membrane diffusional system with respect to the benzoate ester. Concepts here are general and a similar approach can be used to investigate other heterogeneous barriers, living or synthetic. Attention is particularly drawn to the influence of specific binding on the passage of chemicals through cellular membranes and the skin and to the application of these principles in the design of drug delivery systems.

Keyphrases □ Dimethylpolysiloxane barriers, heterogeneous—influence of physical adsorption on molecular flux, equations □ Diffusion, membrane—physical adsorption influence on molecular flux, heterogeneous dimethylpolysiloxane barriers, equations □ Adsorption, physical—influence on molecular flux, lag time relationships, dimethylpolysiloxane heterogeneous barriers □ Membrane diffusion—physical adsorption effects on flux, using heterogeneous dimethylpolysiloxane barriers

The present study deals in part with membranes containing a dispersed silica phase in a continuum of dimethylpolysiloxane polymer. Holliday (1) suggested that the following three criteria are necessary to define a heterogeneous, two-phased polymeric media: (*a*) the geometry, concentration, distribution, orientation, *etc.*, of the dispersed phase; (*b*) the composition or state of matter of the dispersed phase; and (*c*) the composition and state of matter of the continuous phase. In the current study, emphasis is also drawn to the character of the dispersed phase surface; hence, a fourth criteria for characterization is: (*d*) the extent, composition, and properties of the dispersed phase surface or dispersed phase–continuous phase interface.

The dimethylpolysiloxane membranes employed are presumed to contain between 20 and 30% fumed silica filler. The dispersed phase has a large and active surface per unit volume, is randomly oriented, may be considered to be heterogeneous in size (within limits), and is impervious to the diffusing species.

The polymer forming the continuum is an elastomeric silicone rubber which, by itself, has little mechanical strength. It forms an isotropic medium around the filler. It exists above its glass transition point and is without crystallinity at the moderate temperatures of the experiments. Previous investigators (2–5), studying diffusion through dimethylpolysiloxane barriers, found Fick's first law strictly obeyed while Fick's second law was also applicable in limited cases with pure polymer. These membranes have little or no tendency to imbibe water. This noncellulosic quality makes them attractive as membranes for simulation of the drug-transport phenomenon. Fillers, typically silicas or graphites, are incorporated into rubbers to provide mechanical strength. The improved properties result from strong particle–polymer physical interactions, the polymer likely having multiple-site attachment on the particulate surface (6). This implies that significant portions of the dispersed phase surface are occupied by polymer and are unavail-

able for adsorption of additional species. Due to the translational kinetic energy of polymer segments, the available surface at the microscopic level will be in a state of flux, although the total available adsorbing surface at the isothermal condition will be statistically constant.

In the present studies, it is assumed *a priori* that the continuum is little affected by the presence of the filler and that diffusion through the external phase will be unchanged qualitatively and quantitatively on the molecular level. These assumptions are not meant to discount the gross effects of reduced volume available for diffusion and increased averaged diffusional pathlength or tortuosity, τ. Stationary-state transport would be expected to be directly proportional to the continuous phase volume fraction, V_1, and inversely proportional to τ (7). The latter factor also exerts influence on nonsteady-state diffusion.

In the case of fumed silica in dimethylpolysiloxane, another factor is operative in altering and lengthening nonstationary-state barrier penetration; this factor is physical adsorption on the filler surface (3). At any plane in the membrane perpendicular to the vector of diffusion, a transitory equilibrium between diffusant, polymer, and available siliceous surface must be established, partially at the expense of further penetration. Lag times are lengthened, and typical treatment of the diffusional curve generates values for diffusion constants or diffusivities that are significantly distorted. For complex adsorption isotherms, simultaneous solution of Fick's laws with adsorption phenomena are generally not tractable (7). However, Finger *et al.* (8) and Higuchi and Higuchi (7) provided two solutions for special cases of Langmuirian adsorption. They designated as Case I the situation where adsorption is strictly linear with concentration and as Case II the situation where adsorption is constant per unit filler. These solutions are for the extremes of the isotherm. The present studies constitute application and extension of these concepts using heterogeneous dimethylpolysiloxane barriers.

EXPERIMENTAL

Materials—Dimethylpolysiloxane membranes[1] were cut to size for the diffusion cell with a specially made die and washed carefully with deionized water. These membranes were then stored under distilled water until an experiment was initiated, at which time they were again thoroughly rinsed and placed in the diffusion cell. In each complete experiment, the membranes received identical treatment; but from one total experiment to another, storage times in water varied.

Fillerless silicone polymer[2] membranes were prepared in these laboratories. Dimethylpolysiloxane was polymerized between two metal plates separated by 0.051-cm. spacers. Circular membranes were cut as previously described and thoroughly rinsed prior to insertion in the diffusion cell.

The permeants, *p*-aminoacetophenone[3] and ethyl *p*-aminobenzoate[4], were obtained in a highly refined state and were used as received. Deionized water was the sole solvent used in preparing the permeating solutions and the receptor phase.

Equipment—A specially designed diffusion cell, with horizontal placement of compartments and stirring planar with the plane of diffusion, was employed. Particulars concerning the operation of this cell were recounted previously (9). Appearance of diffusant in the receptor compartment was monitored continuously by a spectrophotometer[5] equipped with a flow cell and a 12.7-cm. (5-in.) recorder. Circulation to the flow cell was accomplished by either a proportionating pump[6] or a 23-r.p.m. pump[7], providing flow rates of approximately 2 and 15 ml./min., respectively. The latter was also used in connection with an external donor reservoir in some experiments. Concentrations of diffusing species in the donor phase were determined on a recording spectrophotometer[8].

Procedures—Donor phase solutions were prepared in either of two ways depending on the experimental design. In runs where no external donor reservior was used, excess permeant was equilibrated with water at 37° in a shaker bath. These solutions, including some excess solid, were then transferred *via* a 30-ml. syringe as rapidly as possible to the donor compartment of the diffusion cell, also maintained at 37°. Overflow was piped through a tube to a beaker and discarded.

For runs at concentrations less than saturation, a reservoir or 300-ml. capacity external-jacketed cell was employed. A weighed amount of permeant was placed in the external cell, and either 150 or 300 ml. of deionized water was added, depending on the desired concentration. This solution was stirred with a magnetic stirring bar until all the drug was in solution and the temperature reached 37°. Approximately 18 ml. of the reservoir solution was placed in the donor compartment by syringe, the reservoir was connected to the diffusion cell ports, and its contents were circulated through the cell at 15 ml./min., allowing for a complete change in donor solvent approximately each minute.

In all cases, penetrant, essentially as the free base, was collected in neutral deionized water. Analyses of concentrations on the receptor side indicated that the receptor concentration never exceeded 10% of the most dilute donor concentration and was generally in the 0.1–1% range of that in the applied phase. Therefore, sink conditions existed. Excess drug in the donor compartment or the presence of the external reservoir at subsaturation assured essentially constant donor concentration for a given run.

Calculations—Lag times were obtained by extrapolation of the steady-state portion of the diffusional curves to the time axis. Distances along this axis were measured to the nearest $^1/_{64}$ in. Chart speeds were either 2.54 cm. (1 in.)/min. or 0.25 cm. (0.1 in.)/min., affording estimation of lag times to the nearest second or 10 sec., respectively. An averaged mechanical lag time, the time for the cell contents to be pumped into the lightpath of the spectrophotometer, was determined for each pumping velocity and subtracted from the observed gross value. Mechanical lag times were 15.5 sec. at 15 ml./min. and 1.25 min. at 2 ml./min.

Steady-state slopes were obtained graphically in units of absorbance per minute. These were converted to total steady-state flux, Q_T, in milligrams per second by Eq. 1, using independently determined molar absorptivities, a_m, of 16,800 and 17,200 for *p*-aminoacetophenone and ethyl *p*-aminobenzoate, respectively, a receptor cell volume of 17.8 ml., and the appropriate molecular weight, *MW*:

$$Q_T = \frac{(A/\text{min.}) \times 0.0178 \times MW}{a_m \times 60} = \text{mg./sec.} \qquad \text{(Eq. 1)}$$

The apparent permeability coefficient, P', was calculated from:

$$P' = Q_T \times \frac{h}{AC^0} \qquad \text{(Eq. 2)}$$

where h is the membrane thickness, A is cross-sectional area (10 cm.^{2}), and C^0 represents the concentration in milligrams per milliliter in the applied phase.

Apparent diffusivities were obtained from the lag time relationship of Daynes (10) and Barrer (11):

$$D' = \frac{h^2}{6t_L} \qquad \text{(Eq. 3)}$$

where D' represents the apparent diffusivity, and t_L is the corrected

[1] Silastic sheeting, Dow Corning, Midland, Mich. Dow Corning Medical Products Bulletin 14-184.
[2] Gift from Dow Corning, Midland, Mich.
[3] Eastman Organic Chemicals.
[4] Aldrich Chemical Co.
[5] Beckman DB.
[6] Technicon Autoanalyzer, model 1.
[7] New Brunswick Scientific, model PA-23.
[8] Cary 11.

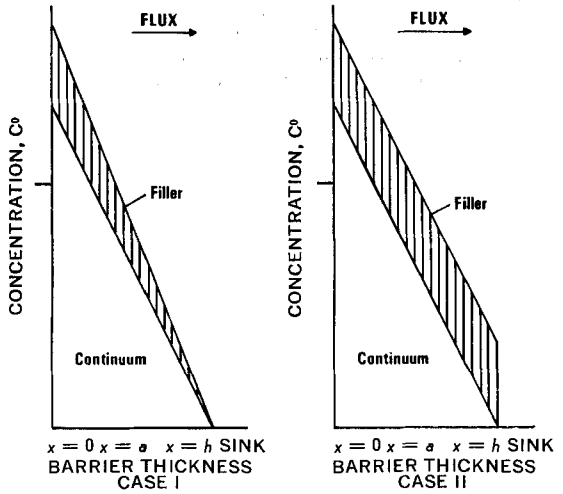

Figure 1—*Plot showing developing concentration gradients in heterogeneous barriers governed by Case I and Case II behaviors, respectively. The crosshatched area represents sorbed permeant; the open area represents the concentration gradient in the continuum. For a given permeant and polymer, the gradient in the polymer would be independent of filler amount and sorption mechanism in the ideal case.*

extrapolated lag time. Apparent partition coefficients, represented by $k_{app.}$, were obtained from the ratio of P' to D'. Steady-state fluxes per unit area, Q, are used in the tables and graphs, and these are exactly an order of magnitude less than the total steady-state flux due to the 10-cm.^{2} membrane cross-sectional area.

THEORETICAL

Diffusion of a molecule through a liquid in the absence of any mixing force requires the formation of a molecular-sized void or hole in the liquid. The energy for formation of a hole is considerable and has been equated with the energy expended in evaporating a molecule of solvent (12). It has been reasoned that a solute molecule occupies each hole formed to which it has access because it would be oscillating 10^{12}–10^{13} times a second and have many kinetic thrusts in the direction of any given hole during the hole's lifetime (13). Thus, the movement of mass through a liquid is dependent on the frequency of hole formation of sufficient size to accommodate the diffusing species. For large molecules relative to the solvent, several solvent molecules must be simultaneously displaced to form occupiable voids. This is the basis for the molecular radius dependency of the diffusion coefficient.

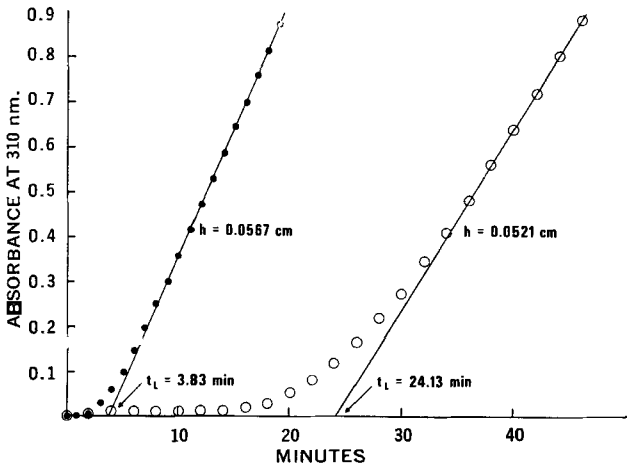

Figure 2—*Diffusional curves as a function of time for the appearance of* p*-aminoacetophenone through pure dimethylpolysiloxane membrane* (●) *and membrane containing filler* (○). *Runs were at 37°. Due to a holdup time in the flow cell lines, the true lag time is 15.5 sec. less than the indicated intercepts.*

Molecular flux through continuous polymer is analogous to flux through liquids. In this case, molecular voids are formed by the random oscillation of polymeric units (14). Hydrogen and other small molecules may require only monomeric unit displacements. Larger diffusional species need cooperative oscillations, possibly involving polymer segments containing tens of units. Obviously, the degree of interaction between polymer chains is a major determinant for the mobility of segments, the ease of hole formation, and, thus, the diffusivity of molecular species. Two factors seriously complicate this simple diffusional model for many polymers: polymer crystallinity and the presence of large percentages of imbibed solvent. Crystallinity introduces regions of very low diffusivity relative to the diffusivity in the surrounding amorphous mass. At a minimum, solvent tends to facilitate the oscillation of polymeric segments by reducing chain interactions (plasticization) and changing permeability. In the extreme, solvent may actually become the diffusional medium itself. Because silicone elastomer is above its glass transition point (point of appearance of crystallinity) at ambient temperature and solvent (water) is denied access by the polymer's physical–chemical nature, these complexities are absent in the present case and this description of diffusion is applicable.

The presence of filler in dimethylpolysiloxane barriers severely complicates interpretation of diffusional data. Most (3), using membranes similar to those employed here, demonstrated that lag times could be increased about 15-fold by as little as 25% by weight silica filler. Changes in stationary-state flux were proportional to the increase in filler content from 0 to 25%. If the assumption that diffusion through the continuum is unaffected by the presence of the filler is strictly true, then the attrition in flux with increasing filler content is attributable only to tortuosity and decreased external phase volume fraction. It is obvious from Most's data (3) that decreasing the volume fraction, V_1, accounts for most of the lost flux and that tortuosity cannot be appreciably greater than 1 (Table IV). For membranes containing inert filler, lag times obtained from typical diffusion curves would be independent of either V_1 or V_2, the respective volume fractions, but dependent on the tortuosity squared as the effective membrane thickness, H, would be equal to τh and the Daynes (10) and Barrer (11) lag time equation would become:

$$t_L = \frac{H^2}{6D} = \frac{\tau^2 h^2}{6D} \qquad \text{(Eq. 4)}$$

A tortuosity of about 4 would be required to produce the expanded lag times observed by Most (3), and this is totally inconsistent with the steady-state data. Identical phenomena were observed in the present studies.

Sorption by the filler provides the only explanation consistent with all facets of the known diffusional behavior. For silica filler, this role is limited to a surface interaction. Although filler phenomena have been widely studied in the rubber industry because of their practical importance there, the only successful attempts to quantitate the actual involvement of active filler were made by Higuchi and Higuchi (7) and by Finger *et al.* (8). These investigators derived equations for the influence of Langmuir adsorption on the movement of penetrant through a heterogeneous barrier. The Langmuir (15) isotherm is:

$$\frac{x}{m} = \frac{abC}{1 + bC} \qquad \text{(Eq. 5)}$$

where x/m is the amount of material adsorbed per unit weight of filler, a and b are constants, and the C is concentration of the equilibrium phase. Lag time equations have been derived for the cases where $1 \gg bC$ and $x/m \simeq abC$ (I) and where $bC \gg 1$ and $x/m \simeq a$ (II). The derived expressions are:

$$\text{Case I} \qquad t_L = \frac{h^2}{6D}(V_1 + KV_2) \qquad \text{(Eq. 6)}$$

$$\text{Case II} \qquad t_L = \frac{h^2}{D}\left(\frac{1}{4} + \frac{K'V_2}{2k_p C^0 D}\right) \qquad \text{(Eq. 7)}$$

Previously undefined terms are K and K', which are constants related to the filler adsorptive capacity; C^0, which is the concentration in the applied (donor) phase; and k_p, which is the true membrane continuum/water (solvent) partition coefficient. A significant modification of the Case I equation is to be advanced in this report.

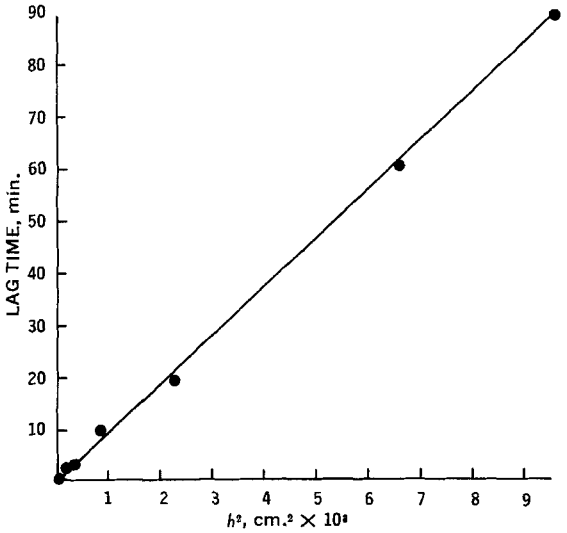

Figure 3—*Plot of lag time,* t_L, versus *the square of membrane thickness,* h^2. *Good correlation is evident for membranes ranging in thickness from* 7.6×10^{-3} *cm. (76 μ) to* 9.80×10^{-2} *cm. (980 μ).*

The mechanisms implicit in these equations may be differentiated by the donor phase concentration dependency in Case II. Total and partial concentration gradients for the two cases in a hypothetical barrier are depicted in Fig. 1. These are arbitrarily drawn to a point $x = a < h$, where x is the distance perpendicular to the diffusional plane. Since a, the point of furthest penetration, is less than h, these are drawn for $t < t_L$. The total area, open and shaded, reflects the total barrier concentration. The shaded area is that portion of the total gradient attributable to adsorption, while the open area represents the gradient in the continuum. It can be seen that at every plane in the barrier up to point a, adsorption is fixed in Case II but proportional to C_x in Case I. Thus, in Case I the concentration at the furthermost point of penetration is zero. This will be true for all $a < h$ and also for $a = h$ when there is a receptor sink. In Case II, a finite concentration entirely due to adsorption exists at a. Finger *et al.* (8) observed Case II behavior for a system in which silica was dispersed in white petrolatum. The present studies, on the other hand, are concerned more with relationships evolving from Case I. The limit as $K \to 0$ for the literature Case I expression is:

$$\lim_{K \to 0} t_L = \lim_{K \to 0} \left[\frac{h^2}{6D} (V_1 + KV_2) \right] = \frac{h^2 V_1}{6D} \qquad \text{(Eq. 8)}$$

implying a volume fraction dependency even for inert filler. It is easy to construct models where V_1 is small; there is no tortuosity to complicate issues and significantly shortened lag times are predicted, *i.e.*, a membrane containing a high volume fraction of inert cylindrical rods oriented perpendicular to the diffusional plane. Facilitation of diffusion leading to reduced lag times is not possible in such circumstances because the lag time would be insensitive to both concentration and area available for diffusion. Actually, the lag time obtained in this example should be exactly equal to that for pure membrane. Thus, Eq. 6 is not strictly applicable, particularly at low values of K.

The Higuchi and Higuchi (7) ratio for Case I lag times focuses on the amount of penetrant in filled membrane relative to fillerless barrier. Total concentration *per se* does not influence the lag time, but the amount of penetrant lost to the adsorbing surface relative to that diffusing in the continuum does. When comparing fillerless and filled membrane, this may be represented as the ratio of the concentration gradients. The respective gradients at any $x = a \leq h$ would be:

$$\text{fillerless} = \frac{C_i - C_a}{a} \qquad \text{(Eq. 9)}$$

$$\text{filled} = \frac{(C_i + BC_i) - (C_a + BC_a)}{a} \qquad \text{(Eq. 10)}$$

where B is a constant proportional to the amount of filler and its ability to adsorb penetrant, C_i is the membrane concentration at the donor membrane interface, and C_a is the membrane concentration at point a; B may be expressed as KV_2, where K is the sorptive capacity and V_2 is the filler volume fraction. For the conditions of a receptor sink, C_a will be zero for all a and the ratio of filled to fillerless gradient will be equal to $1 + KV_2$. Based on this reasoning, the Case I lag time expression is:

$$t_L = \frac{h^2}{6D} (1 + KV_2) \qquad \text{(Eq. 11)}$$

Equation 11 correctly predicts a lag time dependency on only h and D when $K \to 0$ and is used exclusively in all further analysis. Equations 6 and 11 are essentially identical for large values of K. In addition, to be strictly accurate, h may need modification to take into account increased diffusional distance resulting from a nonlinear diffusional pathway (tortuosity).

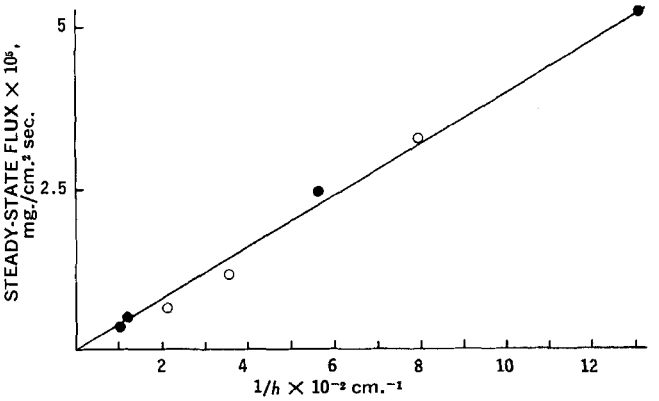

Figure 4—*Plot of steady-state flux,* Q, *against the reciprocal of membrane thickness,* 1/h, *for saturated dose solutions at 37°. The open data points* (○) *indicate nonreinforced membranes; the solid circles* (●) *indicate nylon-reinforced barriers. The nylon obviously had little effect on the permeation velocity.*

EXPERIMENTAL RESULTS

Absorbance changes in the receptor compartment of the diffusion cell accompanying the passage of *p*-aminoacetophenone through a pure dimethylpolysiloxane membrane, 0.0567 cm. in thickness, and a commercially available silica-filled membrane, 0.0521 cm. in thickness, are shown in Fig. 2. The thicknesses were determined at the cessation of each run by the method of Garrett and Chemburkar (2) and represent an average of 10 individual measurements, each at a different location on the membrane surface. It is immediately apparent from Fig. 2 that the lag time was lengthened in the presence of the filler without a correspondingly large decrease in the stationary-state flux. Lag times require correction by 15.5 sec. in this case and were actually 214 and 1430 sec. for fillerless and filled membranes, respectively, in these runs. Data from runs using homogeneous membranes furnish valid values for the specific diffusivity, D, as D' in Eq. 3 becomes D. The average value of D obtained in this manner for *p*-aminoacetophenone was 2.44×10^{-6} cm.²/sec. at 37°. The average value for the permeability coefficient for pure membrane was 7.83×10^{-8} cm.²/sec. The true dimethylpolysiloxane/water partition coefficient for the *p*-aminoacetophenone is calculable from the ratio of P to D and is 3.21×10^{-2}. Furthermore, since saturated aqueous solutions were introduced into the donor compartment, the product of the partition coefficient and the independently determined aqueous solubility yields the dimethylpolysiloxane solubility: 0.317 mg./ml. This latter calculation is valid only if the thermodynamic activity at the membrane–solution interface is the same as in the bulk of the donor solution; *i.e.*, there is no concentration drop across a diffusion layer. Detailed proof that this requisite was met will be provided in a future article. Because the permeability coefficient, P, for fillerless membranes is equal to the product of the specific diffusivity and partition coefficient, Dk_p, but the apparent permeability coefficient, P', for heterogeneous membranes must be adjusted for filler volume fraction and tortuosity:

$$P' = Dk_p \frac{(1 - V_2)}{\tau} = Dk_p \frac{V_1}{\tau} \qquad \text{(Eq. 12)}$$

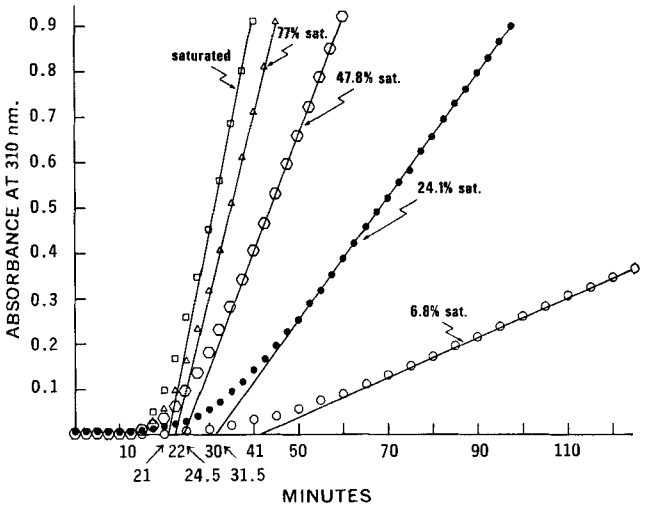

Figure 5—*Absorbance changes at 310 nm. accompanying the diffusion of* p-*aminoacetophenone through dimethylpolysiloxane membranes. The respective curves are for applied phase concentrations of: 9.89 mg./ml. (saturation),* □*; 7.68 mg./ml.,* △*; 4.72 mg./ml.,* ○*; 2.38 mg./ml.,* ●*; and 0.67 mg./ml.,* ○.

it is possible to estimate the ratio of V_1/τ for filled membranes. The average experimental value for *p*-aminoacetophenone was found to be 6.1×10^{-8} cm.²/sec.; P'/P is therefore about 0.78. The permeability was only reduced by roughly 20% by the presence of the filler, while the lag time was extended by a factor of about 7 (Fig. 2).

As a check on the system, a plot of lag time *versus* h^2 for membranes of different thickness should yield a straight line (Eqs. 7 and 11). This is shown in Fig. 3 for *p*-aminoacetophenones, where lag time data for the permeation of a series of membranes varying in thickness from 7.6×10^{-3} to 9.8×10^{-2} cm. are presented. Some of these membranes were reinforced with a nylon netting. Sorption by the netting was assumed to be negligible and, therefore, its presence was not expected to influence lag times (Eq. 11). This appeared to be the case. It was, of course, assumed that the silica/dimethylpolysiloxane ratio was unchanged. Lag times were observed to increase as immersion in water was increased. In the cases of long exposures, a slippery, rinsable film formed on the membrane surface, suggesting some material was leached from within. Because of this variation, membranes deliberately received uniform water treatment and were stored overnight under water and rinsed thoroughly prior to making each run.

In Fig. 4, stationary-state fluxes from the same diffusional runs are plotted against the reciprocal of membrane thickness, $1/h$. A linear relationship was observed despite the presence of nylon reinforcement in several of the barriers, suggesting that the volume fraction occupied by the netting is small and may be discounted. The linearity of steady-state flux to $1/h$ is to be expected only when the total barrier to diffusion exists within the membrane itself. Otherwise, significant deviations would be experienced as thickness is reduced due to relatively increased diffusion layer contributions to the diffusional resistance. However, no significant deviations were experienced. This is attributable to the small solvent/membrane partition coefficient and a greater diffusion coefficient in water relative to the dimethylpolysiloxane barrier.

The two simultaneous solutions of Fick's law and special cases of Langmuir adsorption as expressed in lag times have been given (Eqs. 7 and 11). These two cases can be differentiated by concentration dependency. Therefore, studies were initiated to determine the concentration dependency for *p*-aminoacetophenone and also ethyl *p*-aminobenzoate. In Fig. 5, plots of the raw diffusional curves for *p*-aminoacetophenone are presented for runs at 310 nm., 37°, and varied applied phase concentration ranging from about 7% saturation to saturation, using 0.0476-cm. membranes. It is readily seen that lag times increased with declining concentration. While lag times doubled between the extremes of concentration, the lag time at about 50% saturation was barely distinguishable from that at saturation. The diffusion profile data for all concentrations employed are summarized in Table I. When these data are plotted as lag time *versus* percent saturation (Fig. 6) and compared with the theoretical curves for Cases I and II, it is apparent that although

Table I—Concentration Dependency Data for Permeation of *p*-Aminoacetophenone through 0.0476-cm. Dimethylpolysiloxane Membranes at 37°

Run	Concentration, mg./ml.	Percent Saturation	Corrected Lag Time, min.	Steady-State Flux × 10^5, mg./cm.²/sec.	$D' \times 10^7$, Apparent Diffusivity, cm.²/sec.
1	9.89	100	19.75	1.245	3.19
2	9.73	98.2	22.5	1.130	2.80
3	9.40	95.1	21.25	1.092	2.96
4	7.93	80.2	21.75	0.898	2.89
5	7.06	71.4	19.75	0.964	3.18
6	6.77	68.4	23.25	0.803	2.71
7	5.43	54.9	24.25	0.676	2.60
8	4.70	47.6	23.55	0.689	2.67
9	4.07	41.2	22.25	0.530	2.83
10	4.07	41.2	23.0	0.654	2.74
11	2.67	26.9	29.75	0.396	2.12
12	2.45	24.8	27.5	0.383	2.29
13	2.38	24.1	30.75	0.367	2.05
14	1.33	13.5	35.0	0.216	1.80
15	1.27	12.9	32.5	0.238	1.94
16	0.667	6.7	40.0	0.118	1.57
17	0.350	3.5	40.0	0.062	1.57

Table II—Concentration Dependency Data for Permeation of Ethyl *p*-Aminobenzoate through 0.0476-cm. Dimethylpolysiloxane Membranes at 37°

Run	Concentration, mg./ml.	Percent Saturation	Corrected Lag Time, min.	Steady-State Flux × 10^5, mg./cm.²/sec.	$D' \times 10^7$, Apparent Diffusivity, cm.²/sec.
1	1.735	100	9.8	2.42	6.15
2	1.735	100	10.0	2.23	6.03
3	1.60	92.3	10.3	2.11	5.85
4	1.47	84.7	10.5	2.04	5.74
5	1.33	76.9	9.7	1.98	6.21
6	1.20	69.3	10.8	1.77	5.58
7	1.07	61.6	11.0	1.53	5.48
8	0.935	53.9	10.8	1.51	5.58
9	0.800	46.2	12.0	1.28	5.02
10	0.668	38.5	12.6	0.994	4.78
11	0.533	30.7	12.3	0.847	4.90
12	0.400	23.1	14.4	0.603	4.18
13	0.267	15.4	15.9	0.464	3.79
14	0.133	7.69	17.5	0.198	3.44

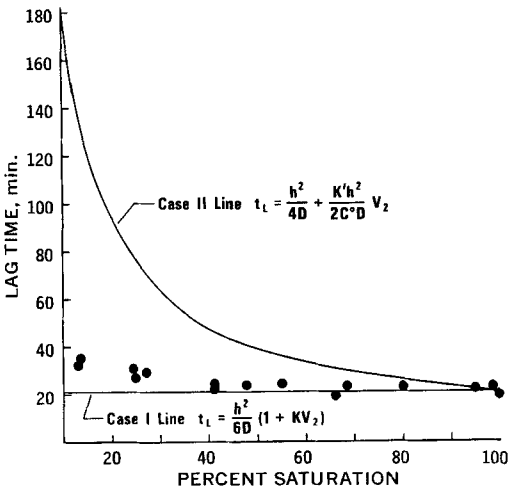

Figure 6—*Plot showing lag time as a function of applied phase concentration for* p-*aminoacetophenone at 37° using 0.0476-cm. membranes. Theoretical lines representing Case I and Case II behavior are superimposed on the plot. These lines were calculated assuming the saturation lag time value, 21.3 min., to be exact.*

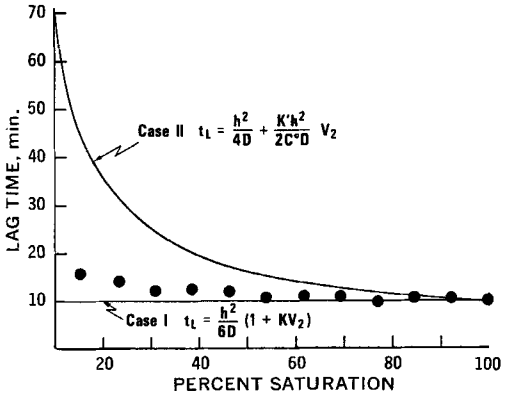

Figure 7—*Plot showing lag time as a function of applied phase concentration for ethyl* p*-aminobenzoate at 37° using 0.0476-cm. membranes. In this case the theoretical lines for Case I and Case II behavior are calculated assuming the 10-min. saturation lag time to be exact;* D *used in these calculations was 2.67 × 10^{-6} cm.² sec.*

Case I is not strictly followed over the entire concentration range, Case II is clearly not applicable. Actually, Case I is a reasonable approximation of the observed diffusional behavior, particularly above 40% saturation. The theoretical curves are based on a 21.3-min. lag time at saturation, an average value for the membranes as processed, and this value is assumed to be exact.

To compare these data with literature data for ethyl *p*-aminobenzoate (3), a similar concentration dependency was initiated for this permeant. The results are summarized in Table II. In Fig. 7, the corrected lag times are plotted against the percent saturation. As in the previous situation, Case I dependency was observed, at least to concentrations less than half-saturation. At the lowest concentrations, lag times deviated from strict Case I behavior. Case II is again completely inconsistent with the experimental data. In this plot, the theoretical curves are drawn assuming the saturation lag time of 10 min. to be correct. Runs were at 37°, using 0.0476-cm. membranes.

It is expected that processes involved in adsorption in the stationary state will be in facile equilibrium with diffusional processes and that steady-state flux for a given membrane thickness will be unaffected by adsorption and only reflect the relative concentration in the applied phase. As seen in Fig. 8 for *p*-aminoacetophenone and in Fig. 9 for ethyl *p*-aminobenzoate, this appeared to be strictly true only at low concentration. At the higher concentrations employed, there were significant deviations from linearity for the ketone and some slighter curvatures for the less water-soluble ester. The deviations are in the right direction to be attributed to the appearance of significant solute–solute interactions. If the total solubility reflects some self-interaction, then activity coefficients would decrease as saturation is approached and account for curvature in either case.

DISCUSSION

Fusion of intermediate Langmuir adsorption behavior or more complex isotherms with Fick's law is not generally manageable. Fortunately, in the present studies the experimental data reasonably fit a relationship for which adsorption is linear with concentration. Under this situation, the Case I adsorption model allows extrapolation of data as a function of filler concentration and adsorptive capacity. Finger *et al.* (8) and Higuchi (16) provided the nonstationary-state relationships governing the permeation of filled systems considered under Case I. When the partition isotherm is linear, Fick's second law need only be modified to account for the amount of permeant adsorbed relative to the concentration in the continuous phase. This factor is directly proportional to the ratio of total concentration gradients in filled and pure systems and leads to the lag time expression given in Eq. 11.

The concentration independence of lag time in Case I has already been stressed, but several other features of this relationship are worthy of note. Lag times are related to the square of the barrier thickness as is the case for homogeneous barriers and Case II as well. Thus, if the simple lag time relationship is applied to the heterogeneous barrier with active filler, an apparent diffusivity is

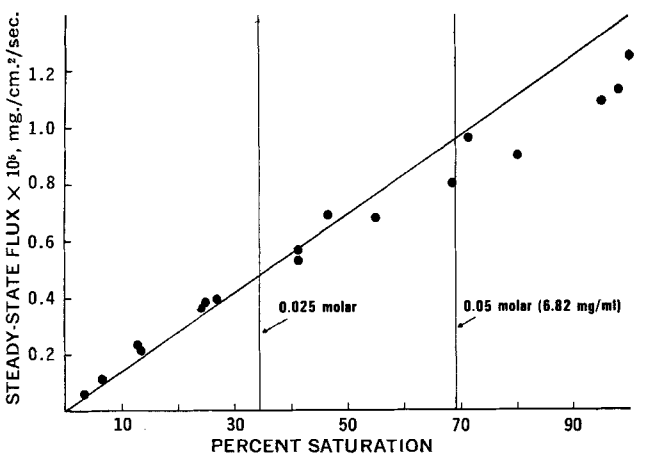

Figure 8—*Plot showing the influence of applied phase concentration of* p*-aminoacetophenone on steady-state flux at 37°. Theoretically, a linear dependency is expected, but there are obvious deviations at high concentrations. Membranes were 0.0476 cm. thick.*

obtained which is independent of membrane thickness for a given filler at a given concentration. The relationship of the apparent diffusivity, D', to more fundamental parameters is given in Eqs. 13 and 14:

$$t_L = \frac{h^2}{6D'} = \frac{h^2}{6D} + \frac{Kh^2}{6D} V_2 \qquad \text{(Eq. 13)}$$

$$\frac{1}{D'} = \frac{1}{D} + \frac{K}{D} V_2 \qquad \text{(Eq. 14)}$$

It can be seen from Eq. 13 that a plot of lag time divided by h^2 against filler volume fraction, V_2, should yield a straight line with an intercept of $1/6D$ and a slope of $K/6D$. Theoretically, one can determine the true diffusion coefficient with membranes of different filler fractions by this method. Similarly, a plot of $1/D'$ *versus* V_2 yields a line with an intercept at $1/D$ and a slope of K/D, again providing estimation of both K and D. The solution of Eq. 14 for D' results in:

$$D' = \frac{D}{1 + KV_2} \qquad \text{(Eq. 15)}$$

Hence, D' is hyperbolically related to V_2.

Two methods are used for estimating diffusivities in polymers: the lag time method in which they are directly calculated and steady-state permeability coupled with equilibrium partition co-

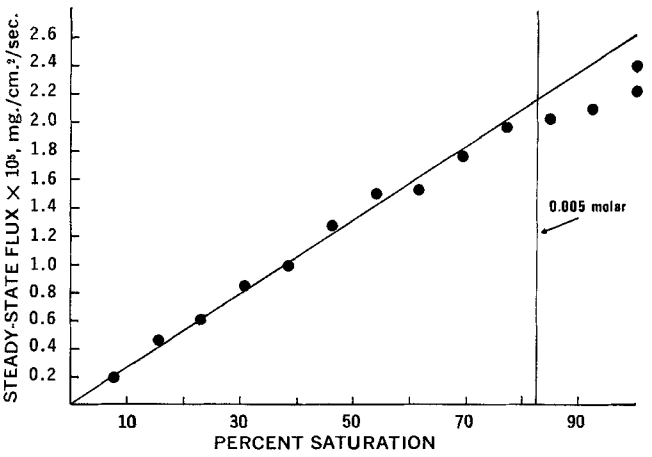

Figure 9—*Steady-state flux of ethyl* p*-aminobenzoate at 37° through 0.0476-cm. membranes as a function of applied phase concentration. Slight, but likely, real deviation from linearity is experienced near saturation concentration. Despite markedly decreased aqueous solubility, the flux is roughly twice that observed for* p*-aminoacetophenone at equivalent percent saturation.*

Table III—Lag Times for the Steady-State Line as a Function of Membrane Type and Adsorption Mechanism

Membrane Type, Adsorption Mechanism	Lag Time Relationship
Homogeneous	$h^2/6D$
Heterogeneous, Case I adsorption	$\frac{\tau^2 h^2}{6D}(1 + KV_2)$
Heterogeneous, Case II adsorption	$\frac{\tau^2 h^2}{D}\left(\frac{1}{4} + \frac{K'}{2k_pC^0}V_2\right)$
Heterogeneous, multiple but independent Case I or Case II adsorption sites	$\frac{\tau^2 h^2}{D}\left(\sum_n\left[\frac{1}{6} + (Kn)V_2\right] + \sum_m\left[\frac{1}{4} + \frac{K'm}{2k_pC^0}V_2\right]\right)$

efficient measurement. Barrer and Chio (17) showed that these methods yield essentially the same results with pure polymers. However, for a heterogeneous barrier, active filler, and Case I sorption, results would not be in agreement by the two methods. Total concentration in the membrane at equilibrium, C_T, may be expressed as:

$$C_T = C_mV_1 + KC_mV_2 \qquad \text{(Eq. 16)}$$

where C_m is the concentration in the external polymeric membrane phase. The equilibrium apparent partition coefficient would be:

$$k_{eq.} = \frac{C_m(V_1 + KV_2)}{C_s} = k_p(V_1 + KV_2) \qquad \text{(Eq. 17)}$$

where C_s is the equilibrium concentration in the bathing solvent. Obviously, C_m/C_s is the true partition coefficient, k_p. The apparent equilibrium diffusivity, $D'_{eq.}$ (the ratio of the apparent permeability constant to the apparent partition coefficient, $k_{eq.}$), is:

$$D'_{eq.} = \frac{P'}{k_{eq.}} = \frac{DV_1}{\tau(V_1 + KV_2)} \qquad \text{(Eq. 18)}$$

which is not equivalent to Eq. 15. Both equations yield $D' = D$ as V_2 approaches zero. If KV_2 is large relative to 1, apparent diffusivities differ by the factor V_1/τ. This factor is the difference between the true and the apparent permeability coefficients. If V_1/τ is not large, the methods should give comparable results. It is interesting and supportive that differences observed by VanAmerongen (18) using heterogeneous barriers are generally in the predicted direction; that is, the equilibrium diffusivity is generally smaller than that obtained using the lag time technique.

The general equation for the steady-state or linear portion of the typical diffusion curve with the boundary conditions previously specified may be expressed as:

$$Q_T = \frac{ADk_pC^0V_1}{\tau h}[t - t_L] \qquad \text{(Eq. 19)}$$

where the lag time, t_L, may be obtained from Table III for the various resolvable situations. The values of both V_1 and τ are equal to 1 in the homogeneous case. A hypothetical example of a Case I

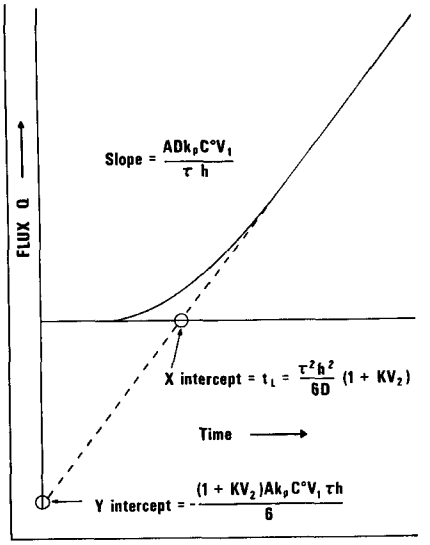

Figure 10—*Theoretical flux curve showing the mathematical values of the intercepts and slope in a diffusional experiment governed by Case I adsorption.*

curve is given in Fig. 10. The equations for slope and intercepts contain five generally independently determinable variables (V_1, V_2, A, h, and C^0) and four unknowns (D, k_p, τ, and K). If τ is not too different from 1, not an unusual situation, estimates of the other unknown parameters may be obtained from a single diffusional run. Otherwise, either D or k_p has to be determined independently. Therefore, in contrast to the opinion of Most (3), the heterogeneous membrane may be characterized diffusionally if the adsorption mechanism is known and is tractable.

In the present case, filler and polymer volume fractions were unknown because commercial polymer was used and this information was not provided. A rough estimate is possible using the permeability coefficient ratio for pure and filled polymer: 0.78 (see *Experimental*). If τ is about 1.1 (see the following paragraph), then V_1 would be about 0.86 and V_2 would be about 0.14. These volume fractions translate to a weight percentage for the filler phase of 27.4, using densities for dimethylpolysiloxane and silica of 0.97 and 2.20, respectively. The weight percent of filler by independent density measurement was 20.6 and thus was only in fair agreement with the steady-state diffusion value.

A rigorous test of the applicability of Eqs. 11 and 13–15 is possible using literature data. Most's (3) recent publication on the passage of ethyl *p*-aminobenzoate through dimethylpolysiloxane barriers containing differing amounts of silica filler is particularly helpful. These data, slightly reworked, are summarized in Table IV. Both V_1 and V_2 were calculated from the weight percentages. The ratio of transmission rates, which are in actuality thickness-averaged steady-state fluxes, provided estimates of τ/V_1, and the product of V_1 times this ratio generated τ. Densities of 0.97 and 2.2 were again used for polymer and filler. Equation 13 predicts that a plot of lag time divided by h^2 against V_2 will be linear. The computer-processed line using this relationship for these data has a correlation coefficient of 0.946 and gives values for D of 8.01×10^{-7} cm.^{2}/sec. and K of 49. Most (3) plotted apparent diffusivity, D', against percent filler

Table IV—Summary of Most's Data (3) on Ethyl *p*-Aminobenzoate Permeation of Dimethylpolysiloxane Membrane, Including Estimates of Volume Fractions and Tortuosity

Weight Percent Filler	V_1	V_2	h, cm.	Transmission Rate $\times 10^5$, μmoles/cm./sec.	Lag Time $\times 10^{-3}$, sec.	$D' \times 10^6$, cm.^{2}/sec.	Relative Transmission Rate, τ/V_1	τ
0	1	0	0.128	1.055	1.50	1.78	1	1
12.5	0.941	0.059	0.139	0.973	13.2	0.242	1.08	1.02
15	0.928	0.072	0.197	0.917	44.9	0.144	1.15	1.07
15	0.928	0.072	0.134(0.144)[a]	0.917	23.8	0.147	1.15	1.07
25	0.872	0.128	0.207	0.834	63.2	0.114	1.27	1.11
25	0.872	0.128	0.128	0.834	22.5	0.119	1.27	1.11

[a] Value required to give reported diffusivity.

Table V—Membrane Solubility, Maximum Rate, Specific Diffusivity, and Partition Coefficient for Ethyl *p*-Aminobenzoate and *p*-Aminoacetophenone at 25 and 37°

Compound	$T°$	Specific Diffusivity, cm.²/sec.	Solubility in Dimethylpolysiloxane[a], mg./ml.	k_p	Maximum Transmission Rate[b]	C_s(Water), mg./ml.
Ethyl *p*-aminobenzoate	27	1.78×10^{-6}	0.83	0.97[d]	1.48×10^{-6}	0.866
	37	(2.67×10^{-6})[c]	1.68			1.74
p-Aminoacetophenone	27	1.63×10^{-6}[c]				
	37	2.44×10^{-6}	0.317	0.0321[e]	7.74×10^{-7}	9.89

[a] Independently determined aqueous solubility, C_s, times k_p. [b] $D \times k_p \times [C_s$. [c] Using a literature E_a of 7.55 kcal./mole for *p*-aminoacetophe none (2). [d] Equilibrium method, Most (3). [e] Lag time method.

which is directly proportional to V_2, and obtained a hyperbolic curve. This is predicted by Eq. 15. If $1/D'$ is plotted against V_2, a straight line is obtained (Fig. 11). The reciprocal of the intercept gives D and was 8.23×10^{-7} cm.²/sec. The value for K obtained with the apparent diffusivity plot was 50.9. The line drawn through the points in Fig. 11 has a correlation coefficient of 0.953. The tortuosity used in a previous calculation was drawn from these data. Weight percent by the relative permeability coefficient method was close to the highest weight percent used by Most (3); therefore, a τ of 1.1 was chosen. Higuchi and Higuchi (7) suggested that tortuosities for uniform spheres will grow linearly up to the point of close packing or a V_2 of 0.77. At this point, τ will be 1.5. The values of τ obtained from Most's data (3) are in good agreement with this hypothesis (Fig. 12). It will be noticed that the arbitrary choice of the unitless parameter, volume fraction, as the measure of mass of adsorbent present makes the value of K unitless also.

The magnitude of K and the resulting product of KV_2 determines the filler effect on the lag time. The K value of 50 for ethyl *p*-aminobenzoate means that a filler volume fraction of 0.02 (about 4% filler by weight) will produce distortions in lag time relative to pure membrane in excess of 100%; 40% filler leads to an order of magnitude increase in lag time.

A comparison of some specific parameters of the ethyl *p*-aminobenzoate and *p*-aminoacetophenone data is given in Table V. Data for two temperatures are given because Most (3) worked at 27° and the present studies were at 37°. Experimental partition coefficients, which are assumed to be relatively temperature insensitive, for the two permeants differ by a factor of 25. However, the specific diffusivities for the two compounds at 27° are virtually identical, which attests to their similar molecular volumes and chemical natures. The 27° value for *p*-aminoacetophenone was calculated using a reported value for the diffusional activation energy of 7.55 kcal./mole (2).

Conceptual application of the present studies extends far beyond specific consideration of dimethylpolysiloxone films. For instance, a rapid method of determining solubility for pure membranes or materials which can be formed into a thick film was demonstrated. This method depends on the thermodynamic activity of the diffusant in the saturated applied phase being equivalent to the activity at the surfacemost layer of the membrane. Both would be equal to the thermodynamic activity of the crystalline solid. The product of the partition coefficient obtained in the diffusional run and the applied phase concentration yields the polymer solubility. This method is particularly valuable for partition coefficients less than one because equilibrium measurement of concentration changes in the applied phase results in small differences in relatively large numbers.

The high specific diffusivities in dimethylpolysiloxane polymer relative to other polymeric materials suggest several practical applications. Based on present theories, hole formation must occur with great frequency, implying that the polymer has great segmental mobility. Use of dimethylpolysiloxane membranes in separation is thus possible; because the material does not imbibe water, these separations may be unique relative to cellulosic barriers. One such specialized application is in the Llewellen and Littlejohn (19) separator, which is the Varian interface between gas chromatograph and mass spectrophotometer. Enrichment of the desired organic at the expense of carrier gas approaches several orders of magnitude per membrane passage (several are used in series).

The use of dimethylpolysiloxane as the polymeric vehicle for drug-containing vaginal rings and implants is also dependent on good diffusant mobility. Kincl *et al.* (20) found that permeability of progesterone through a representative variety of polymeric membranes was 100–1000 times less than through dimethylpolysiloxane. While diffusivity is not the sole factor governing permeability, it is likely the major determinant in this situation. Drug release from implants of materials with diffusivities two to three orders of magnitude less than dimethylpolysiloxane would be extremely slow. For many agents, biological activity would be precluded because effective tissue levels would be neither reached nor maintained.

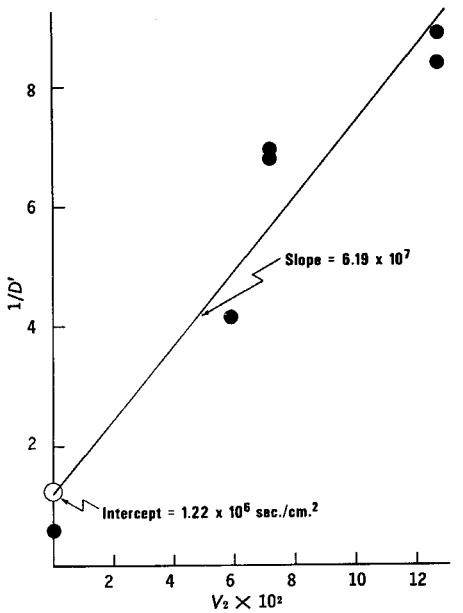

Figure 11—*Fit of Most's data (3) to Case I behavior [the reciprocal of apparent diffusivity, 1/D', should be linear with* V_2 *(Eq. 11)]. The correlation coefficient for the statistical line drawn through the points is 0.953.*

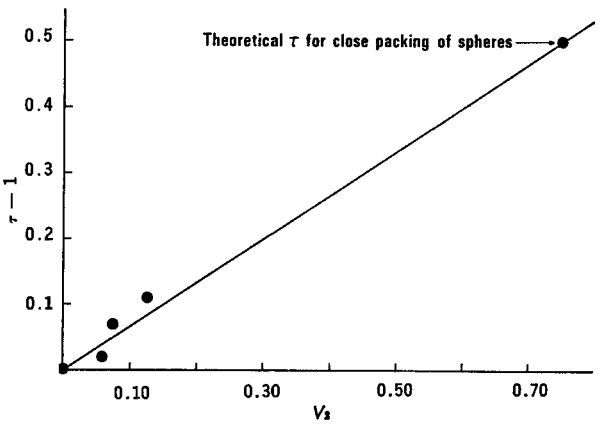

Figure 12—*Plot of* $\tau - 1$ versus V_2 *for Most's ethyl* p*-aminobenzoate data (3) showing that the estimated tortuosities are consistent with theory.*

Understanding of biological membranes is furthered by knowledge of the workings of simpler barriers. The present studies indicate possible effects of specific binding on the nonsteady-state processes governing membrane permeability. From the standpoint of biological membranes, protein binding would have effects analogous to those observed for physical adsorption in the dimethylpolysiloxane films. Both phenomena are dependent on the same basic interaction factors, *i.e.*, hydrogen bonding, hydrophobic bonding, van der Waal's forces, *etc.*, and the simplest cases are mathematically equivalent. Since protein is a major component of living membranes and interacts strongly with a myriad of compound types, one may assume that its presence influences preequilibrium processes involved in transport and distribution of drug and metabolites on the cellular level. However, considering cellular dimensions, it is difficult to ascribe a significance to this relative to all other distribution operations. When macroscopic living barriers such as the skin (stratum corneum), mucosal tissues, and cornea are considered, specific binding is potentially activity determining. The stratum corneum, which is principally protein (keratin and cellular wall remnants), has been reported to be extremely impenetrable relative to other equivalently dense synthetic barriers. Reported diffusivities run to 10^{-13} cm.^{2}/sec. (21). However, diffusivities have been determined using methods that give grossly exaggerated lag times or equilibrium partition coefficients if protein binding is great, either of which directly affect and decrease estimated values of D. Based on these considerations, one can better understand why Scheuplein *et al.* (21) argued that polar molecules permeate slowly through skin not because they are rigorously excluded from the skin but because they are so firmly bound within it.

GLOSSARY OF TERMS

A = area
C^0 = applied phase concentration
C_i = concentration in membrane continuum at donor/membrane interface
C_a = concentration in membrane continuum at point $a \leq h$
C_m = concentration in membrane continuum at equilibrium
C_T = total concentration in heterogeneous membrane, equilibrium condition
D = specific diffusivity, pure membrane
D' = apparent diffusivity, heterogeneous barrier, lag time method
$D_{eq.}$ = apparent diffusivity, heterogeneous barrier, equilibrium method
h = membrane thickness
H = effective diffusional membrane thickness, heterogeneous barrier
K = adsorption constant, Case I
K' = adsorption constant, Case II
k_p = true membrane/solvent partition coefficient
$k_{app.}$ = apparent partition coefficient, heterogeneous barrier, lag time method
$k_{eq.}$ = apparent partition coefficient, heterogeneous barrier, equilibrium method
P = permeability coefficient, pure membrane
P' = permeability coefficient, heterogeneous barrier
Q = flux per unit area
Q_T = total flux
t_L = lag time
V_1 = volume fraction continuous phase, heterogeneous barrier
V_2 = volume fraction filler
τ = tortuosity

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