Evaluation, Control, and Prediction of Drug Diffusion Through Polymeric Membranes II

Diffusion of Aminophenones Through Silastic Membranes: A Test of the pH-Partition Hypothesis

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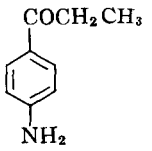
The steady-state and quasi-steady-state diffusions of 4′-aminopropiophenone, 4′-aminoacetophenone, and 3′-aminoacetophenone through various thicknesses of silastic membrane have been studied as functions of temperature, concentration, pH, and various ethanol–water compositions of diffusing and desorbing solutions. The membranes are impermeable to the protonated compounds, and the pKa values can be obtained from the pH profile of the apparent diffusion constants. The applicability of Fick's law was confirmed and the saturation of the membrane and/or limitations of numbers of binding sites are not rate determining. The transport of drug across the membrane is consistent with the partitioning from the diffusing solution into the membrane, diffusion within the membrane, and subsequent partitioning in the desorbing solution. Equations have been established on the basis of an assumed constancy of an intrinsic diffusion constant within the membrane to predict the transport of drugs through membranes separating different solvents where the drug would have different activities and have been experimentally verified. Satisfactory correlation between the apparent diffusion constants from steady-state diffusion studies and the partition coefficient in chloroform–water solutions has been observed for the several compounds. The apparent diffusion constant of 4′-aminopropiophenone from various ethanol–water solutions is linearly related to the reciprocal of its solubility in these solutions.

THE STUDIES reported here on the diffusion and permeation of drugs through polymeric membranes from various solvent systems were initiated to establish and test model systems with solid membranes as homogeneous barriers (1). These may be considered a more realistic simulation of drug transport through solid lipoidal barriers. The purpose was also to quantify those parameters necessary for the evaluation, control, and prediction of drug diffusion through polymeric membranes.

It has been implied that adsorption on surfaces of such polymeric membranes may be rate determining (2–4), that the number of surface binding sites may be finite, that the capacity of the membrane is related to its total number of internal binding sites (5–10), and that diffusion through aqueous diffusion layers on each side of the lipoidal membrane may be rate determining (11). If any but the last of these are so, the diffusion of drugs should not be linearly dependent on the concentration of the diffusing solution. As this concentration is increased, the rates of diffusion should approach a maximum value when adsorption or binding sites are limited. If desorption is rate determining, the rate of diffusion should become independent of membrane thickness as the concentration of the diffusing solutions is increased. These implications demand experimental evaluation to rigorously test the applicability of Fick's laws to diffusion through homogeneous polymer membranes.

This paper (part II of this series) considers the detailed study of the diffusion and permeation of the aminophenones, with specific reference to the antiradiation drug 4′-aminopropiophenone (PAPP), through silastic (silicone rubber) membranes.



4′-aminopropiophenone (PAPP)

EXPERIMENTAL

Materials—The silastic medical grade sheeting (H-0169, H-0293), a dimethyl-siloxane polymer (12), was obtained from the Dow Corning Center for aid to Medical Research, Midland, Mich. It was available in labeled thicknesses of 3, 5, 10, and 20 mil and the actual thicknesses were measured (1).

The following compounds were purchased from

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The authors are grateful to the Dow Corning Center for Aid to Medical Research, Midland, Michigan, for their supplies of the polymeric membranes.

Eastman Organic Chemicals, Rochester, N.Y.: 4′-aminopropiophenone, m.p. 139–140.5° [lit. value 140° (13)]; 4′-aminoacetophenone, m.p. 105–106° [lit. value 106° (13)]; 3′-aminoacetophenone, m.p. 97–99° [lit. value 99° (13)]. All other materials were of analytical reagent grade.

Analytical Methods—The absorbances of the aminophenones were measured in pH 6.8 phosphate buffer solutions against appropriate blanks with a Beckman model DU spectrophotometer in standard 10 mm. light path silica cells at 24 ± 1°. The compound, wavelength used, and molar absorptivity were, respectively: 4′-aminopropiophenone, 307 mμ, ϵ = 16,016; 4′-aminoacetophenone, 312 mμ, ϵ = 13,700; 3′-aminoacetophenone, 327 mμ, ϵ = 1,840. Adherence to Beer's law was confirmed by readings of diluted solutions of a known molarity.

The pKa′ of 100 ml. of 8.56×10^{-5} *M* 4′-aminopropiophenone was determined spectrophotometrically. The pH of the solution was measured on the Beckman expanded scale pH meter standardized with pH 4.0 and 7.0 standard Beckman buffer solutions. An ultraviolet spectrum of this solution was obtained against a distilled water blank on the Cary recording spectrophotometer, model 15. The sample solution in the cell was returned to the bulk solution, and a drop of concentrated HCl was added and the solution stirred. The pH of the solution was measured and the spectra determined again. This procedure was repeated and the absorbances at 307 mμ were plotted against the pH of the solutions. The pH value corresponding to the midpoint of the resultant sigmoidal curve was the half neutralization point taken as the pKa′ of 4′-aminopropiophenone and was 2.42.

Ethanol in aqueous solutions was quantitatively determined with an F & M model 700 gas chromatograph equipped with a flame-ionization detector. The column was a 3.05 cm. (1.2 in.) × 6.4 mm. o.d. stainless steel column packed with 20% Carbowax 20 M on 60–80 mesh Chromosorb W maintained isothermally at 50°. The temperature of the detector was 250° and that of the injection port was 150°. The helium carrier gas was used at a pressure of 30 psig. while hydrogen and air for the flame were used at 10 and 40 psig., respectively. Samples of 5 μl. of aqueous ethanol were injected without any prior treatment. The peak heights were measured and the concentration of the ethanol in the sample was obtained from a calibration curve prepared from ethanol solutions of known concentrations.

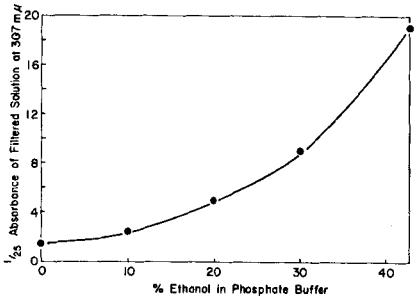

Fig. 1—Solubility of 4′-aminopropiophenone in 6.8 phosphate buffer at 25.0° plotted as absorbance of filtered saturated solutions at 307 mμ, ϵ = 16,016, against the percentage of ethanol in the phosphate buffer.

Solubility Studies—Saturated solutions of the compounds were prepared in pH 6.8 phosphate buffer (ionic strength of 0.3) at 50° and equilibrated at 37.5° in a thermostated shaker bath. The saturated solutions of 4′-aminopropiophenone in pH 6.8 phosphate buffer containing 0, 10, 20, 30, and 40% ethanol by volume were prepared by vigorously shaking the solutions at room temperature in the presence of excess solids and allowed to equilibrate at 25° in the thermostated shaker bath for 48 hr.

The solutions were filtered by suction through electrode isolation tubes which are fitted with a finely porous fritted-glass membrane (E. H. Sargent & Co., Chicago, Ill.). Aliquots of the filtered solution were appropriately diluted with pH 6.8 phosphate buffer and spectrophotometrically analyzed against appropriate blanks. The solubility of 4′-aminopropiophenone in phosphate buffer is shown as a function of ethanol concentration in Fig. 1.

Partition Coefficients—Aqueous pH 6.8 phosphate buffer and chloroform were saturated with respect to each other. The mixtures were separated by a separator and subsequent centrifugation at 3,200 r.p.m. for 5 min. An approximately 5×10^{-4} *M* solution of the compound was prepared in the phosphate buffer presaturated with chloroform. One milliliter of this solution was diluted appropriately with phosphate buffer and spectrophotometrically analyzed (at an absorbance 0.5–0.7) against a blank treated similarly. Five milliliters of the phosphate solution and 5.0 ml. of the chloroform presaturated with aqueous phosphate buffer in a capped stoppered vial were mixed on a Vortex Jr. mixer for 3 min., centrifuged for 3 min. at 3,200 r.p.m., and 1.00 ml. of the aqueous phase was removed, diluted, and spectrophotometrically analyzed. The ratio of the differences in absorbances of the aqueous layer before and after partitioning to the absorbance of the aqueous layer after partitioning was taken as the partition coefficient of the drug in the $CHCl_3$–phosphate buffer system.

Steady-State Diffusion Studies—The equipment and methods used have been described in detail in the prior paper of this series (1).

Effect of Thickness of Membrane on Steady-State Diffusion—Silastic membrane was available in four different thicknesses of 3, 5, 10, and 20 mil. The diffusion of a 1.517×10^{-3} *M* PAPP through these four thicknesses into 200 ml. of 0.12 *N* HCl was studied at 24.9°. A solution of PAPP in pH 6.8 phosphate buffer from one reservoir containing about 8 L of the solution was circulated through four cells, each one fitted with a silastic membrane of different thickness. The samples of 0.12 *N* HCl from the beakers were analyzed as a function of time to monitor the rates of diffusion of PAPP (Fig. 2).

Effect of Temperature on Steady-State Diffusion—The diffusion of PAPP from its solution in pH 6.8 phosphate buffer through 3-mil thick silastic membrane into 200 ml. of 0.12 *N* HCl was studied at seven different temperatures: 24.75°, 24.90°, 30.40°, 31.25°, 33.60°, 37.50°, and 41.0° ± 0.25°. At each temperature the diffusion was studied at four or more concentrations of PAPP in the phosphate buffer solutions. The same diffusion cells were used without changing the membranes to avoid any variation in membrane thickness and in area of the membrane available for diffusion.

Effect of pH on Steady-State Diffusion of PAPP—

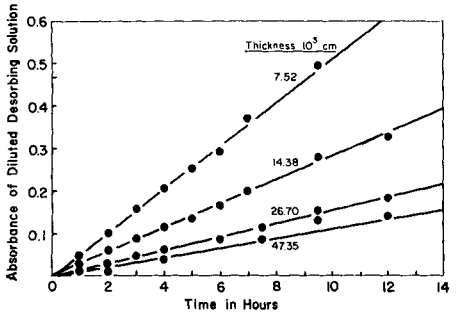

Fig. 2—Diffusion of 4′-aminopropiophenone (C_2 = 1.52×10^{-3} M) *from pH 6.8 phosphate buffer through silastic membranes of different thicknesses at 24.9°. The absorbance at 307 mμ of the desorbing 200 ml. of 0.12* M *HCl solution was monitored as a function of time after a 1:5 dilution with pH 6.8 phosphate buffer.*

The solutions of PAPP were prepared in 0.001 *N*, 0.01 *N*, and 0.1 *N* HCl and pH 3.48, 4.38, and 5.47 acetate buffer and pH 6.70 phosphate buffer. The steady-state diffusion of PAPP from these solutions through 3-mil thick silastic membrane into 200 ml. of 0.12 *N* HCl was studied at 25.0°. The pH values of the solutions were noted before and after the diffusion experiments and were observed to be unchanged. The absorbance of PAPP in the HCl solution in the beaker was measured as a function of time after 1:5 dilution with phosphate buffer. The absorbances of the solutions in the reservoirs, used for the circulation into the diffusion cells, were measured after appropriate dilutions with phosphate buffer.

Steady-State Diffusion of 4′-Aminoacetophenone and 3′-Aminoacetophenone—The diffusion of these two drugs through a 3-mil silastic membrane from their solutions in pH 6.8 phosphate buffer into 120 ml. of 0.12 *N* HCl was studied at 25.0° and 37.5°. The concentrations of the drugs diffusing into HCl were measured spectophotometrically after 1:5 dilutions with pH 6.8 phosphate buffer.

Effect of Alcohols on Steady-State Diffusion of PAPP—The effect of ethanol on the steady-state diffusion of PAPP through 3-mil silastic membrane at 25° was studied by varying the percentages of ethanol in the phosphate buffer (pH 6.8, aqueous) diffusion cell and in the outside desorbing solutions (0.12 *N* HCl). The percentage v/v of ethanol in both solutions and the concentrations of PAPP diffused are given in Table I.

The diffusion of PAPP from its saturated solutions in 0, 10, 20, and 30% v/v ethanol–water through 3-mil silastic membrane into 0.1 *N* HCl containing equivalent percentages of ethanol was studied at 24.3° (Table I). The same diffusion apparatus (Figs. 1 and 2 of *Reference 1*) was also used in the quasi-steady-state diffusion studies of PAPP from 0, 10, 20, and 30% ethanol–water solutions of phosphate buffer into 0, 10, 20, and 30% ethanol–water solutions of phosphate buffer in various combinations. The volume of the diffusing solution in the cell was 0.500 L. and that of the desorbing solution 0.120 L. The concentrations of the desorbing solution were spectrophotometrically monitored as a function of time.

Phosphate buffer (pH 6.8) solutions were prepared 2.0 *M* in ethyl, propyl, isopropyl, and *tert*-butyl alcohol and each contained 0.25 mg./ml. of PAPP. The steady-state diffusion of PAPP from each solution through 3-mil silastic membrane into 200 ml. of 0.12 *N* HCl was measured as a function of time.

TABLE I—APPARENT DIFFUSION CONSTANTS[a] OF 4′-AMINOPROPIOPHENONE[b] AS A FUNCTION OF ETHANOL CONCENTBATION AT 24.60°

% Ethanol in Phosphate Buffer Diffusing Solution	% Ethanol in 0.12 *N* HCl Desorbing Solution	Concn. of PAPP, 10^3 *M*	Apparent Diffusion Constant,[a] 10^{10}L./sec.-cm.
	Set A		
0.0	0.0	1.216	3.49
7.5	7.5	1.402	2.27
15.0	15.0	1.445	1.88
22.5	22.5	1.655	0.97
30.0	30.0	1.561	0.80
37.5	37.5	1.445	0.64
45.0	45.0	1.467	0.46
	Set B		
0	0	1.31	3.53
0	10	1.31	4.02
0	20	1.31	3.92
0	30	1.31	3.92
0	40	1.31	3.92
0	50	1.31	4.10
	Set C		
18	0	1.87	1.84
18	0	2.43	1.93
18	0	2.78	1.96
18	0	3.28	1.85
	Set D		
In water	0.1*N* HCl		
0	0	2.40	3.22
10	10	3.98	2.74
30	30	9.13	1.01
50	50	36.2	0.33

[a] The apparent diffusion constant was obtained from steady-state diffusion studies from ethanol–water phosphate buffer (6.8 pH aqueous) diffusing solutions of constant concentration C_2 through a silastic membrane of thickness X = 7.52×10^{-3} cm. or 3.0 mil and available surface area S = 10.4 cm.² into a desorbing ethanol–water 0.12 *M* HCl solution of a volume V = 0.200 L. The concentrations, C_1, of the desorbing solution where the diffusing species was entirely protonated were monitored spectrophotometrically as a function of time, t, and the obtained slope C_1/t of the plotted data which passed through the origin was used to obtain the apparent diffusion constant, $D = (C_1/t)(XV_1)/SC_2$. [b] The solubility of PAPP in ethanol–water phosphate buffer interpolated from a plot of solubilities *versus* % ethanol were: 10^3 *M*, % ethanol; 2.33, 0.0; 3.15, 7.5; 5.63, 15.0; 9.30, 22.5; 14.43, 30.0; 25.20, 37.5.

Effect of Ethanol on Silastic Membrane—Three steady-state diffusion cells were filled with 0, 10, and 30% ethanolic phosphate buffer solutions and kept in 0.12 *N* HCl solutions containing the same concentrations of ethanol. After 15 hr. the cells were emptied and washed with water, and the steady-state diffusion of PAPP from one solution of PAPP in phosphate buffer circulated in all three cells was studied in the absence of ethanol, inside or outside the cell.

Diffusion of Ethanol Through Silastic Membrane—The steady-state diffusion of ethanol through 3-mil silastic membrane into 200 ml. of 0.12 *N* HCl was studied at 24.6° from absolute ethanol, from phosphate buffer solutions of 0.0, 1.90, 3.01, and 5.06 $\times 10^{-3}$ *M* PAPP containing 18% ethanol, and from phosphate buffer solutions containing 10, 20, 30, 40, and 50% ethanol.

Absolute ethanol was circulated into a diffusion

TABLE II—APPARENT DIFFUSION CONSTANTS[a] OF 4′-AMINOPROPIOPHENONE THROUGH SILASTIC MEMBRANE AT VARIOUS TEMPERATURES

°C.	Concn., C_2, PAPP in Diffusing Solution, 10^4 M	C_1/t Concn. Increase of Desorbing Solution,[b] 10^6 M/L./hr.	$C_1/t\ C_2$ Specific Rate of Concn. Increase of Desorbing Solution,[c] 10^3 hr.$^{-1}$	Diffusion Constant, D[a], 10^{10} L./cm.-sec.
25.74	3.31	2.47	8.30	3.33
	7.21	5.59		
	9.48	7.74		
	11.37	9.12		
	13.99	11.23		
	16.45	13.30		
24.90	3.62	2.98	8.70	3.49
	9.80	8.18		
	12.10	10.23		
	18.30	15.77		
30.40	3.73	3.68	9.00	3.62
	9.21	9.68		
	10.93	10.20		
	16.71	15.30		
31.25	3.65	3.93	10.10	4.06
	9.33	9.43		
	13.74	14.10		
	18.24	21.20		
33.60	3.13	3.75	11.0	4.42
	9.96	11.20		
	14.67	16.50		
	19.11	21.20		
37.50	3.62	4.18	12.00	4.82
	9.37	10.40		
	13.49	16.70		
	17.73	21.20		
41.0	3.64	5.87	14.0	5.62
	9.68	14.40		
	13.99	20.00		
	18.79	27.20		

[a] The apparent diffusion constant, D, was obtained from steady-state diffusion studies from pH 6.5 phosphate buffer diffusing solutions of constant concentrations, C_2, through silastic membrane of thickness, $X = 7.52 \times 10^{-3}$ cm. or 3.0 mil and available surface area, $S = 10.4$ cm.^{2}, into a desorbing 0.12 M HCl solution of a volume $V_1 = 0.200$ L. so that D(L./cm.-sec.) = $(C_1/C_2t)\ (XV_1)/S$, where C_1/t and C_1/C_2t values are obtained as given in the subsequent footnotes. [b] The concentrations C_1 of the desorbing solution, where the diffusing species was entirely protonated, were monitored spectrophotometrically as a function of time, t, in hr., and these values are the obtained slopes, C_1/t in moles/L. of desorbing solution per hr., of the plotted data which passed through the origin. These values represent the slopes of C_1/t *vs.* C_2, where C_2 is the concentration of PAPP in the phosphate buffer diffusing solutions and the slopes of these plots are C_1/tC_2 in hr.$^{-1}$, the rate of increase in concentration of the desorbing solution per unit concentration of diffusing solution per hr.

cell fitted with a 3-mil silastic membrane. About 0.5-ml. samples of 0.12 N HCl were removed at hourly intervals, and 5 μl. of each of these samples was injected into a gas chromatograph for vapor phase analysis of ethanol. The percent ethanol present in the samples was calculated from a calibration curve.

Quasi-Steady-State Diffusion Studies—The quasi-steady-state diffusion cell and the methods previously described (1) were used to study the diffusion of PAPP from 50 and 100 ml. of pH 6.8 phosphate buffer through 5-mil silastic membrane into equal volumes of the same buffer at 25°.

RESULTS

Effect of Drug Concentration on Rate of Diffusion—The slopes, C_1/t, of the plots of concentration of PAPP in the 200 ml. of 0.12 M HCl desorbing solution after steady-state diffusion through 3-mil silastic membrane *versus* time are listed in Table II with the temperatures and the appropriate concentrations, C_2 of PAPP in the pH 6.5 phosphate buffer diffusing solution. Typical plots of these slopes, C_1/t in moles/L./hr., against the respective concentrations, C_2 in moles/L., of the diffusing solutions are shown in Fig. 3. The slopes of these plots, C_1/tC_2 in hr.$^{-1}$, are the specific rates of concentration increase in the desorbing solution per unit concentration of diffusing solution through 3-mil silastic membranes and are also given in Table II. The linear dependence of these diffusion rates, C_1/t, for the same membrane area, thickness, and volumes of diffusing and desorbing solutions on concentration of PAPP in the diffusing solution unequivocally demonstrates that the rate of diffusion through silastic membrane is directly proportional to the concentration of the diffusing drug.

Effect of Membrane Thickness on Rate of Diffusion—The plots of absorbance, $A = \epsilon C_1$ of PAPP in 1:5 diluted samples of the 200 ml. of 0.12 M HCl of the desorbing solution after steady-state diffusion *versus* time, t, for various thicknesses of silastic membrane are given in Fig. 2. The concentration increases with time, C_1/t, derived from the slopes of these plots are listed in Table III as well as the derived specific rates of diffusion (the rates of diffusion in moles of PAPP per cm.^{2} of membrane per sec. per mole/L., C_2, of diffusing solution). When these derived specific rates of diffusion, D/X, are plotted against the reciprocal of the thickness of the membranes, a linear relation is obtained (Fig. 4) with a slope of $3.76 \pm 0.19 \times 10^{-10}$ L./sec.-cm., the apparent diffusion constant D for the diffusion of PAPP through silastic membrane at 24.9°.

Effect of Temperature on Rate of Diffusion—The rates of steady-state diffusion of constant concentrations, C_2 of PAPP decrease with decreasing temperature (Fig. 3) through 3-mil silastic membrane and all are linearly dependent on the concentration, C_2, of the diffusing solution. The slopes, C_1/t, of the PAPP concentrations, C_1, of 200 ml. of 0.12 M HCl desorbing solution as a function of time, t, are given for the various studied temperatures in Table II. The derived specific rates, C_1/tC_2, of concentration increase of desorbing solution, per mole/L., C_2, of diffusing solution as well as the apparent diffusion constants, D, at the various tem-

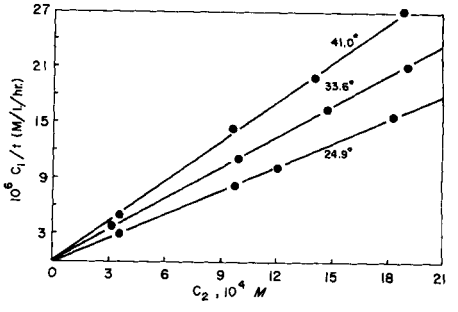

Fig. 3—Rates, C_1/t, of concentration increase in 200 ml. of 0.12 M HCl desorbing solution as a function of concentrations of 4′-aminopropiophenone in pH 6.5 phosphate buffer solution diffusing through 3.0-mil silastic membrane at several temperatures.

TABLE III—DIFFUSION OF 4′-AMINOPROPIOPHENONE AS A FUNCTION OF SILASTIC MEMBRANE THICKNESS AT 24.9°

Labeled thickness (mil)	3	5	10	20
Measured thickness (mil)[a] (10^3 cm.)	2.96 ± 0.05 7.52	5.66 ± 0.09 14.38	10.51 ± 0.10 26.70	18.64 ± 0.06 47.35
Coeff. of variation, %[b]	6.42	6.36	3.62	1.34
Slopes of concn. of desorbing solution *vs.* time, C_1/t($10^5 M$/L./hr.)[c]	1.436	0.749	0.406	0.250
Specific rates of diffusion, D/X (10^8L./sec.-cm.^{2})[d]	5.06	2.64	1.43	0.88

[a]Mean thickness and 95% confidence limits of the mean. [b]Standard deviation divided by the mean value. [c]The concentration, C_1, of the 0.200 L., V_1, of 0.12 *M* HCl desorbing solution was spectrophotometrically monitored as a function of time in hr. and these values are the slopes C_1/t of these linear plots with zero intercepts. [d]The specific rates of diffusion are the rates of diffusion in moles of PAPP per cm.^{2} of membrane, S = 10.40 cm.^{2}, per sec. per mole/L. of diffusing solution, C_2. The conditions were steady-state and the concentration of the diffusing solution was maintained constant, $C_2 = 1.517 \times 10^{-3}$ *M*, and the concentration of the diffusing unprotonated species in the acid desorbing solution was effectively zero. Thus, specific diffusion rate = $D/X = (C_1/t)(V_1/C_2S)$.

peratures are also listed in Table II. The logarithm of the apparent diffusion constants, D, are plotted against the reciprocal of the absolute temperatures, T, in Fig. 5 in accordance with the expression

$$\log D = \log (D)_0 - (\Delta E_a/2.303)(1/T) \quad \text{(Eq. 1)}$$

The estimated activation energies of diffusion through silastic membrane, ΔE_a, as obtained from the slope of these plots, are listed in Table IV for the various compounds. In addition, the determined partition coefficients and solubilities are also given.

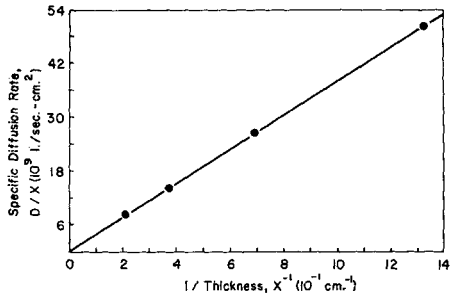

Fig. 4—Effect of thickness, X, of silastic membrane on the specific rates of diffusion, D/X, in moles of PAPP per cm.^{2} of membrane per sec. per mole/L. of phosphate buffer diffusing solution, $C_2 = 1.517 \times 10^{-3}$ M, into 0.12 M HCl desorbing solution at 24.9°.

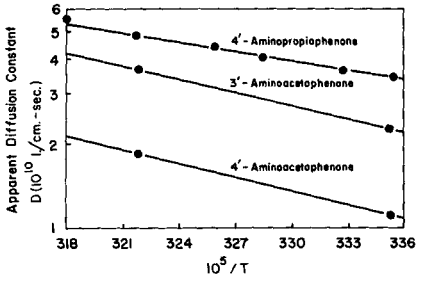

Fig. 5—Arrhenius plots of the logarithm of the apparent diffusion constants, log D, against the reciprocal of the absolute temperature, 1/T, for the diffusion of aminophenones through 3-mil silastic membranes from phosphate buffer solution.

Effect of pH on Rate of Diffusion—The apparent diffusion constants for the steady-state diffusion of PAPP through 2.43-mil silastic membrane into 0.12 *M* HCl from buffered solutions of various pH values with maintained concentrations, C_2, are listed in Table V and are plotted against pH in Fig. 6. The apparent diffusion constant, D, approaches an asymptotic value of 3.66×10^{-10} L./cm./sec. at high pH values and approaches zero at pH values less than one. The pH value corresponding to half the asymptotic value of 1.83×10^{-10} is 2.45, consistent with the experimentally determined spectrophotometric pKa′ of 2.41.

Effect of Alcohols on the Steady-State Diffusion of 4′-Aminopropiophenone (PAPP)—The plots of absorbance, $A = \epsilon C_1$, of PAPP in 1:5 diluted samples of the 200 ml. of 0.12 *M* HCl of the desorbing

TABLE IV—PARTITION COEFFICIENTS,[a] SOLUBILITIES,[b] APPARENT DIFFUSION CONSTANTS,[c] AND ACTIVATION ENERGIES OF DIFFUSION[d] OF AMINOPHENONES

Compd.	4′-Amino-aceto-phenone	3′-Amino-aceto-phenone	4′-Amino-propio-phenone
Partition[a] coefficient at 25.0°	15.97	53.30	134.4
Solubility[b] at 37.5° ($10^3 M$)	24.8	52.2	2.36
Apparent diffusion constants, D^c 10^{10}L./cm.-sec.			
25.0°	1.10	2.21	3.42
37.5°	1.84	3.62	4.82
Activation[d] energy (ΔEa) Kcal./mole	7.55	7.49	4.90

[a] Concentration in chloroform/concentration in pH 6.8 phosphate buffer solution at 25.0°. [b] Solubility in pH 6.8 phosphate buffer at 37.5°. [c] The apparent diffusion constants, D, were obtained from steady-state diffusion studies of maintained concentrations, C_2, in the pH 6.8 phosphate buffer diffusing solution through silastic membrane of thickness X = 7.52 × 10^{-3} cm. or 3.0 mil and available surface area S = 10.4 cm.^{2} into a desorbing 0.12 *M* HCl solution of a volume V_1 = 0.200 L. for PAPP and V_1 = 0.120 L. for the other compounds. The concentration increase of the desorbing solution C_1/t, was spectrally measured as a function of time so that D(L./cm.-sec.) = $(C_1/t)(XV_1/C_2S)$. [d] Calculated from slopes according to plots of the expression: $\log D = \log D - \Delta Ea/2.303\,RT$.

TABLE V—APPARENT DIFFUSION CONSTANTS[a] OF 4′-AMINOPROPIOPHENONE AS A FUNCTION OF pH AT 25.0°

pH	Concn. of PAPP, $C_2 10^3$ M	Apparent[a] Diffusion Constant, 10^{10} L./cm.-sec.
1.30[b]	1.685	0.21
2.00[b]	1.655	1.01
2.45[b]	1.639	1.88
3.48[c]	1.592	2.71
4.38[c]	1.59	3.25
5.47[c]	1.670	3.61
6.70[d]	3.310	3.66

[a] The linear concentration, C_1, increases of the V_1 = 0.200 L. of 0.12 M HCl desorbing solution were spectrally monitored as a function of time, t, and the C/t values obtained from the slope. The diffusion was studied from maintained concentrations, C_2, of the specified buffer solutions through X = 6.09 × 10^{-3} cm. or 2.43-mil silastic membrane with available surface area S = 10.4 cm.^{2}. The apparent diffusion constant was calculated from D(L./cm.-sec.) = $(C_1/t)(XV_1/C_2S)$. [b] HCl. [c] Acetate buffer. [d] Phosphate buffer.

solution after steady-state diffusions through silastic membrane *versus* time, t, for various percentages of ethanol in the diffusing solutions are given in Fig. 7. The derived apparent diffusion constant, D, from the slopes of such plots are given in Table I for various concentrations of ethanol of the diffusing solution and the desorbing solution.

The apparent diffusion constants for PAPP decreased with increasing ethanol concentrations of the phosphate buffered diffusing solution when the PAPP concentrations remained constant (Set A, Table I). Variation in the ethanol concentration of the 0.12 N HCl desorbing solution, where the concentration of the uncharged PAPP was effectively zero and where the diffusing solution had no ethanol, had no significant effect on the apparent diffusion constant (Set B, Table I). Variation in PAPP concentration of an 18% ethanol-containing diffusing solution showed that steady-state diffusion was a linear function of this concentration, and that the apparent diffusion constant (per unit of concentration of the diffusing solution) was truly constant (Set C, Table I).

The steady-state diffusion rates at 24.25° of saturated solutions of PAPP from aqueous saturated solutions with 0, 10, 20, and 30% ethanol through 3-mil silastic membrane into 0.1 N HCl with the same ethanolic concentration are given in Table I, Set D. The increased solubility of PAPP gave a decided increase in the overall rates of diffusion.

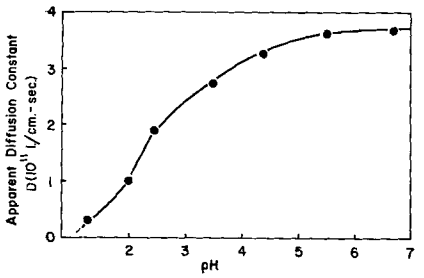

Fig. 6—Apparent diffusion constants for 4′-aminopropiophenone through silastic membrane into 0.12 M HCl desorbing solution at 25.0° against the pH of the diffusing PAPP solutions.

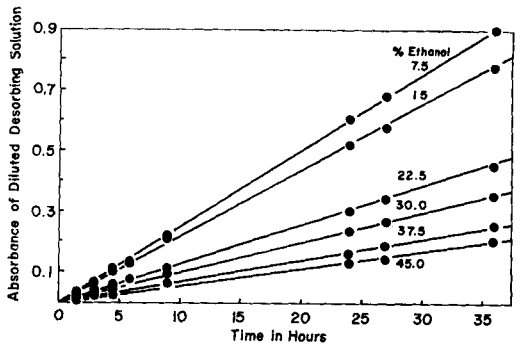

Fig. 7—Diffusion of 4′-aminopropiophenone (C_2 = 1.4 × 10^{-3} M) from various percentages of ethanol–water phosphate buffer (pH 6.8, aqueous) through 3.0-mil silastic membrane at 24.6°. The absorbance at 307 mμ of the desorbing 200 ml. of 0.12 M HCl solution of the same ethanol–water composition was monitored as a function of time after a 1:5 dilution with pH 6.8 phosphate buffer.

However, the apparent diffusion constants decreased with decreasing ethanol concentrations on both sides of the membrane.

The steady-state diffusion rates of PAPP concentrations increase in 200 ml. of 0.12 N HCl desorbing solution per unit concentration of PAPP in alcohol–water phosphate buffer diffusing solution (pH 6.8, aqueous) containing 2.0 M ethyl, propyl, isopropyl, and *tert*-butyl alcohol were 5.1, 6.0, 6.4, and 5.1 × 10^{-3} hr.$^{-1}$, respectively. It could not be concluded that the rates of diffusion of PAPP were significantly modified by variation among these alcohols.

The specific rates of steady-state diffusion of ethanol from phosphate buffer containing 18% ethanol were found to be independent of the PAPP concentration for concentrations up to 5 × 10^{-3} M (Table VI). The specific rates of diffusion of ethanol from phosphate buffer, *i.e.*, per unit of concentration in the diffusing solution, were independent of the concentration of ethanol (10–50%) in the diffusing solution (Table VI). The specific rates of diffusion of PAPP from phosphate buffer through silastic membrane pretreated with ethanol solutions of

TABLE VI—DIFFUSION OF ETHANOL AS A FUNCTION OF 4′-AMINOPROPIOPHENONE CONCENTRATION AT 24.6°

Concn. of Ethanol in Diffusing Solution, %	Concn. of PAPP in Diffusing Solution, 10^3 M	Slope of % Ethanol in Diffusing Solution *vs.* Time, %/hr.	Specific Rate[a] of Diffusion, 10^3 hr.$^{-1}$
18	0	0.032	1.77
18	1.90	0.032	1.77
18	3.01	0.032	1.77
18	5.06	0.032	1.77
10	0	0.0143	1.43
20	0	0.0273	1.37
30	0	0.0453	1.51
40	0	0.0633	1.53
50	0	0.0777	1.56

[a] Calculated for diffusion of ethanol through 3-mil silastic membrane by dividing slope or the plot of the percent ethanol in 200 ml. of 0.12 M HCl desorbing solution in ethanol–water phosphate buffer solution (pH 6.8, aqueous), where area of membrane, S = 10.4 cm.^{2} and thickness of membrane, X = 7.52 × 10^{-3} cm.

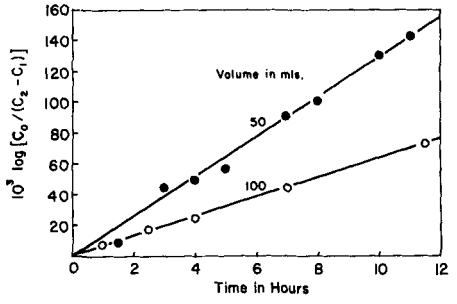

Fig. 8—Plots of log $[C_0/(C_2 - C_1)]$ *against time for quasi-steady-state diffusion of 4'-aminopropiophenone through 5-mil silastic membrane at 25.0°. The* C_2 *and* C_1 *are the concentrations of PAPP in equal volumes of the phosphate buffers of the diffusing solution and the desorbing solution, respectively, where* $C_2 = C_0$ *and* $C_1 = 0$ *at zero time.*

different concentrations were invariant. This indicated that the diffusing properties of these membranes are not altered by ethanol or that any alteration was reversible.

Quasi-Steady-State Diffusion Studies—Quasi-steady-state diffusion differs from steady-state diffusion in that (*a*) the concentrations of the diffusing and desorbing solutions are not held constant; (*b*) the concentration C_2 of the diffusing solution, initially C_0, decreases as the concentration C_1 of the desorbing solution increases; (*c*) as the values of both solutions approach the same equilibrium value with time. The plots of $\log[C_0/(C_2 - C_1)]$ *versus* time are linear for the quasi-steady-state diffusion of PAPP through 5-mil silastic membrane from and to pH 6.8 phosphate buffer at 25° (Fig. 8). The apparent diffusion constants were calculated from the slopes of these plots and were 3.93×10^{-10} and 3.94×10^{-10} L./cm.-sec. for 50-ml. and 100-ml. volumes of the solutions in the arms of the diffusion cell at 25°. These values agree with the estimated diffusion constant obtained from the various steady-state diffusion experiments, *i.e.*, $3.76 \pm 0.19 \times 10^{-10}$ L./cm.-sec. (Tables I, II, IV, V).

DISCUSSION

Fick's Law and Steady-State Diffusion—Fick's first law of diffusion (14–16) states that the rate, dA/dt, of diffusion of moles, A, per unit of time is proportional to the surface area of diffusion, S in cm.^{2}, and the concentration gradient (the rate of change of concentration C' with distance x in cm., dC'/dx) in an isotropic medium:

$$dA/dt = D'SdC'/dx \qquad \text{(Eq. 2)}$$

The experimental steady-state conditions specify that the concentration gradient, dC'/dx, is constant so that at any two planes in the isotropic medium where $x = 0$ at C_2' and $x = X$ at C_1'

$$dA/dt = D'S(C_2' - C_1')/X \qquad \text{(Eq. 3)}$$

In the specific case of diffusion through a membrane of thickness X cm. and surface area S cm.^{2} the steady-state Eq. 3 states that the rate is constant with time for constant concentrations C_2' and C_1', in the first and last monolayers, respectively. If the solutions of concentrations C_2'' and C_1'' of the diffusing species on the diffusion and desorption sides of the membrane, respectively, are in instantaneous equilibrium with their adjacent monolayers in the manner of a partition coefficient, *i.e.*,

$$C_2' = K_2C_2'' \qquad \text{(Eq. 4}a\text{)}$$

$$C_1' = K_1C_1'' \qquad \text{(Eq. 4}b\text{)}$$

the Eq. 3 can be rewritten as

$$dA/dt = D'S(K_2C_2'' - K_1C_1'')/X \qquad \text{(Eq. 5)}$$

Silastic membrane is impermeable to chloride, phosphate, and hydrogen ions (1). The additional fact that the estimated apparent diffusivities of PAPP decreased with increases in the fraction of the concentration that is charged (Fig. 6) confirms that this membrane acts as a lipid-like barrier, permeable only to uncharged species.

Thus the C_i'' terms in the diffusion Eq. 5 refer only to the concentrations of the unionized or uncharged drug in the solutions and are related to total concentrations, C_i by

$$C_i'' = f_iC_i \qquad \text{(Eq. 6)}$$

where f_i is the fraction of the drug that is unionized or uncharged and

$$f_i = K_a/([H^+] + K_a) \qquad \text{(Eq. 7}a\text{)}$$

for an amine such as PAPP whose conjugate acid has a dissociation constant K_a and

$$f_i = [H^+]/([H^+] + K_a) \qquad \text{(Eq. 7}b\text{)}$$

for an uncharged acid of dissociation constant K_a where $[H^+]$ is the hydrogen ion concentration.

The Eq. 5 can be rewritten as

$$dA/dt = D'S(K_2f_2C_2 - K_1f_1C_1)/X \qquad \text{(Eq. 8)}$$

For the special case where $K_1 = K_2 = K$,

$$dA/dt = D'KS(f_2C_2 - f_1C_1)/X = DS(f_2C_2 - f_1C_1)/X \qquad \text{(Eq. 9)}$$

where $D = D'K$ is the apparent diffusion constant or permeability constant for the system of transfer from a diffusing solution through a membrane of X cm. thickness and S cm.^{2} area into a desorbing solution.

In the steady-state diffusion studies of this investigation, the effective concentration $C_1'' = f_1C_1$ of the uncharged diffusing species of PAPP and its analogs was zero at the high acidities of the desorbing HCl solution since $f_1 = 0$ (Eqs. 6 and 7*a*). The concentration C_2'' of the uncharged species was maintained constant in the diffusing solution. The applicable Eq. 9 reduces in this special case to

$$dA/dt = DSf_2C_2/X \qquad \text{(Eq. 10)}$$

which integrates between the limits of zero time and time t to

$$A = C_1V_1 = DSf_2C_2t/X \qquad \text{(Eq. 11)}$$

where A is the amount permeating the membrane in time t. The desorbing solution of volume V_1 was analyzed for its total concentration of the drug, C_1, in moles/L., as a function of time so that plots of the concentration, C_1, *versus* time in seconds provide slopes proportional to the apparent diffusing constant, D, where

$$\text{Slope} = DSf_2C_2/V_1X \quad \text{(Eq. 12)}$$

$$D \text{ (L./cm.-sec.)} = D'K_2 = \text{slope} \cdot (XV_1)/(Sf_2C_2) \quad \text{(Eq. 13)}$$

The validities of Eqs. 11 and 12 have been experimentally verified. The stated conditions of steady-state diffusion give constant rates of diffusion with time (Figs. 2 and 7). The rate of steady-state diffusion of drug through silastic membrane is directly proportional to the concentration of drugs in the diffusing solution, C_2 (Table II, Fig. 3), and this rate is inversely proportional to the thickness of the membrane (Table III, Figs. 2 and 4).

The Eqs. 11 and 12 state that the rates of steady-state diffusion will be directly proportional to the fraction of unionized diffusing drugs and predict that these rates will be lowered to one-half their maxima when $[H^+] = K_a$ or pH = pKa (Eqs. 7, 11–13). This is confirmed by the data of Fig. 6 for PAPP, pKa = 2.42, where the apparent diffusion constants, D (Eq. 13) (actually f_2D) on the assumptions of $C_2'' = C_2$, $f_2 = 1$ are plotted against pH.

The Eqs. 9 and 13 assume that the apparent diffusion constant, D, for steady-state diffusion when $C_1'' = f_1C_1 = 0$ is directly proportional to the partition coefficient, K, of the drug between the diffusing solvent and the membrane. The partition coefficient is a ratio of the activities and/or solubilities (17) so that it may be postulated that

$$D = D'K = D'C_m/C_i = D'S_m\,(1/S_i) \quad \text{(Eq. 14)}$$

where C_m and C_i are the effective concentrations (or activities) of a compound in a membrane and its equilibrated solution, respectively; S_m and S_i are the solubilities in the membrane and its equilibrated solution, respectively.

If it is assumed that drugs in a homologous series have similar intrinsic diffusion constants, D', in the membrane and that the partition coefficients in a chloroform–water system, K_p, are proportional to those in the membrane–water system, K, *i.e.*, $K_p = \alpha K$ where α is a proportionality constant, the apparent diffusion constants, D, should increase with increases in K_p in accordance with Eq. 14. An approximately linear relationship does exist between the apparent diffusion constant, D, and the chloroform–phosphate buffer partition coefficient of the several compounds studied (Table IV).

$$D = 2.3 \times 10^{-12}\,K_p + 0.75 \times 10^{-10} \quad \text{(Eq. 15)}$$

A necessary condition for the plot of D *versus* $1/S_i$ to be linear is that the solubility in the membrane (S_m) is invariant with structural modification of the drug. The data of Table IV confirm the expectation that this is not necessarily so among several drugs.

However, when only the solvent is varied and the diffusion of one drug alone is studied, this necessary condition may be met. Experimental confirmation of Eq. 14 is obtained from the linearity of the plot (Fig. 9) of the apparent diffusion constants of PAPP, D (Table I) obtained from steady-state diffusion studies from ethanolic phosphate buffer solutions through silastic membrane into 0.12 *M* HCl desorbing solution against the reciprocal of the solubilities (Fig. 1) of PAPP, $1/S_i$, in these solutions. Regression analysis showed that the intercept is not significantly different from zero at the 5% level of significance. The slope of the plot of Fig. 9 implies

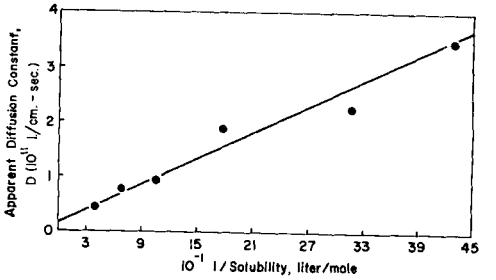

Fig. 9—Plots of apparent diffusion constant D *for the diffusion of 1.5 × 10⁻³M PAPP from various ethanol–water solutions of phosphate buffer (pH 6.8 aqueous) through 3.0-mil silastic membrane into 200 ml. of 0.12* M *HCl desorbing solution against the reciprocal of the solubility in these ethanol–water solutions.*

that the product of the intrinsic diffusion constant and the solubility in the membrane, $D'S_m$, is 8.35×10^{-13} moles/cm.-sec.

Quasi-Steady-State Diffusion—When the concentrations on both sides of a membrane are allowed to equilibrate with time and are monitored by the change of their concentrations with time, these rates can be expressed as (see Eq. 8)

$$dC_1/dt = D'S\,(K_2f_2C_2 - K_1f_1C_1)/XV_1 \quad \text{(Eq. 16}a\text{)}$$

$$dC_2/dt = -D'S\,(K_2f_2C_2 - K_1f_1C_1)/XV_2 \quad \text{(Eq. 16}b\text{)}$$

where V_1 and V_2 are the volumes of the desorbing and diffusing solutions, respectively. When the amounts entering and leaving the membrane are equal for all analytical purposes even though the rate of permeation changes with time as a function of the concentration gradient, this transport is termed "quasi-steady-state diffusion."

The stoichiometry of quasi-steady-state diffusion can be represented by

$$V_1C_1 + V_2C_2 = V_2C_0 \quad \text{(Eq. 17)}$$

and when the value of C_2 from Eq. 17 is substituted into Eq. 16*a* and the resultant expression integrated between the limits of $C_1 = 0$ at $t = 0$ and $C_1 = C_1$ at $t = t$,

$$\log\left\{\frac{K_2f_2C_0 - (K_2f_2V_1 + K_1f_1V_2)\,C_1/V_2}{K_2f_2C_0}\right\} = \frac{-(K_2f_2V_1 + K_1f_1V_2)D'S}{2.303X\,V_1V_2}\,t \quad \text{(Eq. 18)}$$

When both numerator and denominator within the logarithmic term is multiplied by D'.

$$\log\left\{\frac{D'K_2f_2C_0 - (D'K_2f_2V_1 + D'K_1f_1V_2)C_1/V_2}{D'K_2f_2C_0}\right\} = \frac{-(K_2D'V_1f_2 + K_1D'V_2f_1)S}{2.303X\,V_1V_2}\,t \quad \text{(Eq. 19)}$$

A similar expression in terms of C_0 and C_2 results when the value of C_1 from Eq. 12 is substituted in Eq. 16*b*.

If the thermodynamic activities of the drug in the diffusing and desorbing solutions are equal for the same solutions on both sides of the membrane, *i.e.*, $K_1 = K_2 = K$, and when the value of C_0 from Eq. 17 is considered, Eq. 19 reduces to

$$\log \left\{\frac{f_2C_0 - (f_2V_1 + f_1V_2)C_1/V_2}{f_2C_0}\right\} = \log \left\{\frac{f_2C_2 - f_1C_1}{f_2C_2}\right\} = \frac{-(f_2V_1 + f_1V_2)KD'S}{2.303\,XV_1V_2}\,t \quad \text{(Eq. 20)}$$

If $V_1 = V_2 = V$ and $f_2 = f_1 = f$, Eq. 20 reduces to

$$\log \left\{\frac{C_0 - 2C_1}{C_0}\right\} = \log \left\{\frac{C_2 - C_1}{C_1}\right\} = \frac{-2KD'fS}{2.303\,XV}\,t = \frac{-0.869DfS}{XV}\,t \quad \text{(Eq. 21)}$$

where $D = D'K$ is the apparent diffusion constant. This D value can be obtained from the slopes of linear plots of log $(C_2 - C_1)/C_0$ *versus* time for equal volumes of the same phosphate buffer solution in both arms of the quasi-steady-state apparatus (1) (Fig. 8). The linearity is consistent with the expectations of Eq. 21 for quasi-steady-state diffusion. The apparent diffusion constant, $D = 3.94 \times 10^{-10}$ L./cm.-sec., calculated from the slope of such plots, ($f = 1$) was consistent with the highly reproducible apparent diffusion constants 3.66×10^{-10} cm.^{2}/sec. (Table V) for uncharged PAPP obtained from steady-state diffusion data from phosphate buffer into HCl solution at the same temperature for the same silastic membrane.

Quasi-steady-state diffusion (Eq. 20) studies also produced estimates of the apparent diffusion constants $D = KD'$ for PAPP in various percent ethanol–water solutions of phosphate buffer, $f = 1$, diffusing into similar solutions when the volumes were unequal in both arms of the apparatus, $V_2 = 0.500$ L. and $V_1 = 0.120$ L. The obtained values as calculated from the slopes of plots in accordance with Eq. 20 are listed in Set A of Table VII. A new lot of silastic membrane was used in these studies.

Effects of Ethanol on PAPP Diffusion—The rates of steady-state diffusion of PAPP and thus the apparent diffusion constants through silastic membrane decrease with increased concentrations of ethanol in the diffusing solution (Set A, Table I) but are independent of ethanol concentration in the desorbing solution when the effective concentration of the transported drug is essentially zero (Set B, Table I). The specific rates of diffusion (with respect to unit concentrations) or the apparent diffusion constants of PAPP and ethanol from solutions of varying concentrations of PAPP in ethanolic phosphate buffer show negligible variation (Set C, Table I and Table VI). Thus, the diffusions of PAPP and ethanol through silastic appear to be independent processes. Those compounds do not compete or interact within the membrane or on the surfaces for sites. Apparently, the diffusion of the one does not significantly modify the intrinsic diffusivity constant, D', of the other within the membrane.

However, the apparent diffusivity constant of PAPP, $D = D'K$, is modified (Sets A and D, Table I) by varying ethanol concentrations in the diffusing solution. Its independence of the ethanol concentration of the desorbing solution (Set B, Table I), where the effective concentration of PAPP therein is zero ($f_1C_1 = 0, f_1 = 0$) in steady-state diffusion, is consistent with Eqs. 10–13 where the nature of the desorbing solution is not pertinent to the rates of transfer through the membrane. This phenomenon can be assigned to the change in the partition constant, K.

When the diffusing and desorbing solutions are of the same ethanolic concentrations ($K_1 = K_2 = K$) and pH values, ($f_1 = f_2 = f$) in quasi-steady-state diffusion, Eq. 20 is applicable. Thus, when the concentration data is appropriately plotted (Fig. 10) $D'K_i$ values can be obtained from the slope (Set A, Table VII where $f_1 = f_2 = 1$). In these cases the

TABLE VII—CONSTANTS FOR THE QUASI-STEADY-STATE DIFFUSION OF 4′-AMINOPROPIOPHENONE THROUGH, SILASTIC MEMBRANE FOR VARIOUS ETHANOL–WATER CONCENTRATIONS OF DIFFUSING (V_2) AND DESORBING (V_1) 6.8 pH PHOSPHATE BUFFER SOLUTIONS AT 25.3°

Set	% Ethanol in V_2	% Ethanol in V_1	10^{10} L./cm.-sec. $D'K_2$	10^{10} L./cm.-sec. $D'K_1$	$D'K_2V_1 + D'K_1V_2$ 10^{10} L.^{2}/cm.-sec. Obtained[c]	$D'K_2V_1 + D'K_1V_2$ 10^{10} L.^{2}/cm.-sec. Calcd.[d]
A[a]	0	0	2.405	2.405	1.48	1.49
	10	10	1.752	1.752	1.09	1.09
	20	20	1.237	1.237	0.77	0.77
	30	30	0.849	0.849	0.53	0.53
B[b]	0	10	2.405	1.752	1.15	1.16
	0	20	2.405	1.237	1.00	0.91
	0	30	2.405	0.849	0.81	0.71
C[b]	10	0	1.752	2.405	1.40	1.41
	10	20	1.752	1.237	0.93	0.83
	10	30	1.752	0.849	0.70	0.63
D[b]	20	0	1.237	2.405	1.45	1.35
	20	10	1.237	1.752	1.00	1.02
	20	30	1.237	0.849	0.60	0.57
E[b]	30	0	0.849	2.405	1.20	1.30
	30	10	0.849	1.752	0.91	0.98
	30	20	0.849	1.237	0.72	0.72

[a] In this case $D'K_1 = D'K_2 = D$ which are apparent diffusion constants obtained from the slope of the left-hand side of the following equation *vs.* time t, *i.e.*, $\ln C_0V_2/[C_0V_2 - C_1(V_1 + V_2)] = DSt(V_1 + V_2)/XV_1V_2$ where $V_2 = 0.500$ L., $V_1 = 0.120$ L., $S = 10.4$ cm.^{2}, the labeled thickness was 3 mil. [b] In these cases the $D'K_1$ values listed are the apparent diffusion constants DK' of Set A for diffusion from diffusing to desorbing solutions of the same ethanol–water composition of the desorbing solutions in these studies. The $D'K_2$ values listed are the apparent diffusion constants $D'K$ of Set A for diffusion from diffusing to desorbing solutions of the same ethanol–water composition of the diffusing solutions of these studies. [c] The $D'K_2V_1 + D'K_1V_2$ values are obtained from the slopes of the plots of left-hand term of the following equation *vs.* time, t, *i.e.*, $\ln [D'K_2C_0V_2/(D'K_2C_0V_2 - C_1(D'K_2V_1 + D'K_1V_2))] = (DK_2V_1 + D'K_1V_2)St/XV_1V_2$ where C_0, V_1, V_2, S, X are known values, the $D'K_1$ and $D'K_2$ values in logarithmic term are obtained from Set A, and C_1 is experimentally obtained. [d] The $D'K_2V_1 + D'K_1V_2$ values are calculated from the known V_1 and V_2 values and $D'K_2$ and $D'K_1$ values obtained from Set A.

ethanolic water membrane partitioning at the diffusing and desorbing surfaces would be equivalent and $K_1 = K_2 = K$.

If the partition hypothesis (Eq. 4) is correct, these $D'K_i$ values can be used to predict the quasi-steady-state diffusion when the solvents on both sides of the membranes are different and the $D'K_1$ and $D'K_2$ values are not equivalent. The appropriate $D'K_i$ values obtained (Set A, Table VII) for a given ethanol–water mixture can be used to construct the plots of log $[D'K_2C_0 - (D'K_2V_1 + D'K_1V_2)C_1/V_2]/D'K_2C_0$ *versus* time t in accordance with Eq. 19 where $f_1 = f_2 = 1$. The $D'K_2$ values are the apparent diffusion constants for quasi-steady-state diffusion when both solutions (Set A, Table VII) were of the same ethanol–water composition as the diffusing solution (Sets B–E, Table VII). The $D'K_1$ values are the apparent diffusion constants when both solutions (Set A, Table VII) were of the same ethanol–water composition as the desorbing solution (Sets B-E, Table VII). The C_0 (initial concentration of diffusing solution) and C_1 (concentration of desorbing solution at any time) values are experimentally known. The values of $(K_2D'V_1 + K_1D'V_2)$ can be obtained from the slopes of these plots (Fig. 10) in accordance with Eq. 19. These values are given in Sets B–E, Table VII where $V_2 = 0.500$ L. and $V_1 = 0.120$ L. and are in excellent agreement with those calculated from the K_2D' and K_1D' values obtained from the studies with the same ethanol–water composition in both solutions (Set A, Table VII).

Temperature Dependence of Diffusion Through Silastic Membrane—Estimates of the apparent activation energy of diffusion for the several drugs studied (Table IV) were made in accordance with

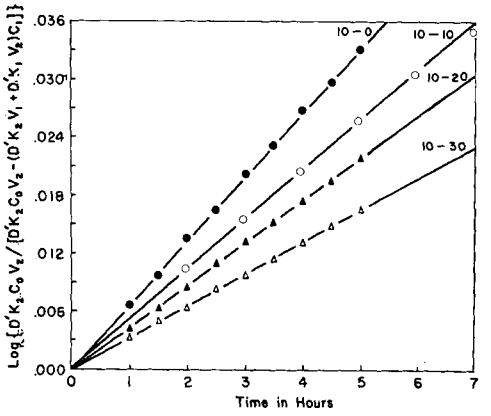

Fig. 10—Examples of plots of a logarithmic function of values against time, t, in accordance with Eq. 19 where $f_1 = f_2 = 1$ *for the diffusion of 4′-aminopropiophenone through silastic membrane from various % ethanol–water diffusing solutions into various % ethanol–water desorbing solutions. The representative plots are labeled accordingly. The slopes of these plots give the* $(K_2D'V_1 + K_1D'V_2)S/2.303XV_1V_2$ *values where* K_2 *and* K_1 *are the partition coefficients between the membrane and the diffusing and desorbing solutions, respectively, where* V_2 *and* V_1 *are the respective volumes, S is the area, X is the thickness of the membrane,* C_0 *is the initial concentration in the diffusing solution, and* C_1 *is the concentration in the desorbing solution as a function of time.*

Eq. 1 from the slopes of the plots of Fig. 5. Since the apparent diffusion constant, D, is a product of the intrinsic diffusion constant D' in the membrane and the partition constant, K in the steady-state diffusion system, it follows from Eq. 14 that

$$\log D' = \log P_D' - \Delta E_D'/2.303RT \quad \text{(Eq. 22)}$$

$$\log S_M = \log P_{S_M} - \Delta E_{S_M}/2.303RT \quad \text{(Eq. 23)}$$

$$\log S_i = \log P_{S_i} - \Delta E_{S_i}/2.303RT \quad \text{(Eq. 24)}$$

see that Eq. 1 may be reinterpreted as

$$\log D = (\log P_D' + \log P_{S_M} - \log P_{S_i}) - (\Delta E_D' + \Delta E_{S_M} - \Delta E_{S_i})/2.303RT \quad \text{(Eq. 25)}$$

and,

$$\Delta E_T = \Delta E_D' + (\Delta E_{S_M} - \Delta E_{S_i}) \quad \text{(Eq. 26)}$$

The apparent energy of diffusion is the sum of the true energy of diffusion inside the membrane and the differences between the heats of solution of the diffusing species in the membrane and the solvent phases. In general the values are approximately double the usual energies of diffusion in solution which are in the range of 3–5 Kcal./mole (18). However, these values are generally obtained for diffusion of large molecules through small molecule liquid solvents. Since the apparent energy of diffusion is perturbed by the heats of solution, changing the diffusing solvent and thus the accompanying heat of solution could increase or decrease the temperature coefficient of apparent diffusion.

Nonsteady-State Diffusion—The rate-determining factor in nonsteady-state transport through a membrane is the rate of diffusion in the membrane. In steady-state transport it is the constant concentration gradient alone and in quasi-steady-state transport both the concentration gradient and the rates of approach to equilibrium of both extramembrane phases are rate determining.

When a membrane is interposed between a solution of the penetrant and the solvent, the transportation of the penetrant is initially a nonsteady-state process and a "time lag" in transport results until the amount leaving the membrane equals the amount entering. This time lag has been used extensively (19–21) for the calculation of the diffusion constant in the nonsteady-state on the premise that a finite amount of time will be needed for a penetrant to traverse the thickness of the membrane before the attainment of a steady state (21). After this initial lag period, when the concentrations on both sides of the membrane are constant, the plot of the amount diffused *versus* time will be a straight line (Eq. 11) which when extrapolated will give an intercept θ on the time axis of

$$\theta = X^2/6D' \quad \text{(Eq. 27)}$$

Use of the authors' apparent diffusion constant, $D = 3.7 \times 10^{-10}$ L./cm.-sec., for the intrinsic diffusion constant D' in Eq. 27 for a membrane thickness $X = 7.52 \times 10^{-3}$ cm. would imply that the intercept of amounts diffused *versus* time would be 7 hr., whereas it is not statistically different from zero. This is consistent with our definition of D as $D'K$. If we assume an excessive error in the zero intercept of as much as 5 min., this would imply that the value of D' is greater than 10^{-8} L./cm.-sec. and that K is less than 10^{-2}.

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Keyphrases

Polymeric membranes—drug diffusion
Silastic membranes—aminophenones, diffusion
Diffusion, steady state—membrane, pH, temperature, ethanol effect
Aminophenones, concentration—diffusion rate
Quasi-steady-state diffusion
Nonsteady-state diffusion

Mechanistic Study of the Influence of Micelle Solubilization and Hydrodynamic Factors on the Dissolution Rate of Solid Drugs

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The influence of micelle-drug solubilization on the dissolution rate has been investigated. The dissolution rates predicted by the diffusion layer model, the Danckwerts theory, and by the rotating disk theory were calculated and compared with experimental data obtained for the benzocaine–polysorbate 80 system. All the parameters involved were independently determined. The different conditions under which each of these theories is applicable have been discussed. Different kinds of dissolution experiments were designed to produce the conditions under which each theory would apply. The theoretical and experimental procedures involved in these studies provide a unique method for distinguishing mechanisms and should be useful in future studies, *e.g.*, in studies of the effects of agitation on mechanisms of interphase transport.

As PART of the authors' program on drug release rates it was decided to conduct experiments on the influence of micelle-drug solubilization on the dissolution rate behavior. There were two reasons for carrying out these studies. First, there has been relatively little work reported in the literature on the effects of solubilization by colloids upon the dissolution rate. Therefore, establishing a relationship between solubilization and dissolution rate appeared to be a worthwhile endeavor. Secondly, as will be seen, the different theories for dissolution rates based upon different hydrodynamic models predict significantly different rate relationships when a solubilizing agent is present. Experimental tests of such theories by other methods (1, 2) are extremely difficult, and, in the authors' opinion, past attempts have not led to convincing results. Thus meaningful information on the hydrodynamical aspects of the dissolution rate process might be obtained by the proposed method of study involving colloidal solubilizing agents.

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