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

Diffusion of Barbiturates, Phenylalkylamines, Dextromethorphan, Progesterone, and Other Drugs

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Silastic membrane demonstrated the greatest permeability among the nine polymeric films studied. The apparent diffusion constants through silastic membrane were determined by steady-state studies for a series of barbiturates and phenylalkylamines and correlated with the determined chloroform/acetate buffer partition coefficients in the former case. The apparent diffusion constants did not correlate with the determined solubilities of the barbiturate series in the diffusing solvent since the solubilities within the membrane have to be considered. Only the uncharged species diffuse through the polymeric membrane and half of the maximal diffusion rate occurs at the pKa′. Diffusion rates were proportional to concentrations in all cases up to the solubility of the diffusing species and Fick's law was fully applicable. Diffusion rates can be varied by changing the diffusing and desorbing solvents and membrane thickness and area. Solvent variation (*e.g.*, water, mineral oil, peanut oil, alcohol) affects the apparent diffusion coefficients of dextromethorphan and progesterone. The rates of diffusion of the studied compounds decrease with their increasing solubility in the diffusing solvent which can be assigned to the preferential partitioning in the solvent rather than the membrane. Diffusion from capsules repeats the rates and is dependent on the same factors as diffusion through films. Solid particles in contact with silastic membrane dissolve in and are transported through the membrane. Release rates from the membrane into surrounding solvents should depend on whether these dissolution rates were of higher or lower orders of magnitude than diffusion through the membrane.

THE APPLICABILITY of Fick's law to the transfer of uncharged drugs through polymeric membranes has been substantiated with respect to aminophenones (1, 2). The apparent rates of diffusion, dA/dt, through a typical solid polymeric membrane, the silicone silastic, have been shown to be proportional to the concentration of the uncharged drug concentration in the diffusing solution, C_2, and inversely proportional to the thickness, X, of the membrane in accordance with the steady- and quasi-steady-state expression of Fick's law,

$$dA/dt = V_1 dC_1/dt = D'S(K_2 f_2 C_2 - K_1 f_1 C_1)/X \quad \text{(Eq. 1)}$$

where C_2 and C_1 are the concentrations of the drug in volumes V_2 and V_1 of diffusing and desorbing solutions, respectively; where f_2 and f_1 are the fractions of the drug concentrations, C_2 and C_1, that are uncharged, respectively; where K_2 and K_1 are the respective partition coefficients for the uncharged species between the membrane and solvents; and where S is the area and D' the intrinsic diffusion constant within the membrane. In general the concentration C_1 of the V_1 volume of desorbing solution was monitored as a function of time.

The silastic membranes are impermeable to HCl, phosphate buffer salts, and protonated aminophenones (1, 2). The apparent diffusion constants $D = D'K$ of various aminophenones through silastic membrane from and to equivalent solvents, *i.e.*, $K_1 = K_2 = K$, where, from Eq. 1,

$$dA/dt = V_1 dC_1/dt = D'KS(f_2 C_2 - f_1 C_1)/X \quad \text{(Eq. 2)}$$

appear to be proportional to chloroform/water partition coefficients. The apparent diffusion constants, $D = D'K$, for 4′-aminopropiophenone from and to solvents of the same composition (or when $f_1 = 0$) were inversely proportional to the solubility of the 4′-aminopropiophenone in the diffusing solution.

The purposes of this investigation were to screen various polymeric films for their permeability to various drugs and to investigate in detail the diffusion of barbituric acid derivatives, phenylalkylamine, dextromethorphan, and progesterone through silastic membrane and potential dosage forms based on this principal. The effects of temperature, pH, and variation of diffusing and desorbing solvents were determined. The relations between the apparent

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diffusion constants with solubilities and oil/water partition coefficients were also investigated.

EXPERIMENTAL

Chemicals—The following compounds were supplied by Abbott Laboratories, North Chicago, Ill. The molar absorptivities, ϵ, are given for the designated wavelengths at which the absorbances were measured: amobarbital, $C_{11}H_{18}N_2O_3$, eq. wt. 226, 236 found, ϵ = 6,520 (238 mμ), pKa′ 7.40; barbital, $C_8H_{12}N_2O_3$, eq. wt. 184, 197 found, ϵ = 10,310 (238 mμ), pKa′ 7.45 [lit. value 7.91 (3)]; butabarbital, $C_{10}H_{16}N_2O_3$, eq. wt. 212, 215 found, ϵ = 10,410 (238 mμ); cyclobarbital, $C_{12}H_{16}N_2O_3$, eq. wt. 236, 245 found, ϵ = 9,880 (238 mμ), pKa′ 7.27 [lit. value 7.50 (3)]; diallylbarbituric acid, $C_{10}H_{12}N_2O_3$, eq. wt. 208, 202 found, ϵ = 9,690 (238 mμ), pKa′ 7.30 [lit. value 7.79 (3)]; mephobarbital, $C_{13}H_{14}N_2O_3$, eq. wt. 246, 250 found, ϵ = 5,730 (238 mμ), pKa′ 7.45; metharbital, $C_9H_{14}N_2O_3$, eq. wt. 198, 198 found, ϵ = 6,540 (238 mμ), pKa′ 7.90; pentobarbital, $C_{11}H_{18}N_2O_3$, eq. wt. 226, 232 found, ϵ = 11,070 (238 mμ), pKa′ 7.65 [lit. value 8.11 (3)]; phenobarbital, $C_{12}H_{12}N_2O_3$, eq. wt. 232, 257 found, ϵ = 10,880 (238 mμ), pKa′ 7.40 [lit. value 7.41 (3)]; secobarbital, $C_{12}H_{18}N_2O_3$, eq. wt. 238, 230 found, ϵ = 9,860 (238 mμ), pKa′ 7.45 [lit. value 8.08 (3)]; thiamylal, $C_{12}H_{17}N_2O_2S$, eq. wt. 254, 290 found, ϵ = 18,660 (304 mμ), pKa′ 6.80; thiopental, $C_{11}H_{18}N_2O_2S$, eq. wt. 242, 246 found, ϵ = 12,100 (304 mμ), pKa′ 7.12.

The following compounds were supplied by Smith Kline & French Laboratories, Philadelphia, Pa.: α-methylphenethylamine hydrochloride, $C_9H_{13}N \cdot HCl$, eq. wt. 172, 165 found, pKa′ 9.07; α-ethylphenethylamine hydrochloride, $C_{10}H_{15}N \cdot HCl$, eq. wt. 186, 203 found; 2-amino-4-methyl-4-phenylpentane hydrochloride, $C_{12}H_{19}N \cdot HCl$, eq. wt. 214, 205 found, pKa′ 9.42; 3-amino-1-phenylbutane sulfate, $(C_{10}H_{15}N)_4 \cdot H_2SO_4$, eq. wt. 198, 242 found, pKa′ 9.30; 1-methyl-5-phenylpentylamine hydrochloride, $C_{12}H_{19}N \cdot HCl$.

The following compounds were supplied by the Upjohn Company, Kalamazoo, Mich. The molar absorptivities, ϵ, are given for the designated wavelengths at which the absorbances were measured: progesterone, ϵ = 16,470 (248 mμ), m.p. 128–130° [lit. value 127–131° (4)]; cortisone, ϵ = 16,000 (238 mμ), m.p. 230–236° [lit. value 236–240° (4)]; hydrocortisone, ϵ = 16,200 (242 mμ), m.p. 217–220° [lit. value 217–220° (4)]; prednisolone, ϵ = 15,200 (242 mμ), m.p. 239–240° [lit. value 240–241° (4)].

Dextromethorphan, pKa′ 8.25, ϵ = 3,002 (277 mμ) was supplied by Vick Divisions Research and Development, Richardson-Merrell Inc., Mt. Vernon, N. Y.

The following compounds were purchased from National Biochemical Corp., Cleveland, Ohio: sulfathiazole, m.p. 200–203° [lit. value 200–204° (4)]; sulfisoxazole, m.p. 195–198° [lit. value 194° (4)]; sulfadiazine, ϵ = 5,370 in alkaline solution (255 mμ), m.p. 256–257° [lit. value 252–256° (4)]; sulfabenzamide, ϵ = 4,480 in alkaline solution (255 mμ), m.p. 181–183° [lit. value 181.2–183.3° (4)].

The peanut and mineral oil used were USP. All other reagents were of analytical grade. The 4′-aminopropiophenone used has been discussed previously (2).

Polymer films tested were an 11-aminoundecanoic acid polymer[1] (5), a polyamide[2] (6), cellulose acetate,[3] cellulose triacetate,[4] and cellulose acetate butyrate,[5] thermoplastic cellulosic films (7), polyethylene type B (8), and polyethylene terephthalate.[6] Polypropylene (10) was supplied by the Avisun Corp., Philadelphia, Pa.; silastic medical grade sheeting H-0169, HO 293 is a dimethylsiloxane polymer (11) and was supplied by the Dow Corning Center for Aid to Medical Research.

Analytical Methods—Spectrophotometric measurement of absorbances at 24.0 ± 1.0° was used for the quantitative estimation of barbituric acid derivatives, steroids, and dextromethorphan in a Beckman model DU spectrophotometer using 10-mm. cells and 0.1 slit width at the wavelengths stated above. The linear relationship between absorbance and concentration was verified in all cases. The barbituric acids were measured in pH 10.1 borate buffer as the molar absorptivities are much higher than in the uncharged form. The absorbances of dextromethorphan and steroids were measured in pH 6.8 phosphate buffer solutions. The solutions of the sulfonamides were made alkaline with NaOH solution. A Cary recording spectrophotometer model 14 was used in screening.

The phenylalkylamines were analyzed by a modification of the method of Gettler and Sunshine (12). A 1.00-ml. aliquot of 1.5–10 × 10^{-5} *M* solution in pH 6.8 phosphate buffer was made alkaline with 0.1 ml. of 2 *N* NaOH, 5.00 ml. of chloroform added, and the mixture agitated. After centrifugation at 3,200 r.p.m. for 3 min., 4.00 ml. of the chloroform solution was removed and 0.20 ml. of freshly prepared methyl orange reagent (1:1 saturated solution of methyl orange and boric acid) was added to this sample. The mixture was again centrifuged, 3.00 ml. of the chloroform solution was removed, and 0.20 ml. of absolute ethanol containing 2% concentrated sulfuric acid was added to this sample. The absorbance of this solution was read at 520 mμ on a Beckman DU spectrophotometer against a phosphate blank prepared similarly. Calibration curves were prepared daily.

The cited pKa′ values were obtained by potentiometric titration at 24.0 ± 1.0° on a Sargent model D automatic titrator and standardized at pH 4.0, 7.0, and 10.0 and are accurate to ±0.05 pH unit. The difference method of Parke and Davis (13) was used and the pKa′ determined from the half-neutralization value of the difference between the titers of equivalent volumes of sample solution and blank necessary to give the same measured pH value. Alkaline solutions of the barbiturates were titrated with standard $HClO_4$; the acid solutions of the phenylalkylamines and dextromethorphan were titrated with standard NaOH.

[1] Rilsan (Nylon 11), May Industries, Inc., Atlanta, Ga.
[2] Polypenco(Nylon 101), Polymer Corp., Reading, Pa.
[3] Kodacel A29, Eastman Chemical Products, Inc., Kingsport, Tenn.
[4] Kodacel TA 401, Eastman Chemical Products, Inc., Kingsport, Tenn.
[5] Kodacel B 298, Eastman Chemical Products, Inc., Kingsport, Tenn.
[6] Mylar polyester type S, E. I. du Pont de Nemours & Co., Wilmington, Del.

Solubility Studies—Saturated solutions of the barbituric acid derivatives in pH 4.7 acetate buffer, ionic strength 0.1, were prepared at 50° and equilibrated at 25° for 48 hr. in a thermostated shaker bath in the presence of excess solids. The solutions were then filtered by suction through electrode isolation tubes, which are fitted with a finely porous fritted-glass membrane (E. H. Sargent and Company, Chicago, Ill.). Aliquots of the filtered solutions were appropriately diluted with pH 10.1 borate buffer and the absorbances measured at the pertinent wavelengths.

Partition Coefficients—Aqueous pH 4.7 acetate buffer and chloroform were saturated with respect to each other. An approximately 5×10^{-4} *M* solution of the barbituric acid derivatives was prepared in the acetate buffer presaturated with chloroform. One milliliter of this solution was appropriately diluted, generally with 10 ml. of pH 10.1 borate buffer, and its absorbance measured at the pertinent wavelength against a blank treated similarly. Five milliliters of the acetate solution and 5.0 ml. of the chloroform presaturated with aqueous acetate buffer in a capped, stoppered vial were mixed on a Vortex Junior 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 with 10 ml. of pH 10.1 borate buffer, and spectrophotometrically analyzed against an acetate buffer blank treated similarly. 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 $CHCl_3$–acetate buffer system.

Screening of Polymer Films for Permeability to Drugs—The cited polymer films in 3 and 5 mil thicknesses were washed with distilled water and dried. Saturated solutions of the cited materials in 0.1 *N* HCl, 0.1 *N* NaOH, pH 6.8 phosphate buffer, propylene glycol, peanut oil, ethanol, mineral oil, ethylene glycol, and polyethylene glycol 200 were prepared. Two milliliters of each saturated solution was put into a serum vial (10-ml. capacity) and the vial stoppered with a holed rubber stopper. A small piece of each membrane was laid upon the stopper and an aluminum cap was then crimped to sandwich the membrane. The serum vial was then inverted and placed into a 60-g. ointment jar containing about 10 ml. of pH 6.8 phosphate buffer. The jars were capped, properly labeled, and set aside for at least 1 week, when the phosphate buffer solutions were analyzed for drug by the methods described. A drug was said to have permeated through a membrane when the peaks at wavelengths corresponding to the $\lambda_{max.}$ values of the drug were observed on the Cary model 15. Experiments with positive results were repeated to avoid erroneous conclusions from leaking vials.

Diffusion Studies—The steady-state diffusions of the barbituric acid derivatives were studied through 3-mil silastic membrane from their solutions in pH 4.7 acetate buffer into pH 10.1 borate buffer at 25 and 37.5°.

Weighed amounts of barbituric acid derivatives were dissolved in small volumes of 1 *N* NaOH and immediately diluted with pH 4.7 acetate buffer solution to 2 l. to obtain solutions which were approximately 5×10^{-3} *M* in barbituric acid derivatives. These were used as reservoir solutions and circulated through the steady-state diffusion cells fitted with 3-mil silastic membranes. The system has been described previously (1). The solutions used on the desorption side of the membrane in the beakers were 200 ml. of pH 10.1 borate buffer. Absorbances of samples were measured as a function of time on the Beckman DU spectrophotometer and the samples were returned to the beakers.

The steady-state diffusion of barbital and pentobarbital through 3-mil silastic membrane from their solutions in acetate, phosphate, and borate buffer solutions of different pH values at 37.5° was also studied.

The steady-state diffusion of the phenylalkylamine salts from borate buffers through 3-mil silastic membrane into 120 ml. of pH 6.8 phosphate buffer was studied at 25°. Samples of the phosphate buffer solutions (1 ml.) were removed every 15 min. and stored in a refrigerator. All the samples were analyzed simultaneously with the standard solutions used to prepare the calibration curve.

The steady-state diffusions of dextromethorphan from peanut oil, mineral oil, and pH 10.1 borate buffer; and progesterone from peanut oil, and a saturated solution in phosphate buffer were studied through 3-mil silastic membrane into pH 6.8 phosphate buffer at 37.5°.

The diffusion of dextromethorphan was also studied from its saturated solutions in peanut oil and mineral oil. The concentration of dextromethorphan in peanut oil was determined by diluting a weighed amount of the filtered solution with chloroform and measuring the absorbance of the solution at 277 mμ against a chloroform blank containing an equivalent amount of peanut oil where the absorbance of a similar solution of a known weight of the drug had been determined. The saturated solution of the dextromethorphan in the mineral oil was filtered and its absorbance was measured against a mineral oil blank. The concentration was calculated from the previously determined absorptivity. The steady-state diffusion apparatus used has been described previously (1).

Silastic capsules (Dow Corning Center for Aid to Medical Research) were small silastic pouches prepared by sealing pieces of tubes (about 6 mm. in diameter and about 2.4 cm. in length) at both ends. These were cleaned externally with water and air dried.

Saturated solutions of 4′-aminopropiophenone in phosphate buffer, solutions of barbital, pentobarbital, and phenobarbital in acetate buffer, and solutions of dextromethorphan in borate buffer, peanut oil, and mineral oil were prepared. The silastic capsules were cut open at one corner and were filled with these saturated solutions. The hole in each of the capsules was sealed by forcing a portion of silastic medical grade adhesive type A (Dow Corning Center for Aid to Medical Research) into and around the hole. The capsules were set aside for 1 day and were tested for leaks by pressing them lightly between fingers. Similarly, capsules containing solvents without drugs were also prepared.

The capsules containing barbital, pentobarbital, and phenobarbital were washed with water and put into 50 ml. of pH 10.1 borate buffer in glass vials. These vials were preequilibrated at 37.5° for about 10 hr. Similarly capsules of 4′-aminopropiophenone and dextromethorphan were put in glass vials containing 50 ml. of 0.12 *N* HCl and pH 6.8 phosphate buffer, respectively. The samples from the vials were assayed spectrophotometrically for the respective compounds.

Diffusion of Solid Progesterone Through Silastic Membrane—One window of the stainless steel steady-state diffusion cell was used. One membrane was placed face down and the available area was covered with powdered, dry progesterone. Another membrane was placed atop and the resultant sandwich was stretched tautly while it was clamped into the window. The cell was immersed in 120 ml. of normal saline and vibrated in the shaker bath at 37.5°. Samples of the solution were removed at intervals and significant absorbance due to progesterone, $\lambda_{max.}$ 248 mμ, was observed on the Cary ultraviolet recording spectrophotometer.

RESULTS

Screening of Polymer Films for Permeability—The spectrophotometric curves of the desorbing solutions were checked for the peaks characterizing the compounds whose diffusion was under test. This method of analysis was sensitive to 10^{-4} *M* concentration in all cases and much more sensitive in the case of steroids. When no drug in the desorbing solution was observed at these sensitivities, the membrane is stated to be impermeable to that drug.

Polyethylene membrane was permeable to 4′-aminoacetophenone in aqueous solutions and in peanut oil and to 4′-aminopropiophenone in ethylene glycol. Both compounds permeated an 11-aminoundecanoic acid polymer membrane[1], from ethanolic solutions. A polymide membrane[2] was permeated by 4′-aminopropiophenone and 3′-aminoacetophenone from 0.1 *N* NaOH and ethanol. Polypropylene was nonpermeable to all the drugs tested.

Substances were leached by phosphate buffer from cellulose triacetate and cellulose butyrate membranes that interfered with the spectrophotometric analyses of the drugs. After compensation for the absorbances of these interfering substances, it was concluded that 4′-aminopropiophenone permeated cellulose triacetate from propylene glycol, ethanol, and polyethylene glycol 200. Positive results were recorded also for barbital in polyethylene glycol 200 and sulfabenzamide in ethanol. Polyethylene terephthalate polyester film[6] was available only in small quantity and was impermeable to all the drugs tested with the available films.

Silastic membrane was permeable to 4′-aminopropiophenone and 3′-aminoacetophenone from all the solvents tested except mineral oil, to progesterone from ethanol, to barbital from ethanol and ethylene glycol, and to phenobarbital from peanut oil, ethanol, polyethylene glycol 200, phosphate buffer, and 0.1 *N* HCl. Silastic membrane allowed permeation of the majority of the compounds screened in measurable quantities and was investigated in further detail.

Steady-State Diffusion Studies—The steady-state diffusion of drugs through silastic membranes was studied with the equipment and by the techniques previously described in detail (1, 2). The concentration, C_2, of the diffusing solution was held constant as was the volume, V_1, of the desorbing solution. The linear slopes, dC_1/dt, of the increase of concentration, C_1, of the desorbing solution with time were determined. The concentrations, f_1C_1, of the uncharged species in the desorbing solution were kept at zero by choosing a pH where the fraction of the drug uncharged, f_1, was effectively zero.

The specific rate of diffusion was obtained by dividing this slope, the rate of increase of total concentration, C_1, of the desorbing solution by the concentration, f_2C_2, of the uncharged species in the diffusing solution. When the slope was obtained from the linear increase in absorbance, A_1, of the desorbing solution with time, this slope, dA_1/dt, was divided by the product of the absorbance, A_2, of the diffusing solution and the fraction, f_2, of the drug uncharged therein since

$$R_S = \text{specific rate of diffusion} = (dA_1/dt)/f_2A_2 = [d(\epsilon C_1)/dt]/f_2\epsilon C_2 = (dC_1/dt)/f_2C_2 \quad \text{(Eq. 3)}$$

Typical plots of the increase of absorbance or concentration with time in the desorbing solutions after diffusion through 3-mil silastic membrane are given in Figs. 1 and 2 for various barbituric

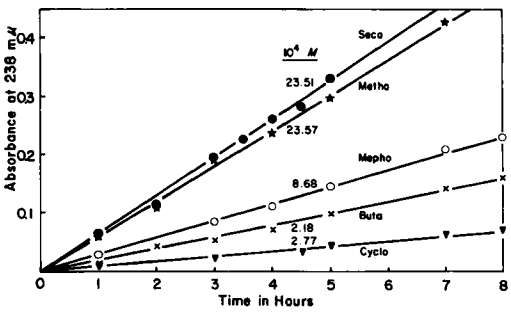

Fig. 1—Absorbance at 238 mμ of 200 ml. of pH 10.1 borate buffer desorbing solution as a function of time on the steady-state diffusion of the stated concentrations of the cited barbitals from pH 4.7 acetate buffer through 3-mil silastic membrane at 37.3°.

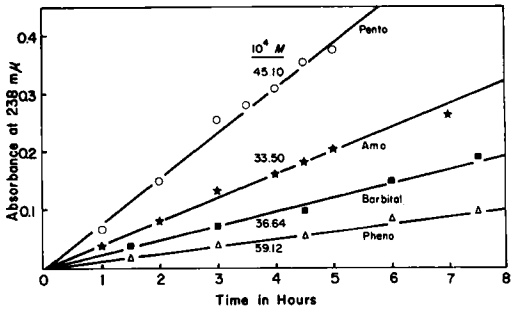

Fig. 2—Absorbance of 238 mμ of 200 ml. of pH 10.1 borate buffer desorbing solution as a function of time on the steady-state diffusion of the stated concentrations of the cited barbitals from pH 4.7 acetate buffer through 3-mil silastic membrane at 37.3°.

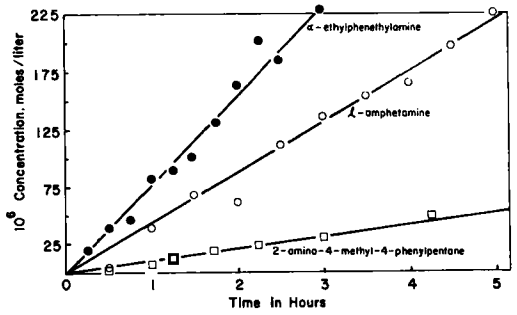

Fig. 3—Concentration of pH 6.8 phosphate buffer desorbing solution as a function of time on the steady-state diffusion of several phenylalkylamines from borate buffer adjusted to the pH corresponding to their pKa' values through 3-mil silastic membrane at 25°. (See Table I.)

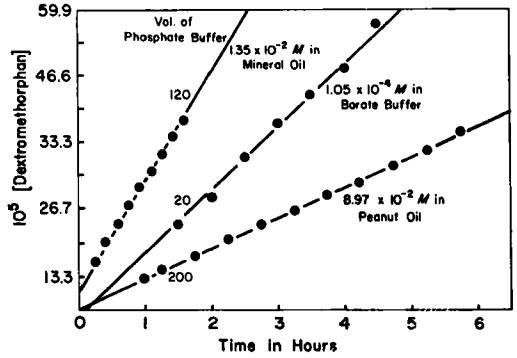

Fig. 4—Concentration of 6.8 phosphate buffer desorbing solution of the stated volumes as a function of time on the steady-state diffusion of dextromethorphan at the cited concentrations from different solutions through 3-mil silastic membrane at 37.5°. The pH of the diffusing solution borate buffer was 10.1.

acid derivatives diffusing from pH 4.7 acetate buffer, where they are unionized, $f_2 = 1$, to pH 10.1 borate buffer where they are ionized, $f_1 = 0$. Typical plots of the diffusion of phenylalkylamines from their partially nonprotonated forms in borate buffers into pH 6.8 phosphate buffers where they are charged, $f_1 = 0$, are given in Fig. 3. Typical plots of the diffusion of dextromethorphan diffusing in its nonprotonated form, $f_2 = 1$, from mineral oil, peanut oil, and pH 10.1 borate buffer into pH 6.8 phosphate buffer, where it would be completely protonated, $f_1 = 0$, are given in Fig. 4.

The apparent diffusion constant, D, was calculated from the rearrangement of Eq. 2 and the determined specific rate of diffusion, $(dC_1/dt)/f_2C_2$ or $(dA_1/dt)/f_2A_2$ as defined in Eq. 3 where $f_1 = 0$,

$$D = XV_1(dC_1/dt)/f_2C_2S \qquad \text{(Eq. 4)}$$

where $X = 7.52 \times 10^{-3}$ cm. for the 3-mil thick silastic membrane, $S = 10.4$ cm.^{2} for the area of the membrane, and V_1 was the maintained volume in liters of the desorbing solution. The fractions of molecules uncharged in the diffusing and desorbing solutions were effectively $f_2 = 1$ and $f_1 = 0$, respectively, for the barbiturates and dextromethorphan. The fraction, f_2, of the phenylalkylamines that were uncharged in the borate buffer diffusing solutions were calculated from the pKa' values of the compounds and the pH values of the borate buffers in accordance with (1),

$$f_2 = [H^+]/([H^+] + K_a) = 10^{-pH}/(10^{-pH} + 10^{-pKa'}) \qquad \text{(Eq. 5)}$$

The concentrations of uncharged phenylalkylamines in the diffusing solutions, their pKa' and pH values, and the observed specific rates of diffusion and apparent diffusion constants are given in Table I.

The determined apparent diffusion constants, solubilities, and partition coefficients for the various barbituric acids are given in Table II. The apparent energies of diffusion, ΔE_a, are calculated from the apparent diffusion constants at the two temperatures studied by

$$\Delta E_a(\text{kcal./mole}) = \frac{10^{-3}(\log D_{37^\circ} - \log D_{24^\circ})2.303R}{(1/T_{24^\circ} - 1/T_{37^\circ})} \qquad \text{(Eq. 6)}$$

where T is the absolute temperature and R is 1.987 cal./degree/mole.

The determined apparent diffusion constants for dextromethorphan from various diffusing solvents are given in Table III.

Further verification of the fact that only nonionized materials diffuse through silastic membranes (1) was obtained from the variation of the apparent diffusion constant, D, on steady-state diffusion into pH 10.1 borate buffer with pH of the diffusing solution on the assumption that $f_2 = 1$ in Eq. 4 (Table IV). The plots of these apparent diffusion constants against pH are shown in Fig. 5. The pKa' values may be considered as the pH values at half the maximum diffusion constant and where dD/dpH is a maximum. These pKa' values for barbital and pentobarbital are 7.50 and 7.72,

TABLE I—APPARENT DIFFUSION CONSTANTS,[a] D, AND SPECIFIC RATES OF DIFFUSION,[b] R_s, OF PHENYLALKYLAMINES THROUGH 3-MIL SILASTIC MEMBRANE AT 25.0° FROM BORATE BUFFER SOLUTIONS INTO pH 6.8 PHOSPHATE BUFFER

Compd.	pKa'	pH	C_2 10^3 M	f_2C_2[c] 10^3 M	R_s[b] 10^2 hr.$^{-1}$	D[a] 10^{10} l./cm.-sec.
α-Methylphenethylamine	9.07	8.93	3.18	1.55	2.84	6.84
3-Amino-1-phenylbutane	9.30	9.40	2.47	1.647	5.00	12.05
1-Methyl-5-phenylpentylamine	9.50	9.60	0.875	0.537	13.41	32.32
α-Ethylphenethylamine	9.30	9.28	1.79	0.917	7.80	18.80
2-Amino-4-methyl-4-phenylpentane	9.42	9.45	0.325	0.190	5.74	13.83

[a] Calculated from $D = XV_1(dC_1/dt)/3{,}600 f_2C_2S$ since $f_1 = 0$, where $X = 7.52 \times 10^{-3}$ cm., and $S = 10.4$ cm.^{2} where $(dC_1/dt)/f_2C_2$ is in hr.$^{-1}$ and $V_1 = 0.120$ l. is the maintained volume of the desorbing solution. [b] $(dC_1/dt)/f_2C_2$, where dC_1/dt is the linear slope of the total concentration in the phosphate buffer solution against time in hours. [c] Calculated from f_2C_2 where C_2 is the maintained concentration of the diffusing solution and $f_2 = [H^+]/([H^+] + Ka') = 10^{-pH}/(10^{-pH} + 10^{-pKa'})$.

TABLE II—APPARENT DIFFUSION CONSTANTS, SOLUBILITIES, AND PARTITION COEFFICIENTS OF BARBITURIC ACID DERIVATIVES

	°C.	C_2 10^3 M	R_S[a] $10^4(dC_1/dt)/C_2$	D[b] 10^{11} l./cm.-sec.	ΔE[c] kcal./Mole	Solubility[d] 10^3 M	Partition Coefficient[e] $CHCl_3$/Acetate Buffer
Amobarbital	24.7	2.97	13.4	5.76	5.1	3.9	20[f]
	37.0	2.80	20.2	8.12			
Barbital	24.1	29.6	0.541	0.216	6.7	38.6	0.80 (0.7)
	37.0	29.6	0.835	0.33			
Butabarbital	24.7	1.96	6.00	2.40	7.2	8.0	9.98
	37.2	2.18	9.87	3.95			
Cyclobarbital	24.7	2.17	2.06	0.82	10.1	35.0	1.36 (13.9)
	37.2	2.44	4.23	1.69			
Diallylbarbituric	24.7	2.34	3.14	1.26	3.6	8.5	3.00
	37.5	2.37	4.04	1.62			
Mephobarbital	24.7	1.01	23.2	9.28	13.6	—	56[f]
	37.2	0.92	61.0	24.4			
Metharbital	24.7	1.32	22.5	9.00	5.5	11.5	56[f]
	37.2	2.78	33.0	13.2			
Pentobarbital	24.1	3.71	11.8	4.72	6.8	3.0	26[f] (28)
	37.0	3.71	19.2	7.68			
Phenobarbital	24.1	4.08	1.64	0.66	6.4	4.6	4.48 (4.7)
	37.0	4.08	2.61	1.04			
Secobarbital	24.7	1.87	22.2	8.88	6.8	7.25	51 (51)
	37.2	1.83	35.6	14.24			
Thiamylal	24.7	0.26	102	40.6	18.2	0.348	high[f]
	37.2	0.42	370	148			
Thiopental	24.1	0.82	216	86.4	6.4	0.82	high[f]
	37.0	0.88	342	137			

[a] Rate of increase per hour of concentration, C_1, of 200 ml. of desorbing solution, pH 10.1 borate buffer, divided by the concentration, C_2, of the diffusing solution of 4.7 pH acetate buffer. This was actually determined from the linear slopes, dA_1/dt, of the plots of absorbance A_1 of the desorbing solution at the wavelengths specified in *Experimental* against time, t, in hours which were divided by the maintained absorbance A_2 of the diffusing solution since $(dA_1/dt)/A_2 = [d(\epsilon C_1)/dt]/\epsilon C_2 = (dC_1/dt)/C_2$ in hr.$^{-1}$. [b] Apparent diffusion constant for the specified barbituric acid derived from steady-state diffusion studies from pH 4.7 acetate 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 pH 10.1 borate buffer solution of volume $V_1 = 0.200$ l. so that D (l./cm. − sec.) = $[(dC_1/dt)/C_2]\ (XV_1)/3600\ S$, where $(dC_1/dt)/C_2$ is given in hr.$^{-1}$. [c] Calculated from $\Delta E_a = [10^{-3}\ (\log D_{37^\circ} - \log D_{24^\circ})\ 2.303R/(1/T_{24^\circ} - 1/T_{37^\circ})]$, where T is the absolute temperature. [d] In pH 4.7 acetate buffer at 25.0°. [e] Parenthetical values are from the literature (14). The acetate buffer was at pH 4.7. [f] These values have large error since the absorbance readings in the acetate buffer were small.

TABLE III—APPARENT DIFFUSION CONSTANTS,[a] D, AND RATES OF DIFFUSION,[b] R, OF DEXTROMETHORPHAN FROM PEANUT OIL, MINERAL OIL, AND pH 10.1 BORATE BUFFER THROUGH 3-MIL SILASTIC MEMBRANE INTO pH 6.8 PHOSPHATE BUFFER AT 37.5°

Dextromethorphan Solution in	Peanut Oil		Mineral Oil	Borate Buffer
	Subsaturated	Saturated	Saturated	Saturated
C_2, 10^2 M	8.97	32.90	1.35	0.0105
R[b], 10^4 M l./hr.	0.6062	2.76	2.10	1.31
V_1, ml.	200	120	120	20
D[a], 10^{11} l./cm.-sec.	2.72	2.02	37.5	501.0

[a] Calculated from $D = XV_1(dC_1/dt)/3600\ f_2C_2S$ since $f_2 = 1$ and $f_1 = 0$, where $S = 7.52 \times 10^{-3}$ cm. and $S = 10.4$ cm.^{2}, where $(dC_1/dt)/f_2C_2$ is in hr.$^{-1}$ and V_1 is the maintained volume of the desorbing solution in liters, and C_1 and C_2 are the total concentrations of the desorbing and diffusing solutions, respectively. [b] dC_1/dt is the linear slope of total concentration in the phosphate buffer solution against time in hours.

respectively, whereas the values from titration were 7.45 and 7.65.

Quasi-Steady-State Diffusion Studies—When nondissociable or nonprotonable compounds such as progesterone are diffused through silastic membrane, there is no way of using buffers to effectively maintain the concentration of the diffusing species as zero in the desorbing solution, *i.e.*, $f_1 = 0$, in the manner that was possible with the previously cited amines and acids. When the same system was used to study the diffusion of progesterone, Eq. 2 is valid where C_2 is maintained constant but C_1 varies with time as $f_2 = f_1 = 1$. Plots of concentration, C_1, of desorbing solution of constant volume, V_1, show decreasing rates of increase with time and approach an asymptotic value as shown in Fig. 6 and the pertinent information is given in Table V.

Diffusion of Drugs from Silastic Capsules—The average area of the silastic membrane in the formulated capsules was 5.58 cm.^{2} with an average membrane thickness of 3.13×10^{-2} cm. However, in this preliminary formulation, the possibilities that some of the silastic adhesive spread over various areas of the capsule modified the thickness and that the capsules were not completely filled must be realized. The observed apparent diffusion constants for various drugs in various solutions from these formulated silastic capsules, on the assumption that the stated available area and thickness are valid, are given in Table VI and compared to those values obtained under the more controlled conditions in all diffusion studies. The comparisons are of the same order of magnitude. When the apparent diffusion constants are related to that of barbital as unity for each method, the

TABLE IV—APPARENT DIFFUSION CONSTANTS,[a] D, OF BARBITAL AND PENTOBARBITAL THROUGH 3.0-MIL SILASTIC MEMBRANE AT 37.3° AS A FUNCTION OF pH

pH	Barbital, D, 10^{13} l./cm.-sec.	pH	Pentobarbital, D, 10^{11} l./cm.-sec.
4.70	33.80	4.60	7.71
6.65	26.08	6.99	7.54
7.30	21.67	7.57	5.58
7.60	15.01	7.90	4.05
8.12	8.83	8.18	3.12
9.15	5.02	8.65	1.53
9.75	2.95	9.05	0.50
10.55	0.65	9.53	0.57

[a] Calculated from $D = XV_1(dC_1/dt)/C_2S$ since $f_1 = 0$, where $X = 7.52 \times 10^{-3}$ cm. and $S = 10.4$ cm.^{2} where V_1 is the maintained volume of the desorbing solution in liters, C_2 is the total concentration of the diffusing solution, and dC_1/dt is the linear slope of total concentration in the desorbing pH 10.1 borate buffer solution against time in seconds.

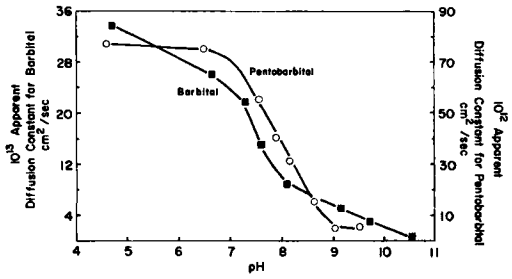

Fig. 5—Apparent diffusion constants of barbital and pentobarbital through 3-mil silastic membranes at 37.3° as a function of pH where no correction has been made for the concentration of uncharged species.

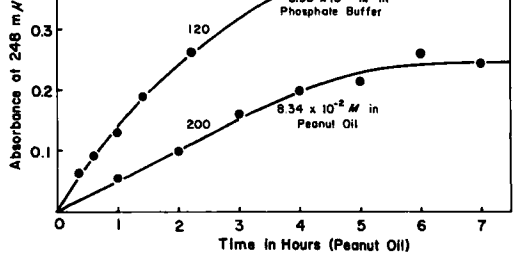

Fig. 6—Absorbance at 248 mμ of the stated volumes of pH 6.8 phosphate buffer desorbing solutions as a function of time on the quasi-steady-state diffusion of progesterone from peanut oil and pH 6.8 phosphate buffer of the stated concentrations through 3-mil silastic membrane at 37.5°.

high degree of correlation of these ratios (Table VI) are truly indicative that the factors affecting diffusion from solution in silastic capsules are the same as those affecting diffusion from solution in the cell.

DISCUSSION

Solid polymeric organic membranes are permeable to uncharged organic molecules which are

TABLE V—APPARENT DIFFUSION CONSTANTS,[a] D, OF PROGESTERONE FROM PEANUT OIL, AND pH 6.8 PHOSPHATE BUFFER THROUGH 3-MIL SILASTIC MEMBRANE INTO pH 6.8 PHOSPHATE BUFFER AT 37.5°

Solution in	Peanut Oil	Phosphate Buffer (Saturated)
Concn., C_2, M	8.34×10^{-2}	5.98×10^{-5}
Volume of phosphate buffer, V_1, ml.	200	120
Apparent diffusion constant, D, 10^{12} l./cm.-sec.	0.38	630

[a] Estimated from the slope of the plot of log $(C_{eq.} - C_1/C_0)$ against time in accordance with the expression log $(C_{eq.} - C_1/C_0) = \log (V_2/V_1 + V_2) - DSt(V_1 + V_2)/(V_1V_2)/2.303X$, where C_1 is the concentration of the desorbing solution of volume V_1 at any time, t, where $C_{eq.}$ is its concentration after final equilibration, C_0 is the concentration of the diffusing solution of volume V_2, S is the area of the 3-mil silastic membrane, and X is the thickness in cm.

lipophilic. In particular, silastic membrane is permeable to the uncharged species of the aminophenones such as *p*-aminoprophenone (1, 2), phenylalkylamines such as amphetamine, steroids such as progesterone, alkaloids such as dextromethorphan, and the barbiturates. These polymeric membranes are impermeable to the charged organic drug and the inorganic ions studied.

The pKa′ values of protonable or dissociating drugs can be determined from the study of rates of steady-state diffusion as a function of the pH of the diffusing solution where half of the maximum diffusing rate at that total concentration is obtained when pH = pKa′ (Fig. 5).

Water and other solvents such as mineral oil do not appear to be readily transported by silastic, although ethanol is transported without modifying the membrane (2).

The classical laws of diffusion appear to hold for silastic membranes so that transport rates in steady-state and quasi-steady-state diffusion can be predicted for particular diffusing and desorbing solutions, their concentrations and pH values from a knowledge of the thickness and area of the membrane, the pKa′ of the diffusing species, and the apparent diffusion constant, $D = KD'$, of the uncharged species.

The latter have now been determined for the several classes of drugs (Tables I–III, V). Only if studies are conducted on thick membranes to determine the intercept value in nonsteady-state diffusion (2, 15–17) can the intrinsic diffusivity constant, D', within the membrane and the actual partition coefficient, K, be separated.

The fact that the rates of transfer (Eqs. 1 and 2) are directly proportional to the concentrations of the diffusing solution up to the limit of the drug's solubility, implies that there is no selective binding to these membranes, no limitations as to sites, and that at all times the concentration in the monolayer on the diffusing side of the membrane is in instantaneous equilibrium with the solution in contact therewith. It also implies and has been confirmed that saturated solutions of drugs diffuse through the membranes at a constant rate.

The apparent diffusion constant, D, can be formulated as a product of the intrinsic diffusion

TABLE VI—APPARENT DIFFUSION CONSTANTS,[a] D, AND SPECIFIC RATES OF DIFFUSION,[b] R_S, OF DRUGS FROM SILASTIC CAPSULES AT 37.5°

Compound	Internal Solution	R_S[b] 10^4 hr.$^{-1}$	D,[a] 10^{11} l./cm.-sec. Silastic Capsules	D,[a] 10^{11} l./cm.-sec. Diffusion Cell	Relative Diffusivities[c] Silastic Capsules	Relative Diffusivities[c] Diffusion Cell
Barbital	Acetate buffer	2.18	0.170	0.338	1.00	1.00
Phenobarbital	Acetate buffer	9.55	0.745	1.05	4.382	3.11
Pentobarbital	Acetate buffer	4.89	3.81	7.71	22.41	22.81
4'-Aminopropiophenone	Phosphate buffer	29.8	38.9	48.2	251.24	142.60
Dextromethorphan	Borate buffer	19.7	154.0	501.0	905.88	1,482.24
Dextromethorphan	Peanut oil	0.967	0.754	2.02	4.38	5.98
Dextromethorphan	Mineral oil	25.0	19.5	37.5	114.71	110.95

[a] Calculated from $D = XV_1 Rs/3600\ S$, where X is the thickness of the membrane in cm. and S is the available surface area in cm.^{2}. [b] The specific rate of diffusion $Rs = (dC_1/dt)/f_2C_2$ is obtained from the slope of the concentration—time in hours plot of the desorbing solution divided by the concentration of the uncharged species in the diffusing solution. [c] Apparent diffusion constant divided by that for barbital from silastic capsules and diffusion cell, respectively.

constant, D', within the membrane, and the operational partition coefficient for the uncharged species between the membrane and the solvent when the diffusing and desorbing solvents are the same (Eq. 2). Another confirmation of this hypothesis is the linear relation between the apparent diffusion constant, D, of a series of barbituric acids for diffusion through silastic membranes and their partition coefficients between acetate buffer solution and chloroform (Fig. 7). Knowledge of rank order of such partition should permit prediction of relative diffusion through such membranes. No significant correlation exists for apparent diffusion constants with solubility or its reciprocal in the diffusing solution for the barbiturate series. This is readily understandable since

$$D = D'K = D'C_m/C_i = D'S_m(1/S_i) \quad \text{(Eq. 7)}$$

where C_m and C_i are the concentrations in the equilibrated monolayer of the membrane and the concentration in the contacting solution, respectively; and where S_m and S_i are the respective solubilities. The apparent diffusion constant would be inversely proportional to the reciprocal of the solubility in the solvent only if the solubility of each drug of a homologous series were the same in the membrane. The fact that the apparent diffusivities, D, are proportional to partition coefficients but not to the solubilities in the case of barbiturates (Table II) denies this assumption.

An interesting result of this analysis is the conclusion that a species in solution can be separated

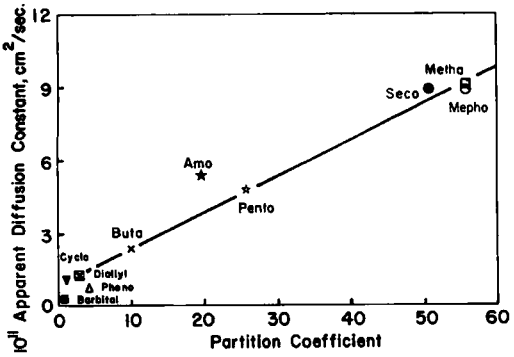

Fig. 7—The apparent diffusion constants of various barbitals diffusing through 3-mil silastic membrane at 25.0° as a function of their partition coefficients between 4.7 pH acetate buffer and chloroform.

from ionic or salt contaminants and concentrated in a desorbing solvent wherein it has a greater activity or solubility than the diffusing solvent. At final equilibrium, the rate of diffusion $dA/dt = 0$ and from Eq. 1.

$$K_2f_2C_2 = K_1f_1C_1 \quad \text{(Eq. 8)}$$

so that, when Eq. 7 is considered,

$$\frac{C_1}{C_2} = \frac{K_2f_2}{K_1f_1} = \frac{f_2}{f_1}\cdot\frac{S_1}{S_2} \quad \text{(Eq. 9)}$$

so that the ratio of the concentrations in both desorbing and diffusing solutions at equilibrium is proportional to the ratio of their solubilities, S_i, in these solutions. In the specific cases of immiscible solvents, these are equivalent to the partition coefficient of the compound in these solvents. In the general case of miscible solvents, such as was shown for ethanol and water (2), these ratios may be considered as hypothetical partition coefficients.

These studies on diffusion through silastic membranes and the fact that solid materials such as progesterone and other steroids in contact with the membrane do permeate (18–21) permits one to conceive of such membranes as isotropic media capable of dissolving drugs in a solid solution with all the operational properties of true solutions. The rates of diffusion within the membrane are dependent on the concentration gradients within them and the distance, X, of traversal. The overall rates of diffusion from solid particles of drug should be dependent on whether or not the rates of dissolution of these particles in contact with the membrane are rate determining. Such particles suspended in a polymer matrix should have rates of dissolution proportional to their surface area in contact. Release rates from the membrane into surrounding solvents would depend on whether these dissolution rates were of higher or lower orders of magnitude than diffusion within the membrane.

SUMMARY

Various polymer films were screened for permeability to various drugs dissolved in several solvents. Detailed attention was placed on the diffusion of a series of barbituric acid and phenylalkylamines, and apparent diffusivities could be correlated with chloroform–acetate buffer partition coefficients. It was ascertained that Fick's law for solid poly-

meric membranes is operative with respect to the concentrations of uncharged organic compounds. Apparent diffusion constants from various solvents were obtained from steady-state and quasi-steady-state studies. Solid materials in contact with such membranes modified to act as potential pharmaceutical dosage forms were studied and demonstrated that basic diffusional information could be used to evaluate, predict, and control such diffusion.

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Keyphrases

Polymeric membranes—drug diffusion
Silastic membranes—diffusion rates
Capsules, silastic—drug diffusion
Solid particles—membrane transport
Diffusion—steady state
Potentiometric titration—pKa values
UV spectrophotometry—analysis
Colorimetric analysis—spectrophotometer

Effect of a Dimethylpolysiloxane Fluid on the Stability of Menadione

By RONALD T. TURNBULL* and KENNETH E. AVIS

The nonaqueous solvents presently in use as parenteral vehicles possess certain disadvantages or have limited application. The silicone fluids have certain physical, chemical, and biological properties which would appear to make them suitable for parenteral formulations. Accelerated thermal and light stability studies were carried out on a dimethyl silicone fluid of 20 centistokes viscosity and corn oil using menadione as the medicinal compound for study. Based on predictions from the accelerated thermal studies, it was found that the dimethyl silicone fluid was superior to corn oil. Corn oil was found to be superior to the dimethyl silicone in retarding photodegradation of menadione at room temperature. Since greater emphasis must be placed on the ability of the vehicle to retard thermal changes in a chemical compound, the experimental results indicate that the dimethyl silicone fluid of 20 centistokes viscosity is superior to corn oil as a vehicle for menadione.

AQUEOUS SYSTEMS are normally preferred for liquid dosage forms intended for parenteral administration because body systems are aqueous and absorption of the drug generally occurs more readily from an aqueous system. However, a number of therapeutic agents, because of their solubility characteristics, can only be formulated in nonaqueous solvent systems. Although the number of such agents is considerably less than those requiring aqueous systems, they are vital to our therapeutic armamentarium.

The nonaqueous vehicles most commonly used are the fixed oils. All of these, however, have disadvantages in use, such as: the development of rancidity with aging, potential allergenic reactions in sensitive individuals and local tissue reac-

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