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

Methods and Reproducibility of Steady-State Diffusion Studies

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The equipment and methods for the study of drug diffusion through polymeric membranes are described. Among studies conducted on a given day, diffusion rates were reproducible within a coefficient of variation of 3.2 percent. Variation in ionic strength from 0.1–0.4 and the variations in hydrostatic head studied had no significant effect on the rates of diffusion of 4′-aminopropiophenone from 6.8 phosphate buffer through silastic membrane into 0.12 *N* HCl. Silastic membrane is shown to be impermeable to phosphate buffer and hydrogen and chloride ions.

THE POSSIBLE mechanisms for the passage of nutrients and drugs across a succession of membranes in the living organism have been explained on their postulated similarity to the transport or diffusion processes in artificial membranes (1–5).

Diffusion is characterized by the tendency of molecules to migrate from a region of high concentration to a region of lower concentration, but is more rigorously stated with respect to chemical potentials or activities rather than concentrations. The membrane is an imperfect barrier separating two fluids and hinders free diffusion of a substance in an isotropic medium.

Dialysis is due to sieve action and is largely dependent on the molecular weight of the diffusate and the viscosity of the solvent in accordance with the Sutherland and Einstein equation (6). Dialysis membranes may be considered as heterogeneous barriers in the sense that they possess pores. The ease of transport is generally a measure of the probability of a solvated molecule entering and diffusing through these pores. There is little selectivity in the separation of two closely related molecules except when their size is approximately that of the size of the pore (7). In general, the solvent as well as the solute is transported; membranes which allow salt transport are permeable to water (8).

Many polymeric membranes, such as copolymers based on polyoxyethylene glycols and polyethylene terephthalate, act as homogeneous barriers to free diffusion (7). Transport may be generally dependent on the relative adsorption of the molecules diffusing to the face of the membrane and solubility of these molecules in the membrane. Lyman and co-workers (7, 9, 10) have prepared synthetic membranes with the express intent of endowing them with specific characteristics which would transfer substances by an adsorption and solubility mechanism and not by sieve action. Variation in copolymer ratios of the synthetic membranes variably affected the transfer rates of glucose and urea. These observations were consistent with postulates of different degrees of association or partitioning with the membranes (11).

Studies on the diffusion of drugs from solution through polymeric substances that cannot be considered as dialysis have been limited. Johnson (12) has studied the diffusion of drugs in cross-linked thiolated gelatin and has observed that both ionic and nonionic drugs diffuse in accordance with Fick's law, which implies dialysis. No rigorous dependence of diffusivity on molecular weight can be concluded among the compounds studied.

The extensive use of polymeric materials for packaging purposes in the pharmaceutical industry has led to the investigation of polymer-drug interactions (13–18). It has been concluded from pH-sorption studies that undissociated acids interact with the basic amide groups of the polyamide nylon through hydrogen bonding. The rate-determining step was stated to be the diffusion of the solute within the polymer. The number of binding sites are finite and Langmuir or Freundlich adsorption models are applicable. Decreased solvent polarity decreased the extent of sorption.

Model systems for the kinetics of drug transport through lipoidal barriers have been studied recently. A series of nonpolar liquids have been selected as models of living membranes between aqueous phases (19–22). The purpose was to obtain values which could be employed to cor-

Received December 18, 1967, from the College of Pharmacy, University of Florida, Gainesville, FL 32601

Accepted for publication February 14, 1968.

Presented in part to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

Abstracted in part from a thesis submitted by P. B. Chemburkar to the University of Florida, in partial fulfillment of Doctor of Philosophy degree requirements.

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

relate the structures, solubilities, and partition coefficients of drug molecules with their ability to pass through different membranes.

The studies reported in this series 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. 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. This is of practical importance in the light of recent pharmaceutical interest in the applications of such phenomena to the design of new dosage forms (7, 9, 10), particularly with reference to silicone rubber or silastic membranes (23, 24).

This first paper of the series describes the apparatus and techniques used to study steady-state and quasi-steady-state diffusion through such a lipid-like polymeric membrane and statistically evaluates the reproducibility of the former.

EXPERIMENTAL

Materials—The silastic medical grade sheeting (H-0169, H-0293), a dimethyl-siloxane polymer (25) was obtained from the Dow Corning Center for aid to Medical Research, Midland, Michigan. They were available in labeled thicknesses of 3, 5,10, and 20 mil. The actual thickness was obtained from the difference of measurements between two sheets of hard-surfaced paper and of the thickness of the two sheets alone. A micrometer screw with an accuracy of 0.1 mil was used at 10 equally spaced sites on seven different 2.54 cm. × 2.54 cm. square patches.

The 4′-aminopropiophenone, m.p. 139–140.5°, lit. value 140° (26), was purchased from Eastman Organic Chemicals, Rochester, New York. All other materials were of analytical reagent grade.

Analytical Methods—The absorbance of 4′-aminopropiophenone, 307 mμ, ϵ = 16,016 was measured in pH 6.8 phosphate buffer solutions against an appropriate blank with a Beckman model DU spectrophotometer in standard 10-mm. light path silica cells at 24.0 ± 1.0°.

Steady-State Diffusion Cells, Assembly, and Procedure—The steady-state diffusion cell designed was a modification of the cell used by Lyman *et al.* (10). An exploded schematic view of the diffusion cell is shown in Fig. 1. It consisted of two stainless steel plates (6.35 cm. × 5.1 cm. × 3.8 mm.), a glass T joint, two silicone rubber gaskets (2.57 cm. i.d. × 2.95 cm. o.d. × 0.16 cm. thick), and a set of four stainless steel nuts and bolts.

Each of the stainless steel plates had a hole in the center, 2.57 cm. in diameter. Around this hole there was a border 0.43 cm. in width from the perimeter of the hole and recessed 2 mm. into one face of the stainless steel plate. The silicone gaskets fitted into the recessed borders around the holes. The two plates had four holes in four corners for the stainless steel bolts.

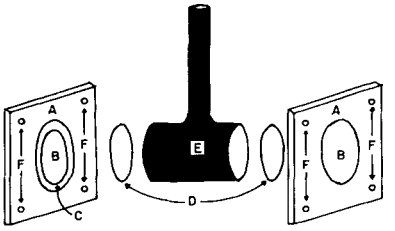

Fig. 1—Diffusion cell used for steady-state diffusion. Key: A, stainless steel plates (6.35 cm. × 5.1 cm. × 3.2 mm.), B, hole in stainless steel plate (2.57 cm. in diameter); C, recessed border around hole B (0.43 cm. in width from the perimeter of the hole and recessed 2 mm. into the stainless steel plate); D, silicone rubber gaskets (2.57 cm. i.d.; 2.95 cm. o.d.; 0.16 cm. thick); E, glass T joint with horizontal glass cylinder (2.6 cm. in diameter, 3 cm. long) and vertical stem (0.8 cm. in diameter and 11 cm. long); F, holes for stainless steel bolts.

The glass T joint consisted of a 3 cm. long hollow glass cylinder 2.60 cm. in diameter joined in its center at right angles on one side to an 11 cm. long glass tube 0.8 cm. in diameter to form a hollow T-shaped device. The two annular edges of the glass cylinder fitted into the recessed borders against the gaskets in the plates.

A 5.1 cm. × 5.1 cm. square of membrane under study (after washing with distilled water and drying in air) was positioned between the recessed border of each of the plates and a silicone rubber gasket. The open ends of the glass cylinder were then fitted into the recessed borders on the face of the silicone rubber gaskets. The whole assembly was held in position by a set of four nuts and bolts passing through the holes in the corners of the plates. The volume of the assembled cell was approximately 22 ml. and the total area of the two membranes available for diffusion was 10.4 cm.^{2}.

The diffusion cell was filled with 20 ml. of the buffered solution of the drug under study and was placed in either a 200 (or 400) ml. beaker which contained either 120 (or 200) ml. of solution into which the drug was to diffuse. The level in the cell was maintained about 3.88 cm. above the horizontal portion of the inverted T joint. This was effected by pumping the drug solution from a 2-L. reservoir through one channel of a Durrum 12-channel Dial-A-Pump (Durrum Instrument Corp., Palo Alto, California) at a rate of 25–30 ml./min. to a tube opening at the diametric center of the horizontal portion of the inverted glass T joint of the assembled diffusion cell. Another pump channel removed the solution back to the reservoir at a rate of 35–40 ml./min. through a tube whose opening was positioned in the stem of the cell at the level of the solution in the beaker (Fig. 2). The net results were to provide excellent agitation of the solution in the cell, maintain a constant level at the positioning of the opening of the effluent tube, renew the cell's contents every few min., and maintain a constant concentration therein (Fig. 2).

The beaker was covered with a Parafilm membrane (American Can Company, Neenah, Wisconsin) taped to the sides of the beaker with a hole in it

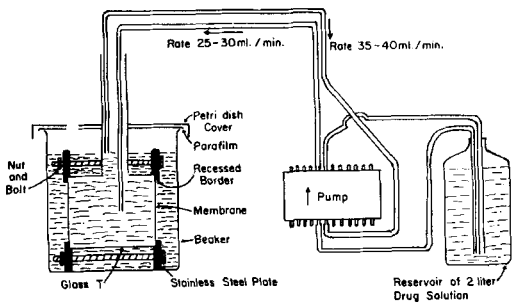

Fig. 2—Diffusion apparatus and pump assembly for steady-state diffusion studies.

for the stem of the diffusion cell. Over this was placed a plastic Petri dish with one hole for the stem and another for sample removal. This construction immobilized the diffusion cell in the beaker and minimized evaporation or contamination of the solution in the beaker (Fig. 2). The beakers with their respective diffusion cells were fitted rigidly in a metal rack inserted in the water contained in the thermostatted shaker bath (American Instrument Co., Silver Spring, Maryland) which was operated at 108 strokes per min. of 3.8 cm.

Prior to initiating any study, the beaker and its contents and the reservoir and its contents were equilibrated at the temperature of the study for about 10 hr.

At the end of each experiment, the volume and pH of the solutions in the beakers and the diffusion cells were measured. The pH values did not change throughout the course of an experiment for all studies.

Reproducibility of Steady-State Diffusion Studies—The reproducibility of diffusion studies was tested by studying the diffusion of 4′-aminopropiophenone, PAPP, from 22.0 ml. of its saturated solution in pH 6.53 ± 0.02 phosphate buffer through 3 mil silastic membrane into 184 ml. of 0.12 *N* HCl at 37.3° ± 0.1°. The cell solution contained excess undissolved PAPP and additional agitation was afforded by bubbling nitrogen through the cell. Samples (1.00 ml.) of the beaker solution of phosphate buffer were removed every hr. for 8–10 hr. Each sample, diluted with 4.00 ml. of pH 6.8 phosphate buffer (μ = 0.3) was measured at 307 mμ. Five separate experiments were performed on each of 5 days. Typical data for one such day are given in Table I.

Effect of Hydrostatic Pressure on Steady-State Diffusion—Solutions of PAPP ($1.70 \times 10^{-3} M$) in pH 6.8 phosphate buffer were circulated into four diffusion cells. The suction tubes of the channels returning the solutions from the diffusion cells to the reservoir were adjusted at four different levels (see Fig. 3) in the stem of the diffusion cell. The levels of the tubes were 0, 1.3 cm., 2.54 cm., and 7.62 cm. above the level of the solution in the beaker. The higher rate of pumping the solution from the cell to the reservoir over that of pumping the solution from the reservoir to the cell, kept the level in the cell constant at the level of the suction tube orifice. The rate of diffusion was monitored by spectrophotometric analysis of the samples from the beaker.

Effect of Ionic Strength on Steady-State Diffusion—A 100-ml. solution of 0.4 *N* HCl containing 2.5 Gm. of PAPP was prepared. Twenty-milliliter aliquots of this solution were added to 170, 330, 500, and 670 ml. of pH 6.8 phosphate buffer with an ionic strength of μ = 1.2. The solutions were then diluted with distilled water to 2 L. to obtain solutions of PAPP of the same concentrations in phosphate buffer but with ionic strengths of 0.102, 0.198, 0.300, and 0.402, respectively. The pH values of these solutions were 6.69, 6.73, 6.75, and 6.78, respectively. These solutions were then circulated in four diffusion cells to study the diffusion of PAPP through silastic membrane into 200 ml. of 0.12 *N* HCl at 23.0°.

TABLE I—STEADY-STATE DIFFUSION OF 4′-AMINOPROPIOPHENONE FROM 22.0 ML. SATURATED SOLUTION ($2.36 \times 10^{-3} M$) IN pH 6.5 PHOSPHATE BUFFER THROUGH 3-MIL SILASTIC MEMBRANE INTO 184 ML. OF 0.12 *N* HCl AT 37.3°[a]

Hr.	Absorbance[a] at 307 mμ in HCl Solution 1	2	3	4	5
0	0.007	0.004	0.008	0.014	0.006
1.00	0.134	0.141	0.116	0.121	0.112
2.00	0.234	0.224	0.232	0.207	0.209
3.00	0.357	0.319	0.340	0.287	0.319
4.00	0.478	0.428	0.460	0.395	0.433
5.00	0.560	0.515	0.532	0.470	0.505
6.00	0.663	0.602	0.653	0.559	0.612
8.00	0.886	0.815	0.875	0.722	0.825

[a] The desorbing sample solutions surrounding the cell were diluted 1:5 with pH 6.5 phosphate buffer before measurement of absorbance at 307 mμ.

Permeability of Silastic Membrane to Phosphate Buffer Salts and Hydrochloric Acid—A steady-state diffusion cell was assembled with 5-mil thick silastic membrane in position. It was filled with about 20 ml. of distilled water. The cell was kept in a 400-ml. beaker containing about 250 ml. of pH 6.5 phosphate buffer (μ = 1.2). A sample of distilled water from the cell was tested after 15 hr. for the presence of PO_4^{3-} by the ammonium molybdate test (27).

Another diffusion cell filled with 20 ml. distilled water was kept in a beaker containing 250 ml. of 0.1 *N* HCl solution. The distilled water inside the cell was tested for the presence of chloride ions after 11 hr. by the silver nitrate test (27). The pH of the distilled water was also measured.

Quasi-Steady-State Diffusion Cell, Assembly, and

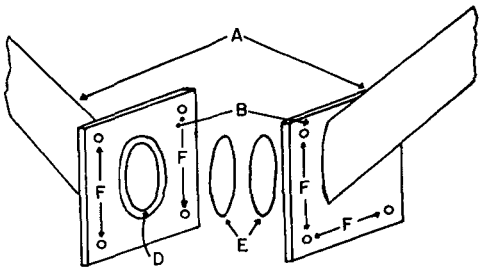

Fig. 3—Diffusion cell used for quasi-steady-state diffusion. Key: A, stainless steel cylinders (3.81 cm. in diameter, 17.8 cm. long); B, stainless steel plates (6.35 cm. × 6.35 cm. × 3.2 mm.); C, hole in stainless steel plate (3.1 cm. in diameter); D, recessed border around hole C (0.8 cm. in width from perimeter of the hole and recessed 2 mm. into the stainless steel plate); E, silicone rubber gaskets (3.1 cm. i.d.; 3.8 cm. o.d.; 3 mm. thick); F, holes for stainless steel bolts.

Procedures—The quasi-steady-state diffusion cell (Fig. 3) consisted of two stainless steel plates (6.35 cm. × 6.35 cm. × 3.2 mm.). Each of these plates was welded to one end of a stainless steel tube (3.81 cm. in diameter and 17.8 cm. long) at an angle of 45°. Each plate had a hole in the center (3.1 cm. in diameter) with a circular border 0.8 cm. in width from the perimeter of the hole and recessed 2 mm. into the face of the plate. The plates had four holes in the four corners for the stainless steel bolts. Two silicone rubber gaskets (3.1 cm. i.d. × 3.8 cm. o.d. × 3 mm. thick) fitted into the recessed border around the holes in the plates. A square of the membrane under study after washing with distilled water and drying in air was clamped between the two silicone rubber gaskets placed in the recessed borders in the plates. The plates were then clamped together with four stainless steel nuts and bolts. The diffusion cell when assembled formed a V-shaped device and held 150 ml. of solution in each of the tubes. The area of the membrane available for the diffusion was 7.55 cm.^{2}.

The solutions in the arms of the quasi-steady-state diffusion cell were agitated by the thermostated shaker bath in which the cell was immersed and wired to the shaker tray.

The cell was initially equilibrated in the thermostated shaker bath for about 8–10 hr. with 100 ml. of the appropriate buffer solution in both arms. Subsequently these solutions were removed by suction and a previously thermally equilibrated 50 ml. or 100 ml. solution of fresh appropriate buffer was added to one arm and an equal volume of thermally equilibrated solution of the drug in the buffer was added to the other arm. The open ends of the arms were covered with Parafilm. At regular intervals, samples from both arms of the diffusion cell were removed and spectrophotometrically analyzed for drug against the appropriate blanks until the differences in absorbances became small. The volume and pH of the solutions in both arms were measured at the end of the experiment.

RESULTS AND DISCUSSION

Impermeability of Silastic Membranes to Salts and Acid—The ammonium molybdate reagent solution (28) gave a yellow colored solution when mixed with an equal volume of 4.8×10^{-4} *M* solution of phosphate buffer. A faintly yellow colored solution was obtained with 9.60×10^{-6} *M* phosphate buffer solution. The sample from the diffusion cell kept for 15 hr. in a beaker containing phosphate buffer did not yield a precipitate or a colored solution with this reagent. It was therefore concluded that phosphate buffer salts do not diffuse significantly through silastic membrane.

A white turbid solution was obtained when 4×10^{-5} *M* solution of HCl was acidified with nitric acid and an equal volume of 10% silver nitrate solution was added. A sample from the diffusion cell kept for 11 hr. in a beaker containing 0.1 *N* HCl did not yield a turbid solution when treated similarly. Also, the 6.45 pH of the solution in the cell was constant for the time interval. It was therefore concluded that HCl does not diffuse significantly through silastic membrane.

Reproducibility of Steady-State Diffusion Studies—An example of the typical data obtained from a steady-state diffusion study of saturated solutions of PAPP in 6.5 phosphate buffer through a 3-mil silastic membrane into 200 ml. of 0.12 *N* HCl (where the concentration of the diffusing species, uncharged PAPP, is effectively zero) is given in Table I for five different cells run simultaneously on 1 day at 37.5°. The absorbances at 307 mμ of PAPP in the desorbing solution were monitored as a function of time, and when plotted against time are straight lines that appear to have zero intercepts.

The data of Table I were statistically analyzed (28–30) to determine linear regression against time, and it was concluded that the hypothesis that the intercepts were zero could not be rejected at the 5% level. The coefficient of variation for values among the slopes of the 5 replicate studies (Table I) conducted on 1 day was 7.0%.

Studies of five replicate diffusion experiments that resulted in data similar to Table I were repeated on each of 5 days. The slopes of the linear plots of concentration of the desorbing solution *versus* time and the analysis of variance (28–30) of these slopes are given in Table II. There was no significant difference between the slopes on the same day and between the slopes on different days. The estimates of variances were: for error, $\sigma_{E^2} = 0.0029$; for replicates, $\sigma_{R^2} = 0.000609$; and for days, $\sigma_{D^2} = 0.0042$. The coefficient of variation for all slopes was 12% and for the means of the slopes on differ-

TABLE II—REPRODUCIBILITY OF 4′-AMINOPROPIOPHENONE DIFFUSION THROUGH SILASTIC MEMBRANE[a]

	Slopes of Concentration of Desorbing Solution *Versus* Time[b]				
Days	1	2	3	4	5
1	0.491	0.482	0.467	0.404	0.425
2	0.531	0.476	0.517	0.444	0.496
3	0.695	0.452	0.501	0.518	0.506
4	0.537	0.483	0.434	0.471	0.509
5	0.509	0.493	0.550	0.592	0.422

Analysis of Variance

Source of Variation	*df*	*SS*	Mean Square	*F* Ratio	Components of Variance
Replicates (*R*)	4	0.021305	0.005326	1.84 N.S.[c]	$\sigma_{E^2} + 4\,\sigma_{R^2}$
Days (*D*)	4	0.018229	0.004557	1.58 N.S.[c]	$\sigma_{E^2} + 4\sigma_{D^2}$
Error (*E*)	16	0.046222	0.0028888		σ_{E^2}
Total	24	0.085756			

[a] Steady-state diffusion of 4′-aminopropiophenone from saturated solution (2.35×10^{-3}*M*) in phosphate buffer through 3-mil silastic membrane into 200 ml. of 0.12 *N* HCl at 37.5° where in the latter solution the PAPP is fully protonated. [b] Moles of PAPP diffused per hr. would be 0.200 time these slope values which are in moles/L./hr. [c] N.S.—not significant.

ent days was 5.3%. This would include the inherent errors of the measurements and the variations among the membranes.

In subsequent experiments where nitrogen purging was not used, the variability among repetitive experiments was even less. For example, in a similar steady-state diffusion experiment at 23.0° through 3-mil silastic membrane where the PAPP concentration was 1.79×10^{-3} moles/L., the ionic strengths and the slopes of plots of concentration in desorbing solution *versus* time in 10^5 moles/L./hr. were: 0.102; 1.25; 0.198; 1.24; 0.300; 1.30; 0.402; 1.31. The coefficient of variation of the slopes was 3.2%, well within the 7.0% calculated for the variation in slopes of the five replicated nitrogen purged diffusion studies conducted in 1 day. These data showed that ionic strength had no significant effect on steady-state diffusion of PAPP through silastic membranes.

Another example is a similar steady-state diffusion experiment at 25.0° through 3-mil silastic membrane where the PAPP concentration was 1.70×10^{-3} moles/L. The number of inches the level of the solution in the cell was above that of the desorbing solution in the beaker (Fig. 3) and the slopes of the plots of concentration in desorbing solution *versus* time in 10^5 moles/L./hr. were: 0.00 in.; 1.42; 0.50 in.; 1.46; 1.00 in.; 1.39; 3.00 in.; 1.45. The coefficient of variation of the slopes was 1.5%. These data showed that hydrostatic pressure exerted by variation of the levels in the diffusion cell within the limits studied had no significant effect on the rate of diffusion of PAPP through silastic membrane.

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Keyphrases

Polymeric membranes—drug diffusion
4′-Aminopropiophenone—diffusion
Diffusion cell, steady state—diagram
Hydrostatic pressure—steady-state diffusion effect
Ionic strength—steady-state diffusion effect
Silastic membranes—permeability
Quasi-steady-state diffusion cell—diagram