Diffusion Layer Effects on Permeation of Phenylbutazone through Polydimethylsiloxane

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Abstract □ The permeation of phenylbutazone through polydimethylsiloxane was studied under conditions of varying membrane thickness, stirrer speed, and pH. The results are described in terms of the two-phase model of general transport theory and provide experimental evidence of its usefulness. It was found that permeation rates are controlled by the aqueous diffusion layer at the membrane surface, especially when permeation cells equipped with thin membranes are weakly stirred. Gentle agitation and thin membranes exist in the intestinal tract, so that drug absorption rates *in vivo* may be limited by a diffusion layer. Diffusion layer control may lead to a breakdown of the pH–partition theory because the ionic and nonionic forms of the drug diffuse through the aqueous diffusion layer. The diffusion of phenylbutazone in polydimethylsiloxane did not obey Fick's law of diffusion.

Keyphrases □ Phenylbutazone—diffusion layer effects on permeation through polydimethylsiloxane □ Permeation, drug—phenylbutazone through polydimethylsiloxane, diffusion layer effects □ Diffusion layer—effects on permeation of phenylbutazone through polydimethylsiloxane □ Polydimethylsiloxane—permeation of phenylbutazone, diffusion layer effects □ Membranes, polydimethylsiloxane—permeation of phenylbutazone, diffusion layer effects

As part of the drug absorption studies being carried out in these laboratories, the effects of dissolution rate, excipients, nutrients, pH, surfactants, and other materials on the permeation rate of drugs *in vitro* were investigated (1–3). During this work, it was found that the pH dependence of phenylbutazone permeation through polydimethylsiloxane membranes (3) could not be described by the pH–partition theory, as has usually been the case for drug permeation through synthetic membranes (1, 4–6). Breakdown of the pH–partition theory may arise from permeation of ions through the membrane or from aqueous diffusion layer effects at the membrane surface. Since permeation of ions through polydimethylsiloxane is unlikely, it appears that diffusion layer effects are responsible for the observed deviations from the pH–partition theory.

A two-phase model (7) of drug absorption was chosen to describe the experimental results. This model is suitable when the experimental conditions are chosen to maintain zero concentration of drug at the desorbing surface of the membrane. From the work of Suzuki *et al.* (7), it can be shown, for weak acids, that:

$$\frac{m}{C_0} = \frac{D_m K_p A}{l}\left\{1 + e^{2.303(\mathrm{pH}\,-\,\mathrm{pKa})} + \frac{1}{T}\right\}^{-1} \qquad \text{(Eq. 1)}$$

where:

$$T = \frac{D_a l}{K_p h D_m} \qquad \text{(Eq. 2)}$$

In these equations, m is the permeation rate of drug through the membrane; C_0 is the concentration of drug in the perfusing solution; D_m and D_a are the diffusion coefficients of the drug in the membrane and in the solution, respectively; K_p is the partition coefficient of the drug between the membrane and the solution; A and l are the area and thickness of the membrane, respectively; pKa is the ionization constant; and h is the thickness of the aqueous diffusion layer in contact with the membrane. Equation 1 reduces to the equation obtained from pH–partition theory if T^{-1} is small and can be neglected (8). The term T^{-1} is not negligible if the permeation rate is dependent upon or controlled by the aqueous diffusion layer in contact with the membrane. Conditions leading to diffusion layer control are low rates of agitation and very thin membranes.

Deviations from the behavior predicted by the pH–partition theory have been observed in experiments involving animal membranes (9–11), in cells constructed especially to demonstrate the diffusion layer problem (12), and in buccal absorption (13, 14). The effect of alkyl chain length on the diffusion layer has been reported (15). The phenylbutazone permeation results described in this paper, however, appear to be the first deviation involving a widely used drug and a synthetic rubber membrane. To ascertain whether the two-phase model is applicable to these results and to investigate some consequences of diffusion layer control, the effects of membrane thickness and stirrer speed on the permeation of phenylbutazone through polydimethylsiloxane were measured.

EXPERIMENTAL

Permeation Experiments—The effect of membrane thickness on permeation rate was measured using a cell similar to that described by Garrett and Chemburkar (4), except that the membranes were attached to the cells with silicone adhesive. Stirring rate experiments were done in the system depicted schematically in Fig. 1. The cells were placed in a beaker, at 37.0 ± 0.1°, containing drug solution buffered with a citric acid–disodium phosphate system having an ionic strength of 1.20. The desorbing solution within the cell was borate buffer at pH 10, ionic strength 0.78, ensuring a virtually zero concentration of unionized phenylbutazone within the cell. During the experiment, the change in concentration of the drug on both sides of the membrane was negligible and a steady rate of permeation was achieved. The drug concentration in the desorbing solution was measured by pumping the solution continuously through a UV spectrophotometer set at 265 nm. Phenylbutazone USP reference standard was used for the Beer's law calibration, giving a molar absorptivity of 21,050.

Agitation—During experiments designed to investigate the effect of membrane thickness on the permeation rate, the internal and external solutions were stirred gently to prevent the formation of concentration gradients within the solutions. In the stirring rate experiments, a three-bladed stainless steel impeller was mounted 3.2 cm above the membrane (Fig. 1). The impeller, 5 cm in diameter, had blades mounted at an angle of about 45° to the shaft, which was turned to drive the solution down onto the membrane.

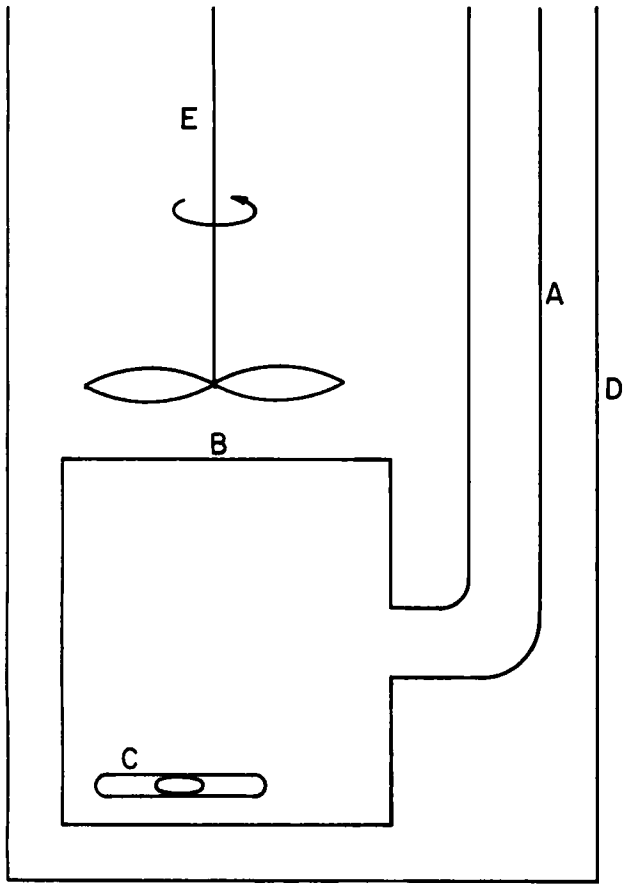

Figure 1—*Schematic diagram of the apparatus used to study stirring rate effects. Glass cell A with polydimethylsiloxane membrane B is stirred internally by magnetic stirring bar C. The cell is mounted in beaker D containing drug solution and stirred by impeller E.*

The shaft was driven by an adjustable stirrer[1] and the rate was measured with a tachometer. The inside of the cell was stirred to prevent the formation of concentration gradients.

Partition Coefficients—Weighed segments of polydimethylsiloxane membrane were immersed in buffered solutions of phenylbutazone, pH 4.0, for 48 hr at 37.0 ± 0.1°. Upon removal from the drug solution, the membrane was rinsed under distilled water, quickly patted dry, and placed in a borate buffer solution, pH 10, at 37°. The concentration of desorbed drug in the buffer was measured spectrophotometrically after allowing 48 hr for desorption. The density of the membrane was estimated from its weight and physical dimensions to be 1.13 g cm^{-3}.

Materials—Phenylbutazone[2] was used throughout. The thicknesses of the polydimethylsiloxane membranes were found by direct measurement to be 0.003[3], 0.015[4], and 0.025[4] cm. All are believed to contain about 30 parts of silica filler per 100 parts of polymer.

RESULTS AND DISCUSSION

The steady-state permeation rate of phenylbutazone through the polydimethylsiloxane membranes was measured under varying conditions of pH, agitation, and membrane thickness. The results were plotted as moles of drug permeated *versus* time. From these graphs the steady-state slope, m, and time lag, t^*, were estimated. Time lag is the point at which the extrapolated steady-state rate intersects the time axis.

[1] Fisher Stedi-Speed.
[2] Ciba Geigy Co., Montreal, Canada.
[3] General Electric Co., Schenectady, N.Y.
[4] Dow-Corning Co., Midland, Mich.

Table I—Parameters Used to Calculate Theoretical Curves for Varying Membrane Thickness

Membrane Thickness, cm	D_mK_p, (cm^2 sec^{-1}) × 10^5	T	pKa	Area, cm^2
0.003	8.16 ± 0.85	0.0093	4.5	8.62
0.015	6.41 ± 0.42	0.061	4.5	8.62
0.025	6.81 ± 0.98	0.082	4.5	8.62

Table II—Parameters Used to Calculate Theoretical Curves for Varying Agitation Rates

Agitation Rate, rpm	D_mK_p, (cm^2 sec^{-1}) × 10^5	T	pKa	Area, cm^2
47 ± 1	8.01 ± 0.28	0.119	4.5	4.46
372 ± 4	6.72 ± 0.56	0.54	4.5	4.46

Effect of Membrane Thickness—Permeation rates over a range of pH values were measured for membranes 0.003, 0.015, and 0.025 cm thick. The results are given in Fig. 2 as plots of m/C_0 *versus* pH. Figure 2 also includes theoretical curves of m/C_0 *versus* pH calculated from Eq. 1. Values of D_mK_p (by definition the permeability coefficient, $P = D_mK_p$) and T were adjusted by trial and error to give the best fit to the data for each membrane. The values used are given in Table I and, for D_mK_p, are in good agreement with those reported previously (3). Equation 2 predicts that the ratio of the membrane thicknesses will be the same as the ratio of T for each membrane. The actual ratios are 1:5:8.3 and 1:6.5:8.8, respectively. The difference between the actual and predicted values, which exceeds the experimental error, may arise from differences in filler content and cross-link density in the membranes studied. Variation in the latter would have a direct bearing on K_p and D_m. The displacement to the right of the m/C_0 curves (Fig. 2) as the membrane thickness decreases is a consequence of increasing diffusion layer control of the permeation process. Diffusion layer control may lead to a breakdown of the pH–partition theory because both the ionic and nonionic forms of the drug diffuse through the boundary layer. If diffusion is membrane controlled, only the nonionic form of the drug enters and diffuses through the membrane. The rate of partitioning into the membrane depends upon the concentration of nonionized drug in the solution, a function of the pH of the solution and the pKa of the drug.

The walls of the GI tract consist of a relatively thick diffusion layer (the mucus) and a relatively thin membrane (the cell wall). Under these conditions, diffusion layer control of the absorption rate might be expected. The *in vivo* absorption of acidic drugs may not, therefore, be adversely affected by the pH of the intestine to the extent predicted by the pH–partition theory. This postulate is corroborated to some extent by the observation that the peak blood level in human subjects given phenylbutazone in solution is observed within 30 min of ingesting the drug (16), although absorption from the stomach, while unlikely, cannot be precluded. Diffusion layer effects may account for the abnormalities observed by Hogben *et al.* (9) and Nogami and Matsuzawa (10, 11), making

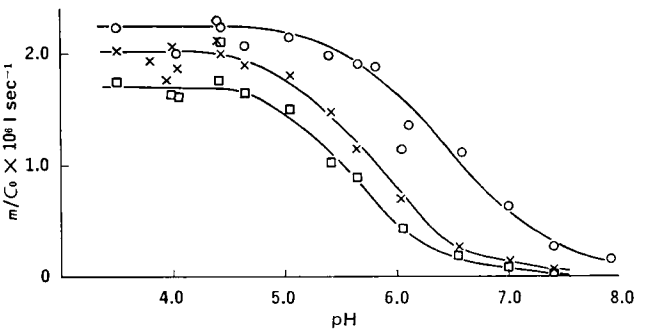

Figure 2—*Plot of* m/C_0 versus *pH. Membrane thicknesses were:* ○, *0.003 cm;* ×, *0.015 cm; and* □, *0.025 cm.*

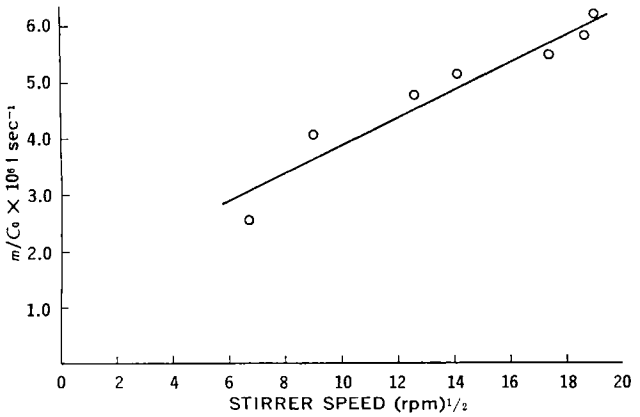

Figure 3—*Plot of* m/C_0 versus *the square root of the stirrer speed; pH = 5.03, l = 0.015, and* A = *4.46 cm².*

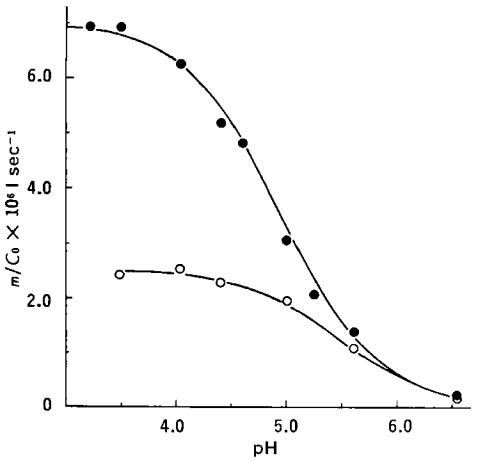

Figure 4—*Plot of* m/C_0 versus *pH; l = 0.015 cm, and* A = *4.46 cm². Stirring speeds were:* ○, *47 rpm; and* ●, *372 rpm.*

it unnecessary to invoke special mechanisms to account for their experimental results.

Effect of Agitation—According to Levich (17), the thickness of a diffusion layer is inversely proportional to the square root of the velocity at which liquid flows past the surface giving rise to the layer. In the present system, liquid is impelled onto the membrane surface and flows across the membrane at a velocity proportional to the stirrer speed, at least at low stirrer speeds. Under diffusion-controlled permeation, the term [exp 2.303(pH − pKa)] in Eq. 1 becomes small compared to T^{-1} and Eq. 1 reduces to:

$$\frac{m}{C_0} \sim \frac{AD_a}{h} \qquad \text{(Eq. 3)}$$

Equation 3 predicts that a plot of m/C_0 *versus* the square root of the stirrer speed will be linear, as was the case for data obtained at pH 5.03 (Fig. 3).

The effect of pH on the permeation rate through 0.015-cm membranes was measured at two levels of agitation, 47 ± 1 and 372 ± 4 rpm. The results are given in Fig. 4 along with the curves calculated from Eq. 1. The parameters used to obtain the best fit of Eq. 1 to the data are given in Table II. While D_mK_p remained essentially unaffected by the stirring rate, T increased by a factor of 4.5, thus showing its dependence on the diffusion layer h (Eq. 2). As the stirring rate increased, the thickness of the unstirred boundary diffusion layer decreased and the rate at which drug permeated the membrane increased. If stirring rates were increased sufficiently, the permeation rate would no longer be controlled by the aqueous diffusion layer.

Diffusion Coefficient—The diffusion coefficient of phenylbutazone in polydimethylsiloxane was determined by the time lag method and the permeation solubility method (18). Under steady-state conditions:

$$t^* = \frac{l^2}{6D_m} \qquad \text{(Eq. 4)}$$

where D_m is the diffusion coefficient of phenylbutazone in the studied membrane and l is the thickness of the membrane. The diffusion coefficients were (1.3 ± 0.7) × 10^{-7} and (1.3 ± 0.5) × 10^{-7} cm² sec^{-1} for the 0.015- and 0.025-cm membranes, respectively (Table III). The poor experimental reproducibility (coefficient of variation of 30–40%) is typical of the time lag method. Siegel and Coughlin (19) discussed the difficulties associated with this method.

The partition coefficient of phenylbutazone in equilibrium between the 0.025-cm polydimethylsiloxane membrane used in these experiments and aqueous buffer, pH 4.0, is 83 ± 9, based upon the mean of three experiments. The diffusion coefficient (0.025-cm membrane) calculated from the permeability coefficient (Table I) and the partition coefficient ($P = D_mK_p$) is 8.2 × 10^{-7} cm² sec^{-1}, significantly greater than the value obtained by time lag measurements (Table III).

The lack of agreement between the two methods indicates non-Fickian diffusion behavior and is not unexpected in view of the work of Most (20) and Flynn and Roseman (21), who studied the effect of silica filler on diffusion in polydimethylsiloxane. Diffusion in polyethylene membranes was recently shown to be non-Fickian (22–24). All polyethylenes are partially crystalline and do not meet the Fickian requirement of homogeneity, which was one boundary condition assumed in the derivation of the relationship $P = D_mK_p$. Since few polymeric membranes are actually homogeneous, it appears that the time lag and the permeation solubility methods are of limited practical applicability for the determination of diffusion coefficients.

Table III—Lag Times and Diffusion Coefficients

0.015-cm Membrane		0.025-cm Membrane	
t^*, sec	D_m, (cm² sec^{-1}) × 10^7	t^*, sec	D_m, (cm² sec^{-1}) × 10^7
420	0.9	360	2.8
420	0.9	1140	0.9
480	0.8	840	1.2
240	1.6	1080	0.9
300	1.3	660	1.5
180	2.1	900	1.1
360	1.0	720	1.4
120	3.1	1200	0.8
360	1.0	720	1.4
540	0.7	1260	0.8
540	0.7	960	1.1
180	2.1	780	1.3
420	0.9	540	1.9
350 ± 138	(1.3 ± 0.7) × 10^{-7}	860 ± 267	(1.3 ± 0.5) × 10^{-7}

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Diffusion of Benzocaine from Ointment Bases

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Abstract □ The release of benzocaine from oleaginous, absorption, emulsion (water-in-oil and oil-in-water), and water-soluble ointment bases *via* dialysis through a cellulose membrane to an aqueous sink was studied at 37.5°, and benzocaine release from some commercially available products was compared with experimental preparations. The rate of release was found to be greater from water-soluble bases than from other bases and was generally dependent on the concentration of drug in the base. An explanation is offered for the case in which the rate of release is not concentration dependent.

Keyphrases □ Benzocaine—release from various ointment bases, dialysis through cellulose membrane □ Ointment bases—comparison of rate of release of benzocaine, dialysis through cellulose membrane □ Vehicles—diffusion of benzocaine from various ointment bases

It is well recognized that one important function of an ointment base is the control it exerts over the release and, therefore, the therapeutic activity of the medication it carries. For topical preparations, there are two general approaches to the formulation problem of maximizing the absorption of the active ingredient from the vehicle. One approach is to include an agent that affects the barrier function of the epidermis, and the second is to alter the physical characteristics of the vehicle and, thus, the diffusion of the drug from the vehicle to the skin (1). When considering only the second approach, an experimental procedure that measures the release of drug from an ointment base should be of value in determining a base of choice for the formulation of an active ingredient. The methods available for measuring the release of drug from a semisolid were recently reviewed (2). Although some investigators have tried to develop models for the prediction of the relative release rates of a drug from various vehicles, it is generally felt to be impossible (2). Before it can be said that a drug is released best by a specific base, the release rates must be compared by some experimental means.

Local anesthetics have been widely used in therapeutic, diagnostic, and surgical situations because of their ability to inhibit pain and itch sensations by reversibly blocking both generation and conduction of impulses in nervous tissue. These agents have been administered by a variety of routes, but topical application for the relief of pain and pruritis is generally used by the lay public. A significantly large number and variety of these products are readily available for purchase as nonprescription items. Among the categories of products marketed that frequently include a local anesthetic in their formulation are burn and sunburn preparations, hemorrhoidal products, throat sprays and lozenges, eczema and psoriasis remedies, teething lotions, otic products, and topical first-aid preparations. Benzocaine (ethyl *p*-aminobenzoate) is an extensively used local anesthetic and is commercially available in concentrations varying from a declared amount of 0.5 to 20.0%.

An excellent method has been reported to measure the effectiveness of local anesthetics when applied to the intact skin of human subjects (3). Thirty commercially available products and some specially formulated solutions were evaluated with respect to their ability to block the sensation of itch and burning induced by an electrical current. Not all of the commercial products contained benzocaine; but of those that did, only one was found to be effective in obtunding the sensation of itch and burning associated with electrical stimulation of an area burned with UV light.

The purposes of this investigation were to: *(a)* utilize a simple dialysis cell method to compare the ef-