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Ultrasonically mediated solute permeation through polymer barriers

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The effects of ultrasound on the permeation of benzoic acid through polydimethylsiloxane, and hydrocortisone through cellulose was investigated. Ultrasonic irradiation resulted in a 23% increase in the permeability coefficient of hydrocortisone in a cellulose film. A 14% increase in permeability coefficient was observed for benzoic acid in a polydimethylsiloxane film. The effects of ultrasound on stagnant aqueous diffusion layers, membrane-solution interfacial temperature, membrane integrity, and diffusant stability were investigated. These factors were not responsible for the observed increases in permeability.

Ultrasound has been reported to enhance solute permeation through biological and polymer barriers. A wide variety of drug agents have been used in conjunction with ultrasound in-vivo and in-vitro and were discussed in a recent literature survey by Skauen & Zentner (1984).

Griffin & Touchstone (1963, 1972) and Griffin et al (1965) studied the penetration of hydrocortisone into swine muscle and nerve tissue after ultrasonic massages with topical hydrocortisone preparations. Hydrocortisone concentrations were found to be over 300% higher in muscle tissue when a hydrocortisone ointment was applied with ultrasound than without ultrasound. Solute permeation in cellulose barriers was shown to be increased by ultrasound. An increase of over 400% in the permeation of potassium chloride and sodium chloride by use of high intensity ultrasonic irradiation was reported (Lenart & Auslander 1980). Mendez et al (1976) observed increased permeation of deuterium oxide through cellulose by ultrasonic irradiation.

Although there have been reports in the literature on the use of ultrasound to enhance solute permeation through membrane barriers, there have been no systematic investigations in which the known parameters of solute permeation have been adequately controlled. Our purpose was to study the effects of ultrasound on solute permeation through model membrane barriers under well controlled in-vitro conditions. Ultrasonic effects on stagnant aqueous diffusion layers, membrane-solution interfacial temperature, equilibrium partition coefficients, and potential structural or chemical changes in diffusant or polymer barriers were investigated.

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Ultrasonic effects on two solute-membrane systems were selected for investigation: a hydrocortisone-cellulose system and a benzoic acid-polydimethylsiloxane system. These systems were distinctly different and served as effective models for the mechanistic investigation of ultrasonic effects. The solute-membrane combinations were chosen from considerations of acceptable permeability characteristics, solute aqueous solubility, and membrane-solute partition coefficients. The mechanism of solute permeation in cellulose and polydimethylsiloxane (PDS) membranes in the absence of ultrasound have been established and described (Fritzinger et al 1971; Kincl et al 1968).

MATERIALS AND METHODS

Materials

Benzoic acid (Fisher Scientific Company, Fair Lawn, NJ, ACS grade) and hydrocortisone (Sigma Chemical Company, St Louis, MO) were used as received. Thin layer chromatographic analysis indicated all reagents were pure. All other reagents were of analytical grade and were used as received.

Polydimethylsiloxane (PDS) membranes (Silastic, medical grade non-reinforced, Dow Corning Corp., Midland, MI) 0·0127 cm thickness were used as received. Cellulose membranes (Spectrapor-3, Spectrum Medical Instruments, Los Angeles, CA) were received in dry, non-hydrated form.

Determination of partition coefficients

Partition coefficients (K) were defined as the ratio of the solute concentration in the polymer phase to that in the solution phase at equilibrium.

The volume and concentration of the benzoic acid solution used in the partition coefficient determinations were the same as those used in the permeation

experiments. Benzoic acid solution (100 ml, 1 mg ml^{-1}) with pH adjusted to 2·0 with HCl, was equilibrated with rectangular sheets of PDS (3·8 × 4·0 × 0·0127 cm). The benzoic acid solution concentration was monitored for 72 h with equilibration attained after approximately 24 h. Constant temperature (25 °C) was maintained with intermittent shaking throughout the equilibration period. After equilibration the membrane was placed in 20 ml of ethanol with continuous stirring for 12 h at room temperature (20 °C) to extract the benzoic acid. This was repeated twice with three rinses of ethanol between extractions. There was no detectable benzoic acid in the last extraction volume of ethanol indicating complete extraction. The ethanol extraction aliquots were combined and the concentration of benzoic acid determined by UV spectroscopy.

The effects of ultrasound on the equilibrium partition coefficients were investigated by ultrasonically irradiating PDS samples pre-equilibrated in benzoic acid solution. Temperature was maintained at 25 °C. Ultrasonic treatment lasted for 30 min at a power level of 33 W which corresponded to time and power levels used in a typical permeation experiment. Extraction of benzoic acid was then performed as previously outlined.

Partition coefficients of hydrocortisone in cellulose were approximated by the volume fraction of water within the hydrated membrane; direct measurements resulted in high variability. The variability was the result of the low levels of hydrocortisone that partitioned into the cellulose polymer. It has been experimentally verified by Ginzburg & Katchalsky (1963) that partition coefficients of hydrophobic solutes in water-swollen membranes such as cellulose were closely approximated by the volume fraction of water within the hydrated membrane. The volume fraction of water in the hydrated cellulose membranes at 25 °C was determined by surface drying the hydrated cellulose film between filter paper and then weighing. The cellulose film was then vacuum oven-dried to constant weight. The volume of water within the film was determined from the wet weight, dry weight, and the density of water. The total volume of the hydrated film was determined from the wet weight and the density of the film as measured with a pycnometer. The technique was previously described by Kaufmann & Leonard (1968). Thicknesses of the hydrated cellulose membranes were determined from geometric considerations (i.e. thickness = volume/(length × width)) and were consistent with direct measurements using a micrometer.

The effects of ultrasound on the volume fraction of water within the cellulose membranes were investigated by ultrasonically irradiating previously hydrated cellulose membranes. Temperature was maintained at 25 °C. Ultrasonic treatment lasted for 60 min at 33 W which corresponded to time and power levels used in a typical permeation experiment. The volume fraction of water within the hydrated membrane was then measured as previously outlined.

Permeation methods

Permeation experiments were performed with specially designed diffusion cells which allowed for vertical separation of a solute donor reservoir compartment from a receptor compartment. Fig. 1 shows a cross-sectional schematic view of the diffusional apparatus. The polymer membranes (D)

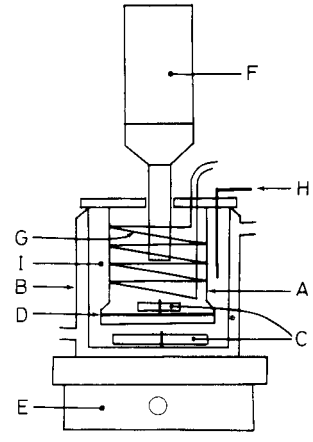

FIG. 1. Cross-sectional view of diffusion apparatus. Key: (A) donor half cell, (B) jacketed beaker receptor cell, (C) magnetic stir bars, (D) membrane, (E) magnetic stirrer, (F) sonicator probe, (G) stainless steel cooling coil, (H) sampling port.

were mounted in the polycarbonate donor half cell (A) between the cell flange and the faceplate. The polymer membranes were not supported. The faceplate was secured to the flange with six nylon screws. The length of the donor half cell was 8·5 cm with an inside diameter of 4·4 cm. The volume of the donor cell was 125 ml. The total membrane area available for diffusion was 15·2 cm^2. The donor cell (A) was positioned in a glass, jacketed beaker (B) serving as the receptor compartment (I). Water at constant temperature was pumped through the jacketed beaker with a circulating water bath (Lauda/

Brinkmann, model RC-20T, Westbury, NY) providing temperature control accurate to ±0·25 °C. Stirring was provided in both compartments by placing a magnetic stir bar (C) directly on the membrane surface (D) in the donor cell and another stir bar (C) in the receptor compartment 2 cm from the membrane surface. Both magnetic stir bars were driven by an external magnetic stirrer (E) at a controlled speed (900 rev min^{-1} unless otherwise stated). Ultrasound at a frequency of 20 kHz was provided by a Branson model 200 sonifier (Branson Sonic Power Company, Danbury, CT). The ultrasonic probe (F) equipped with a flat titanium tip, having 1 cm^2 of surface was centrally positioned in the donor compartment. The probe was submerged 3 cm into the donor solution and was 3 cm from the membrane surface. Ultrasonically mediated experiments were performed with 33 W of ultrasonic power input to the donor solution as determined by the instrument's power meter which was confirmed calorimetrically. Ultrasound at 20 kHz is routinely used for cell membrane disruption applications and was similarly utilized in the present studies as a method for membrane agitation. Continuous cavitation was indicated by the presence of characteristic cavitational noise.

Because the use of ultrasound in solutions may result in thermal effects, the donor cell was fitted with a stainless steel cooling coil (G). Water at constant temperature was pumped through the coil at a controlled rate with a peristaltic pump (Master Flex Pump with variable speed drive, model 7553, Cole Parmer Instrument Co., Chicago, IL) to ensure proper temperature control during ultrasound experiments. Temperature was continuously monitored in both the donor and receptor phase solutions and was controlled to ±0·25 °C of the desired temperature level at all times.

Aqueous solutions of benzoic acid and hydrocortisone served as the donor reservoirs. The pH of the benzoic acid solutions were set at 2·0 with HCl to maintain the benzoic acid in the undissociated form (pK_a = 4·2). The concentrations of benzoic acid and hydrocortisone were 1 and 0·2 mg ml^{-1}, respectively. In all cases the volume in the donor and receptor compartments was maintained at 100 and 190 ml, respectively. Deionized water was used in the receptor compartment for the hydrocortisone diffusion studies while an HCl buffer (pH 2·0) was used for the benzoic acid studies.

The PDS membranes were initially rinsed with deionized water for 30 min and then wiped with ethanol. Cellulose membranes were hydrated in running tap water for 24 h and then rinsed three times in 2 litres of deionized water for 30 min. The same membrane was used for all permeation experiments to eliminate variability. After each experiment the membrane was rinsed with deionized water for about 3 min. All experiments were performed in at least triplicate (n = 3 to 10) with the coefficient of variation less than 3% for replicate runs.

The appearance of diffusant in the receptor compartment was determined by UV spectroscopy (Cary model 219 spectrophotometer Varian Instruments, Palo Alto, CA). Initially the receptor compartment was diffusant-free. Samples (2 ml) were taken from the sampling port (H) in the receptor compartment at appropriate time intervals with a glass syringe. The sample volume was replaced with deionized water or HCl buffer to maintain constant volume. The mass of diffusant lost due to sampling was included in subsequent calculations.

Membrane-solution interfacial temperature

During the ultrasonically mediated permeation of benzoic acid through the PDS membrane, the temperature in the membrane-donor solution interfacial region was continuously monitored using a fine wire thermocouple probe (0·0127 cm diameter iron-constantan, Omega Engineering Inc. Stamford, CT) and a digital thermometer (Omega Engineering Inc. Stamford, CT). The temperature in the cellulose membrane-donor solution interfacial region was monitored in like fashion. The internal temperature of the PDS membrane was also monitored during sonication by embedding the thermocouple probe between two sheets of PDS membrane sealed with silastic medical grade adhesive type A (Dow Corning Corp. Midland, MI). Ultrasonic power input to the system was set at 33 W. The bulk solution temperature was maintained at 25 °C.

Ultrasonic effects on membranes and diffusants

Permeability coefficients of hydrocortisone in cellulose and benzoic acid in PDS were determined before, during, and after the membranes were ultrasonically irradiated. Permanent changes in the permeability properties of the membranes subsequent to ultrasonic exposure would be a clear and sensitive indication of an ultrasonically induced change in the membrane structure.

Characterization of stagnant aqueous diffusion layers

Stirring speeds were measured with a digital photo-tachometer (Model 8211, Cole Parmer Instrument Co., Chicago, IL). Permeability coefficients at 25 °C

were determined in each solute-membrane system at stirring speeds ranging from 830 to 1000 rev min^{-1}. Permeability coefficients of benzoic acid in PDS during ultrasonic irradiation were also determined as a function of stirring at 25 °C. The ultrasonic power input to the donor solution was set at 33 W.

RESULTS AND DISCUSSION

Partition coefficients of 0·649 ± 0·020 and 0·626 ± 0·010 (n = 4 to 6) were determined for benzoic acid in PDS and hydrocortisone in cellulose, respectively. Membranes from the same manufacturer lots were used in all determinations to avoid variation in the measurements. Ultrasonic irradiation did not significantly affect the partition coefficients in either solute-membrane system (Table 1).

Table 1. Values of partition coefficients determined with and without ultrasound at 25 °C.

System	h (cm)	Partition coefficient (K) Control	Ultrasound
Benzoic acid-PDS	0·0127	0·649 ± 0·019	0·655 ± 0·012
Hydrocortisone-cellulose	0·0055	0·626 ± 0·010	0·619 ± 0·005

Values represent the means ± s.d., n = 4 to 6.

Equation 1 may be used to describe the diffusion of solute across a membrane barrier under conditions where the concentration in the donor and receptor phase solutions vary with time. A complete derivation of equation 1 has been given previously (Jacobs 1935; Flynn et al 1974). The analysis assumes: (i) a quasi-steady state exists; (ii) the mass of diffusant in the membrane is negligible in comparison with that in the donor solution; (iii) the receptor phase is initially diffusant-free. Equation 1 was applicable to the present studies.

$$\left(\frac{V_d V_r}{V_d + V_r}\right) \ln\left[\frac{M_d V_r}{M_d V_r - M(V_r + V_d)}\right] = \frac{DAKt}{h} \quad (1)$$

where M_d = mass of diffusant in donor phase (mg), M_r = mass of diffusant in receptor phase (mg), M = net mass of diffusant transferred (mg), V_d = volume of donor phase (ml), V_r = volume of receptor phase (ml), K = the equilibrium membrane-solution partition coefficient, D = the effective diffusion coefficient ($cm^2\ s^{-1}$), A = membrane area (cm^2), t = time (s), h = thickness of membrane (cm). A plot of:

$$\ln\left[\frac{M_d V_r}{M_d V_r - M(V_r + V_d)}\right]$$

vs time yielded a straight line with a slope equal to:

$$\left(\frac{V_d + V_r}{V_d V_r}\right) \frac{DAK}{h} \quad (2)$$

The permeability coefficient, P, defined as:

$$P = \frac{DK}{h} \quad (3)$$

was calculated from the slope. With independent measurements of the partition coefficient and membrane thickness, the diffusion coefficient, D, was calculated. The diffusion and permeability coefficients measured represented observed or effective coefficients and include porosity and torturosity features of the membrane barriers.

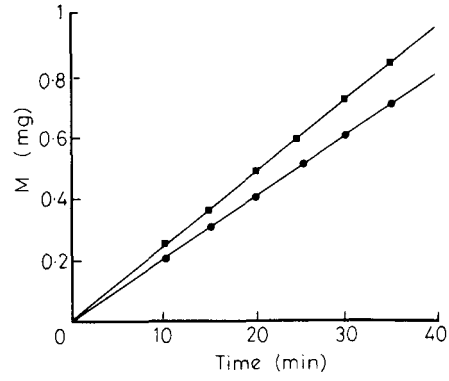

FIG. 2. Amount (net mass of diffusant transferred, M) of benzoic acid diffused through a PDS barrier versus time at 25 °C. Key: (●) control; (■) ultrasound.

Fig. 2 was a typical plot of the amount diffused versus time for the benzoic acid-PDS system with and without ultrasonic irradiation. Similar plots were obtained with the hydrocortisone-cellulose system. The curves represent least squares linear regression lines. Correlation coefficients were >0·999 in all cases. Lag times were not apparent since the same membrane was used in each experiment and contained diffusant at time zero. The increased slopes observed with ultrasound were due to increased solute flux. Tables 2 and 3 summarize the experimen-

Table 2. Effects of ultrasound on the permeation of benzoic acid in PDS at 25 °C.

	Flux ($\mu g\ min^{-1}\ cm^2$)	P × 10^5 ($cm\ s^{-1}$)	D × 10^7 ($cm^2\ s^{-1}$)
Control	1·356 ± 0·013	2·232 ± 0·023	4·368 ± 0·044
Ultrasound	1·541 ± 0·031	2·535 ± 0·050	4·961 ± 0·098

Values represent the means ± s.d., n = 3 to 10.

Table 3. Effects of ultrasound on the permeation of hydrocortisone in cellulose at 25 °C.

	Flux ($\mu g\ min^{-1}\ cm^2$)	$P \times 10^5$ ($cm\ s^{-1}$)	$D \times 10^7$ ($cm^2\ s^{-1}$)
Control	21·618 ± 0·617	3·136 ± 0·073	2·754 ± 0·064
Ultrasound	26·514 ± 1·01	3·849 ± 0·086	3·382 ± 0·065

Values represent the means ± s.d., n = 3 to 10.

tally determined values of flux, permeability coefficients (P), and diffusion coefficients (D) for control and ultrasound experiments. The permeability coefficient of benzoic acid in PDS was increased by 14% over control values by ultrasonic irradiation. Hydrocortisone permeability in cellulose was increased by 23% over control values by ultrasonic irradiation. Statistical analysis (Student's *t*-test) indicated a significant increase in the diffusion coefficient, permeability coefficient and flux in both diffusional systems with ultrasound ($P < 0·001$).

Schwan & Carstensen (1974) and Herrick & Krusen (1954) have shown that ultrasound can produce significant thermal effects in aqueous solutions and solids with localized heating at the interface of two dissimilar substances. Skauen (1974) and Pauly & Schwan (1971) have suggested that these effects occurred mainly from cavitation and absorption of the ultrasonic energy. The temperature, measured by the fine wire thermocouple in the benzoic acid solution-PDS membrane interfacial region was found to be constant at 25 °C during the ultrasound diffusion experiment as shown in Fig. 3. The internal temperature of the PDS polymer was also stable at 25 °C over the same time period.

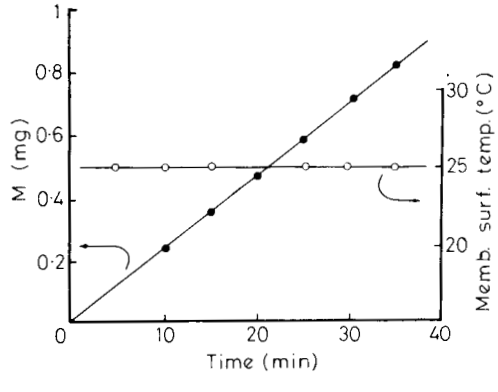

FIG. 3. Amount (M) of benzoic acid diffused through PDS membrane and membrane surface-donor solution interfacial region temperature versus time during ultrasonic irradiation.

Similar results were obtained with the cellulose barrier with no localized heating of the membrane-solution interface observed.

Physical and chemical changes in biological tissues and macromolecules are known to result from exposure to ultrasound of a wide range of frequencies (20 kHz to 6 MHz) and intensities (1 to 1000 W cm^{-2}) as summarized by Skauen & Zentner (1984). The potential degradational effects of ultrasound on the solute-membrane system under study were investigated. The permeability characteristics of membranes which had not been ultrasonically irradiated were the same as those which were previously ultrasonically irradiated (Table 4). This indicated that no permanent changes in the physical or chemical characteristics of the membranes occurred as a result of ultrasonic irradiation. Thin layer chromatography of benzoic acid and hydrocortisone indicated no ultrasonically induced degradation. A single spot was detectable by both UV and iodine complexation. The R_F values of ultrasonically irradiated benzoic acid and hydrocortisone were identical with pure samples. These findings were supported by FT–IR and UV analysis with identical spectra of the diffusant molecules observed before and after exposure to ultrasound.

Table 4. Permeability coefficients ($P \times 10^5$ cm s^{-1}) of benzoic acid in PDS and hydrocortisone in cellulose before ultrasonic treatment of membrane, and after ultrasonic pretreatment of membrane at 25 °C.

System	Before ultrasound treatment	After pretreatment with ultrasound
Benzoic acid-PDS	2·253 ± 0·004	2·245 ± 0·027
Hydrocortisone-cellulose	3·132 ± 0·081	3·139 ± 0·075

Values represent the means ± s.d., n = 3 to 9.

In poorly stirred systems, stagnant aqueous diffusion layers may significantly add to the total resistance to diffusion. Under these conditions, the total diffusional barrier may be considered to be the sum of several individual resistances in series as described previously (Flynn & Yalkowsky 1972). According to equation 4, the ith diffusional resistance, R_i has been defined as the reciprocal of the ith permeability coefficient, P_i, in the ith lamina.

$$R_i = \frac{1}{P_i} = \frac{h_i}{D_i K_i} \qquad (4)$$

where h_i, D_i and K_i are the thickness, diffusivity, and partition coefficient in the ith barrier, respectively. The total resistance, R_t, to diffusion is the sum of the individual resistances. One special case involves a trilaminate series barrier sequentially composed of a stagnant aqueous donor layer, a polymer membrane, and a stagnant aqueous receptor layer. In this case, the thickness of the total barrier to permeation includes the stagnant aqueous diffusion layers at the membrane-solution interfaces. Flynn & Yalkowsky (1972) and Flynn et al (1972) studied the effects of stagnant aqueous diffusion layers on measured permeabilities and derived the following:

$$P = \frac{KD_mD_a}{h_mD_a + KD_m\Sigma h_a} \quad (5)$$

The subscripts 'a' and 'm' refer to the aqueous phases and membrane phase, respectively. The Σh_a term is the sum of the thicknesses of the stagnant aqueous diffusion layers. When the membrane resistance to permeation is much greater than the resistance of the stagnant aqueous diffusion layers, or correspondingly, the product h_mD_a is much greater than $KD_m\Sigma h_a$ the permeability coefficient is effectively reduced to KD_m/h_m. Under these conditions the permeability is a function of only membrane terms.

Dyer & Nyborg (1960) have shown that ultrasonic cavitation and microstreaming may produce significant agitation in aqueous systems. Ultrasonic disruption of stagnant aqueous diffusion layers in poorly stirred diffusional systems would decrease the total barrier resistance and lead to higher permeation rates. The characterization of stagnant aqueous diffusion layers in the present study was made by empirically determining the limiting impeller speed at which further increases in speed produced no measurable change in the observed permeability. The technique was described previously (Ginzburg & Katchalsky 1963; Lane & Riggle 1958). The observed permeability coefficient of benzoic acid in PDS increased with the rate of mechanical stirring up to approximately 900 rev min^{-1} (Fig. 4). Above 900 rev min^{-1} the observed permeability coefficient was constant and was assumed to represent the limiting permeability of the membrane. The observed permeability coefficient of hydrocortisone in cellulose, measured as a function of stirring, was determined to be constant over the entire range of stirring speeds studied (Fig. 5). It was concluded that for the hydrocortisone-cellulose system the critical impeller speed was below 800 rev min^{-1} and the contribution of stagnant aqueous diffusion layers to the overall resistance was minimal.

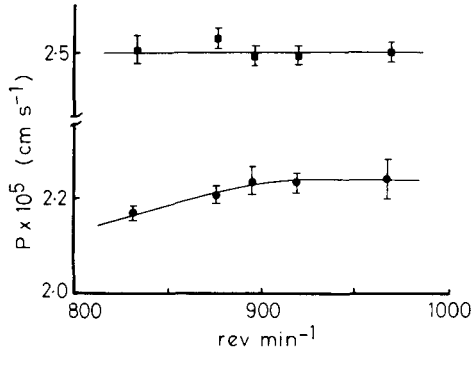

FIG. 4. Plot of observed permeability coefficient (P) of benzoic acid in PDS versus stirring speed at 25 °C with and without ultrasound. Each data point represents the mean ± s.d., n = 2 to 3. Key: (●) control; (■) ultrasound.

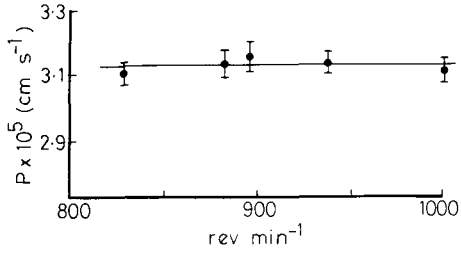

FIG. 5. Plot of observed permeability coefficient (P) of hydrocortisone in cellulose versus stirring speed at 25 °C. Each data point represents the mean ± s.d., n = 2 to 3.

Ginzburg & Katchalsky (1963) have observed that stagnant aqueous diffusion layers may still be present above the empirically determined limiting stirring speeds. However considering the stirring conditions in the present study, the total thickness of these layers was likely to be considerably less than 100 μm. Theoretical calculations of the membrane resistance and stagnant aqueous diffusion layer resistance can be made using Equation 4 if D_a, D_m, and Σh_a are known. These calculations were made (Table 5) assuming that Σh_a was 100 μm and that the diffusion coefficients of benzoic acid in PDS and hydrocortisone in cellulose measured in the present study represented the true membrane diffusion coefficients (D_m). Literature values of the aqueous diffusivities (D_a) of benzoic acid and hydrocortisone were used in the calculations as reported by Ho et al (1976), Goldberg & Higuchi (1968) and King & Brodie (1957).

The contribution of stagnant aqueous diffusion layers to the total diffusional resistance as shown in

Table 5. Stagnant aqueous diffusion layer contribution to diffusional resistance.

System	$D_a \times 10^5$ ($cm^2 s^{-1}$)	Aqueous resistance ($s cm^{-1}$)	Membrane resistance ($s cm^{-1}$)	Total resistance ($s cm^{-1}$)
Benzoic acid-PDS	1·11	901	44 800	45 701
Hydrocortisone-cellulose	0·70	1429	31 888	33 317

Stagnant aqueous diffusion layer thickness (Σh_a) was assumed to equal 100 μm in both cases.

Table 5 was 2% for the benzoic acid-PDS system and 4% for the hydrocortisone-cellulose system. Assuming ultrasound completely disrupted these layers and that this was the only mechanism of ultrasonically increased permeation, the ultrasonic enhancement of permeability would be expected to be only 2% for the benzoic acid-PTDS system and 4% for the hydrocortisone-cellulose system. This is much less than the observed ultrasonically meditated increases of 14% for the benzoic acid-PDS system and 23% for the hydrocortisone-cellulose system.

Permeability coefficients of benzoic acid in PDS measured with ultrasound in conjunction with mechanical stirring were invariant with stirring conditions (Fig. 4). At stirring speeds less than 900 rev min^{-1}, where the thickness of stagnant aqueous diffusion layers become more pronounced, the data suggested that the ultrasonic treatment was disrupting stagnant aqueous diffusion layers. If stagnant aqueous diffusion layers were not disrupted by ultrasound, one would expect the ultrasonic permeability curve to shadow the permeability curve without ultrasound, and fall off at the lower stirring speeds where stagnant aqueous diffusion layers significantly contribute to the total barrier resistance. This behaviour was not observed. It was also clear from Fig. 4 that the enhanced permeability resulting from ultrasound was not exclusively due to disruption of stagnant aqueous diffusion layers as indicated by the significant increase in permeability at stirring speeds greater than 900 rev min^{-1} where it was determined that diffusional resistance from stagnant aqueous diffusion layers was minimal.

The permeability of hydrocortisone in cellulose and benzoic acid in PDS has been shown to be enhanced by ultrasound. The known parameters of permeation have been controlled in all cases. The effects of ultrasound go beyond simple increases in bulk temperature or agitation and do not produce permanent changes in the membrane barrier or diffusing solute.

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