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Ion-paired drug diffusion through polymer membranes

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Summary

Studies of ion pair formation and permeation in non-aqueous media through model synthetic membranes were performed with the aim of lipophilization of ionic drugs for transport across hydrophobic barriers. Ion pair formation was characterized utilizing conductivity, NMR and electromotive force. The permeation experiments were performed using 3 model hydrophobic membranes, dense hydrophobic, porous hydrophobic and hydrophobic–hydrophilic balanced membranes. It was found that the ion-paired drugs attained electrical neutrality and lipophilic characteristics and consequently, had enhanced permeation through hydrophobic membranes. Both partition and pore mechanisms contributed to ion pair diffusion.

Introduction

In general, hydrophobic drugs permeate through both hydrophobic membranes and hydrophilic membranes and hydrophilic or ionized drugs readily diffuse through hydrophilic membranes. Kim et al. (1980) described "partition-pore" type mechanisms which may be used to interpret these transport phenomena. Permeation studies using ionic or hydrophilic drugs with hydrophobic membranes, however, have been unsuccessful. This is primarily due to weak partitioning and low diffusivity of the drug in the membrane. Yet, most drugs utilized in clinical treatments are ionic salts or weak acids and bases which are ionized at physiological pH. Hence, the delivery of ionizable drugs through hydrophobic barriers is of great practical interest, but remains a relatively new and unknown area of research.

Several approaches for enhancing ionic/hydrophilic drug permeation through hydrophobic membranes have been researched including iontophoresis (Sloan, 1986), prodrug design (Higuchi, 1973) and aqueous ion pair complex formation (Tomlinson, 1982). Although these methods show promise in some cases, their application is limited. In the case of iontophoresis, long-term application cannot be achieved since constant external current is utilized. Prodrug design requires chemical modification of drug structures and complicated physical model development to account for simultaneous diffusion and bioconversion. Aqueous ion pair complex formation is mainly induced by hydrophobic interactions which require the presence of bulky hydrophobic groups in both drug ions and counterions.

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Thus, selection of drugs or counterions is restricted. Sufficient dosage is difficult to achieve since the complexes have low solubility products, above which micelle formation or aggregation occurs. Toxicity problems of the counter-ion must also be considered.

Ionic drug permeation through hydrophobic membranes may be facilitated by non-aqueous ion pair formation. Ionized drugs form ion pairs in low dielectric media. The equilibria for this process can be described by Eqn. 1, where A^+B^- represents the electrostatically associated species, the ion pairs.

$$A^+ + B^- \overset{K_a}{\rightleftarrows} A^+B^- \quad (1)$$

The major contribution to the binding energy between ions arises from coulombic interactions. The electrostatic coulombic energy is given by:

$$E = \frac{Z_1 Z_2 e^2}{\epsilon r} \quad (2)$$

where Z_1e and Z_2e are the charges of the ions, r denotes the distance separating the ions and ϵ is the dielectric constant. Thus, it can be seen that the dielectric constant of the medium is an important factor influencing ion pair formation, although non coulombic contributions such as solvation, polarizability of ions and hydrogen bonding, etc., may also be involved.

According to Bjerrum's theory (1926), ion pair formation is dependent on the critical distance d within which ions are stabilized as ion pairs, and is expressed as:

$$d = \frac{Z_1 Z_2 e^2}{2\epsilon kT} \quad (3)$$

where k is Boltzmann's constant and T is the absolute temperature. This equation also demonstrates the importance of the dielectric constant in ion pair formation. The thermal energy and electrostatic energy is equal at the critical distance. Therefore, expressions for the two energies were equated to derive the equation. It can be deduced that in non-aqueous systems where the solvent dielectric constants are less than 40, strong interaction between the ions leads to significant ion pair formation (Fuoss, 1949; Bult, 1983).

One hypothesis is that the ion pairs formed in non-aqueous systems will attain electrical neutrality and consequently, lipophilic characteristics. Hence, hydrophilic ionizable drugs may be readily delivered across hydrophobic barriers via ion pair formation, without modification of the drug structures.

In this manuscript, the ion pair formation of drugs will be characterized utilizing conductivity measurements, NMR and electromotive force. Based on the hypothesis, a mechanistic investigation of ion-paired drug permeation in non-aqueous systems will be presented using the model synthetic membranes listed below:

(1) silicone rubber membrane (dense hydrophobic membrane model)

(2) microporous polypropylene membrane (porous hydrophobic membrane model)

(3) hydroxyethyl methacrylate/styrene copolymer membrane (*p*-HEMA/styrene) (hydrophobic–hydrophilic balanced membrane model)

Materials and Methods

Preparation of polymer membranes

Silicone rubber membrane. A dimethylsiloxane prepolymer base (Silastic, 382 Medical Grade Elastomer, Dow Corning) was placed in a beaker and stannous octoate, a cross-linking agent (0.2% w/w), was added. The solution was completely mixed to ensure homogeneous curing, and then degassed under vacuum and allowed to cure between polystyrene plates separated by a spacer at 23° C for 24 h.

Porous polypropylene membrane. This membrane was obtained commercially (Celgard 2400, Celanese). The micropores in the asymmetric hydrophobic polypropylene network were developed by applying a stretching stress, the average pore size was specified as 0.1 μm.

p-HEMA/styrene membrane. Medical grade HEMA (2-hydroxyethyl methacrylate) was obtained as a gift from Hydron Laboratories and was used without further purification. Styrene (Al-

drich) was purified by distillation under reduced pressure and stored at 4°C. The *p*-HEMA/styrene membranes were synthesized by free radical polymerization. 2,2′-Azobisisobutyronitrile (Polysciences) was used as an initiator at a concentration of 7.84 mmol/liter monomer. Also, 0.3 mole% of cross-linker, ethyleneglycoldimethacrylate was used. Several mixtures of different monomer concentrations in glass vials werre purged with nitrogen gas to remove residual oxygen for 20 min and injected into a polymerization mold consisting of two polyethylene plates separated by a spacer. The polymerization was conducted at 60°C for 5 days, then the molds were soaked in distilled water for 1 day. The membranes were removed and placed into a water/methanol (1 : 1 v/v) mixture for 7 days to eliminate unreacted monomer.

Conductivity measurements

Conductance of drug solutions was measured at 23°C by a conductance-resistance meter (YSI model 34, YSI Scientific) and a pyrex cell with a cell constant of 1.00 cm^{-1}. Equivalent conductance, Λ, was calculated by the relationship:

$$\Lambda = \frac{1000k}{c} \tag{4}$$

where k is specific conductance and c is the normal concentration of drug.

NMR measurements

^{13}C-NMR spectra were recorded on a FT-NMR spectrometer (NR/200, AF series, IBM Instruments) connected to a cryomagnet system (90 mm, 4.7 Tesler magnet) running at 50.327 MHz. Tetraethylammonium chloride was used as an internal reference. 0.3 M solutions of drugs were made in certain solvents and 1 ml samples were placed in glass tube cells. The probe temperature was 23°C.

Permeation experiments by electromotive force (EMF)

A silver–silver chloride (Ag–AgCl) electrode for applying voltage across the membrane in the diffusion cells was prepared. This electrode is commonly used in both aqueous and nonaqueous systems (Strehlow, 1976). Two silver wires (4 cm) were soldered to a copper wire which contained a 1.5 V battery and a 1 K resistor in series. The silver wire (anode) and the copper wire (cathode) were immersed in a 0.1 M potassium chloride solution to create a AgCl coating on the wire. The electrodeposition was continued until the silver wire was coated with dark gray silver chloride. The housing for the electrode was prepared using a glass pasteur pipet. The smaller end of the pipet was flame sealed with an asbestos insert such that micropores remained after sealing. The housing was filled with a saturated potassium chloride solution and the AgCl-coated silver wire was inserted. To examine the EMF effect on ionic drug permeation, an electrode with a charge opposite to the drug ion was placed in the receiver chamber and the other electrode was placed in the donor chamber of the diffusion cell. The voltage was supplied by a voltage generator (EC 103 Minicell Power Supply, E-C Apparatus Corp.). Detailed procedures for diffusion experiments are described in the next section.

Diffusion experiments

Two-compartment glass diffusion cells with each chamber having a 130 ml volume were utilized for the diffusion experiments. The two compartments were separated by a polymer membrane with an area of 14.7 cm^2. The receiver and donor compartments were filled with pure medium and drug solution, respectively. The initial drug concentration was 1 mg/ml. Each chamber was stirred at 1550 rpm by a glass stirrer with an external motor to minimize the boundary layer effect. The polymer membranes were pre-equilibrated with the pure medium for 2 days prior to use. During permeation, 1 ml samples were withdrawn from the receiver chamber and replaced with pure solvent at given time intervals. The concentration of the samples was assayed spectrophotometrically (Perkin-Elmer Lambda 7 UV/VIS spectrophotometer, Perkin-Elmer Corp.). All diffusion experiments were conducted at 23°C.

Measurement of partition coefficients

A solution depletion technique was employed for the determination of the partition coefficient,

K_d, based on the following equation:

$$K_d = \frac{(C_0 - C_s)V_s}{C_s V_m} \quad (5)$$

where C_0 and C_s are the initial and equilibrium drug concentration, respectively, V_s is the volume of the solution and V_m is the volume of the swollen membrane. A membrane sample with a volume of approximately 1 ml was placed in 5 ml of drug solution. The concentration of the drug solution was equal to that used in permeation studies. Equilibrium was reached after 1 week and the drug concentration in solution was measured spectrophotometrically. The volume of the swollen membrane was measured based on its buoyant force in the medium and evaluated using the following equation:

$$V_m = \frac{W_{pa} - W_{ps}}{d_s} \quad (6)$$

where W_{pa} and W_{ps} are the weights of swollen membrane in air and the medium, respectively, and d_s is the density of the medium. W_{ps} could be directly measured by supporting the swollen membrane in the medium with a thin coiled wire which was directly attached to a balance. This method is applicable only if the density of the swollen membrane was higher than the medium.

Treatment of permeation results

From the data obtained in the diffusion experiments, permeation coefficients were calculated from the following equation (Zentner, 1978) which was derived by modifying Fick's law:

$$\ln\left(1 - \frac{2C_t}{C_0}\right) = \frac{-2AU}{Vl} \cdot t \quad (7)$$

where C_t is the solute concentration in the receiver chamber at a certain time t, C_0 is the initial solute concentration in the donor chamber, A is the permeable area of membrane, U is the permeation coefficient, V is the compartment volume, and l is the thickness of the membrane. A plot of $-Vl/2A \cdot \ln(1 - 2C_t/C_0)$ versus t yields a straight line with a slope equal to the permeation coefficient. Diffusion coefficients, D, were calculated by dividing the permeation coefficient by the partition coefficient.

$$D = \frac{U}{K_d} \quad (8)$$

Calculation of solute molecular size and self-diffusion coefficient

An estimation of solute molar volume was made utilizing an atomic or group contribution method, based on the assumption that the solute molecules are spherical (Wilke, 1949; Flynn, 1974). The solute molecular radius was calculated from the following equation:

$$r^2 = (3V/4\pi N_0)^{2/3} \quad (9)$$

where r is the solute molecular radius, V is the molar volume of solute and N_0 is Avogadro's number. To obtain self-diffusion coefficients, the Stokes-Einstein equation was used:

$$D_0 = \frac{kT}{6\pi\eta r} \quad (10)$$

where D_0 is the self-diffusion coefficient, k is Boltzmann's constant, and η is the medium viscosity.

Swelling measurements of polymer membranes

The membrane was placed in the appropriate solvent until its weight remained constant. In general, equilibrium was achieved in 1 week. After measuring the weight of the swollen membrane, the membrane was vacuum-dried until the weight remained constant, then, the weight of the dry membrane was measured. The swelling ratio of the membrane was expressed as the weight percent solvent in the swollen membrane.

Results and Discussion

Conductivity measurements

Solution conductivity is proportional to the current that is transported through the solution in

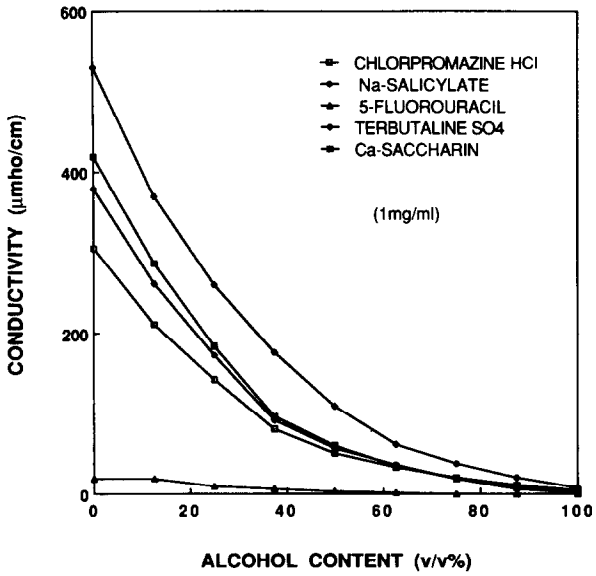

Fig. 1. Conductivity of drugs in propylene glycol/water mixtures.

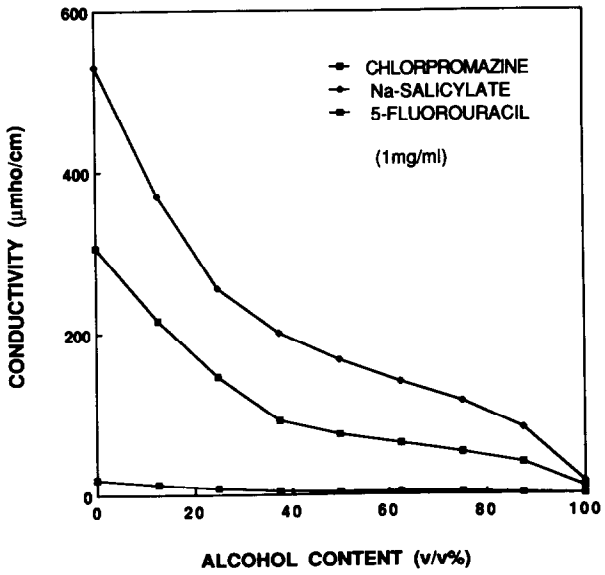

Fig. 3. Conductivity of drugs in isopropanol/water mixtures.

the conductivity cell. In solutions which contain ionic species, the conductivity of the solution is largely dependent on the population of ions. The ion pairing process involves charge neutralization which can be observed via conductivity measurements. Therefore, conductivity measurements of several ionic drug salts were conducted in binary gradient mixtures of aqueous and non-aqueous solvents (Figs. 1–3). The drug concentration was the same as in the diffusion experiments. The non-aqueous solvents were alcohols, such as propylene glycol, ethanol and isopropanol.

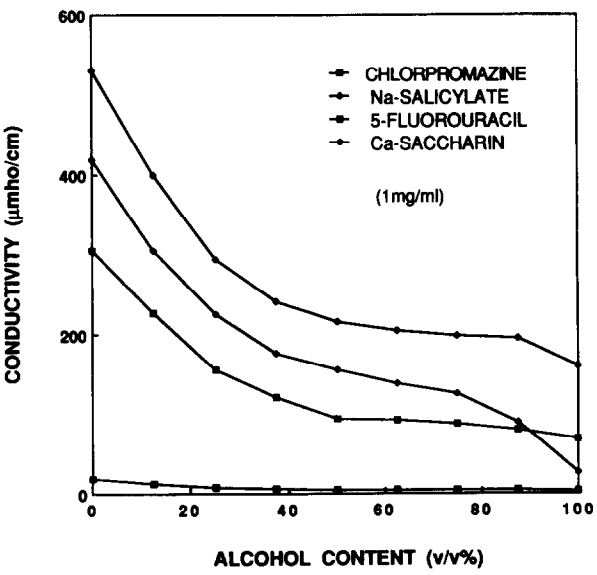

Fig. 2. Conductivity of drugs in ethanol/water mixtures.

As shown in Figs. 1–3, the solution conductivity of the ionic salts varied significantly as a function of solvent composition. The highest conductivities were observed in pure water where the drug salts were almost completely ionized. The conductivities decreased significantly as the alcohol content increased for all the ionic drugs, indicating a gradual decline in the concentration of the conductive ionic species. Thus, it is presumed that ion pair formation was induced by increasing the relative amount of non-aqueous medium. This effect is due to the lowering of the medium dielectric constant which is known to be an important factor affecting coulombic interactions between oppositely charged ions, which is the driving force for ion pairing.

It is possible, however, that changes in conductivity resulted from changes in the media. In order to examine this effect and to reaffirm the formation of ion pairs, conductivity of 5-fluorouracil, a neutral compound, was measured as a reference (see Figs. 1–3). The change in conductivity of

5-fluorouracil by varying the solvent composition was not significant compared to that of the ionic drug salts. The conductivity of pure media was found to be negligibly small in all cases; therefore, the decrease in conductivity of the drug salts was mainly due to the formation of electrically neutral ion pairs. It was noteworthy that in pure low dielectric medium, i.e. isopropanol ($D = 18.3$), that both the ion-paired species and the intrinsically neutral compound, 5-fluorouracil had low conductivities.

Conductivity measurements of the model ionic compounds manifested evidence of ion pair formation in non-aqueous media. However, the results were limited in providing quantitative estimations of ion pair formation since the conductivity of ionic compounds may be influenced by factors such as ion mobility. Another method to explain ion pair formation is by the relationship between equivalent conductivity and drug concentration based on the following equation (Fuoss, 1949):

$$\Lambda = \Lambda_0 - (a\Lambda_0 + b)\sqrt{c} \tag{11}$$

where Λ is equivalent conductivity, Λ_0 is equivalent conductivity at infinite dilution, c is the concentration in gram equivalents per liter, and a and b are constants dependent on dielectric constant, temperature and viscosity. In general, strong electrolytes, i.e. salts, which are completely ionized in aqueous solutions conform to this equation, yielding straight lines with small negative slopes. For weak electrolytes such as acetic acid, however, the equivalent conductivity falls off rapidly as concentration increases corresponding to ionic association. The degree of dissociation, α, is described by the Arrhenius equation:

$$\alpha = \frac{\Lambda}{\Lambda_0} \tag{12}$$

The ionic drugs used in these studies were strong electrolytes in aqueous media, but were expected to behave like weak electrolytes in non-aqueous media due to the effect of ion pairing.

Fig. 4 shows a plot of the equivalent conductivity of a model ionic compound, sodium salicylate,

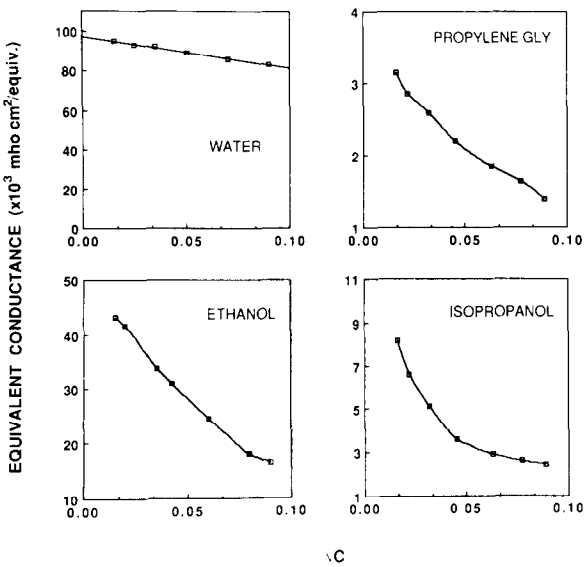

Fig. 4. Equivalent conductivity of sodium salicylate in several media.

based on Eqn. 11. In water, a linear relationship was observed, with a very small negative slope, indicating the predominance of the ionized species. In contrast, the compound in non-aqueous media yielded curves with large slopes. This result demonstrates that significant ion pair formation occurred in the non-aqueous media. The larger negative slope was indicative of a greater degree of ion pair association.

Quantitative analysis of the ion pair formation was performed using the Shedlovsky equation (Fuoss, 1949):

$$\frac{1}{\Lambda S} = \frac{K_a}{\Lambda_0^2} c\Lambda f^2 S + \frac{1}{\Lambda_0} \tag{13}$$

where K_a denotes the ion pair association constant, f is the activity coefficient of the solute, and S can be written as:

$$S = 1 + \frac{a\Lambda_0 + b}{\Lambda_0}(c\alpha_0)^{1/2} \tag{14}$$

$$\alpha_0 = \frac{\Lambda}{\Lambda_0} S \tag{15}$$

TABLE 1

Ion pair association constants of ionic drugs in water, propylene glycol (PG), ethanol (EtOH) and isopropanol (IP)

	Water (78.3) [a]	PG (32.0) [a]	EtOH (24.3) [a]	IP (18.3) [a]
Sodium salicylate	≈ 0	486	1252	2314
Sodium diclofenac	≈ 0	650	1115	2969
Sodium warfarin	≈ 0	459	1229	1453
Hydralazine HCl	≈ 0	435	–	–
Terbutaline SO_4	≈ 0	522	–	–

[a] Dielectric constant.

where α_0 is the degree of dissociation for an ion pair. Initial values for Λ_0 were estimated by an extrapolation based on Eqn. 11. Several iterations resulted in a refined Λ_0 value. A plot of $1/\Lambda S$ versus $c\Lambda f^2 S$ yielded a straight line with a slope K_a/Λ_0^2 from which the association constants were obtained.

The ion pair association constant for several ionic drugs in non-aqueous media were measured and the results are tabulated in Table 1. It was observed that ion pair association was enhanced as the medium dielectric constant decreased. The variation in the association constant among the different ionic drugs was not great in a given medium. Therefore, the medium dielectric constant appeared to be the major factor governing ion pair formation.

NMR measurements

Additional characterization of non-aqueous ion pair formation was attempted using ^{13}C-NMR. NMR can be utilized to investigate ionic interactions on a molecular level, which cannot be done with conductometric studies. Sodium salicylate was selected as a model ionic compound. This compound contains an anionic carboxylic group. When the sodium counter-ion associates with the carboxylic anion during the ion pairing process, the electronic environment around the ionic center of salicylate ion will be altered. Therefore, the magnitude of the ion pair formation was expected to be represented by the chemical shifts of the carbon atoms adjacent to the ion pairing site. On the basis of this concept, ^{13}C-NMR spectra of sodium

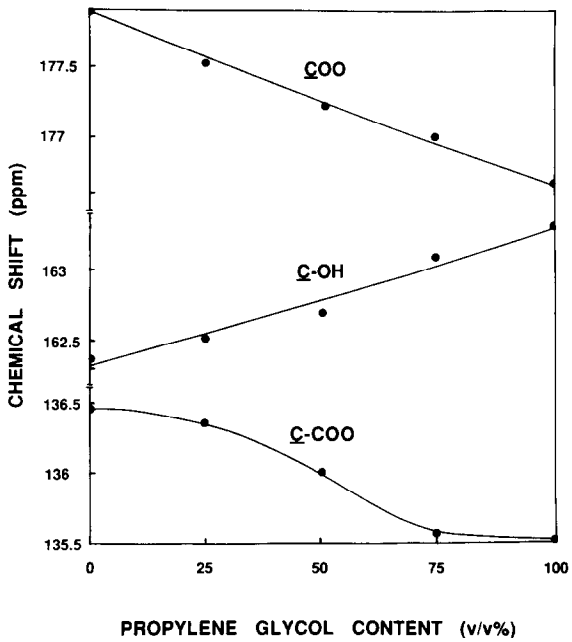

Fig. 5. ^{13}C-NMR chemical shifts of sodium salicylate in propylene glycol/water mixtures.

salicylate was measured in binary gradient mixtures of propylene glycol, a model ion pairing medium, and water, an ionizing medium.

The carboxylic carbon peak of sodium salicylate appeared around 177 ppm, and the peak of the next adjacent carbon in the benzene ring was around 135 ppm. The peak for the hydroxyl carbon appeared around 162 ppm. The rest of the benzene ring carbon peaks range from 118 to 132 ppm. The chemical shifts of ^{13}C-NMR peaks for sodium salicylate are shown in Fig. 5. The carboxylic carbon peak shifted upfield as the propylene glycol ratio of the media increased. The peak of the next adjacent carbon also showed an upfield shift. This behavior was attributed to ion pair formation with increasing propylene glycol content. Shindo et al. (1976) investigated the ^{13}C-NMR chemical shifts of the carbon atom in a carboxylic acid at different pHs. It was found that the carboxylic carbon peak shifted upfield as the amount of unionic (protonized) carboxylic group increased at low pH levels. In terms of charge neutralization of the carboxyl anion, the protonization in acid–base equilibria and the ion pairing in low dielectric media would be expected to exert

similar effects on the chemical shift of the carboxylic carbon. Therefore, it was confirmed that the chemical shift of the carboxylic carbon of sodium salicylate was due to ion pair formation.

Noticeable downfield shifts with increasing propylene glycol content were also observed for the carbon atom attached to the hydroxyl group. This indicates that the positive sodium counter-ion also interacted with the hydroxyl group causing deshielding of the adjacent carbon atom. The chemical shifts of other benzene ring carbons remained relatively unchanged indicating no interaction with the counter-ion.

To reaffirm the above interpretations, chemical shifts of salicylic acid in water at pH 10 and propylene glycol were compared to the spectra for sodium salicylate in the same solvents. In water, salicylic acid showed the same chemical shifts as sodium salicylate, this was expected since the species were identical. The carboxylic carbon peak of salicylic acid in propylene glycol appeared more upfield (174.65 ppm) than that of sodium salicylate (176.65 ppm). This observation suggests that ion pairing in sodium salicylate may not be as strong as the covalent bond in salicylic acid.

Effect of electromotive force on permeation in membranes

Permeation experiments with model ionizable drugs through *p*-HEMA membranes were conducted in water, an ionizing medium and propylene glycol, an ion pairing medium. Fig. 6 shows the permeation of sodium salicylate through a *p*-HEMA membrane in water. When steady-state permeation was reached, voltage (43 V) was applied across the membrane. The permeation was substantially enhanced by the electromotive force, thus the total flux of sodium salicylate could be expressed as follows:

$$J = -D\left(\frac{dC}{dx} + \frac{ZF}{RT}DC\frac{de}{dx}\right) \qquad (16)$$

where Z is the charge of the solute, F is the Faraday constant, and de/dx is the additional driving force of the electrical potential gradient. The effect of the electric field was to enhance the flux of ions. After removal of the electromotive

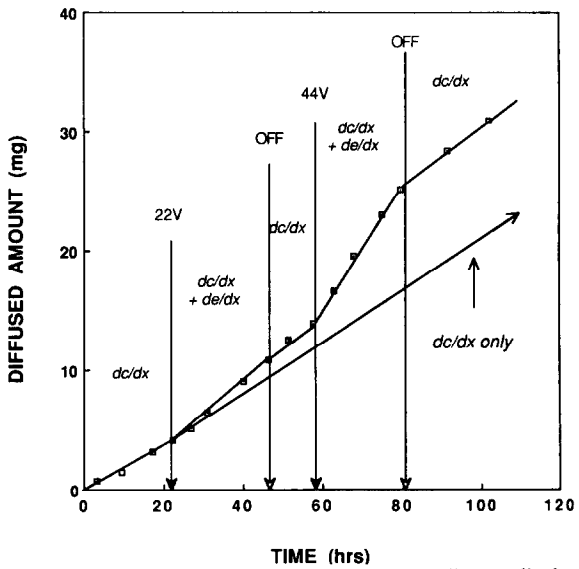

Fig. 6. Effect of electromotive force on sodium salicylate permeation through *p*-HEMA membrane in water.

force, the permeation of sodium salicylate was dependent only on dC/dx. In contrast, the application of an electric field had little effect on sodium salicylate permeation through the membrane in ion pairing media, such as propylene glycol, isopropanol and ethanol (not shown). In order to determine the effect of electromotive force on the membrane itself, permeation of 5-fluorouracil, an intrinsically neutral compound, was conducted in both aqueous and non-aqueous media. The application of the electric field had no effect on permeation. Thus, these results show that species in non-aqueous systems were predominantly electrically neutral ion pairs.

Permeation studies through polymer membranes

Case 1. Ion-paired drug permeation through dense hydrophobic membrane

The model dense hydrophobic membrane used in the permeation studies was silicone rubber. This hydrophobic membrane is permeable to hydrophobic compounds such as steroids (Roseman, 1972), and relatively impermeable to hydrophilic compounds due to their poor partitioning into the polymer.

Permeation experiments with the model drugs,

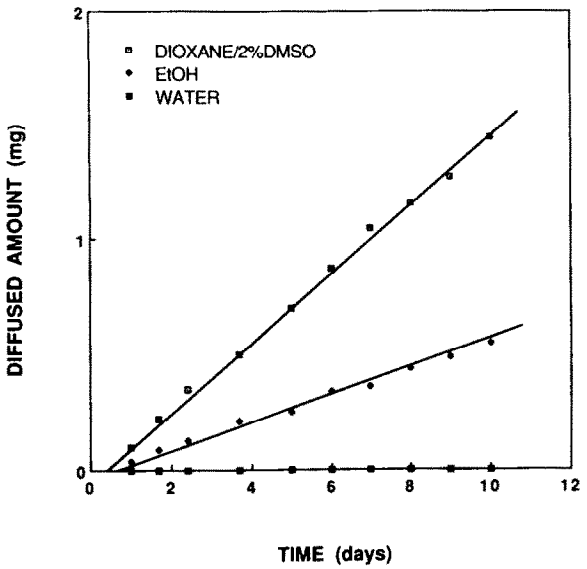

Fig. 7. Permeation of sodium salicylate through silicone rubber membrane in dioxane/2% DMSO, ethanol and water.

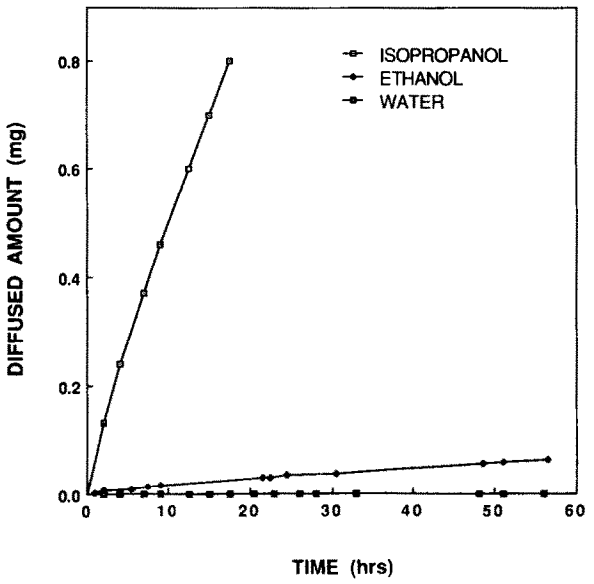

Fig. 8. Permeation of sodium warfarin through silicone rubber membrane in isopropanol, ethanol and water.

sodium salicylate and sodium warfarin, were conducted to investigate the diffusion of ion-paired drugs in several non-aqueous media. An aqueous medium was employed as a reference system in which the drugs will exist as ionic species. As shown in Fig. 7, no permeation of sodium salicylate occurred in water. In contrast, significant permeation was observed in non-aqueous media, such as ethanol and dioxane (2% DMSO was added to dioxane to improve drug solubility). Similar results were obtained using another model drug, sodium warfarin, i.e. no permeation in the aqueous medium and significant permeation in the non-aqueous media (isopropanol and ethanol) (Fig. 8).

The impermeability of the hydrophobic membranes to the ionized drugs in aqueous media can be explained by the Born energy of charging (Parsegian, 1969). This theory predicts a large energy difference between an ion in water and an ion within a non-polar membrane. The ion-paired drugs were electrically neutral and without an electrostatic energy term. Thus, the activation energy for the neutral ion pairs to partition into the hydrophobic membrane is much lower than for the ions. Consequently, the permeation of ion pairs through the membrane is greater than the permeation of ions. These facts suggest that the ion-paired drugs in the non-aqueous media diffused primarily via a partition type mechanism. This phenomenon is illustrated in Fig. 9.

Higher permeability was observed in isopropanol and dioxane than in ethanol. Two factors may contribute to this difference. These are the dielectric constants of the media and the swelling of the membrane. The dielectric constants of dioxane/2% DMSO ($D \cong 2$) and isopropanol ($D = 18.3$) are lower than that of ethanol ($D = 24.3$). The lower dielectric media contain more ion pairs, a diffusable species, which leads to higher flux. The other factor was membrane swelling. The swelling ratios were about 18% in both dioxane and isopropanol and 3% in ethanol. The ion-paired drugs were associated with the solvent and the ion pair stabilization was primarily due to coulombic forces. Thus, solvent partitioning was accompanied by ion pair permeation. Permeation occurred through the membrane with 3% swelling ratio in ethanol. In this low swelling range, permeation has rarely been observed for hydrophilic solutes through a dense hydrogel, such as *p*-HEMA with 5 mol% cross-linking (Kim, 1980). This *p*-HEMA membrane allowed only hydrophobic solute per-

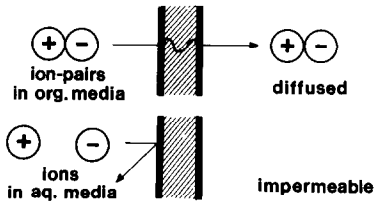

Fig. 9. Schematic illustration of ion-paired drug permeation through silicone rubber membrane; dense hydrophobic membrane model.

meation and showed 10% swelling in water. It is possible that pore channels were not present in the hydrophobic silicone rubber membrane with low ethanol swelling (3%). Therefore, permeation of sodium salicylate was primarily as neutral ion pairs via a partition mechanism.

In the case of dioxane or isopropanol, the solvent partitioning into the membrane was high (18%). Thus, both pore and partition permeation mechanisms were involved.

Case 2. Ion-paired drug permeation through porous hydrophobic membrane

The model membrane used in this study was a Celgard membrane, a hydrophobic polypropylene network containing micropores. Discrete micropores of 0.1 μm in diameter were uniformly dispersed in the polymer network and the porosity was about 35% (Bierenbaum, 1974). This membrane is a good model barrier which contains both porous channels and a hydrophobic nature. Permeation experiments with model ionic drugs and the Celgard membrane were performed in non-aqueous and aqueous systems (Fig. 10). The permeation of the drugs was dependent mainly upon the solvent nature, i.e. aqueous or non-aqueous. The transport of ionized drugs in water did not occur. This was primarily due to the lack of water partitioning into the membrane. In non-aqueous media, marked permeation of the ionic drugs was observed due to the wetting of the hydrophobic pores. Thus, ionic drugs were found to be permeable through hydrophobic pores via both the wetting nature of the solvent and the ion pair formation in non-aqueous systems. A schematic illustration of the permeation mechanism is shown in Fig. 11.

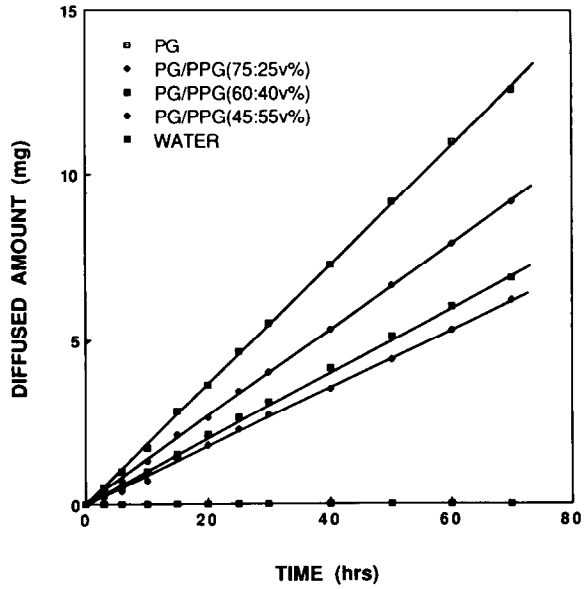

Fig. 10. Permeation of sodium diclofenac through Celgard membrane in non-aqueous versus aqueous media. PG, propylene glycol; PPG, polypropylene glycol 400.

The permeation rate decreased with increasing percent of polypropylene oxide, a more viscous medium than propylene glycol. This fact suggests that medium viscosity is an important factor controlling the rate of drug permeation through hydrophobic pores.

This model study was an extreme case in which diffusion channels consist solely of hydrophobic pores. In addition to the partition type mechanism previously suggested, this model study indicated that ionic drug transport can also be enhanced in the presence of porous channels in hydrophobic barriers.

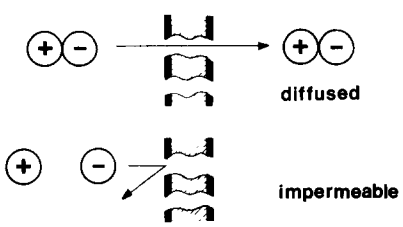

Fig. 11. Schematic illustration of ion-paired drug permeation through Celgard membrane; porous hydrophobic membrane model.

TABLE 2

Permeation of sodium warfarin and warfarin base through p-HEMA / styrene (ST) membranes in propylene glycol (PG) and water

Monomer feed composition (w/w%)		Sodium warfarin		Warfarin	
		PG	H_2O	PG	H_2O [a]
p-HEMA	U	3.04×10^{-8}	3.03×10^{-8}	5.20×10^{-8}	3.78×10^{-8}
	K_d	0.69	2.07	0.73	2.30
	D	4.41×10^{-8}	1.46×10^{-8}	7.15×10^{-8}	1.64×10^{-8}
p-HEMA/ST(95 : 5)	U		3.09×10^{-9}		1.12×10^{-8}
	K_d		1.52		1.88
	D		2.03×10^{-9}		0.60×10^{-8}
p-HEMA/ST(90 : 10)	U	4.89×10^{-8}	≈ 0	5.93×10^{-8}	≈ 0
	K_d	0.74	–	0.78	–
	D	6.61×10^{-8}	≈ 0	7.60×10^{-8}	≈ 0
p-HEMA/ST(70 : 30)	U	6.07×10^{-8}	≈ 0	6.62×10^{-8}	≈ 0
	K_d	0.80	–	0.80	–
	D	7.59×10^{-8}	≈ 0	8.28×10^{-8}	≈ 0
p-HEMA/ST(50 : 50)	U	3.79×10^{-8}	≈ 0	7.12×10^{-8}	≈ 0
	K_d	0.76	–	0.83	–
	D	4.92×10^{-8}	≈ 0	8.58×10^{-8}	≈ 0

U = permeation coefficient (cm^2/s); K_d = partition coefficient; D = diffusion coefficient (cm^2/s); ($n = 3$, S.D. < 5%).[a] Permeation was conducted at pH 10.

Case 3. Ion-paired drug permeation through hydrophilic–hydrophobic balanced membranes

Case 1 and 2 studies were models for ion-paired drug permeation through dense hydrophobic and porous hydrophobic membranes, respectively. To further substantiate the diffusion mechanism involved in ion-paired drug permeation, hydrophilic–hydrophobic balanced membranes were selected as model membranes. The membranes were HEMA/styrene copolymers with varying degrees of hydrophobicity, i.e. styrene content. Tested drugs included sodium warfarin, an ionic drug and warfarin, a neutral analog. Permeation studies with the drugs were conducted in an ion pairing medium, propylene glycol, and in an ionizing medium, water. The permeation results are summarized in Table 2. From the data in Table 2, a plot of diffusivity of sodium warfarin versus styrene composition of the membrane is given in Fig. 12.

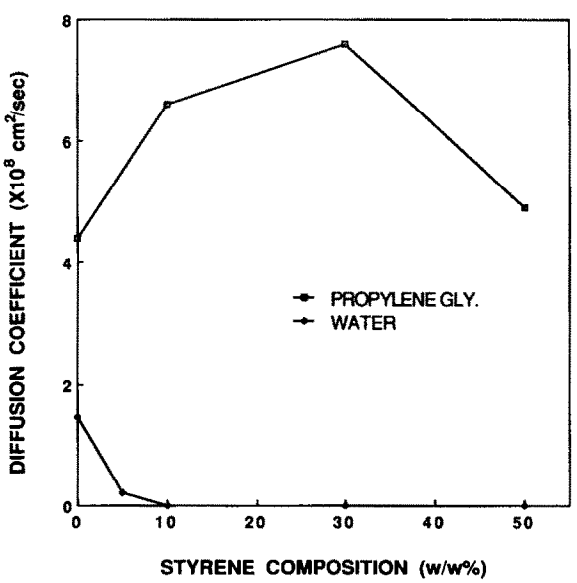

Fig. 12. Permeation of sodium warfarin through *p*-HEMA/styrene membranes in propylene glycol and water.

The permeation of sodium warfarin in propylene glycol was enhanced by increasing membrane hydrophobicity up to 30% styrene. At higher styrene compositions (50%), a decrease in diffusivity was observed. The partition coefficient followed a similar trend (see Table 2). Prior to the analysis of this result, a description of the permeation system in propylene glycol is necessary.

(1) The polymer membranes contain 3 major

components for drug permeation, the hydrophobic styrene, the relatively hydrophilic HEMA, and the solvent. The solvent phase may be divided into two regions, one is polymer associated medium and the other is bulk medium with fluctuating pores. Thus, it was expected that both partition and pore channels exist for drug permeation.

(2) The pore volume fraction is approximately the same for all membranes, i.e. the membranes showed nearly equivalent swelling (73.5%, S.D. = 1.1).

(3) Both ion-paired drugs and ions coexist at equilibrium.

Both the ion-paired and ionized drugs in propylene glycol could permeate through the pore channels. It was considered that the lipophilic ion pairs could also diffuse via the hydrophobic partition channels. As the hydrophobicity of the membrane increased, the ion pair permeability increased whereas, ion permeation gradually decreased. When the membrane was highly hydrophobic ($\approx > 40\%$ styrene ratio), the permeability of ions dropped significantly, and therefore, the total permeation decreased. This fact may indicate the presence of a partition mechanism for lipophilic ion paired drug diffusion.

The permeation behavior of sodium warfarin in water was considerably different (also see Fig. 12). The ion permeability markedly decreased with increasing styrene content. Thus, the permeation was considered to occur primarily through the relatively hydrophilic HEMA or aqueous phase. An overall schematic illustration of the mechanism for sodium warfarin permeation is given in Fig. 13.

Diffusion mechanisms were confirmed by permeation experiments with warfarin base, an intrinsically hydrophobic compound. In propylene glycol, a continuous increase in the diffusion rate of warfarin base with increased membrane hydrophobicity was observed (Fig. 14). The partition coefficient also showed a similar trend (see Table 2). This contrasting behavior (as compared to sodium warfarin) was due to the absence of ions in the permeation system of warfarin base. Aqueous permeation studies with warfarin were also conducted at a pH of 10, at which warfarin base is

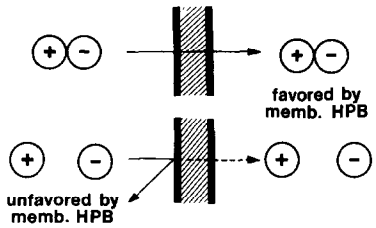

Fig. 13. Schematic illustration of ion-paired drug permeation through *p*-HEMA/styrene membranes; hydrophobic–hydrophilic balanced membrane model.

completely ionized ($pK_a = 5.1$). The diffusing species were identical to the case of aqueous sodium warfarin permeation. As expected, the results were similar to aqueous sodium warfarin permeation. Therefore, it was confirmed that the partition mechanism was operative in the permeation of ion-paired drug through hydrophobic membranes.

Mechanistic investigations of ion-paired drug permeation focusing on the pore mechanism were also performed. An important point is that ions and ion pairs have different molecular sizes. This difference becomes significant for trimer salts, i.e. terbutaline sulfate and calcium saccharin, for which the ion pair (actually ion triplet) is more than twice as large as the ions. Since the ion-paired drugs can also diffuse via pore channels, the permeation results should reflect a difference due to the effect of size. On the basis of this hypothesis, membrane permeation experiments with ionic drugs, with varying molecular sizes were conducted in propylene glycol and water. The results were analyzed using the free volume relationship described by Yasuda et al. (1969).

$$\ln\left(\frac{D_m}{D_0}\right)\alpha - \frac{Bq_2}{V_f}\left(\frac{1}{H} - 1\right) \tag{17}$$

where D_m is the diffusion coefficient of the solutes in the membrane, D_0 is the solute self-diffusion coefficient, Bq_2 is proportional to the solute cross-sectional area (πr^2), V_f is the molar free volume of solvent and H is the degree of solvation. This equation implies that the diffusivity through the membranes decreases as the solute size increases. Table 3 summarizes the permeation results with ionic drugs of varying sizes through a

TABLE 3

Permeation of ionic drugs with different sizes through p-HEMA membrane in water

Drug	r^2 (Å^2)	D_0 (cm^2/s)	U (cm^2/s)	K_d	D_m (cm^2/s)	$\ln(D_m/D_0)$
Sodium salicylate	10.07	7.62×10^{-6}	2.78×10^{-7}	1.36	2.04×10^{-7}	−3.62
Hydralazine HCl	10.88	7.34×10^{-6}	2.87×10^{-7}	1.67	1.72×10^{-7}	−3.75
Calcium saccharin	10.74	7.36×10^{-6}	1.32×10^{-7}	0.79	1.67×10^{-7}	−3.79
Terbutaline SO_4	17.74	5.74×10^{-6}	5.10×10^{-8}	1.68	3.04×10^{-8}	−5.24
Sodium diclofenac	17.78	5.72×10^{-6}	5.79×10^{-8}	1.58	3.66×10^{-8}	−5.05
Warfarin	19.62	5.45×10^{-6}	3.78×10^{-8}	2.30	1.64×10^{-8}	−5.81
Sodium warfarin	19.62	5.45×10^{-6}	3.03×10^{-8}	2.07	1.46×10^{-8}	−5.92
Chlorpromazine HCl	20.60	5.32×10^{-6}	3.70×10^{-8}	2.30	1.61×10^{-8}	−5.80

r^2: molecular radii of drugs were calculated based on ion size. D: $n = 3$, s.d. < 5%

p-HEMA membrane in water. A plot of $\ln(D_m/D_0)$ versus r^2 by ionic sizes is given in Fig. 15. The plot exhibited linearity, indicating the size dependence of solute diffusivity. Wisniewski et al. (1980) investigated hydrophilic solute permeation through hydrogel membranes and elucidated a governing pore mechanism for hydrophilic solute permeation based on the observed linear size dependence from the plot of $\ln(D_m/D_0)$ versus r^2. Accordingly, it was determined that ionized solutes permeated via a pore mechanism due to their hydrophilic characteristics.

Data for permeation of the drugs in propylene glycol through p-HEMA/styrene (7 : 3 w/w%) membranes is presented in Table 4. Plots of $\ln(D_m/D_0)$ versus r^2 for each ion pair are shown in Fig. 16. Overall, permeation was size dependent, with deviations. The ion pair size dependence suggests that the permeating species was predominately the ion-paired drugs. Significant deviation from linearity was observed with drugs which form ion triplets, such as calcium saccharin and terbutaline sulfate. As mentioned previously, the size difference between ions and ion pairs for these drugs is large. The observed deviations indicated that the actual sizes of the ion triplets were

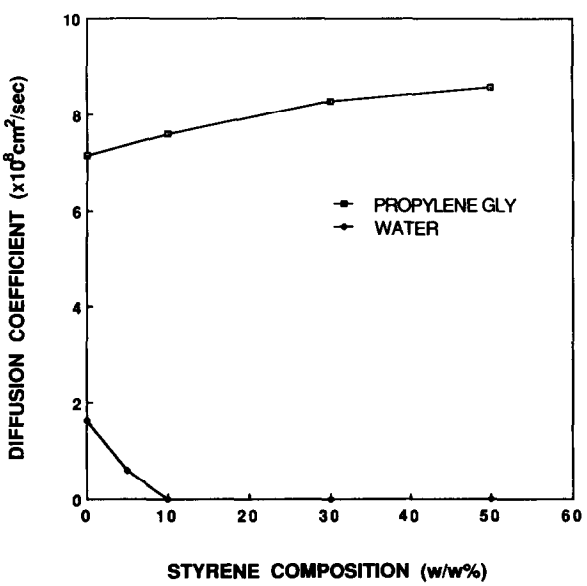

Fig. 14. Permeation of warfarin base through p-HEMA/styrene membranes in propylene glycol and water.

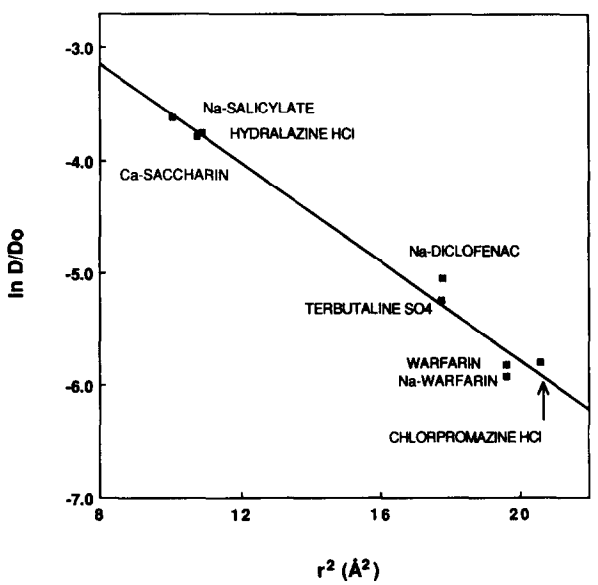

Fig. 15. Dependence of ionized drug permeation on the solute molecular size through p-HEMA membrane in water.

TABLE 4

Permeation of ionic drugs with different sizes through p-HEMA / styrene membrane (7 : 3 w / w %) in propylene glycol

Drug	r^2 (Å^2)	D_0 (cm^2/s)	U (cm^2/s)	K_d	D_m (cm^2/s)	ln(D_m/D_0)
Sodium salicylate	11.39	1.43×10^{-7}	1.08×10^{-7}	0.89	1.21×10^{-7}	−0.17
Hydralazine HCl	12.60	1.36×10^{-7}	1.02×10^{-7}	0.92	1.11×10^{-7}	−0.20
Calcium saccharin	17.34	1.16×10^{-7}	4.90×10^{-8}	0.88	5.57×10^{-8}	−0.73
Sodium diclofenac	18.80	1.11×10^{-7}	6.32×10^{-8}	0.89	7.10×10^{-8}	−0.44
Warfarin	(19.80)	1.09×10^{-7}	6.62×10^{-8}	0.80	8.28×10^{-8}	−0.27
Sodium warfarin	20.58	1.06×10^{-7}	6.07×10^{-8}	0.80	7.59×10^{-8}	−0.33
Chlorpromazine HCl	21.88	1.03×10^{-7}	6.59×10^{-8}	0.89	7.40×10^{-8}	−0.33
Terbutaline SO_4	29.69	5.74×10^{-8}	2.94×10^{-8}	1.38	2.13×10^{-8}	−0.99

r^2: molecular radii of drugs were calculated based on ion pair size. D: $n = 3$, S.D. < 5%.

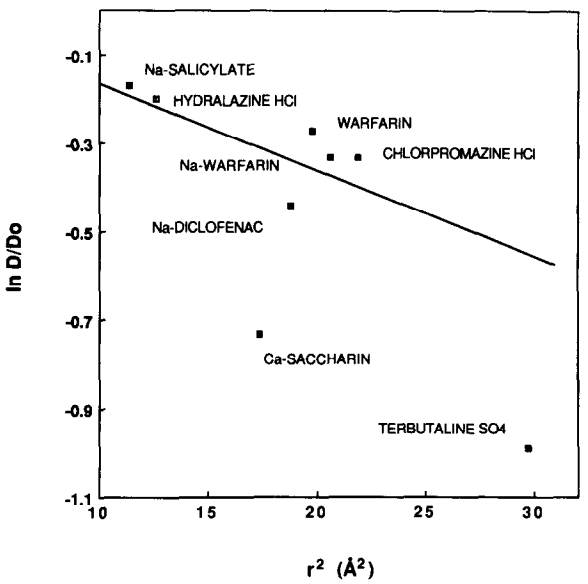

Fig. 16. Permeation of ion-paired drugs with different sizes through *p*-HEMA styrene (7:3 w/w%) membrane in propyleneglycol.

even larger than the calculated values. This is probably due to solvent association between the two large ions of an ion triplet. Overall, the size dependence studies provided additional evidence for ion-paired drug permeation.

Conclusion

Ionic drug salts form electrically neutral ion pairs in non-aqueous media. The ion-paired drugs could permeate through hydrophobic membranes due to their lipophilicity. Both pore and partition mechanisms contribute to ion pair diffusion.

The concept of ion pair formation was found to be a valuable tool for the lipophilization of ionic drugs for transport through hydrophobic membranes.

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