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Ion-pairs of ibuprofen: increased membrane diffusion

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Abstract

The purpose of the present study was to determine the influence of pH and ion-pairing on the permeation of ibuprofen across polydimethylsiloxane (PDMS) membrane. The solubility of ibuprofen sodium was determined at a range of pH values. Saturated solutions were then used to determine the influence of pH on diffusion across PDMS as a model membrane. The apparent partition coefficient of ibuprofen sodium between n-octanol and phosphate buffer at various pH values was also investigated. Organic salts of ibuprofen using ethylamine, diethylamine, triethylamine and ethylene diamine as counter-ions were synthesized and the influence of these counter-ions on the permeation of ibuprofen was studied. The presence of ion-pairing was confirmed using ^{1}H NMR and ^{13}C NMR. Diffusion studies at different pH values (4.0, 5.0, 6.0, 7.0 and 8.0) indicated that ibuprofen sodium flux increased significantly with increasing pH from 4.0 to 7.0. Above pH 7.0 a decrease in diffusion was observed. The permeability coefficient increased with an increase in the amount of unionized acid. The apparent partition coefficient was directly related to the steady-state flux. The steady-state flux of ibuprofen increased up to 16-fold using different counter-ions. The highest flux was measured from ibuprofen triethylamine. The flux of ibuprofen salts across a lipophilic membrane can be increased by formation of ion-pairs. The extent of enhancement is associated with the lipophilicity, extent of ion-pairing and reduction in charge over the drug molecule.

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Introduction

Most of the clinically accepted drugs for delivery through the skin are of low molecular weight, lipophilic and effective at low doses. However, the majority of drugs are weak acids or bases, and are ionized under normal physiological conditions. The human stratum corneum acts as a significant barrier for the skin penetration of these hydrophilic ionizable drugs. Charged species are known to be poor penetrants across skin, other biological membranes and non-porous polymers. Their permeation coefficient has been estimated to be about 10^4 times smaller than for the respective uncharged species (Swarbrick et al 1984). Many strategies, including the use of penetration enhancers, have been exploited to increase the penetration of drugs through the stratum corneum (e.g. Walters & Hadgraft 1993; Hadgraft 1999; Asbill et al 2000; Barry 2001). However, as many of the skin penetration enhancing chemicals have the potential to cause skin irritation (e.g. Kanikkannan & Singh 2002), more effective and safer penetration enhancement techniques need to be developed.

The formation of ion pairs has been investigated for the enhancement of membrane permeability and hence bioavailability of hydrophilic ionized molecules. The theory is that when oppositely charged molecules interact, this association reduces or neutralizes the overall electrostatic charge of the ion-pair molecule that is formed. The consequent increase in lipophilicity of the ion-pair compared to the ion results in increased permeation of the molecule through a membrane (e.g. intestinal, skin or synthetic).

Early studies on ion-pair transport focused on absorption from the gastrointestinal tract. Wilson and Wiseman were among the first to test the ion-pair hypothesis for the lipophilization of the ionic drug tropsium (Wilson & Wiseman 1954). They reported an enhanced transfer rate across everted intestine using alkylsulphonates as counter-ions. Gasco and colleagues reported an increase in the bioavailability of propranol in the presence of taurodeoxycholate (Gasco et al 1984). Furthermore, hexylsalicylate was found to be capable of enhancing the bioavailability of hydrophilic drugs such as pholedrine and bretylium after oral and rectal application respectively.

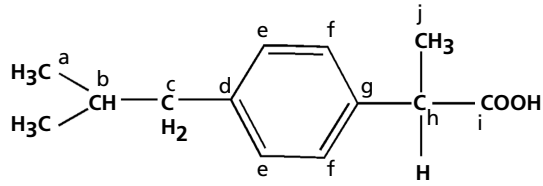

Figure 1 Structure of ibuprofen molecule.

The concept of forming ion-pairs to increase the skin permeability of hydrophilic drugs has also been reported (Hadgraft et al 1985, 1986; Young et al 1988; Pedersen 1990). Kadono and colleagues (1998) reported increased penetration through shed snakeskin of salicylate by ion-pair formation with alkylamines. Megwa and colleagues also found increased skin penetration and local tissue deposition of salicylate in the presence of alkylamines (Megwa et al 2000a). In a further study, these researchers showed that secondary, tertiary and quaternary amines increased the permeation of salicylates through human epidermal membranes in vitro (Megwa et al 2000b). Permeability enhancement was greatest with tertiary amines and was found to increase with alkyl chain length. Increase in skin penetration of lignocaine (Valenta et al 2000) and ondansetron (Takahashi & Rytting 2001) by ion-pair formation has also been reported. Although most of these studies describe the ion-pair approach as the means to increase the permeation of drugs across biological and synthetic membranes, few have provided direct evidence of ion-pair formation.

The objective of this study was to determine the significance of ion-pair formation on the permeation of ibuprofen (Figure 1). The solubility of ibuprofen sodium was measured over a range of pH values. The saturated solutions obtained from the solubility determination were used to measure the diffusion at various pH values through a polydimethylsiloxane (PDMS) membrane. In further investigations, the effect on membrane permeability of a number of amine counter-ions was examined. Nuclear magnetic resonance (NMR) spectroscopy was used to identify the presence of ion-pair formation between ibuprofen and the respective amine counter-ion. In addition, the partition characteristics of ibuprofen sodium and various organic ibuprofen salts were examined using an n-octanol–aqueous buffer system.

Materials and Methods

Materials

Ibuprofen sodium, ethylamine hydrochloride, diethylamine hydrochloride, triethylamine hydrochloride and ethylene diamine dihydrochloride were from Sigma (St Louis, MO). PDMS membrane (thickness 0.005″) was from Pillar Surgical (CA). HPLC-grade acetonitrile and methanol (Fisher Scientific, USA) were used, and all other chemicals were of analytical grade.

High-performance liquid chromatography

A Waters liquid chromatographic system equipped with a model 717 plus auto sampler, model 600S controller and 996 photodiode array detector was used. Separation was achieved on a Symmetry C_{18} column (5 μm, 3.9 × 150 mm i.d., Waters Inc., MA) at ambient temperature with an in-line pre-filter. Integration was undertaken using Millenium$^{3.2}$ software.

The mobile phase consisted of dilute phosphoric acid adjusted to pH 2.2:acetonitrile (40:60) filtered through a 0.45 μm membrane filter (Durapore membrane filter, Millipore). The mobile phase was continuously degassed before and during use. The flow rate was 1.0 mL min^{-1} and the detection wavelength was 220 nm. The retention time for ibuprofen was ~4.8 min. Calibration curves were calculated on peak area measurements.

NMR spectroscopy

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using a Bruker Avance 300 spectrometer (Karlsruhe, Germany). Samples were dissolved in deuteromethanol and chemical shifts (δ) for hydrogen and carbon resonance reported in ppm relative to TMS.

Solubility–pH profile

An excess of ibuprofen sodium was added to phosphate buffers with pH values of 4.0, 5.0, 6.0, 7.0 and 8.0 in screw-capped vials and stirred in the dark at 25 °C for 48 h. The pH of the resultant mixture was determined during this period and adjusted to the required value by adding phosphoric acid or KOH. The mixtures were then centrifuged at 10 000 g for 10 min and the supernatants analysed for ibuprofen content using HPLC. The pH of the solutions was confirmed after centrifugation. All experiments were repeated four times.

Synthesis of ibuprofen ion-pairs

Equimolar amounts of ibuprofen sodium and amine hydrochloride (ethylamine hydrochloride, diethylamine hydrochloride, triethylamine hydrochloride or ethylene diamine dihydrochloride) were dissolved in methanol and stirred for 24 h. The cloudy mixture was then filtered through a 0.45 μm membrane filter (Durapore). The precipitate was collected, weighed and was proven to be sodium chloride (NaCl) by reaction with silver nitrate. The molar yield of sodium chloride was more than 90% of expected amount in every synthesis. The solvent from the clear filtrate solution obtained after filtration was evaporated and the residue was dried in vacuo for 24 h with P_2O_5 as a drying agent. The salts were dissolved in deuteromethanol and ^{1}H NMR and ^{13}C NMR used to confirm the presence of ion-pair in solution.

Permeation experiments

In-vitro permeation studies across PDMS membrane were performed in Pyrex glass Franz-type diffusion cells. The

membrane was immersed in deionized distilled water for 1 h before use. PDMS membrane (cross-sectional area 1.18 cm^2) was then mounted between the donor and receptor compartments of diffusion cells and the assembly held in place with a plastic clamp. The diffusion unit was immersed in a water bath at 37 °C. Phosphate buffer pH 7.0 (approx. 3.5 mL) was the receptor fluid. For permeation at different pH values the donor phase was 1 mL of the saturated solution at that particular pH. After equilibration with the buffer, 1.0 mL of the donor solution was added to the donor cell. A magnetic stirrer driven by an external magnet continuously stirred the receptor compartment at the same speed for all cells. Samples of the receptor phase were withdrawn and replaced by drug-free buffer at appropriate times throughout the 6 h period of the experiment. The ibuprofen content in the receptor phase was determined using HPLC. Experiments were repeated four times.

The cumulative amount of drug released through the PDMS membrane, Q(t), was determined from $Q = (CV)/A$, where C is the concentration of ibuprofen (sodium) in the receptor compartment in $\mu g\,mL^{-1}$ for the corresponding sample time t, V is the volume of fluid in the receptor phase and A is the diffusional area of the membrane. The flux of ibuprofen through the membrane into the receptor from each of the formulations was determined from the slope of the plot of cumulative amount in the receptor phase vs time and expressed as $\mu g\,cm^{-2}\,h^{-1}$. Permeability coefficients were calculated for ibuprofen for each formulation.

Apparent partition coefficient

The apparent partition coefficients were investigated between n-octanol and phosphate buffers at various pH values. Each phase had been pre-saturated with the other by equilibration overnight before the experiments. A known amount of ibuprofen sodium was dissolved in buffers of different pH values to which n-octanol was added. The mixture was stirred continuously for 24 h at 25 °C. After phase separation, the ibuprofen content in the buffer was analysed by HPLC. Since the initial amount of ibuprofen sodium was known, the amount in the organic phase was determined by difference.

Diffusion and partition of ibuprofen ion-pairs

The apparent partition coefficients and the diffusion studies were performed as described above. Phosphate buffer pH 7.0 was used as an aqueous phase for the determination of the apparent partition coefficient. The diffusion studies were conducted containing 2% solutions of ibuprofen or its equivalent of the amine salt, using propylene glycol as the solvent. The ibuprofen content was analysed using HPLC.

Statistical analysis

The difference between the flux of ibuprofen for the infinite dose application (saturated solutions) at different pH values and for different ibuprofen salts was assessed using multiple regression with pair-wise comparison. One-way ANOVA, followed by Tukey's HSD post-hoc test, was used for assessing the difference in solubility due to pH or salts.

Results and Discussion

Solubility

Ibuprofen is relatively non-polar and accordingly its highest solubility is obtained in solvents of lower solubility parameter values, such as acetone, ethyl acetate and lipophilic alcohols. Solubility decreases in most polar solvents. By replacing the acidic proton by sodium, the region of maximum solubility is shifted to larger solubility parameter values as compared to the parent acid (Bustamante et al 2000). As expected, the solubility of ibuprofen sodium (pKa = 4.45; Avdeef et al 1998) increases with increasing pH. The solubility profile is summarized in Table 1. The solubility at pH 7 and 8 is significantly greater than at pH 4, 5 and 6 ($P < 0.001$). There is no significant difference in solubility from pH 7 to 8.

Solvent–membrane interactions

Percutaneous absorption involves partitioning of a solute from its vehicle into the skin and subsequent diffusion of solute through the skin. Identical solute flux would be expected from solutions in which the solute had equal

Table 1 Solubility, log P values (n-octanol:buffer), permeability coefficient and steady-state flux through PDMS membrane for ibuprofen sodium at different pH values.

pH	Solubility ($mg\,mL^{-1}$)	log P	k_p ($cm\,h^{-1}$)	Fraction unionized	Flux ($\mu g\,cm^{-2}\,h$)
4	0.028 ± 0.0007		2.2977	73.81	64.131 ± 1.8
5	0.156 ± 0.008	3.28 ± 0.007	0.398	21.98	62.36 ± 0.91
6	1.0 ± 0.05	2.42 ± 0.02	0.187	2.74	187.10 ± 12.3*
7	340.51 ± 31.3	0.92 ± 0.04	0.00081	0.28	277.23 ± 4.23*
8	299.035 ± 21.4	0.63 ± 0.01	0.0001262	0.03	37.834 ± 3.5*

Values represent the mean ± s.d. (n = 4). *Significantly different from value at pH = 4; $P < 0.002$.

thermodynamic activity. Non-ideal behaviour is a result of solute and/or solvent interaction with the membrane (Twist & Zatz 1988a; Jiang et al 1998). In this situation the physicochemical properties of the barrier will change depending on the interaction involved. It is therefore often difficult to interpret results because of the highly complex nature of the stratum corneum. A synthetic membrane, such as PDMS membrane, offers advantages concerning the physicochemical properties of the diffusional barrier, including perm selectivity, high diffusivity, thickness control, and less stringent storage and handling requirements. Moreover, Twist & Zatz (1988b) suggest that solvents (e.g. water, glycerin, propylene glycol and polyethylene glycol 400) are not sorbed to a significant extent by this material and behave as ideal vehicles; permeation from these vehicles is therefore considered to be a function only of permeant activity. Hence to determine the appropriate permeant activity and to eliminate membrane–solvent–solute interaction, PDMS membrane was chosen for the studies. Propylene glycol and water were used as solvents since they are not significantly sorbed by this membrane. The flux through PDMS membranes is usually faster as compared to the human skin barrier, but the permeability relationships and trend are very similar (Valenta et al 2000).

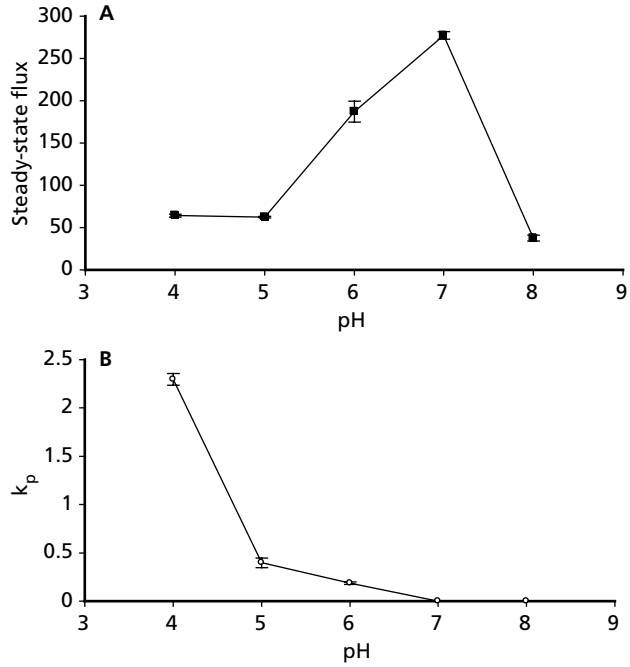

Figure 2 Relationship between steady-state flux (A) and permeability coefficient k_p (B) with respect to change in pH.

pH and penetration

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that has been formulated into a number of topical preparations. Its solubility and diffusion parameters as a function of pH have been documented (Watkinson et al 1994; Hadgraft & Valenta 2000). The low solubility of ibuprofen is one of the factors responsible for its reduced transfer across the skin. Sodium salts are more soluble than the parent drug, thereby increasing the amount of drug in solution in the aqueous vehicle. However, increasing the polar nature of the permeant reduces its tendency to permeate the lipophilic stratum corneum. The overall effect on permeation is a combination of these effects.

Donor depletion was observed at pH 4, 5 and 6, therefore flux was calculated using the cumulative amounts from the first four sampling times. The highest flux was determined at pH 7 (Table 1). The flux increased as the pH increased from pH 4 to pH 7 and then decreased as shown in Figure 2. The total flux (J_{tot}) of a permeant through a membrane is a composite term, contributed to by the diffusion of both the ionized and unionized moieties. The transport across the membrane can be described by the permeabilities of the ionized and unionized species and their respective concentrations $k_{p(ion)}$, $k_{p(union)}$, c_{ion}, and c_{union} (Hadgraft & Valenta 2000):

$$J_{tot} = (k_{p(union)} \times c_{union}) + (k_{p(ion)} \times c_{ion})$$

The ambient pH and the pK_a give the relative amounts of ionized and unionized species. In the case of ibuprofen sodium, flux at lower pH is dominated by the first term (unionized species), whereas at higher pH it is dominated by the second term (ionized species). Figure 3 shows the relationship between permeability coefficient as a function of the percentage of unionized ibuprofen present. The percentage of drug that was ionized or unionized at a particular pH was calculated using the Henderson–Hasselbach equation.

A linear relationship ($y = 31.984x + 1.322$; $r^2 = 0.978$) between the permeability coefficient and fraction ionized suggests that the diffusion was mostly as a result of partition and transfer of unionized ibuprofen present in the donor phase, and the insignificant intercept indicates the contribution of ionized species. A plot of permeability as a function of pH (Figure 2) also follows a reasonable trend that would be expected of an acidic compound. The permeability coefficient of the ibuprofen sodium increases

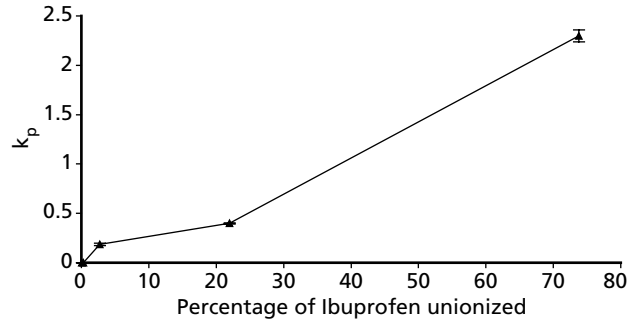

Figure 3 Relationship between percentage of ibuprofen unionized and permeability coefficient.

with decrease in pH. The highest permeability coefficient was determined at pH 4 (Figure 2), when more than 50% of ibuprofen sodium is unionized ($pK_a = 4.45$, (Avdeef et al 1998)). It is interesting to note that the steady-state flux of ibuprofen sodium is greater at higher pH, whereas its permeability coefficient is higher at lower pH when the fraction of unionized species is greater. This suggests that at higher pH the lower permeability of the ionized species is more than compensated for by the increased solubility, which is consistent with the findings of previous studies (Watkinson et al 1994).

Partitioning experiments

The apparent partition coefficients between n-octanol (representative of skin lipids) and phosphate buffers at various pH values are presented in Table 1. As expected, the octanol:buffer partition coefficient increased with decreasing pH from pH 8 to 5. The drug concentration in the aqueous phase at pH 4 was below the limit of detection, indicating a very high partitioning into octanol for the unionized species.

NMR spectroscopy

The goal of both the ^1H and ^{13}C NMR measurements (see Tables 2, 3a and 3b) was to obtain evidence for the presence of ion-pair formation between ibuprofen (Figure 1) and respective amine salts from the chemical shift changes to protons and carbons near the cationic and anionic charges. Ion-pair formation is an indicator of increased permeability of the salt through skin.

Comparison of the proton spectra of ibuprofen and ibuprofen sodium, and the amine hydrochloride and ibuprofen salts in CD_3OD showed no significant changes in chemical shifts (Table 3a). Relative to the chemical shifts in the corresponding amine, the ^1H NMR spectra of the primary, secondary, tertiary and quaternary ethylamine hydrochloride and ibuprofen cations show small deshielding shifts in both the methylene and methyl protons adjacent to the nitrogen (Table 2). The protons on the carbon adjacent to the nitrogen are recognized by their downfield position in the salt as compared to the free amine. The deshielding effect for primary, secondary and tertiary amine salts is smaller in the ibuprofen salts than in the corresponding hydrochlorides, which is indicative of greater charge neutralization and ion-pair formation. The largest downfield chemical shift was observed in the methylene group in the quaternary salts where charge separation is greatest, and therefore charge neutralization least, because of steric hindrance.

^{13}C NMR provided significant evidence for ion-pair formation between ibuprofen and the corresponding amine. The carboxylic acid group in ibuprofen (RCOOH) shows a chemical shift of carbon (i) at 178.55 ppm while the sodium salt ($RCOO^-Na^+$) shows the carboxylate anion at 186.67 ppm (Table 3b). Based on these values for complete protonation (or deuteration) in the acid and complete ionization in the sodium salt, intermediate chemical shift values reflect the degree of charge neutralization resulting from interaction between the carboxylate anion and the nitrogen cation in the ibuprofen amine salts. The ammonium salt (181.96 ppm) indicates considerable charge neutralization, which may be partly stabilized by solvation of an ion-pair, including hydrogen bonding interactions as well as electrostatic attraction. Less charge neutralization occurs in the quaternary salt (183.39 ppm), where hydrogen bonding interactions cannot occur and close contact between the charges is sterically hindered. The degree of neutralization in the quaternary salt is equivalent to that observed for the primary amine (183.56 ppm) but must result from a different mode of interaction in each case. As the lipophilic character resulting from increased ethyl substitution of the amine salts increases, ion-pair formation, as indicated by chemical shift changes as a measure of charge neutralization, is favoured. This is shown by a decrease in the chemical shift values from the primary (183.56 ppm), to

Table 2 ^1H and ^{13}C chemical shifts of amines, amine hydrochloride and ibuprofen amine salt.

	^1H		^{13}C	
Amine	CH_2	CH_3	CH_2	CH_3
1°	2.69	1.12	37.20	18.39
2°	2.63	1.13	44.64	14.95
3°	2.58	1.07	47.25	11.51
4°	–	–	–	–
Amine hydrochloride	CH_2	CH_3	CH_2	CH_3
1°	3.05 (+0.36)	1.35 (+0.23)	36.44 (−0.76)	13.31 (−5.08)
2°	3.09 (+0.46)	1.35 (+0.22)	43.77 (−0.87)	11.88 (−3.07)
3°	3.27 (+0.69)	1.38 (+0.31)	48.02 (−0.77)	9.63 (−1.88)
4°	3.34	1.32	53.50	7.87
Ibuprofen amine salt	CH_2	CH_3	CH_2	CH_3
1°	2.91 (+0.22)	1.24 (+0.12)	36.05 (0.39)	13.31 (−5.08)
2°	2.96 (+0.33)	1.25 (+0.12)	43.49 (−0.28)	11.77 (−3.18)
3°	3.21 (+0.63)	1.33 (+0.26)	–	9.39 (−2.12)
4°	3.30	1.30	53.44	7.79

Table 3a ^{1}H NMR chemical shift (δ) of ibuprofen and its salts for proton on carbon.

	RCOOH	Na^+ $RCOO^-Na^+$	1° $RCOO^-N^+H_3Et$	2° $RCOO^-N^+H_2Et_2$	3° $RCOO^-N^+HEt_3$	4° $RCOO^-N^+Et_4$	Diamine $RCOO^-N^+H_3$ $CH_2CH_2NH_2$
a	0.92	0.92	0.89	0.89	0.91	0.89	0.90
b	1.87	1.84	1.84	1.84	1.85	1.83	1.84
c	2.47	2.45	2.44	2.44	2.46	2.44	2.44
e	7.11	7.07	7.06	7.07	7.1	7.05	7.06
f	7.24	7.32	7.27	7.27	7.23	7.28	7.27
h	3.61	3.61	3.57	3.58	3.68	3.56	3.58
j	1.46	1.46	1.42	1.43	1.44	1.41	1.42

Table 3b ^{13}C NMR spectra of ibuprofen and its salts.

	RCOOH	Na^+ $RCOO^-Na^+$	N^+H_4 $RCOO^-$ N^+H_4	1° $RCOO^-N^+H_3Et$	2° $RCOO^-N^+H_2Et_2$	3° $RCOO^-N^+HEt_3$	4° $RCOO^-N^+Et_4$	Diamine $RCOO^-N^+H_3$ $CH_2CH_2N\ H_2$
a	22.90	22.91	22.90	22.94	22.96	22.87	22.89	22.93
b	46.15	46.21	46.24	46.26	46.26	46.19	46.25	46.25
c	31.48	31.54	31.61	31.64	31.64	31.58	31.65	31.63
d	139.74	140.25	140.92	140.57	140.74	139.96	140.42	140.74
e	128.33	128.39	128.44	128.47	128.49	128.40	128.52	128.46
f	130.34	129.87	130.16	130.07	130.13	130.41	129.97	130.13
g	141.54	142.85	141.81	142.83	142.45	141.67	143.08	142.39
h	46.34	49.97	–	–	–	–	–	–
i	178.55	186.67	181.96	183.56	182.79	178.74	183.39	183.126
j	19.23	20.21	19.86	20.21	20.08	19.26	20.27	20.06

the secondary (182.79 ppm) and to the tertiary amine (178.74 ppm). The similarity of the chemical shifts for ibuprofen and the tertiary amine salt indicates a high degree of charge neutralization, which is consistent with extensive close ion-pair formation. Tertiary amines have been previously reported to form more stable ion-pairs when compared with primary and secondary amines (Megwa et al 2000b). Similar, but smaller, chemical shift changes are observed in the methyl group (j) and the aromatic ring carbon (g). Correlation of the chemical shifts of the amine salts of ibuprofen with the carbon (h) adjacent to the carboxylate anion is not possible because this signal is obscured by the solvent protons. The similarity of the chemical shift for the carboxylate carbon in the primary amine salt with the mono ibuprofen salt of ethylene diamine is consistent with a similar degree of interaction between these primary amine salts and the carboxylate anion.

Relative to the corresponding amines, the ^{13}C NMR spectra of the cations in the primary, secondary, tertiary and quaternary hydrochloride and ibuprofen salts show significant deshielding in the cation of the methylene carbon and increased shielding of the methyl carbon (Table 2). This reversal of shielding may be due to the conformational location of the methyl groups with respect to the C–C bonds. Nevertheless there is a consistent correlation between the chemical shift changes observed in all four series of salts. Similar, but smaller, chemical shift differences are observed in the methylene carbon of the ibuprofen salts compared with the hydrochloride salts, again indicating greater charge neutralization and ion-pair formation. No significant change is observed in the methyl carbons between the ibuprofen and hydrochloride salts. These measurements therefore provide evidence for the existence of an ion-pair between ibuprofen and amines in solution. The conclusion based on NMR measurements that the tertiary amine has the largest degree of ion-pair formation is in agreement with the changes observed in the diffusion rates for primary, secondary and tertiary salts.

An ion-pair is a pair of oppositely charged ions held together by Coulomb attraction without formation of a covalent bond. Experimentally, an ion-pair behaves as one unit in determining conductivity, kinetic behaviour, osmotic properties, etc. Following Bjerrum, oppositely charged ions with their centres closer together than a distance of:

$$q = (8.36 \times 10^6\ z^+z^-)/(\varepsilon_r T)\ \text{pm}$$

are considered to constitute an ion-pair ('Bjerrum ion pair'). z^+ and z^- are the charge numbers of the ions, and ε_r is the relative permittivity (or dielectric constant) of the medium. Solvents with lower dielectric constant favour formation of an ion-pair. The distance q increases with temperature and high-temperature solvents behave in this respect as solvents of lower dielectric constants, permitting long-range ion-pairing (Yizhak 1999). Since the dielectric constant for propylene glycol is lower than

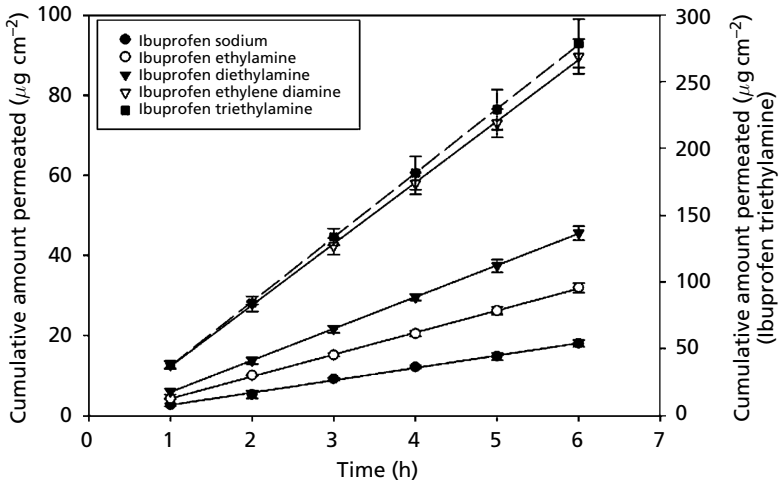

Figure 4 Comparison of diffusion profiles of different ibuprofen ion-pairs from propylene glycol through PDMS membrane.

Table 4 Steady-state flux and log P values of ibuprofen ion-pairs.

Salt type	log P	Flux
Ibuprofen sodium	0.92 ± 0.04	3.09 ± 0.091
Ibuprofen ethylamine	0.967 ± 0.02	5.42 ± 0.092*
Ibuprofen diethylamine	1.12 ± 0.03	7.91 ± 0.14*
Ibuprofen triethylamine	1.18 ± 0.03	48.14 ± 1.34*
Ibuprofen ethylene diamine	1.11 ± 0.02	15.31 ± 0.35*

Each value represents the mean $\pm$ s.d. ($n = 4$). *Significantly different from ibuprofen sodium, $P < 0.0005$.

methanol and we have evidence for ion-pair formation in methanol, we assumed ion-pair formation of ibuprofen with various amine counter-ions in propylene glycol. Propylene glycol has been used as the solvent for studying the penetration experiments, as specified in the methods section.

Ibuprofen salts and diffusion through PDMS membrane

Propylene glycol was used as a solvent since it is not significantly sorbed by the PDMS membrane (Twist & Zatz 1988b). The measured apparent partition coefficients of the salts into n-octanol seems to be in agreement with their lipophilicity (Table 4). Ibuprofen showed the highest partition coefficient with triethylamine as a counter-ion, followed by diethylamine and ethylamine. The partition coefficient of ibuprofen ethylene diamine was similar to that of diethylamine.

All the salts showed higher steady-state flux for ibuprofen through the PDMS membrane as compared to the sodium salt (Figure 4). Ibuprofen ethylene diamine is plotted on the right-hand y-axis, whereas the other salts are plotted on the left-hand y-axis. The highest steady-state flux was measured from ibuprofen triethylamine, followed by ibuprofen ethylene diamine, ibuprofen diethylamine and ibuprofen ethylamine. Although the partition coefficient of ibuprofen ethylene diamine was similar to ibuprofen diethylamine, its steady-state flux is almost twice that of ibuprofen diethylamine.

Conclusions

The results of this study suggest that it is possible to enhance the flux of salts across lipophilic membranes using an ion-pair approach. The degree of enhancement is associated with the lipophilicity, extent of ion-pairing and reduction in the charge over the drug molecule.

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