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The dermal delivery of lignocaine: influence of ion pairing

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Abstract

The purpose of the present study was to determine the significance of ion pairing on the permeation of lignocaine. Results of diffusion studies through polydimethylsiloxane (PDMS) at different pH values 4.0, 6.0, 7.0, 8.0 indicated that lignocaine hydrochloride (L-HCl) flux significantly increased with the amount of unionized base. In order to see if similar results could be obtained using human skin, permeation runs were performed with human skin at pH of 4.0, 5.5 and 7.0. These values were chosen to simulate an appropriate range of physiological conditions. Results of the experiments with human epidermis showed increasing L-HCl flux with increasing pH, confirming the trends seen with PDMS membranes. A linear relationship was found between the apparent partition coefficient and the steady state flux. Further experiments were conducted at donor pH 4.0 to minimise the contribution of the unionized species. Although an excess of different ions such as nitrate, mesylate and bromide increased the apparent partition coefficient, the steady state flux was not significantly increased. The steady state lignocaine flux was increased up to 2.45-fold using different counter ions. The highest flux was measured from lignocaine morpholinopropane sulfonate (L-mps). It is possible to enhance the flux of salts across lipophilic membranes by using an ion pair approach. The degree to which this is possible depends on the lipophilicity of the counter ion, the medium in which the ion pair forms, and the ionic strength.

Keywords: Lignocaine; Percutaneous absorption; Silicone membrane; Human epidermis; pH effect; Ion pairing

1. Introduction

Many attempts have been made to provide effective anaesthesia of the skin in order to suppress pain from burning, itching, surgical operations, injections and dermatological diseases. However to achieve sufficient anaesthetic effect on intact skin, repeated application and high concentration of the drug up to 30% are required (Lubens et al., 1974; Akerman et al., 1979). Therefore it is of great interest to enhance penetration of anaesthetics such as lignocaine, a weak base, which is commonly used as the soluble hydrochloride. Although lignocaine in its base form can permeate more easily through skin because of its higher lipophilicity the ionic form

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dominates at physiological pH of the skin surface (4.2–6.5) (Katz and Poulsen, 1971). The objective of this work was to determine the significance of ion pairing on the permeation of lignocaine. In the first part lignocaine-HCl (L-HCl) diffusion was measured from donor solutions held at different pH values 4.0, 6.0, 7.0, 8.0 through a silicone (polydimethylsiloxane, PDMS) membrane model. In order to imitate a more physiologically acceptable range, permeation through human epidermis was measured from donor solutions at pH 4.0, 5.5 and 7.0. In further investigations the effects of different counter ions were examined together with an assessment of a PDMS membrane as a model for stratum corneum. In addition, the partition characteristics of various organic lignocaine salts were examined using n-octanol.

2. Materials and methods

2.1. Materials

Lignocaine hydrochloride and lignocaine were from Sigma (St. Louis, MO), 3-(*N*-morpholino)propanesulfonic acid, n-octanesulfonic acid and benzoic acid were from Merck (Germany). PDMS of thickness 300 μm was supplied by Samco (UK).

2.2. Synthesis of lignocaine salts

2.2.1. Lignocaine nitrate

Equimolar amounts of lignocaine base and ammonium nitrate were dissolved in methanol and stirred for 10 h. The solvent was evaporated, the residue was suspended twice in toluene and dried.

2.2.2. Lignocaine sulfonates

To an aqueous solution of 3-(*N*-morpholino)propanesulfonic acid (or n-octylsulfonate) an equimolar amount of lignocaine in small portions was added. The solution was stirred for 24 h. Then, the solvent was removed in vacuo and the solid residue was dried for 24 h.

2.2.3. Lignocaine benzoate

Equimolar amounts of lignocaine and benzoic acid, dissolved in diethyl ether, were mixed and stirred for 8 h. The solvent was removed in vacuo, the residue was dissolved twice in toluene and dried.

The structure and composition of the resulting salts were analysed and confirmed by ^{1}H-NMR (Bruker Avance 300 MHz) and IR (Perkin Elmer FT-IR instrument SPECTRUM 1000) spectroscopy.

2.3. Diffusion through an artificial membrane

In vitro diffusion studies with PDMS (polydimethylsiloxane) membranes were performed using Franz-type glass diffusion cells. Each donor compartment was filled with 1.0 ml of 2% (w/v) lignocaine hydrochloride (L-HCl) in buffer solution (phosphate buffer 0.05 M). The pH was adjusted to the required value by adding phosphoric acid or KOH. In order to maintain sink conditions, the receptor phase consisted of buffer pH 3.5 (Green and Hadgraft, 1987). It was stirred continuously and maintained at 32°C throughout the experiment. The receptor phase was replaced hourly with fresh buffer solution and L-HCl content analysed using HPLC at a flow rate of 1 ml/min at 260 nm. The stationary phase was a C-18 ODS 5-μm column (24×4.6 mm). A mobile phase of acetonitrile: 0.05 M phosphate buffer: triethylamine (20:80:1), adjusted to pH 4.0, was used. Samples of 20 μl were injected. The retention time for lignocaine was $\sim$7.1 min. Calibration curves were calculated on the basis of peak area measurements.

2.4. Diffusion through human epidermis

Permeation studies were performed using heat separated female human abdominal epidermis from a post-operative source (Bronaugh et al., 1981). To simulate acceptable in vivo physiological conditions, experiments were conducted using buffer donor solutions at pH 4.0, 5.5 and 7.0. Each permeation study was run for 10 h. To ensure sink conditions, the receptor solutions consisted of buffer pH 3.5. The receptor solutions were analysed for L-HCl content by HPLC.

2.5. Apparent partition coefficient

The apparent partition coefficients were investigated between n-octanol and phosphate buffer (0.05 M) at various pH values. The pH was adjusted after adding the counter-ion. n-Octanol pre-saturated with buffer was used. L-HCl and an excess amount of counter ion were dissolved, the pH adjusted and stirred continuously for 20 h at 32°C. The stirring time was determined empirically. After phase separation the lignocaine content was analysed in the buffer by HPLC. Since the amount of lignocaine initially used was known, the amount in the organic phase could be determined by difference. The weights of the samples were corrected so that they related to lignocaine base.

2.6. Diffusion and partition with excess of ions

The pH was fixed at 4.0 for all experiments. At this pH the concentration of free base is less than 0.015% and the contribution of this species can be considered negligible. Diffusion studies of L-HCl were performed with a fivefold molar excess of nitrate, bromide and mesylate as their sodium salts. The apparent partition coefficients were also determined. In the case of nitrate, additional measurements of the apparent partition coefficients were estimated with two different molar ratios of L-HCl: nitrate 1:15 and 1:25.

2.7. Diffusion and partition of lignocaine salts

The apparent partition coefficients as well as diffusion studies were performed as described above. The lignocaine content was analysed by HPLC, the method being separately calibrated for each salt. For lignocaine benzoate (L-benz) the analysis was modified since benzoate interfered. An excess of 10% HCl was added to the solution of L-benz. The weak benzoic acid was displaced and the precipitated benzoic acid removed by shaking with diethyl ether three times. The lignocaine content in the buffer was analysed by HPLC.

2.8. Statistical data analysis

Results are expressed as the means of at least three experiments $\pm$ S.D. Statistical data analysis was performed using the t-test with $P < 0.05$.

3. Results and discussion

3.1. Influence of pH

The log D values of L-HCl at pH 4.0, 6.0, 6.8, 7.0 and 8.0 were determined and are shown in Table 1. Values were also estimated using ACD software (ACD Software, Toronto, Canada). The experimental values can be compared to calculated ones (Fig. 1). There is good agreement between the results at high pH when the predominant species is unionized. The trend is the same at lower pH values but the predicted values are, in general, higher than those found experimentally. It is generally recognized that partition of ionized material is insignificant and it is im-

Table 1
Experimental and calculated (ACD software) log D values for n-octanol and steady state fluxes of lignocaine-HCl through a PDMS membrane at different pH values ($n = 3$)[a]

pH	Log D (experimental)	Log D (calculated)	Fraction ionized (μg/cm^2 per h)	Flux
4.0	-1.09 ± 0.4	-0.73	0.99	1.47 ± 0.029
5.5	-0.7 ± 0.02	-0.4	0.99	27.75 ± 2.3
6.0	-0.62 ± 0.5	-0.07	0.99	33.2 ± 1.33
6.8	-0.34 ± 0.05	0.64	0.93	200 ± 1.2
7.0	-0.02 ± 0.01	0.83	0.89	325 ± 27
8.0	1.72 ± 0.07	1.72	0.44	636 ± 130

[a] The predicted log D for the neutral species is 2.36.

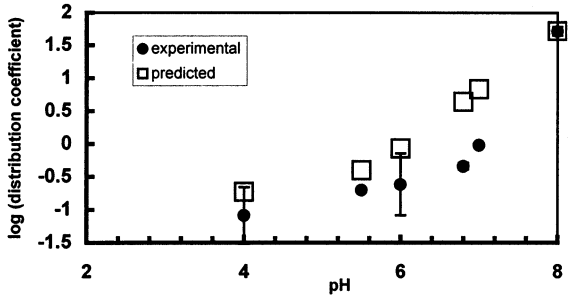

Fig. 1. A comparison between the experimental log D values and those predicted using ACD software.

pressive, therefore, that the agreement is as good as it is. The absolute values will be dependent on a number of factors including the nature of the counter ions present and the ionic strength of the aqueous phase. The counter ions present will be considered later.

Diffusion experiments using an artificial silicone membrane were conducted over a 6-h period. The cumulative amount per unit area of drug released through PDMS membrane, $Q(t)$, was determined from $Q=(CV)/A$ where C is the L-HCl concentration in the receiver compartment in μg/ml for the corresponding sample time t. V is the volume of fluid in the receptor phase and A is the diffusional area of the cell. The lag time was very short and the slope of the best fit line gives the steady state flux J of L-HCl (μg/cm^2 per h). In order to determine the influence of the degree of ionisation, diffusion studies at pH 4.0, 6.0, 6.8, 7.0 and 8.0 were performed. The highest steady state flux (636 μg/cm^2 per h) was determined at pH 8.0 when more than 50% L-HCl is unionized (pK_a 7.9; Siddiqui et al., 1985). This can be seen in Table 1. The results indicated that the L-HCl flux significantly increased with the amount of unionized base. As seen in Fig. 2 an exponential relationship is obtained between the steady state flux and apparent partition coefficient.

The ionized part f_{ion}, can be calculated according to the following equation (Martin et al., 1975):

$$f_{ion} = 100/[1 + 10^{(pH + pK_a)}] \quad (1)$$

The total flux (J_{tot}) of drug through the membrane is a composite term which can be attributed to transport of both the ionized and unionized moieties. The transport properties can be described by the permeabilities of the ionized and unioinized species and the respective concentrations $k_{p\ (ion)}$, $k_{p\ (union)}$, $c_{(ion)}$, $c_{(union)}$.

$$J_{tot} = k_{p\ (union)} * c_{(union)} + k_{p\ (ion)} * c_{(ion)} \quad (2)$$

The flux at the lowest pH will be dominated by the second term. Using a series of simultaneous equations with the fixed equation being that for pH 4.0, it is possible to obtain values for, $k_{p\ (ion)}$, and $k_{p\ (union)}$. These are provided in Table 2.

There is a large discrepancy for the different values, probably the result of inherent variability in some of the flux values, particularly at pH 8.0. Fig. 3 shows a comparison between the experimental data and calculated values using Eq. (2) and the mean k_p values given in Table 2.

Fig. 4 shows the steady state flux as a function of the fraction of unionized lignocaine present in the donor phase. If diffusion was solely as a result of partition and transfer of the unionized species, a linear relation would be expected. The deviation from linearity suggests other processes such as ion-pairing are significant. It is also possible to

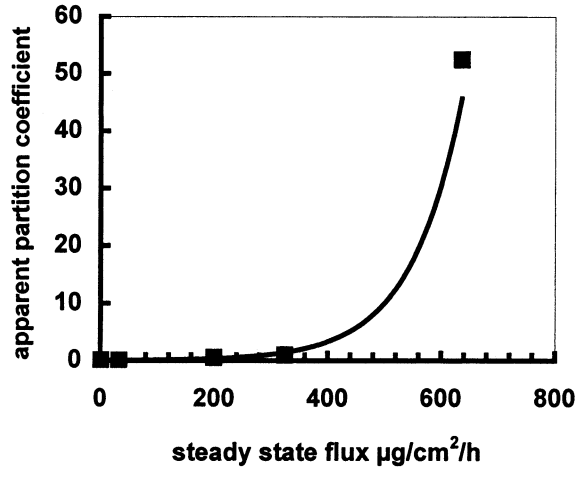

Fig. 2. The relationship between apparent partition coefficient and steady state flux (through PDMS membranes) of lignocaine-HCl at various values of pH.

Table 2
The permeabilities (cm/h) through the PDMS membrane for the different species

	pH 6	pH 6.8	pH 7.0	pH 8	Mean ± S.D.
$k_{p\ (union)}$	0.13	0.02	0.15	0.06	0.089 ± 0.059
$k_{p\ (ion)}$	5.7×10^{-5}	7.1×10^{-5}	5.5×10^{-5}	6.6×10^{-5}	$6.2 \pm 0.7 \times 10^{-5}$

compare the ratio of the permeabilities for the unionized and ionized species. The ratio of the mean values is 1435. The diffusion of the two species through PDMS would be expected to be similar since their sizes are similar. The major determinant would therefore be the ability of the two species to partition into a lipophilic environment. Using the ACD software, the ratio of the predicted distribution coefficients is 1435. There appears to be very good agreement between the values despite the fact that in the experiment the partition medium is PDMS whereas the predicted ratio is for octanol. However it should be noted that there is some error in the ratio determined for the experimental values.

In order to see if similar results could be obtained using human skin, permeation experiments were performed. Epidermal membranes were used and donor phases at pH 4.0, 5.5 and 7.0. These pH values were chosen to simulate conditions which could be used in topical formulations (Katz and Poulsen, 1971).

In the case of skin, where diffusion is significantly slower, it is far less clear whether or not steady state conditions have been established. Therefore, a different data analysis is used which takes into account the non-steady state region. Using a non-linear curve fitting method as described by Pellett et al. (1997) a value of the steady state flux can be determined from data which include values in the non-steady state region. Using a computer fitting program (EasyPlot 4.01, Cherwell Scientific Software), the permeability coefficients at steady state were evaluated (Table 3).

The permeability coefficients were calculated using the Potts and Guy equation and the log D values using ACD software. The steady state fluxes of lignocaine-HCl through human epidermis were calculated using the measured apparent permeabilities and multiplying by the applied concentrations ($n = 3$). The results of the experiments with human epidermis showed increasing L-HCl flux with increasing pH, confirming the trends seen with PDMS membranes (Table 1). This is in accordance with literature data obtained with hu-

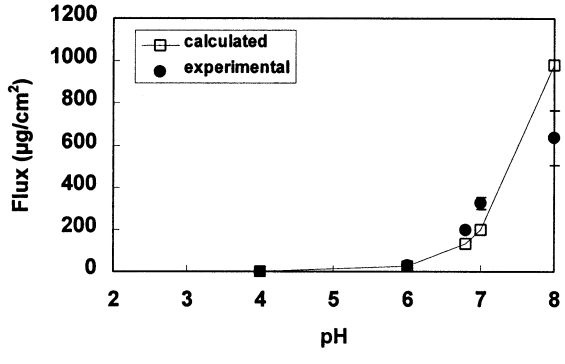

Fig. 3. A comparison between the experimental data and calculated values using Eq. (2) and the mean k_p values given in Table 2.

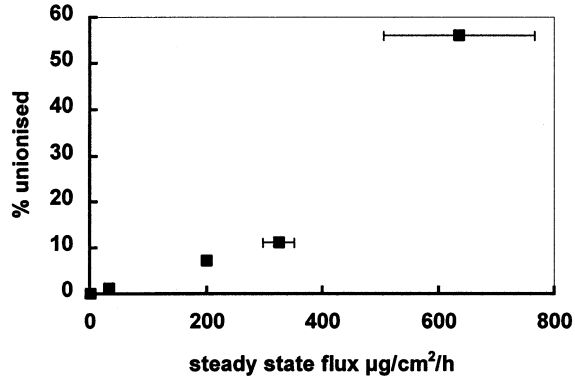

Fig. 4. The relationship between the steady state flux through the PDMS membrane and the percent of unionized lignocaine in the donor phase.

Table 3
Values of the apparent permeability coefficient and estimated permeability coefficient

pH	k_p (cm/h)	Estimated k_p (cm/h)	Flux (μg/cm^2 per h)
4.0	1.33×10^{-5}	2.25×10^{-5}	1.2 ± 1.2
5.5	3.39×10^{-5}	3.86×10^{-5}	13 ± 2
7.0	1.40×10^{-4}	2.88×10^{-4}	118 ± 30

man epidermis. Kushla and Zatz (1991) and Siddiqui et al. (1985) obtained similar results after a diffusion experiment lasting 10 h. As seen in Fig. 5 there is a linear relationship between the distribution coefficient and the steady state flux.

There are direct comparisons that can be made between the behaviour of the fluxes through the two different membranes (Fig. 6). Although the flux through the PDMS is, as expected, faster than that through the skin there appears to be a very similar relationship between the two when the effect of pH is examined.

It is possible to estimate the permeabilities expected using the Potts and Guy equation (Potts and Guy, 1992). Usually this equation is used solely for unionized permeants. However it is possible to use log D values rather than log P. The values obtained using this approach are provided in Table 3. Considering all the assumptions made there is remarkable agreement between the measured values and those predicted by the Potts and Guy equation.

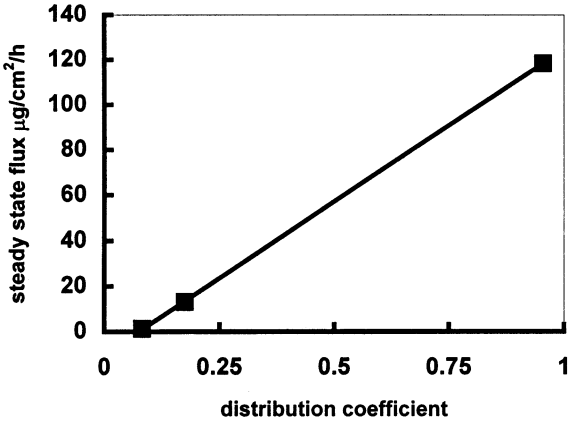

Fig. 5. The relationship between the steady state flux through human epidermis and the distribution coefficient for lignocaine.

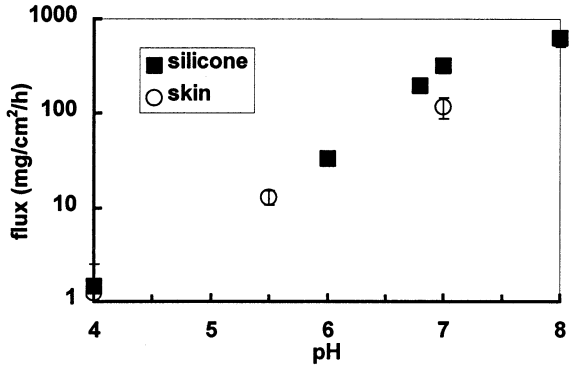

Fig. 6. The relationship between the steady state flux and pH for PDMS and human skin.

3.2. Influence of excess ions on the transfer through PDMS membranes

All experiments were conducted at pH 4.0 to minimise the contribution of the unionized form to the partition process. At this pH the concentration of the free base can be considered negligible. Although the log D is increased by the presence of the ions (nitrate, bromide and mesylate (Table 4) the steady state flux of lignocaine-HCl across PDMS was not significantly increased (Fig. 7).

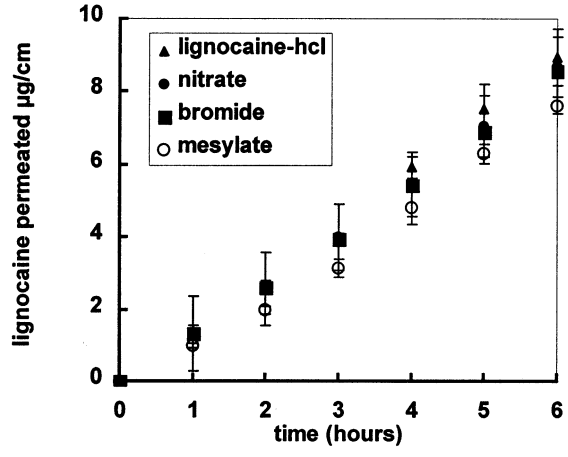

Fig. 7. The permeation of lignocaine hydrochloride through a PDMS membrane in the presence of a molar excess (5:1) of nitrate, bromide and mesylate ions.

Table 4
Log D of lignocaine-HCl with a molar excess (5:1) of different ions, and the steady state flux through PDMS membranes[a]

Ion type	Log D	Flux (μg/cm^2 per h)
Lignocaine-HCl	-1.09 ± 0.4	1.47 ± 0.03
With nitrate	-0.35 ± 0.016	1.40 ± 0.11
With bromide	-0.39 ± 0.07	1.39 ± 0.01
With mesylate	-0.48 ± 0.014	1.21 ± 0.04

[a] pH 4.0; $n = 3$.

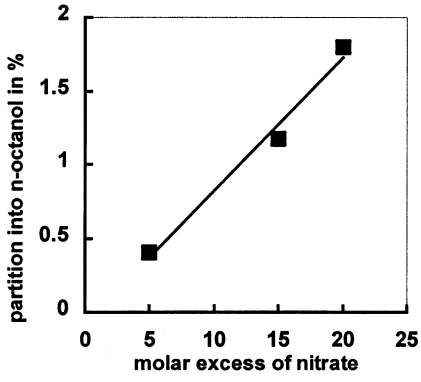

Fig. 8. The influence of an excess of nitrate ions on the partitioning of lignocaine hydrochloride.

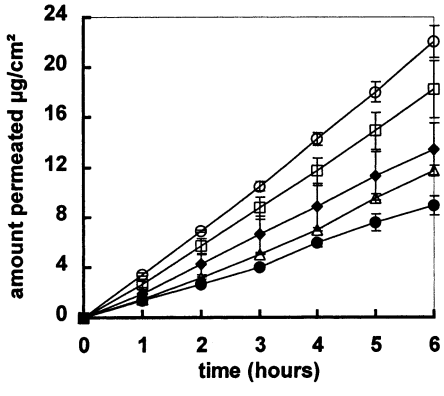

Fig. 9. Comparison of diffusion profiles of different lignocaine salts at pH 4.0 through PDMS membranes. -●-, L-HCl; -▲-, L-mps; -◆-, L-os; -△-, L-benz; -□-, L-nitrate.

Table 5
Log D of different lignocaine salts with corresponding calculated log P values for the parent acids of the counter ion present

Salt type	Log D	Log P	Flux (μg/cm^2 per h)
L-HCl	-1.09 ± 0.4	–	1.47 ± 0.03
L-benz	-0.84 ± 0.05	1.89	1.85 ± 0.06
L-os	0.62 ± 0.03	2.82	2.22 ± 0.4
L-nitrate	-0.43 ± 0.03	-0.03	2.95 ± 0.32
L-mps	-0.84 ± 0.05	-0.92	3.60 ± 0.17

This indicates that these anions have only a weak ability to promote diffusion. There is evidence that nitrate has a significant influence on the partition behaviour into n-octanol since a relationship exists between partition and excess nitrate present (Fig. 8).

3.3. Lignocaine salts and diffusion through PDMS

All experiments were conducted at pH 4.0 to minimise the contribution of the unionized species. Whereas the measured apparent partition coefficients into n-octanol of the salts (from high to low) L-os > L-nitrate > L-mps > L-benz > L-HCl (Table 5) are almost in agreement with their lipophilicity, as determined by the calculated log P (ACD software) of the parent acid, the steady state flux does not correlate.

The highest steady state flux was measured from L-mps as 3.6 μg/cm^2 per h (Fig. 9). The highest tendency to partition into n-octanol was measured from L-os but the steady state flux is 1.6-fold lower than from L-mps. Although the apparent partition coefficient of L-nitrate is similar to that of L-HCl with excess of sodium nitrate the steady state flux of the lignocaine from L-nitrate is 2.1-fold higher than from the latter.

All steady state fluxes from the L-salts are higher than from L-HCl (Table 4).

4. Conclusions

Many publications deal with the importance of the salt form with respect to the unionized drug

(Cascella and Feldmann, 1980; Swarbrick et al., 1984; Neubert, 1989; Pardo et al., 1992; Mattani et al., 1994; Kadono et al., 1998). The major advantage of the salt form is related to improved solubility. However, when the salt contains both an organic cation and anion, the salt could possess a residual degree of hydrophobicity despite its ionic character. It has been reported that salts of this type may behave as ion pairs and they can be transported through hydrophobic membranes. Since the ability of lignocaine to form an ion pair with organic acids has been reported (Nash et al., 1992; Vajragupta and La-ong, 1994; Karami and Beronius, 1998) the partition and diffusion behaviour was further evaluated and novel L-salts considered. The pH values selected for the studies should not alter the barrier characteristics of the stratum corneum. Between 4 and 10 there appears to be little change in hydration, swelling or permeability characteristics of human skin (Barry, 1983). Therefore any changes in lignocaine flux result from changes in the relative amount of the two species, ionized and unionized, present in solution and not from any direct enhancer activity on the stratum corneum. The formation of ion pairs, which enhance skin permeability, has been postulated for several lignocaine salts (Vajragupta and La-ong, 1994). The experiments were conducted at pH 7.4 through pig skin but none of the salts had a significantly higher partition coefficient than L-HCl. At this pH more than 24% of lignocaine is unionized and this species contributes significantly to the flux. Another paper describes the preparation of lignocaine-n-alkanoate ion pairs by direct acid base reaction (Nash et al., 1992). Permeation through hairless mouse skin showed an increased steady state flux from the salts compared to lignocaine. A possible explanation for this increase can be based on their lipid solubility characteristics.

This paper shows that for both PDMS and human skin there are similarities in the behaviour, the larger the unionized fraction the higher the flux. The presence of excess ions such as nitrate, mesylate and bromide showed a similar but significant increase in their log D value compared to L-HCl.

However, the steady state flux through PDMS was not significantly increased. These anions do not have a big effect on the diffusion compared to L-HCl. There may be several explanations for this. The partitioning medium of n-octanol may not be reflecting the more hydrophobic nature of the PDMS membrane. Also the flux is a product of partition and diffusion and although the more lipophilic counter ion promotes partition, the diffusing species, the ion pair, is larger and will therefore result in slower transport.

There is a linear relationship between the partition coefficient of nitrate ion pair and the molar excess of nitrate ions, which indicates that nitrate can have a positive effect. For the transport experiment with the excess amount of nitrate, the steady state flux was not increased, whereas in the salt form the steady state flux of lignocaine was increased 2-fold compared to L-HCl flux. One of the reasons may be the different ionic strength in the donor solution. In the case of excess nitrate, the nitrate was added as sodium nitrate to the L-HCl solution in a molar ratio 5:1. When the L-nitrate salt was used, the amount of L-nitrate dissolved related directly to the amount of free base.

The partition coefficients of the synthesised salts are almost in agreement with the lipophilicity of the counter ions. However, a correlation with the steady state flux could not be found. This is especially the case for L-os which shows a high partition into n-octanol whereas the steady state flux is comparable to that of L-benz. One reason could be a hydrophobic interaction between the open chain hydrocarbons (C-8) of the octanesulfonate of the salt and the PDMS membrane.

It is possible to enhance the flux of salts across lipophilic membranes by using an ion pairing approach. The degree to which this is possible depends on the lipophilicity of the counter ion, the medium in which the ion pair forms and the ionic strength of the donor solution. There are significant differences between PDMS and stratum corneum but the trends observed are similar.

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