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On iontophoretic delivery enhancement: Ionization and mobility of lidocaine hydrochloride in propylene glycol

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Abstract

The structure of lidocaine hydrochloride (LidHCl) in propylene glycol (PG), a solvent known to enhance transdermal delivery of drugs, and the mobilities of the different kinds of ionic species appearing in this system was investigated at 25.0°C by precision conductometry. The molar conductivity was determined at several concentration between 0.4 and 10 mM and the data analysed using the conductance equation of Fuoss-Hsia and Fernandez-Prini (FHFP equation). For concentrations of up to ≈ 1.2 mM no higher aggregates that $LidH^+$ were found. Using a two-parameter analysis of the equilibrium, $LidH^+ \Leftrightarrow Lid + H^+$, we obtained the acid dissociation constant, $K_a(LidH^+) = 2.5 \cdot 10^{-7}$ (molar scale); $pK_a = 6.60$, and the limiting molar conductivity, $\lambda_0(LidH^+) = 0.2675$ cm$^2/\Omega$ per mol. For concentrations above 1.2 mM there is strong evidence of formation of ion-pairs, $LidH^+Cl^-$. The ion-pair association constant was estimated to $K_p \approx 40$ indicating that about 15% of the electrolyte is in the form of $LidH^+Cl^-$ at the highest concentration (10 mM) investigated.

Keywords: Iontophoresis; Lidocaine hydrochloride; Propylene glycol; Enhancer; Molar conductivity; Ionic conductivity; Ion pairs

1. Introduction

It is well documented that iontophoresis can be used to enhance transdermal delivery of many drugs. Further increase in the rate of permeation may be achieved by addition of various chemical agents to the drug. A synergetic effect between iontophoresis and certain chemical agents has been observed. Such a synergetic effect was found by Bhatia et al. (1997) studying the enhancing effect of, e.g. oleic acid in combination with ethanol and propylene glycol, respectively, on the in vitro permeability of luteinizing hormone releasing hormone (LHRH) through porcine epidermis.

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By passive delivery, transdermal in vitro studies, Kushla and Zatz (1990) have shown that cationic surfactants may remarkably increase the flux of lidocaine through human skin from saturated systems in propylene glycol-water mixtures. It has also been demonstrated that such surfactants are effective in increasing the corneal permeation of pilocarpine nitrate (Mikkelson et al., 1943), penicillin (Godbey et al., 1979) and ketorolac (Fu and Lidgate, 1986). Kushla et al. (1993) investigated the anaesthetic activity of several topical lidocaine formulations containing 20% propylene glycol. They found that all formulations containing propylene glycol produced significantly greater anesthesia compared with the formulations without propylene glycol. Sarpotdar and Zatz (1986) report an in vitro study of the penetration enhancement of lidocaine through hairless mouse skin in the presence of propylene glycol. They observed that the concentration of propylene glycol strongly affects the steady state flux.

To optimise the conditions in iontophoretic delivery of local anesthetics, and because of the obvious importance of propylene glycol (PG) as an enhancer in various formulations, we decided to investigate, by electrical precision conductance measurements, the behaviour of lidocaine hydrochloride in pure PG at 25°C with respect to ionization and transport properties.

2. Experimental

2.1. Reagents

Crystalline lidocaine hydrochloride monohydrate ($LidHCl \cdot H_2O$) and propylene glycol (PG), $CH_3CH(OH)CH_2OH$, were obtained from Sigma.

The density of the solid $LidHCl \cdot H_2O$, 1.1961 g/cm^3, at room temperature was determined by means of an Acc Pyc 1330 density meter.

The solvent medium, PG, was of HPLC grade (min. 99.5%; water content $< 0.02\%$; chloride $< 0.01\%$). Its electrolytic conductivity was determined to $\kappa = 4.85 \cdot 10^{-9}/\Omega$ per cm. For the dielectric constant of PG we obtained $\epsilon = 29.65 \pm 0.15$ at 25.00 ± 0.1°C using a Ferisol M 803 A Q-meter. The literature value, $\eta = 0.43887$ P at 25°C, for the viscosity of the solvent, (Venkateswara Sastry and Kalidas, 1985) was used in the calculations.

Potassium chloride (Merck, suprapur), used to calibrate the conductivity cell, was dried at 130°C and stored in a desiccator.

Aqueous solutions of KCl and stock solutions of LidHCl in PG were prepared on weight basis. Because of the high precision of the method used all weights were corrected for the buoyancy effect of the air. The density of the stock solution was determined by means of a DMA 02 C digital precision density meter (Sjöberg et al., 1996). In calculating concentrations of diluted samples the density of the solution was assumed to vary linearly with the molality of the solute.

2.2. Conductance measurements

The equipment employed and the technique used to determine the molar conductivity, Λ, of solutions of lidocaine hydrochloride in propylene glycol at 25.00 ± 0.02°C were the same as previously described for this salt in water and in 1-octanol as solvent media (Sjöberg et al., 1996; Karami et al., 1997) with the exception that portions of the stock solution were added to the initially pure solvent in the conductivity cell using 10 ml 'plastic Once®' syringes. The exact amounts of the stock solution added to the cell were determined by difference weighing of the syringe.

For each concentration of the salt resistance measurements were performed at five different frequencies, v, in the interval from 2 to 5 kHz. Ordinarily, the resistance, R, is extrapolated to infinite frequency (i.e. to $1/v = 0$) assuming a linear relationship between R and $1/v$. For the present system, however, we found a slight curvature in this graph. A typical example of this kind is shown in Fig. 1 for a 4.25 mM solution of LidHCl in PG. The curve in this graph refers to a polynom of order 2.

The results of the conductance measurements are summarised in Table 1, where the molar conductivity of LidHCl, corrected for the conductivity of the solvent, is given at different concentrations between 0.4 and 10.0 mM.

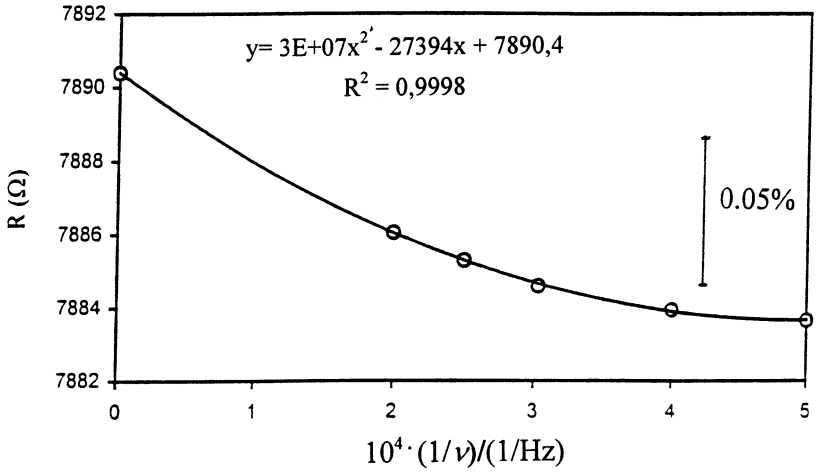

Fig. 1. Extrapolation of resistance to infinite frequency for 4.25 mM LidHCl in PG at 25°C.

3. Analysis of conductivity data

For the concentration range of lidocaine hydrochloride in propylene glycol here concerned it appears reasonable to assume that the ionic species $LidH^+$, H^+, and Cl^-, appear besides electrically neutral species, lidocaine molecules (Lid) and ion-pairs, $LidH^+Cl^-$ and H^+Cl^-. For 1:1-electrolytes triple ions should, according to theory (Fuoss and Accascina, 1959), not appear below a critical concentration, c_0, given by the expression (Eq. (1)),

$$c_0 = 3.2 \cdot 10^{-7} \epsilon^3 \quad (1)$$

Table 1
Molar conductivity of lidocaine hydrochloride in propylene glycol at 25.0°C

$10^4 \cdot c$ (M)	Λ (cm^2/Ω per mol)	$10^4 \cdot c$ (M)	Λ (cm^2/Ω per mol)
4.098	2.30368	48.922	1.96789
6.057	2.26773	56.213	1.94053
9.082	2.23412	63.342	1.91431
12.289	2.19165	69.704	1.89185
16.400	2.15348	76.132	1.87435
20.923	2.11960	82.454	1.85652
34.000	2.03673	88.130[a]	1.84357
38.298	2.01751	93.950[a]	1.83138
42.506	1.99502	100.045[a]	1.81187

[a] These concentrations were not included in computing the conductance parameters because they exceed, according to theory (Fuoss and Accascina, 1959), the critical concentration for triple ion formation.

where ϵ is the dielectric constant of the solvent. For PG at 25°C, $c_0 = 8.34$ mM. The calculation of conductance parameters from our conductivity data in Table 1 will be restricted to concentrations below this critical value.

Hence, we will consider the following equilibria (Eqs. (2)–(4)),

$$LidH^+ \overset{K_a}{\Leftrightarrow} Lid + H^+ \quad (2)$$

$$H^+ + Cl^- \overset{K}{\Leftrightarrow} H^+Cl^- \quad (3)$$

$$LidH^+ + Cl^- \overset{K_p}{\Leftrightarrow} LidH^+Cl^- \quad (4)$$

where K_a is the acid dissociation constant of $LidH^+$, and K and K_p are the ion-pair association constants for formation of H^+Cl^- and $LidH^+Cl^-$ ion-pairs, respectively.

3.1. The dissociation equilibrium, $LidH^+ \Leftrightarrow Lid + H^+$

In analysing our conductance data we will assume that, for the four lowest concentration points, $12.289 \cdot 10^{-4} \geq c \geq 4.098 \cdot 10^{-4}$ M, ion-pair formation according to Eq. (3) and Eq. (4) may be neglected. This assumption will be discussed below. For the infinitely dilute solution, when the electrolyte is completely dissociated into Lid, H^+ and Cl^-, the molar conductivity is equal

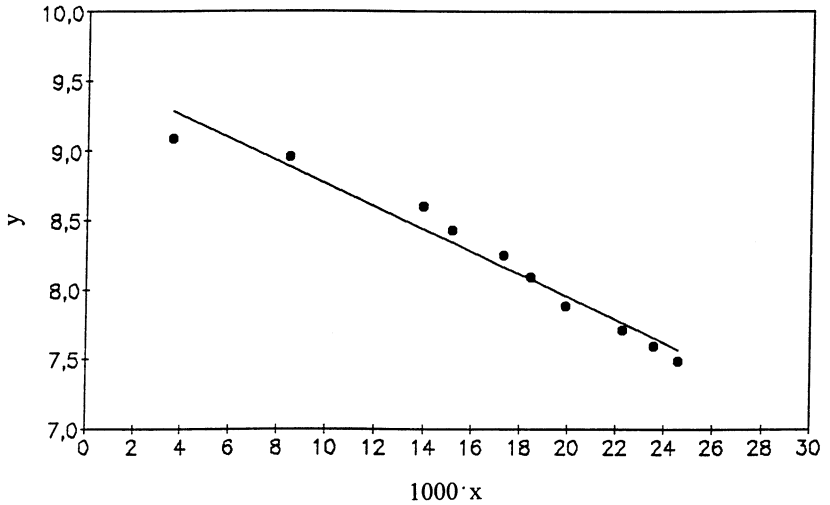

Fig. 2. Graph according to Eq. (7) for HCl in PG at 25°C. Calculations based on conductance data of Venkateswara Sastry and Kalidas (1985).

to the limiting molar conductivity of hydrochloric acid, Λ_0(HCl).

The degree of dissociation of $LidH^+$ is denoted by α. Hence, the fractions of $LidH^+$, H^+ and Cl^- are equal to $(1-\alpha)$, α and unity, respectively. The concentration dependence of the molar conductivity of LidHCl in this high dilution range can now be expressed,

$$\Lambda = m[\lambda_0(LidH^+)(1-\alpha) + \lambda_0(H^+)\alpha + \lambda_0(Cl^-)] \quad (5)$$

where m is a previously defined mobility correction factor (Karami et al., 1997), which corrects Λ for ion atmosphere effects. The λ_0's are the limiting molar conductivities of the species indicated.

The single ion conductivities, $\lambda_0(H^+)$ and $\lambda_0(Cl^-)$, were estimated from literature data using the following procedure.

Venkateswara Sastry and Kalidas (1985) report conductivity data for hydrochloric acid in propylene glycol at 25°C. To obtain the ion-pair association constant, K, of H^+Cl^- and Λ_0(HCl) the FHFP conductance equation (Fuoss and Hsia, 1967, 1968; Fernandez-Prini, 1969),

$$\Lambda = \Lambda_0 - S(c\alpha)^{1/2} + Ec\alpha \log(c\alpha) + J_1 c\alpha - J_2(c\alpha)^{3/2} - Kc\alpha\gamma^2\Lambda \quad (6)$$

in its linearised form,

$$y = \Lambda_0 - K \cdot x \quad (7)$$

combined with the law of mass action for the equilibrium Eq. (3) and the Debye-Hückel equation (Robinson and Stokes, 1965) for the mean molar activity coefficient of free ions, was fitted to the HCl conductivity data according to the iterative method previously outlined for LidHCl in 1-octanol (Karami et al., 1997). The distance parameter in the Debye-Hückel equation and in the FHFP conductance Eq. (6) and Eq. (7) was set equal to the Bjerrum radius, which for univalent electrolytes in PG at 25°C is equal to 9.45 Å. A graph according to Eq. (7) for the final values of K and Λ_0(HCl) is shown in Fig. 2. This procedure yielded $K = 82$ (molar scale) and Λ_0(HCl) = 9.58 cm^2/Ω per mol.

To split Λ_0(HCl) into the individual limiting ionic conductivities, $\lambda_0(H^+)$ and $\lambda_0(Cl^-)$, access to transport numbers are required. To the knowledge of the authors no such data for HCl in PG are available in the literature. However, for a series of alcohols including propan-1-ol, propan-2-ol, 2-methylpropan-1-ol, butan-1-ol and butan-2-ol (De Lisi et al., 1976) estimated cation transport numbers for HCl in these alcohols at 25°C are in the range from 0.77 to 0.85. Hence, we decided tentatively to use $t_+ = 0.8$ for the

cation transport of HCl in PG. This yields $\lambda_0(H^+) = 7.66$ and $\lambda_0(Cl^-) = 1.92$ cm^2/Ω per mol.

The acid dissociation constant K_a for $LidH^+$ (equilibrium 2) and the limiting molar conductivity of this ion, $\lambda_0(LidH^+)$, resulting in the best fit of Eq. (5) to the four lowest concentration points (c,Λ) in Table 1 were determined according to the procedure described for $LidH^+$ in aqueous solution (Sjöberg et al., 1996).

In Fig. 3 it is shown how the standard deviation in Λ, $\sigma(\Lambda)$, for the difference between experimental and calculated values of Λ depend on $\lambda_0(LidH^+)$ for different values of K_a. The corresponding contour diagram, Fig. 4 illustrates how $\sigma(\Lambda)$ depends on these two parameters. The 'total minimum' (denoted 'x') was found at $K_a = 2.5 \cdot 10^{-7}$ (molarity scale), i.e. $pK_a(LidH^+) = 6.60$ and $\lambda_0(LidH^+) = 0.2675$ cm^2/Ω per mol.

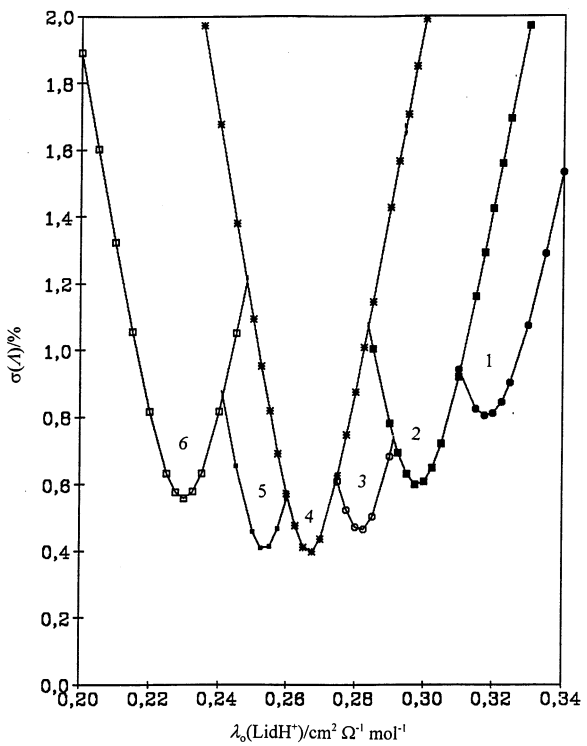

Fig. 3. Standard deviation plot for varying K_a and λ_0 ($LidH^+$). Fit of Eq. (5) to the four lowest concentration points in Table 1 for LidHCl in PG. The curves 1–6 refer to 10^7. $K_a = 1$, 1.5, 2, 2.5, 3 and 4, respectively.

As noted above we have in this low concentration range neglected formation of ion-pairs ψ (H^+Cl^- and $LidH^+Cl^-$) in calculating the acid dissociation constant, K_a, of $LidH^+$. On basis of the H^+Cl^- association constant, $K = 82$, above the concentration of H^+Cl^- ion-pairs is found to be $\approx 3\%$ of that of free protons at a total concentration of $4.098 \cdot 10^{-4}$ M and $\approx 10\%$ at $12.289 \cdot 10^{-4}$ M (the concentration limits used in calculating K_a). The corresponding values for ion-pairs of $LidH^+Cl^-$ relative to free $LidH^+$ ions are at the same concentration limits ≈ 1 and 3%, respectively (estimates based on the $LidH^+Cl^-$ association constant, $K_p = 40$, below).

As can be seen in Fig. 5, however, the calculated Λ vs concentration curve according to Eq. (5) fits quite well to the four lowest concentration points. This may be taken as evidence that the slight formation of H^+Cl^- and $LidH^+Cl^-$ ion-pairs in this low concentration range does not affect the calculated dissociation constant, K_a, significantly. With increasing concentration, however, the experimental points show an increasingly negative deviations from the calculated curve. We interpret this effect to be caused by formation of significant quantities of $LidH^+Cl^-$ ion-pairs. This matter will be discussed in the next section.

3.2. The ion-pair formation equilibrium, $LidH^+ + Cl^- \Leftrightarrow LidH^+Cl^-$

It has been previously shown that 1:1-electrolytes in methanol, the dielectric constant of which at 25°C ($\epsilon = 32.63$) is close to that of propylene glycol ($\epsilon = 29.65$), are subject to slight ion-pair formation (Beronius et al., 1970). Hence, in propylene glycol as solvent it appears most reasonable to assume that ion-pairs of $LidH^+Cl^-$ may be present in equilibrium with free $LidH^+$ and Cl^- ions.

To calculate the association constant, K_p, for formation of $LidH^+Cl^-$ ion-pairs the linearized FHFP Eq. (7) was iteratively fitted, as described for HCl above, to the 15 experimental points in Table 1 below the critical concentration for triple ion formation ($c_0 = 8.34$ mM). A graph according to Eq. (7) is shown in Fig. 6. Though an apparently straight line is obtained (regression coeffi-

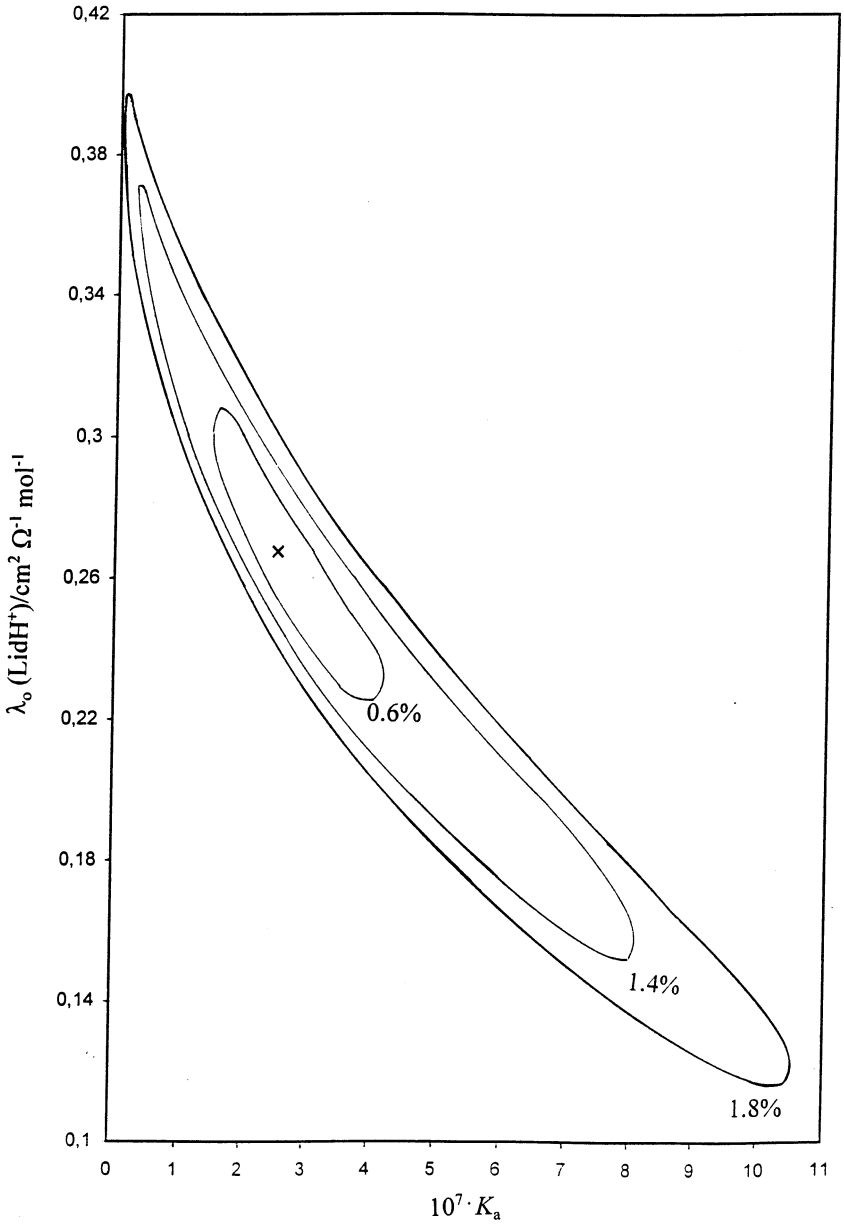

Fig. 4. Contour diagram showing the dependence of $\sigma(\Lambda)$ on $\lambda_0(\mathrm{LidH}^+)$ and K_a. The figure on the lines represent percentage standard deviation. Calculations based on data for LidHCl in PG according to Table 1 for $c_{max} = 1.23$ mM (four lowest concentration points). The best fit point, denoted x, corresponds to $K_a = 2.5 \cdot 10^{-7}$ and $\lambda_0(\mathrm{LidH}^+) = 0.2675$ cm^2/Ω per mol.

cient 0.999) a close inspection indicates that there might be a slight curvature (convex downwards) in this graph. This effect may be due to the fact that we have neglected the contribution of free protons to the conductivity due to the (slight) dissociation of LidH^+. If this is so, there should be a trend in K_p with the concentration interval studied. Hence, we repeated the calculation of K_p

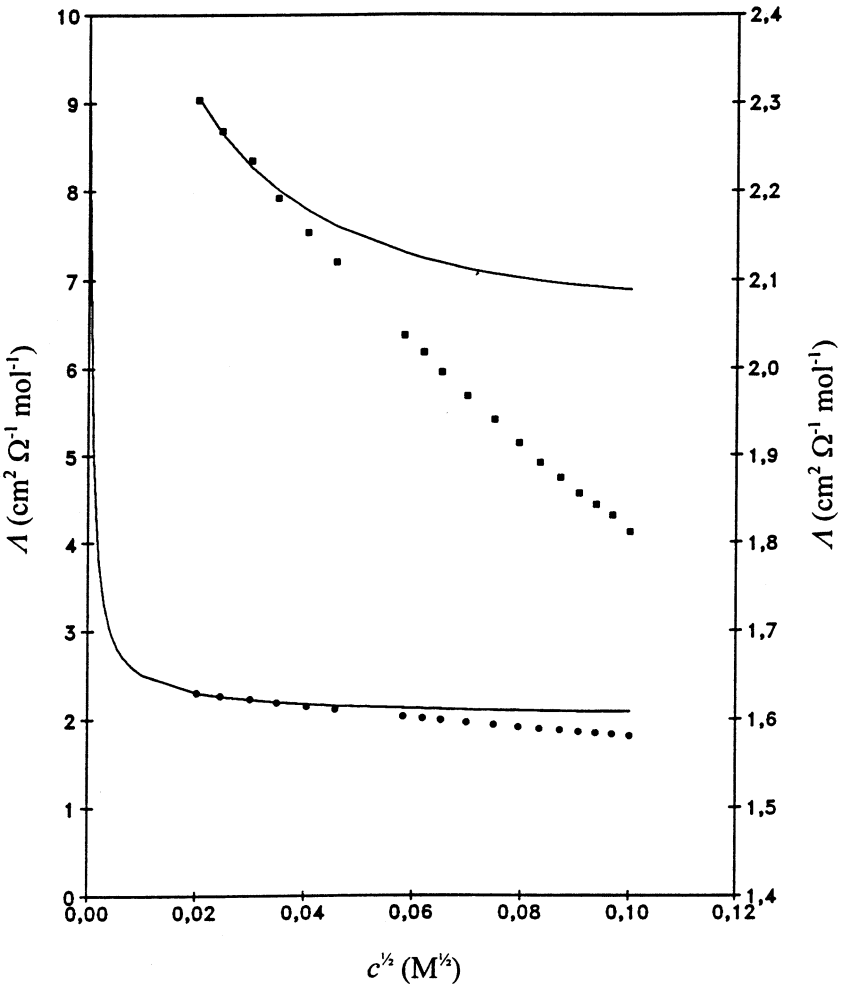

Fig. 5. Dependence of Λ on concentration of LidHCl in PG according to Eq. (5) fitted to the four lowest concentration points in Table 1. The increasing negative deviations between Eq. (5) and the experimental points with increasing concentration indicates formation of ion-pairs ($LidH^+Cl^-$). The upper curve, referring to the right hand side y-axis, is an enlargement in the vertical direction of lower one.

after removing the point at the lowest concentration, then again after removing the two lowest concentration points, and so on. The result is shown as the upper curve in Fig. 7, where K_p has been plotted as a function of the lower limit of the LidHCl concentration interval. A very slight decreasing trend in K_p with increasing lower limit of the interval is indicated. Hoping to obtain a constant K_p-value each experimental point was corrected for the contribution of free protons to the conductivity. The dependence of K_p on the lower concentration limit is, after this correction, shown as the lower curve in Fig. 7. Now we find a slight increase in K_p upon increasing the lower concentration limit. These calculations show, however, that the disturbing effect of the dissociation of $LidH^+$ on the computed ion-pair association constant, K_p, is quite small. The two curves in Fig. 7 tend asymptotically to a value of $K_p \approx 40$.

Fig. 8 shows the corresponding dependence of Λ_0(LidHCl) on the lower limit of the concentra-

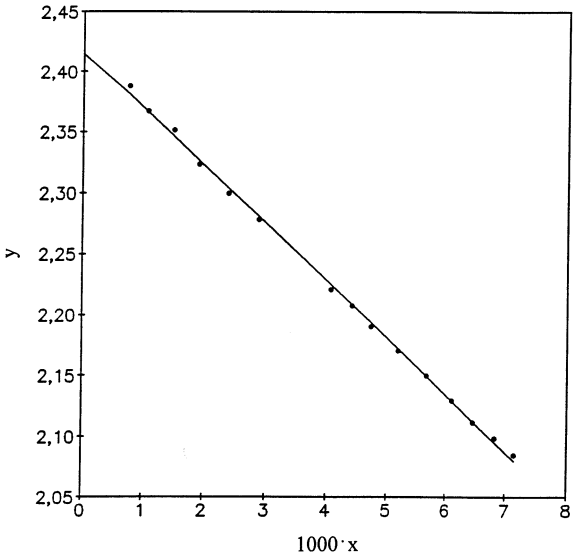

Fig. 6. Best fit of Eq. (6) in its linearized form, Eq. (7), to the conductance data of LidHCl in Table 1; $c_{max} = 8.25$ mM.

tion interval before and after correcting the conductivity of the solution for the dissociation of $LidH^+$. The two curves converges asymptotically towards $\Lambda_0(LidHCl) \approx 2.35$ cm$^2/\Omega$ per mol, which is not far from the corresponding Λ_0-value, 2.19 cm$^2/\Omega$ per mol, obtained as the sum of the limiting ionic conductivities of $LidH^+$ and Cl^- according to the alternative method of computation in Section 3.1 above.

4. Discussion

Inspection of Fig. 5 indicates that Eq. (5), derived on the assumption that the only equilibrium of importance is that between $LidH^+$, Lid and H^+, fits the experimental points quite well up to a total LidHCl concentration of about 1.2 mM. Above this concentration there is strong evidence of formation of $LidH^+Cl^-$ ion-pairs (experimental points deviating negatively from the calculated curve).

On basis of the equilibrium constants above, $K_a = 2.5 \cdot 10^{-7}$ for the dissociation of $LidH^+$ and $K_p = 40$ for the formation of $LidH^+Cl^-$ ion-pairs, the concentrations of the $LidH^+Cl^-$, $LidH^+$, and electrically neutral Lid molecules were computed as a function of the total concentration of lidocaine hydrochloride. Mean molar activity coefficients were calculated as above according to the Debye-Hückel equation. The results are shown in graphic form in Fig. 9, which indicates that free $LidH^+$ ions strongly dominate over both $LidH^+Cl^-$ ion-pairs and neutral Lid molecules in the entire concentration interval studied. Only a very small fraction of the salt appears as electrically neutral Lid molecules.

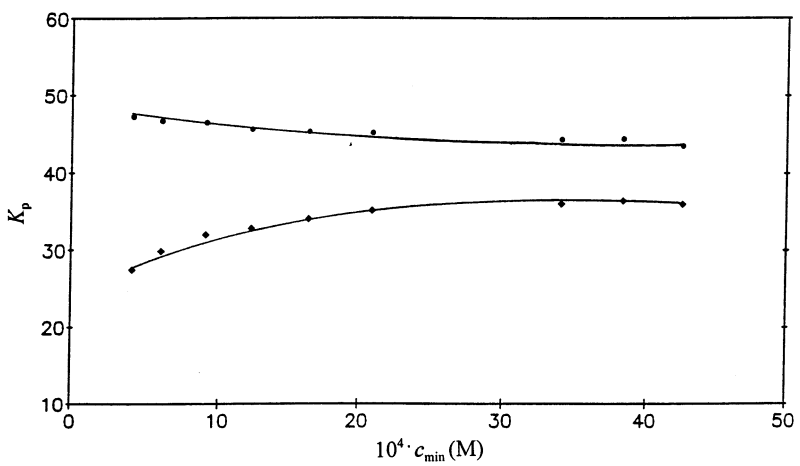

Fig. 7. Upper curve: Ion-pair association constant, K_p, as a function of the lower limit of the concentration interval of LidHCl in PG assuming negligible dissociation of $LidH^+$. The lower curve is the corresponding one obtained after correcting the conductivity of the solution for the contribution of free protons due to the slight dissociation of $LidH^+$. Conductance data according to Table 1 for $c_{max} = 8.25$ mM.

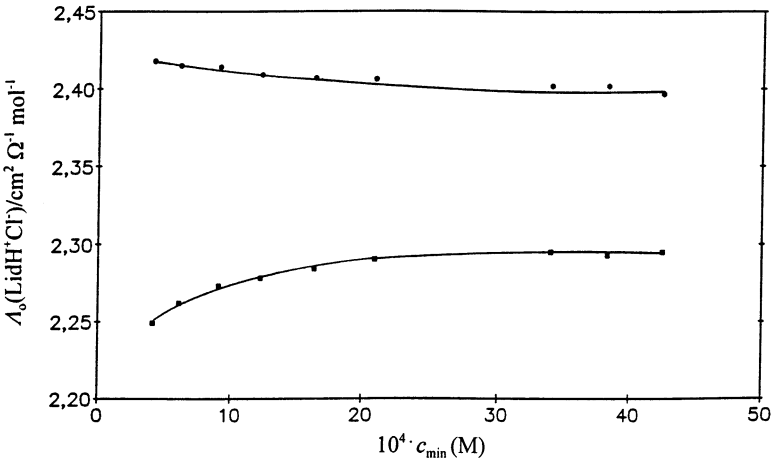

Fig. 8. Dependence of Λ_0(LidHCl) on the lower limit of the concentration interval before and after correcting the conductivity of the solution for the dissociation of $LidH^+$ (compare top and bottom curves, respectively).

From an iontophoretic point of view it is desirable that the fraction of the electrolyte in the form of charged species ($LidH^+$) is as large as possible. Fig. 10 shows how the fraction of the salt in this charged form varies with the total concentration of lidocaine hydrochloride. In extremely dilute solutions increasing concentration results in an increase in the fraction of free $LidH^+$ ions up to a total concentration of about 0.5 mM. In this low concentration range dissociation of $LidH^+$ into Lid and H^+ is the dominating process. At this concentration, corresponding to the maximum in the graph, there is an onset of formation of measurable amounts of $LidH^+Cl^-$ ion-pairs, the extent of which increases with the salt concentration. This results in a gradual decrease in the fraction of free $LidH^+$ ions with increasing concentration. At the highest concentration investigated, 10 mM, the fraction of $LidH^+Cl^-$ ion-pairs is about 15% of the total concentration of lidocaine hydrochloride.

Lidocaine hydrochloride has been previously studied at 25°C by the present method in water (Sjöberg et al., 1996) and 1-octanol (Karami et al., 1997) as solvent media. Propylene glycol is, with respect to ionization power, intermediate in character between these two solvents. This fact is reflected by the different kind of charged and non-charged species appearing in detectable amounts in these solvent media (Table 2).

In water as solvent no higher aggregates than $LidH^+$ are detected (Sjöberg et al., 1996). Water and propylene glycol are similar with respect to their influence on the electrolyte with the exception that LidHCl is subject to slight ion-pair formation in PG. The behaviour of LidHCl in 1-octanol differs markedly from that in water and PG. In 1-octanol the $LidH^+$ ion appears to be practically undissociated and there is in this solvent strong evidence of formation of ion-pairs as well as triple ions (Karami et al., 1997).

5. Conclusions

The aim of the present study was to obtain a firm basis for optimising the conditions in iontophoretic delivery of drugs involving enhancers. Lidocaine hydrochloride in pure propylene glycol was used as a model system. Propylene glycol was selected as solvent because of its documented importance as an enhancer. By means of electrical precision conductance measurements and application of advanced conductance theory it was found possible to characterise this system on a molecular level.

The dependence of the molar conductivity of the electrolyte was investigated at 25.0°C over the concentration interval from 0.4 to 10 mM. The data were analysed with respect to dissociation of

$LidH^+$, formation of ion-pairs, $LidH^+Cl^-$, and mobilities of the ionic species involved.

$LidH^+$ was found to behave as a very weak electrolyte ($pK_a = 6.60$) and is subject to slight ion-pair formation with the chloride ion; ion-pair association constant $K_p \approx 40$ on the molarity scale. Up to a total concentration of about 0.5 mM dissociation of $LidH^+$ is the dominating process. Above this concentration measurable amounts of $LidH^+Cl^-$ ion-pairs are formed. The extent of ion-pair formation increases to about 15% of the total concentration of lidocaine hydrochloride at the highest concentration, 10 mM, investigated.

Comparison with conductance data for this anaestheticum in water and 1-octanol as solvent media clearly demonstrate the tremendous effect of the character of the solvent on the behaviour of the drug with respect to formation of charged and uncharged species in the solution.

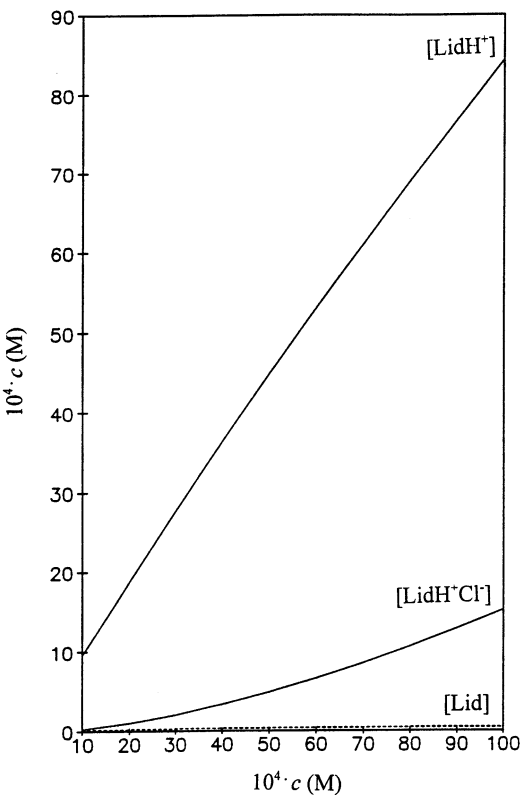

Fig. 9. Concentrations of different species in solutions of LidHCl in PG as a function of total concentration indicating a strong domination of free $LidH^+$ ions over ion-pairs, $LidH^+Cl^-$, and neutral lidocaine molecules, Lid.

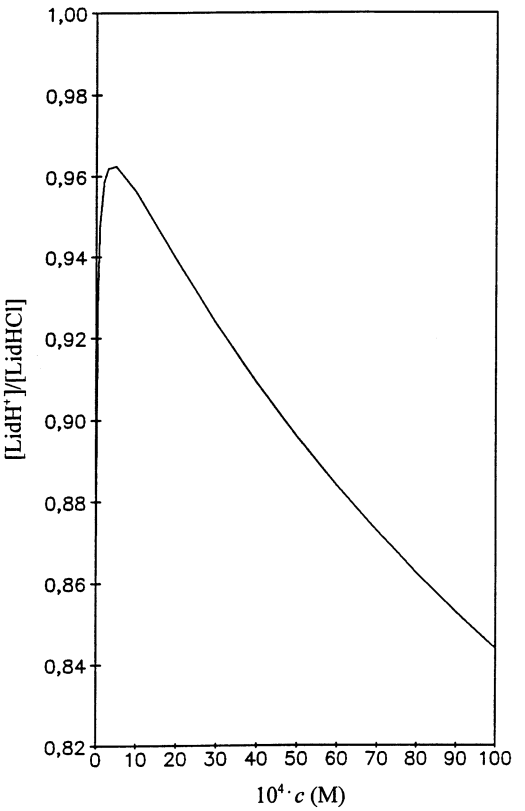

Fig. 10. Fraction of the drug in the form of $LidH^+$ as a function of total concentration of LidHCl in PG.

Table 2
Measurable amounts (*) of charged and uncharged species of lidocaine hydrochloride in the concentration interval 0.2–10 mM at 25°C

Solvent	Water	Propylene glycol	1-Octanol
ϵ	78.3	29.65	9.85
$LidH^+$	*	*	*
Cl^-	*	*	*
Lid	*	*	—
H^+	*	*	—
$LidH^+Cl^-$	—	*	*
$(LidH)_2Cl^+$	—	—	*
$LidHCl_2^-$	—	—	*

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References

Beronius, P., Wikander, G., Nilsson, A.-M., 1970. Conductance and association of alkali iodides in methanol and ethanol. Z. Physik. Chem. N.F. 70, 52–61.

Bhatia, K.S., Gao, S., Singh, J., 1997. Effect of penetration enhancers and iontophoresis on the FT-IR spectroscopy and LHRH permeability through porcine skin. J. Control. Release 47, 81–89.

De Lisi, R., Goffredi, M., Livery, V.T., 1976. Effect of water on proton migration in alcoholic solvents. Part 4. Conductance of hydrogen chloride in butan-2-ol and in ethanol. J. Chem. Soc. Faraday I. 72, 436–447.

Fernandez-Prini, R., 1969. Conductance of electrolyte solutions. A modified expression for its concentration dependence. Trans. Faraday Soc. 65, 3311–3313.

Fu, R.C., Lidgate, D.M., 1986. In vitro rabbit corneal permeability study of ketorolac tromethamine, a non-steroidal anti-inflammatory agent. Drug Dev. Ind. Pharm. 12, 2403–2430.

Fuoss, R.M., Accascina, F., 1959. Electrolytic Conductance. Interscience, New York.

Fuoss, R.M., Hsia, K.-L., 1967. Association of 1-1 salts in water. Proc. Natl. Acad. Sci. USA 57, 1550–1557.

Fuoss, R.M., Hsia, K.-L., 1968. Association of 1-1 salts in water. Proc. Natl. Acad. Sci. USA 58, 1818.

Godbey, R.E.W., Green, K., Hull, D.S., 1979. Influence of cetylpyridinium chloride on corneal permeability to penicillin. J. Pharm. Sci. 68, 1176–1178.

Karami, K., Sjöberg, H., Beronius, P., 1997. Ionization conditions for iontophoretic drug delivery. Electrical conductance and aggregation of lidocaine hydrochloride in 1-octanol at 25°C. Int. J. Pharm. 154, 79–87.

Kushla, G.P., Zatz, J.L., 1990. Evaluation of a noninvasive method for monitoring percutaneous absorption of lidocaine in vivo. Pharm. Res. 7, 1033–1037.

Kushla, G.P., Zatz, J.L., Mills, O.H. Jr., Berger, R.S., 1993. Noninvasive assessment of anesthetic activity of topical lidocaine formulations. J. Pharm. Sci. 82, 1118–1122.

Mikkelson, T.J., Chrai, S.S., Robinson, J.R., 1943. Competitive inhibition of drug-protein interaction in eye fluids and tissues. J. Pharm. Sci. 62, 1942–1945.

Robinson, R.A., Stokes, R.H., 1965. Electrolyte Solutions, 2nd ed. Butterworths, London.

Sarpotdar, P.P., Zatz, J.L., 1986. Evaluation of penetration enhancement of lidocaine by nonionic surfactants through hairless mouse skin in vitro. J. Pharm. Sci. 75, 176–181.

Sjöberg, H., Karami, K., Beronius, P., Sundelöf, L.-O., 1996. Ionization conditions for iontophoretic drug delivery. A revised pK_a of lidocaine hydrochloride in aqueous solution at 25°C established by precision conductometry. Int. J. Pharm. 141, 63–70.

Venkateswara Sastry, V., Kalidas, C., 1985. Conductances of HCl and HBr in water-propylene glycol mixtures. Ind. J. Chem. 24A, 658–660.