ELSEVIER

International Journal of Pharmaceutics 141 (1996) 63–70

international journal of pharmaceutics

Ionization conditions for iontophoretic drug delivery. A revised pK_a of lidocaine hydrochloride in aqueous solution at 25°C established by precision conductometry

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Received 28 February 1996; revised 29 May 1996; accepted 2 June 1996

Abstract

The electrical conductance of lidocaine hydrochloride ($LidH^+Cl^-$) in aqueous solution at 25.00°C has been established by precision conductometry over a concentration interval from 0.3 to 6.6 mM. Assuming any ion pairing between the $LidH^+$ and Cl^- ions to be negligible, a conductance equation has been derived in which the equilibrium between $LidH^+$, Lid and H^+ is considered. This equation involves the dissociation constant of $LidH^+$, K_a, and the limiting molar conductivity of $LidH^+$, $\lambda_0(LidH^+)$, as adjustable parameters. The mobility correction factor used to correct the mobility of the ions for ion atmosphere effects is in accord with the conductance function of Fuoss, Hsia, and Fernandez-Prini (FHFP equation). A computer program was developed to find the values of K_a and $\lambda_0(LidH^+)$ resulting in the best fit of the conductance equation to the experimental points (minimum standard deviation between experimental and computed Λ-values). With the distance parameter set equal to the Bjerrum radius, $q = 0.357$ nm, we obtained pK_a ($LidH^+$) = 7.16 (molarity scale), $\lambda_0(LidH^+) = 17.87$ cm^2 Ω^{-1} mol^{-1}. Our pK_a-value is 0.7 units lower than the previously reported potentiometrically determined value, 7.85.

Keywords: Iontophoresis conditions (prerequisites); Lidocaine hydrochloride; Molar conductivity; Ionic conductivity; Ion size

1. Introduction

Modern drug delivery systems tend, for many reasons, to comprise an increasing number of sophisticated technical devices. Specialized drugs are often very costly. Hence, it is essential that as little as possible is lost during the delivery process. It is from the medical point of view essential that the rate of delivery may be effectively controlled. Often direct and simple routes into the living body are desired.

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PII S0378-5173(96)04616-9

Iontophoresis is a technique by which charged bioactive molecules are transferred from an electrolytic solution into and through a tissue by means of a direct electric current (Masada et al., 1989; Banga and Chien, 1988; Bellantone et al., 1986). Though this technique has been used during several decades for specific delivery purposes there is still considerable lack of basic knowledge of this phenomenon (Glikfeld et al., 1988; Miller and Smith, 1989). In a typical in vivo iontophoretic system, two electrodes are placed on the skin and connected to a power supply. The bioactive material is placed in a conducting medium, normally an aqueous solution, between the 'active' electrode and the skin and the circuit completed by a second 'passive' electrode and the skin.

Iontophoretic drug delivery has many advantages over passive transdermal delivery, which is restricted to relatively small and lipophilic compounds, e.g. straightforward control of the amount delivered by the use of a constant current (Phipps et al., 1989). In comparison with peroral administration, the first passage through the liver is avoided by directing the drug directly into the blood system. Furthermore, iontophoresis appears from many different points of view to be an attractive method of administration. Systematic toxicity is virtually eliminated because of the minute amounts of drug delivered, yet the concentration of locally administrated drug may be relatively high. Fear of administration, especially in comparison with the use of syringe and needle, would also be eliminated (Gangarosa et al., 1978).

A condition for iontophoretic delivery of drugs is that the drug molecule is in an ionized state with either a positive or a negative charge. Non-ionic drugs may be transported iontophoretically into the body provided a charge can be introduced into the drug molecule or by electroosmosis.

The mobility of charged drugs depend upon several factors, e.g. concentration, interactions between the ionic species themselves, interactions between the ions and the solvent molecules, size of the charged drug molecule, polarity of the solvent, etc. A systematic investigation of these effects may be of great help in selecting drugs suitable for iontophoretic delivery and to establish optimum conditions in the iontophoretic procedure. For those drugs where the degree of ionization is pH dependent, the efficiency of iontophoretic delivery varies with pH. An example of this kind is the hydrochloride salt of a local anesthetic, where an increase in pH results in conversion of positively charged molecules into electrically neutral species (Gangarosa et al., 1978).

The aim of the present investigation is to study lidocaine hydrochloride in aqueous solution, especially the ionization and mobility of the $LidH^+$ ion, by means of precision conductometry and application of advanced conductance theory.

2. Experimental

Lidocaine hydrochloride monohydrate for injection was obtained as a gift from Astra Pain Control AB, Södertälje, Sweden (Broberg et al., 1991). Chromatographic analysis indicated a purity of 99.8%. This sample was used in the conductance measurements denoted Series 1 below. The lidocaine hydrochloride monohydrate used in Series 2 was obtained from Sigma, USA.

The conductivity of the deionized water used as solvent was $\kappa = 1.18 \cdot 10^{-6}$ and $6.83 \cdot 10^{-7}$ Ω^{-1} cm^{-1} in Series 1 and 2, respectively. Potassium chloride (Merck) for calibration of the two different types of conductivity cells used was of suprapur grade.

Solutions of potassium chloride for calibration of the conductivity cells and stock solutions of lidocaine hydrochloride were prepared on weight basis. Due to the high precision of the techniques used, all weights were corrected to vacuo. The densities of the stock solutions were determined by means of a DMA O2 C digital precision density meter (Anton Paar K.G., Graz, Austria).

2.1. Conductance measurements, Series 1

In the first series of conductance measurements, a 50-ml conductivity cell of the kind previously described (Nilsson et al., 1970) was used. The cell, fitted with bright platinum electrodes, was con-

nected to a Leeds and Northrup 4666 high-precision conductivity bridge. The cell was kept in a constant temperature kerosene bath at 25.00 ± 0.02°C.

The cell constant, 0.42311 cm^{-1}, was determined using an aqueous potassium chloride solution (Lind et al., 1959). The cell resistance, R, was determined at several frequencies, ν, from 0.3 to 5 kHz and the resistance was plotted against the inverse of the frequency. The linear part of this curve, obtained within the 2–5 kHz range, was extrapolated to infinite frequency, i.e. to $1/\nu = 0$. A typical example of a graph of this kind is shown in Fig. 1 for a 2.45 mM LidHCl solution. Such an extrapolation is necessary in order to obtain conductivity data free of relaxation effects.

Dilute lidocaine hydrochloride solutions were prepared by adding portions (3–12 ml) of the LidHCl stock solution directly into the conductivity cell containing a predetermined weight of conductivity water. The stock solution was added using a calibrated Dosimat E 535 precision buret (Metrohm Herisau), kept in an air thermostat at 25.00 ± 0.02°C. The densities of the diluted solutions were calculated assuming the density to vary linearly with the concentration of the electrolyte.

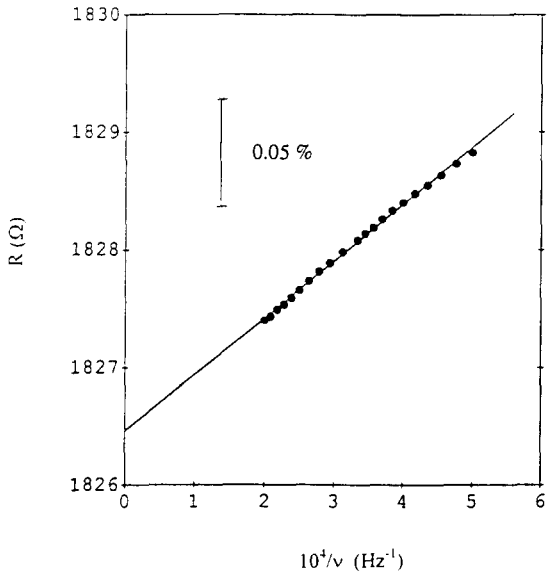

Fig. 1. Extrapolation of resistance to infinite frequency for an aqueous 2.45 mM LidHCl solution at 25°C. The experimental points correspond to the 2–5 kHz frequency range.

Table 1
Molar conductivity of lidocaine hydrochloride in water at 25.00°C

$10^4 \cdot c$ (M)	Λ (cm^2 Ω^{-1} mol^{-1})	$10^4 \cdot c$ (M)	Λ (cm^2 Ω^{-1} mol^{-1})
Series 1		*Series 2* (continued):	
8.0952	95.825	7.9897	96.171
12.336	95.125	9.5567	96.036
16.361	94.799	10.596	95.703
20.546	94.284	13.174	95.431
24.494	94.095	15.725	95.153
28.578	93.683	18.250	94.962
32.697	93.449	20.747	94.720
36.780	93.072	25.665	94.238
		28.086	94.055
Series 2		30.482	93.884
2.6922	98.612	32.853	93.544
3.2271	98.341	35.200	93.646
3.7609	98.044	39.824	93.208
4.2935	97.832	44.356	92.969
5.3553	97.124	65.724	91.915
6.4125	96.665		

Resistance measurements were performed for each concentration at four different frequencies between 2 and 5 kHz and extrapolated to infinite frequency as outlined above. The results of these measurements are given in Table 1, where the molar conductivity, Λ, is quoted at the different concentrations investigated.

2.2. Conductance measurements, Series 2

The acid dissociation constant of $LidH^+$ evaluated from the data in Series 1 was found to deviate by nearly one pK_a unit from the value determined potentiometrically by Löfgren (1948). Hence it was decided to perform a second series of measurements. In this series, the concentration range investigated was considerably increased to cover the interval from 0.269 to 6.57 mM.

It may be noted that for the present system, it is not meaningful to extend the concentration interval towards still lower concentrations because of the disturbance of the ions in the solvent itself. Ideally, in precision measurements of electrical conductance, the correction for the conductivity of the solvent should be negligible.

In the second series a conductivity cell of the Daggett–Bair–Kraus type (Daggett et al., 1951), fitted with bright platinum electrodes, was used. Its capacity was 1200 ml. About 1000 ml of conductivity water was initially transferred to the cell. The exact amount was determined by difference weighing. The cell was kept at 25.00 ± 0.02°C in the air thermostat mentioned above. Portions of the stock electrolyte solution (KCl for calibration and LidHCl, respectively) were then successively added using the Dosimat E 535 precision buret kept in the same thermostat as the cell. Resistance measurements were performed at four different frequencies from 2 to 5 kHz and extrapolation to infinite frequency performed as outlined above. The value $k = 0.06695 \pm 0.00022$ cm^{-1} of the cell constant was obtained. The results are given in Table 1.

3. The conductance equation

In deriving a conductance equation for $LidH^+Cl^-$ in water as solvent, it will be assumed that the electrolyte is completely dissociated with respect to the chloride ion and that the $LidH^+$ ion dissociates into neutral Lid molecules and H^+ ions.

The assumptions that any pairing between the $LidH^+$ and Cl^- ions is negligible appears to be most reasonable, since the minimum distance between the centers of charge of these ions would not be far from the Bjerrum radius, $q = 3.6$ Å, for 1:1-electrolytes in water as solvent at 25°C. The Bjerrum radius corresponds to that distance of charge between a cation and an anion where the electrostatic attraction energy is of the same order as the thermal energy of the solvent molecules. Hence, the system studied may be represented by the scheme

$$LidH^+Cl^- \rightarrow LidH^+ + Cl^-, \quad (1a)$$

$$LidH^+ \overset{K_a}{\Leftrightarrow} Lid + H^+. \quad (1b)$$

Denoting by α the degree of dissociation of $LidH^+$, the fractions of LidHCl present as conducting species, $LidH^+$, H^+ and Cl^-, are equal to $(1-\alpha)$, α and unity, respectively.

The concentration dependence of the molar conductivity of LidHCl may now be written

$$\Lambda = m[\lambda_0(LidH^+)(1-\alpha) + \lambda_0(H^+)\alpha + \lambda_0(Cl^-)], \quad (2)$$

where m is a mobility correction factor, which corrects Λ for ion atmosphere effects, and $\lambda_0(LidH^+)$, $\lambda_0(H^+)$ and $\lambda_0(Cl^-)$ are the limiting molar conductivities of the species indicated.

The problem now consists in evaluating, from the experimentally established concentration dependence of the molar conductivity of $LidH^+Cl^-$, the dissociation constant, K_a, of $LidH^+$ and the limiting molar conductivity, $\lambda_0(LidH^+)$, of the $LidH^+$ ion. The remaining limiting molar conductivities in Eq. (2), $\lambda_0(H^+)$ and $\lambda_0(Cl^-)$, can be obtained from independent literature data.

4. Analysis of conductance data

The thermodynamic dissociation constant, K_a, for the equilibrium (Eq. (1b)) between $LidH^+$, Lid and H^+ is defined in terms of activities of the different species involved, i.e.

$$K_a = \frac{a(Lid)\cdot a(H^+)}{a(LidH^+)}. \quad (3a)$$

Assuming the activity coefficients of $LidH^+$ and H^+ to be equal and that of the electrically neutral Lid molecule to be unity, we obtain

$$K_a = \frac{c(Lid)\cdot c(H^+)}{c(LidH^+)} = \frac{c\alpha^2}{(1-\alpha)}, \quad (3b)$$

where c is the total concentration of lidocaine hydrochloride.

The dependence of the mobility correction factor, m, on the free ionic concentration, c_i, may, according to the conductance equation of Fuoss and Hsia (1967, 1968) and Fernandez-Prini (1969), referred to as the 'FHFP' equation, be expressed

$$m = (\Lambda_0 - S\cdot c_i^{1/2} + E\cdot c_i\cdot \log c_i + J_1\cdot c_i - J_2\cdot c_i^{3/2})/\Lambda_0, \quad (4)$$

where S and E are coefficients which depend on the limiting molar conductivity, Λ_0, the dielectric

constant, ε, the viscosity, η, of the solvent, and the temperature, while J_1 and J_2 depend, in addition, on a distance parameter, R, the maximum distance between centers of charge of paired ions (Justice, 1971; Beronius, 1975, 1976; Lee and Wheaton, 1978a,b, 1979).

The dissociation of $LidH^+$ into neutral Lid molecules and H^+ ions does not change the ionic strength of the solution, which is numerically equal to the total concentration, c, of $LidH^+Cl^-$.

To establish reliable values of $\lambda_0(H^+)$ and $\lambda_0(Cl^-)$, the experimental conductance data according to Shedlovsky (1932) for HCl in the concentration range $0.02841 < c < 1.5768$ mM were reanalyzed by means of the FHFP equation. Complete ionization in the entire concentration range was assumed. The values $\varepsilon = 78.3$, for the dielectric constant, and $\eta = 0.8903$ cP ($8.903 \cdot 10^{-4}$ N s m^{-2}), for the viscosity of the solvent (Robinson and Stokes, 1965), were used. The distance parameter was set equal to the Bjerrum radius, $q = 3.57$ Å. The best fit of the conductance equation to the experimental data was obtained for $\Lambda_0 = 426.16$ cm^2 Ω^{-1} mol^{-1}. This value is identical to the sum of the limiting ionic conductivities, $\lambda_0(H^+) = 349.81$ and $\lambda_0(Cl^-) = 76.35$ cm^2 Ω^{-1} mol^{-1}, according to data in the monograph of Robinson and Stokes (1965). Hence, we used these values of the limiting ionic conductivities of H^+ and Cl^- in the conductance Eq. (2) for lidocaine hydrochloride.

The following calculation procedure was used to obtain the limiting ionic conductivity and dissociation constant of $LidH^+$, $\lambda_0(LidH^+)$ and K_a, respectively.

Using Eqs. (2), (3b) and (4) together with a preselected value of $\lambda_0(LidH^+)$ and K_a, respectively, a value of Λ was calculated for each concentration, c_i, of lidocaine hydrochloride investigated. The difference, $\Delta\Lambda_i = [\Lambda_i(\text{expt}) - \Lambda_i(\text{calc})]$, between the experimental and calculated Λ-values was then determined for each experimental point (c_i, Λ_i) and then the relative standard deviation

$$\sigma(\Lambda) = [\Sigma(\Delta\Lambda_i/\Lambda_i)^2/(N-2)]^{1/2}, \quad (5)$$

where N is the number of experimental points. These calculations were repeated for a series of $\lambda_0(LidH^+)$-values using a fixed value of K_a. The graph in Fig. 2 shows for Series 2 how the percentage standard deviation in Λ depends on $\lambda_0(LidH^+)$ for a number of different K_a-values.

A three-dimensional representation of the dependence of the percentage standard deviation in molar conductivity of LidHCl on the two parameters investigated, $\lambda_0(LidH^+)$ and K_a, is shown in Fig. 3. The 'total' three-dimensional minimum was taken as the best values of $\lambda_0(LidH^+)$ and K_a.

For these final values of $\lambda_0(LidH^+)$ and K_a, we obtained $m = 0.9705$ for the mobility correction factor according to Eq. (4) at the highest concentration, 6.57 mM, investigated.

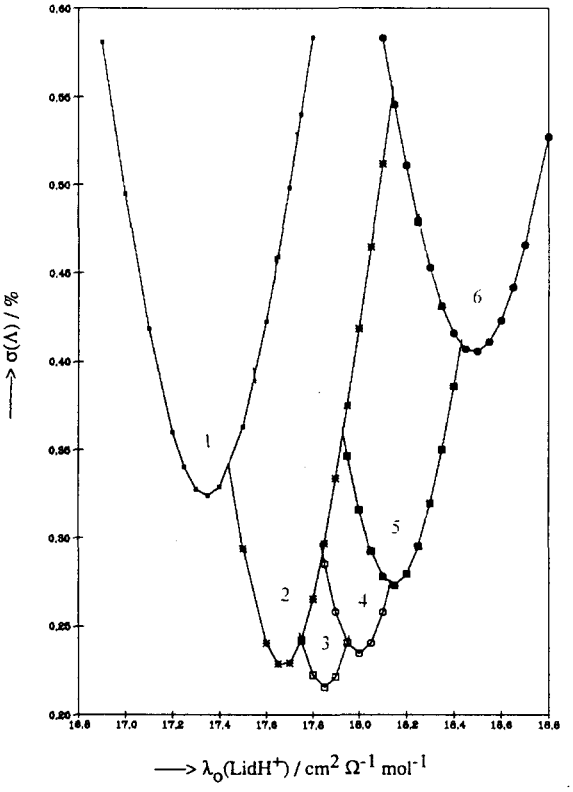

Fig. 2. Dependence of standard deviation of Λ on limiting molar conductivity of the $LidH^+$ ion for LidHCl in aqueous solution at 25°C. The curves 1–6 refer to the following values of the dissociation constant: $10^8 \cdot K_a = 10.0$, 8.00, 7.00, 6.22, 5.50 and 4.00, respectively. The calculations are based on the conductance data Series 2 in Table 1.

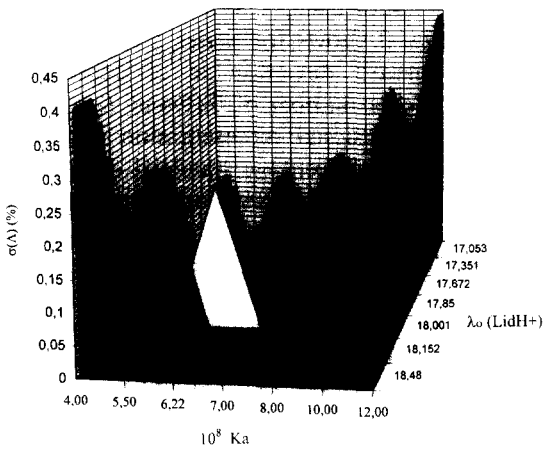

Fig. 3. A three-dimensional representation of the dependence of $\sigma(\Lambda)$ on K_a and Λ_0 for the same system as in Fig. 2. Best fit parameters: $K_a = 6.928 \cdot 10^{-8}$ (molar scale); $\Lambda_0 = 17.87$ cm^2 Ω^{-1} mol^{-1}; $\sigma(\Lambda) = 0.21\%$.

5. Results and discussion

A compilation of our results is given in Table 2 together with pK_a determined potentiometrically by Löfgren (1948). The data indicate that the pK_a according to the conductometric method is about 0.7 pK_a units lower than the value of pK_a based on potentiometry.

In Fig. 4, the molar conductivity is given as a function of the total concentration, c, of LidHCl. The fulldrawn curves represent Eq. (2) fitted to the experimental points of Series 2. The upper curve is an enlargement in the vertical direction of the lower one (right hand side scale). For infinite dilution, the lower curve extrapolates to the limiting molar conductivity of HCl, Λ_0(HCl) = 426.16 cm^2 Ω^{-1} mol^{-1} (outside the range of the diagram).

Table 2
Comparison of conductance data for LidHCl according to the present investigation with data according to Löfgren (1948)

pK_a	Λ_0 (cm^2 Ω^{-1} mol^{-1})	Reference
7.204	17.70	Series 1
7.159	17.87	Series 2
7.855	—	Löfgren (1948)

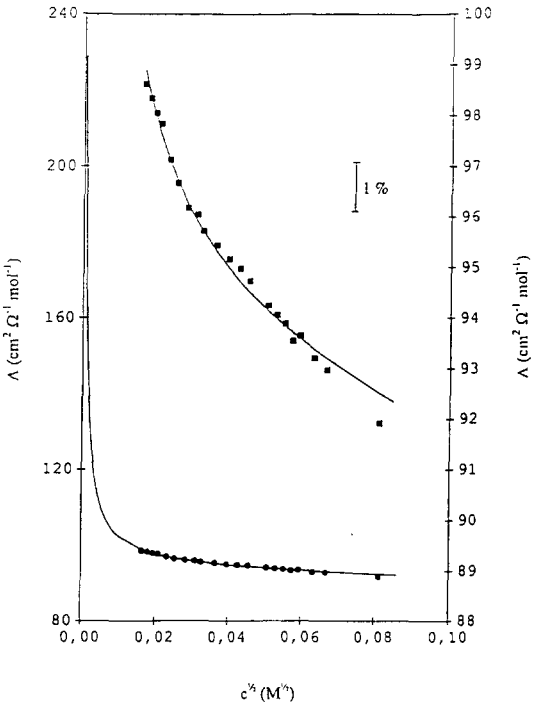

Fig. 4. Dependence of molar conductivity of LidHCl(aq), according to Series 2, on concentration at 25.00°C. The fulldrawn curves represent Eq. (2) fitted to the experimental points. The upper curve, which is an enlargement in the vertical direction of the lower one, refers to the right hand side y-axis. The lower curve extrapolates at infinite dilution to the limiting molar conductivity of HCl, 426.16 cm^2 Ω^{-1} mol^{-1} (not shown in the diagram).

Inspection of the upper curve in Fig. 4 suggests a systematic deviation of the experimental points from the calculated one for total concentrations of lidocaine hydrochloride exceeding about 4 mM. The equation of the fulldrawn curve was derived on the assumption that the only species present are uncharged Lid molecules, $LidH^+$ ions and free hydrogen and chloride ions. Possibly other association processes might be in operation at concentrations exceeding 4 mM. A more extensive experimental material and perhaps complementary experimental methods would be necessary to answer this question.

From an iontophoretic point of view, it is essential that the fraction of the active substance present in ionic form is as large as possible. In Fig. 5, the fraction of lidocaine hydrochloride in

the form of $LidH^+$ is given as a function of the total concentration of LidHCl. The graph indicates that more than 97% of the electrolyte is present as $LidH^+$ at total concentrations exceeding 0.1 mM. For total concentrations of lidocaine hydrochloride below this concentration there is a rapid decrease in the fraction $[LidH^+]/[LidHCl]$ because of the dissociation of $LidH^+$ into Lid and H^+.

The mobility of an ion is directly proportional to its molar conductivity (Robinson and Stokes, 1965). The limiting molar conductivity of the $LidH^+$ ion, $\lambda_0(LidH^+)$, in aqueous solution is of the same order as that of higher members of the homologue series of quaternary ammonium ions. These bulky ions may to a good approximation be regarded as spherical. Molecular models and volumes have been used to estimate the radii of these ions (Robinson and Stokes, 1965). In the graph, Fig. 6, the limiting molar conductivity of Me_4N^+, Et_4N^+, Pr_4N^+, Bu_4N^+ and Am_4N^+ has been plotted as a function of the ion radius. The arrow indicates the limiting molar conductivity of the $LidH^+$ ion. The graph indicates that the mobility of the $LidH^+$ ion is the same as that of a spherical ion of about 5.2 Å radius.

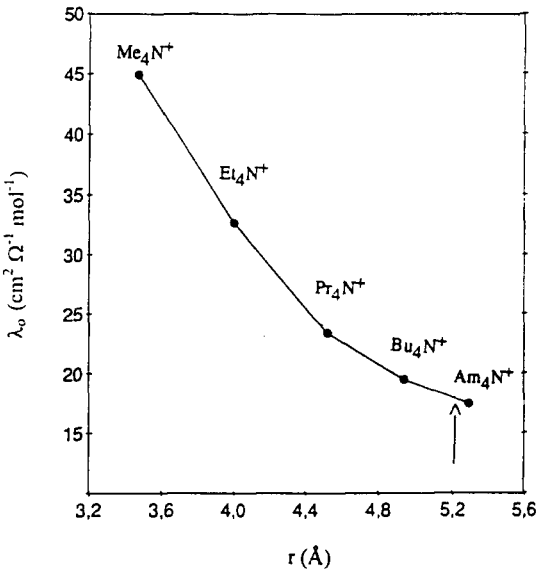

Fig. 6. Limiting molar conductivity of quaternary ammonium ions in aqueous solution at 25°C as a function of the ion radius according to Robinson and Stokes (1965). The arrow indicates the limiting ionic conductivity of the $LidH^+$ ion.

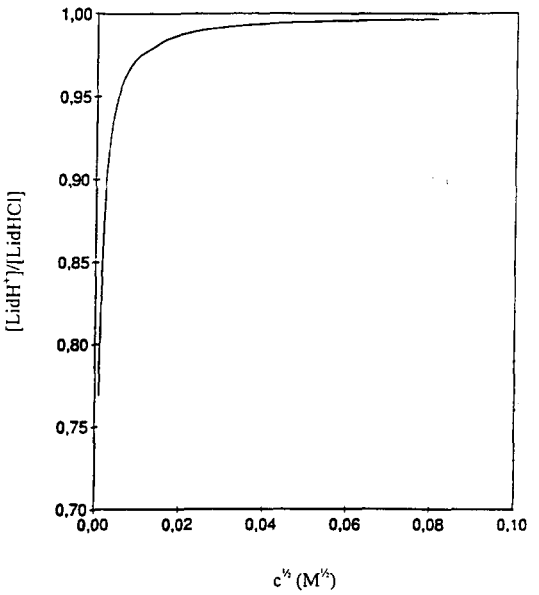

Fig. 5. Fraction of lidocaine hydrochloride present in the form of $LidH^+$ as a function of the total concentration of LidHCl in aqueous solution at 25°C.

6. Conclusions

In the present study, which is the starting point of research aiming to optimize the conditions in iontophoretic drug delivery, the dissociation and mobility of the $LidH^+$ ion in aqueous solution at 25°C has been determined by precision conductometry. Access to accurate values of these parameters is of fundamental importance to optimize the iontophoretic procedure. Almost identical values of pK_a and $\lambda_0(LidH^+)$, respectively, were obtained in two series of measurements performed under partially different experimental conditions. The value of pK_a obtained is, however, almost one pK_a unit lower (i.e. K_a about one power of ten higher) than that previously determined by potentiometry. Our observation suggests that there might be a systematic deviation in pK_a according to these two experimental methods (Löfgren, 1948). From an applied point of view

the difference observed is sufficiently large to be of practical importance.

Acknowledgements

The authors are grateful to Astra Pain Control AB, Södertälje, Sweden for their kind support. Financial support from the Swedish Research Council for Engineering Sciences and from the Swedish Natural Science Research Council is gratefully acknowledged.

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