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Short Communication

On iontophoretic delivery enhancement: ionization and transport properties of lidocaine hydrochloride in aqueous propylene glycol

Kiomars Karami, Nadia Merclin, Fredrik Brounéus, Per Beronius *

Physical Pharmaceutical Chemistry, Uppsala University, Uppsala Biomedical Center, P.O. Box 574, SE-751 23 Uppsala, Sweden

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Abstract

The ionization and transport properties of lidocaine hydrochloride (LidHCl) in aqueous propylene glycol (PG) containing 20% PG by weight was studied by means of electrical precision conductometry. For drug concentrations exceeding about 1.7 mM a slight formation of $LidH^+Cl^-$ ion-pairs is indicated; ion-pair association constant, $K_p = 1.73$ (molar scale). A two variable analysis of the experimental data yielded $K_a = 1.5 \times 10^{-8}$ for the acid dissociation constant of $LidH^+$, i.e. $pK_a = 7.82$, and the limiting ionic conductivity, $\lambda_o(LidH^+) = 21.73$ cm^2 S mol^{-1}. To enable evaluation of single ion conductivities the proton transport number of HCl in the present solvent mixture was determined using the moving boundary method.

Keywords: Lidocaine hydrochloride; Iontphoresis; Enhancer; Propylene glycol (PG); Molar conductivity; Transport number

1. Introduction

The rate of skin permeation of drugs by transdermal iontophoretic delivery may be significantly increased by addition of various enhancing agents to the drug formulation (Potts and Guy, 1997). Kushla and Zatz (1990) found an enhancing effect on the flux of lidocaine through human skin using aqueous propylene glycol (20% PG by weight) as a base for formulation of this local anesthetic. Previously the ionization and mobility of lidocaine hydrochloride in water (Sjöberg et al., 1996) and in pure propylene glycol (Karami and Beronius, 1998) as solvent media have been investigated by precision conductometry. In this paper the results of a similar investigation of the behavior of lidocaine hydrochloride in aqueous propylene glycol (20% PG by weight) are reported.

Propylene glycol, HPLC grade, minimum 99.5%, and lidocaine hydrochloride monohydrate, were obtained from Sigma, USA. Analytical grade Millipore water was used. Properties of solvent mixture at 25.0°C: electrolytic conductiv-

* Corresponding author.
E-mail address: per.beronius@bmc.uu.se (P. Beronius)

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ity, $\kappa = 7.48 \cdot 10^{-7}$ S cm^{-1}; dielectric constant, $\varepsilon = 69.30 \pm 0.03$ (Ferisol M 803A Q-meter); viscosity, $\eta = 1.769 \pm 0.010$ cP (Ubbelode viscometers). The dependence of the molar conductivity, Λ, on drug concentration for solutions of LidHCl at 25.00 ± 0.02°C were determined as previously described (Karami and Beronius, 1998). The results of the conductance measurements are summarized in Table 1.

The following equilibria were assumed in analyzing the conductance data:

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

$$\mathrm{LidH^+} + \mathrm{Cl^-} \overset{K_p}{\Leftrightarrow} \mathrm{LidH^+Cl^-} \quad (2)$$

where the K's indicated are thermodynamic equilibrium constants. Estimates indicate that the concentration of free protons would be very low. Hence, any possible formation of $\mathrm{H^+Cl^-}$ ion-pairs was not considered in analyzing the conductance data. In calculating K_a it was assumed that for the five lowest concentration points, $c \leq 1.682$ mM, ion-pair formation according to Eq. (2) was negligible. On these assumptions we have for this low concentration range the following expression for the molar conductivity,

$$\Lambda = m[\lambda_0(\mathrm{LidH^+})(1-\beta) + \lambda_0(\mathrm{H^+})\beta + \lambda_0(\mathrm{Cl^-})] \quad (3)$$

where β is the degree of dissociation of $\mathrm{LidH^+}$, the λ_0's are the limiting molar conductivities of the species indicated, and m is a mobility correction factor, correcting for ion atmosphere effects cf. Karami and Beronius (1998).

Table 1
Molar conductivity of LidHCl in aqueous propylene glycol (20% PG by weight) at 25.0°C

$10^4 \times c$ (M)	Λ (cm^2 S mol^{-1})	$10^4 \times c$ (M)	Λ (cm^2 S mol^{-1})
4.141	54.964	50.498	52.197
6.205	54.713	60.147	51.960
8.808	54.464	71.631	51.642
12.423	54.134	84.337	51.325
16.824	53.823	98.405	51.001
21.960	53.484	113.47	50.612
27.949	53.100	128.93	50.289
34.730	52.807	145.00	49.955
42.132	52.552	163.00	49.626

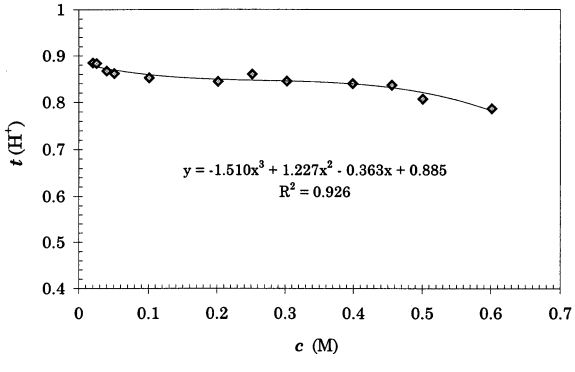

Fig. 1. Dependence of cation transport number of hydrochloric acid on concentration in H_2O/PG solution (20% PG by weight) at 25°C.

At infinite dilution the limiting molar conductivity of LidHCl is equal to that of hydrochloric acid, previously determined to 281.55 cm^2 S mol^{-1} by Venkateswara Sastry and Kalidas (1985). To separate this quantity into $\lambda_0(\mathrm{H^+})$ and $\lambda_0(\mathrm{Cl^-})$ appearing in Eq. (3) the transport number of the proton of hydrochloric acid in the present solvent mixture was determined at 25.0 ± 0.4°C using the moving boundary method, cf. Robinson and Stokes (1965). The equipment used was similar to that described by MacInnes and Longsworth (1932). The current was kept constant using a current stabilizer and measured by means of a Fluke 25 Multimeter. Measurements were performed for several concentrations of HCl and extrapolated to infinite dilution according to Fig. 1. This procedure yielded the proton transference number $t_+ = 0.885$ and hence, $\lambda_0(\mathrm{H^+}) = 249.17$ and $\lambda_0(\mathrm{Cl^-}) = 32.38$ cm^2 S mol^{-1}.

A two parameter analysis of the conductance data in the LidHCl lower concentration range ($c \leq 1.682$ mM), cf. Karami and Beronius (1998), yielded the acid dissociation constant, $K_a = 1.5 \times 10^{-8}$ of $\mathrm{LidH^+}$ ($\mathrm{p}K_a = 7.82$), and $\lambda_0(\mathrm{LidH^+}) = 21.73$ cm^2 S mol^{-1}.

The upper curve in Fig. 2 shows that Eq. (3) fits the five lowest concentration points quite well. For increasing concentrations, the experimental points show an increasingly negative deviation from the calculated curve indicating significant formation of $\mathrm{LidH^+Cl^-}$ ion-pairs.

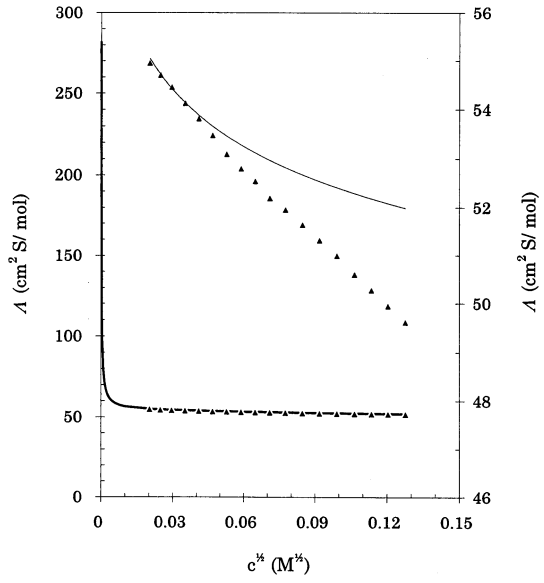

Fig. 2. Dependence of molar conductivity on concentration for LidHCl in H_2O/PG (20% PG by weight) at 25°C according to Eq. (3) fitted to the five lowest concentration points in Table 1. The upper curve refers to the right hand side y-axis and is an enlargement in the vertical direction of the bottom curve.

Estimates indicate that any dissociation of $LidH^+$ into neutral Lid molecules and protons in the higher concentration range studied ($c \geq 2.196$ mM) might be neglected. Hence, using the data in this concentration range it is possible to estimate the limiting molar conductivity, Λ_0 of LidHCl, and subsequently, $\lambda_0(LidH^+)$, and also the ion-pair association constant, K_p, for formation of $LidH^+Cl^-$ ion pairs according to the equilibrium (2). An iterative procedure, similar to that outlined for LidHCl in pure propylene glycol (Karami and Beronius, 1998) based on the FHFP conductance equation (Fuoss and Hsia, 1967, 1968; Fernandez-Prini, 1969), yielded $K_p = 1.73$ to be compared with $K_p = 40$ for pure propylene glycol as solvent medium (Karami and Beronius, 1998). The value $\lambda_0(LidH^+) = 23.37$ cm^2 S mol^{-1} obtained from the higher concentration range is not far from the corresponding value, 21.73 cm^2 S mol^{-1}, derived above from the data in the lower concentration range.

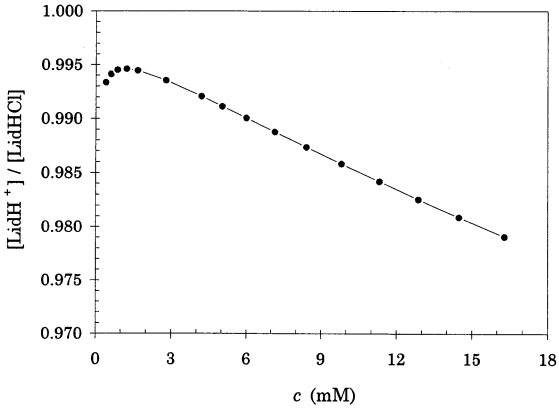

Fig. 3. Dependence of the fraction of $LidH^+$ ions on total LidHCl concentration in H_2O/PG solution (20% PG by weight) at 25°C.

In designing an optimal iontophoretic drug reservoir it is necessary to consider the extent of ionization as well as the mobilities of the drug molecules in the reservoir medium. As indicated in Fig. 3, the fraction of the drug in the form of $LidH^+$ at first increases with increasing total LidHCl concentration. However, this effect is counteracted by the gradual increase in formation of electrically neutral $LidH^+Cl^-$ ion-pairs. As a consequence, the fraction of the drug in the form of $LidH^+$ reaches a maximum and then decreases (Fig. 3). The maximum of this curve, corresponding to a fraction of 99.5% of the drug in the form of $LidH^+$, appears at a total drug concentration of about 1 mM.

Summing up, in this study the various species of lidocaine hydrochloride present in aqueous propylene glycol (20% PG by weight) have been identified and also quantified by electrical precision conductance measurements. Furthermore, the effect of the total drug concentration on the relative amounts of the various charged and uncharged species present has been established.

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References

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

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.

Karami, K., Beronius, P., 1998. On iontophoretic delivery enhancement: ionization and mobility of lidocaine hydrochloride in propylene glycol. Int. J. Pharm. 168, 85–95.

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.

MacInnes, D.A., Longsworth, L.G., 1932. Transference numbers by the method of moving boundaries. Chem. Rev. 11, 171–230.

Potts, R.O., Guy, R.H., 1997. Mechanisms of Transdermal Drug Delivery, first ed. Marcel Dekker Inc., New York.

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

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 & HBr in water-propylene glycol mixtures. Ind. J. Chem. 24A, 658–660.