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# Diffusive transport properties of some local anesthetics applicable for iontophoretic formulation of the drugs

Fredrik Brounéus, Kiomars Karami, Per Beronius *, Lars-Olof Sundelöf

*Physical Pharmaceutical Chemistry, Uppsala University, Uppsala Biomedical Center, PO Box 574, S-751 23, Uppsala, Sweden*

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**Abstract**

As part of a general study to improve the iontophoretic delivery of local anaesthetics of the amide type, the diffusion properties of the hydrochloride salts of bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine and ropivacaine, were studied in a 1% w/w agarose hydrogel. A source drug solution (25 mM) was placed in contact with the gel and, after an appropriate time, the drug concentration profile in the gel was analyzed to give a diffusion coefficient, $D$. The values of $D \times 10^{10}$ expressed in $m^2\ s^{-1}$ were: (bupi) 6.71, (eti) 6.71, (ropi) 6.39, (mepi) 7.31, (lido) 7.49 and (prilo) 7.76. For comparative reasons, the diffusion coefficient for LidHCl in an aqueous solution according to the Nernst–Hartley relation for the diffusion of ion-pairs was calculated, hereby taking into account ionic activity of $LidH^+$ and $Cl^-$. The diffusion coefficient thus obtained was $7.76 \times 10^{-10}\ m^2\ s^{-1}$ at infinite dilution. The relationship between the molecular weight of the compounds and the diffusion coefficient was investigated. 

*Keywords:* Diffusion coefficient; Local anesthetic; Hydrogel; Agarose; Iontophoresis

## 1. Introduction

Hydrogels are interesting media with respect to formulation of iontophoretic patches. Such hydrogels are utilized as drug reservoirs and contact interfaces between the skin and the electrodes (Phipps et al., 1989; Iomed Clinical Systems, 1998). In transdermal iontophoresis, in addition to paracellular transport, an important route of entry for the drug molecules through the skin is the aqueous pores, i.e. hair follicles and sweat ducts (Roberts et al., 1997; Banga and Chien, 1988; Chen et al., 1998). Thus, the diffusive transport properties of drugs in water and water-based hydrogels would be interesting from an iontophoretic point of view.

It has earlier been shown that the diffusion of low molecular weight substances in 1 wt.% agarose gel does not differ significantly from the diffusion in water (Korsmeyer, 1991). In this study, the diffusion coefficients of the hydrochloride salts of six different local anaesthetics, viz bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine and ropivacaine were determined in a hydrogel composed of 1% w/w agarose in deionized water.

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

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## 2. Materials and methods

All local anaesthetics: hydrochloride salts of bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine and ropivacaine, were kindly supplied by AstraZeneca, Södertälje, Sweden. Agarose was obtained from Sigma, USA. Deionized water was used to prepare hydrogels and solutions.

To determine the molar absorbance coefficients of the drug substances, a standard curve with absorbance plotted as a function of concentration was constructed for each substance. The concentrations of the solutions were within the range of 0.025–5.00 mM.

The results are shown in Table 1. For prilocaine, the wavelength used does not correspond to $\lambda_{max}$. This choice is due to the high molar absorbance that would otherwise render the con-

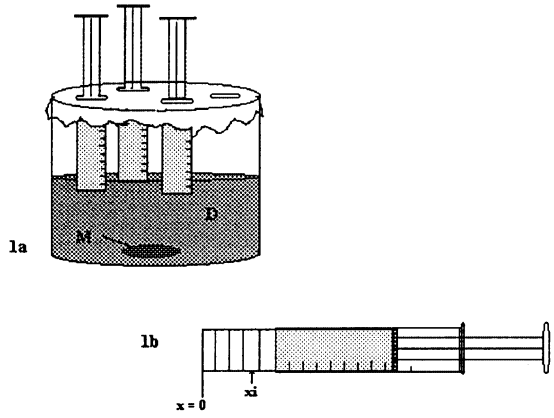
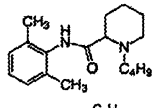
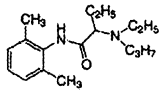
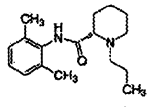
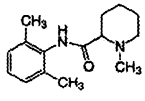
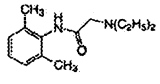
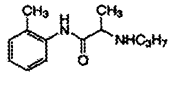



Fig. 1. Gel filled syringes in a magnetically stirred (M) drug solution (D) thermostatted to 25°C (a). A gel-filled syringe being sliced after terminated diffusion time (b).

Table 1
Molecular structures, molecular weights, and molar absorbance coefficients, $\varepsilon$, for the local anesthetic substances

| Substance | Structure | $M$ (g mol$^{-1}$) | λ (nm) | ε ( cm$^{-1}$ mol$^{-1}$ L) |
|---|---|---|---|---|
| Bupivacaine |  | 289.0 | 262.0 | 408.0 |
| Etidocaine |  | 277.2 | 263.0 | 473.3 |
| Ropivacaine |  | 274.9 | 262.0 | 436.2 |
| Mepivacaine |  | 246.8 | 265.0 | 433.8 |
| Lidocaine |  | 234.8 | 263.0 | 450.0 |
| Prilocaine |  | 220.8 | 270.0 | 562.2 |

struction of a standard curve for prilocaine in the same concentration range as the other local anaesthetics impossible. The measurements for prilocaine at 270 nm were highly reproducible, and this choice of wavelength was found to have no significant effect on the determination of the concentrations.

A 1% w/w agarose hydrogel was cast in syringes with tops cut off and dipped into a 25 mM drug solution, thermostatted to 25°C (Upadrashta et al., 1993), see Fig. 1a. After about 72 h, the gels were pushed out and sliced into 10 segments each (Fig. 1b). The density of the 1% agarose gel was experimentally determined to $1.069 \pm 0.022$ g cm$^{-3}$ by measuring the volume and weight of eight separately cast gel segments. The radius of the gel was set to 7.75 mm, corresponding to half of the inner diameter of the syringe.

Each gel segment was weighed and the volume of the disk, $V_{gel}$, was calculated. The segments were then immersed in deionized water in a series of test tubes. Due to the large concentration difference between the first and the last gel segments, 7 and 4 ml of water were added to the test tubes containing the first five and the five last segments, respectively. After about 3 h, the absorbances of the solutions in the test tubes were measured with a Milton Roy, Spectronic GeneSys5 spectrophotometer. The time required for complete drug release from the gels into the release solutions had earlier been examined.

From the absorbance data the drug concentration of the release solution was determined. The concentration of the drug in the gel segment was calculated using the following equation:

$$c_{gel} = c_{solution}\left(\frac{V_{gel} + V_{solution}}{V_{gel}}\right). \quad (1)$$

The diffusion coordinate, $x$, was taken as the distance from the syringe end to the middle of each gel disk. The concentration profile is given by

$$c(x, t) = c_0 \,\mathrm{erfc}\left(\frac{x}{2\sqrt{D\,t}}\right), \quad (2)$$

from which $D$ can be calculated; $c_0$ is the drug solution concentration (25 mM) and $t$ is the diffusion time (Upadrashta et al., 1993).

If $x/2(Dt)^{1/2}$ is denoted $\beta$, then the error function complement of $\beta$, erfc($\beta$), can be expressed,

$$\mathrm{erfc}(\beta) = \frac{2}{\sqrt{\pi}} \int_{\beta}^{\infty} \mathrm{e}^{-\zeta^2}\, \mathrm{d}\zeta, \quad (3)$$

where,

$$\mathrm{d}\zeta = \frac{\mathrm{d}x}{2\sqrt{D\,t}}..$$

A computer program, constructed in Microsoft Excel®, was utilized to fit the theoretical concentration profile Eq. (2) to the experimental data (Sjöberg et al., 1999). The theoretical concentration profile was generated with a constant interval between the different $x$-values, set as the largest experimental distance divided by 100. Fig. 2 shows the gel concentration profile for lidocaine hydrochloride (LidHCl). The drawn line represents the computer generated theoretical concentration profile according to Eq. (2). The dots are the experimentally observed concentrations.

By adjusting $c_0$ for each experimental value of $x$ and minimizing the sum of the squared differences between the experimental and theoretical concentrations, the diffusion coefficient for each drug in the agarose hydrogel was determined.

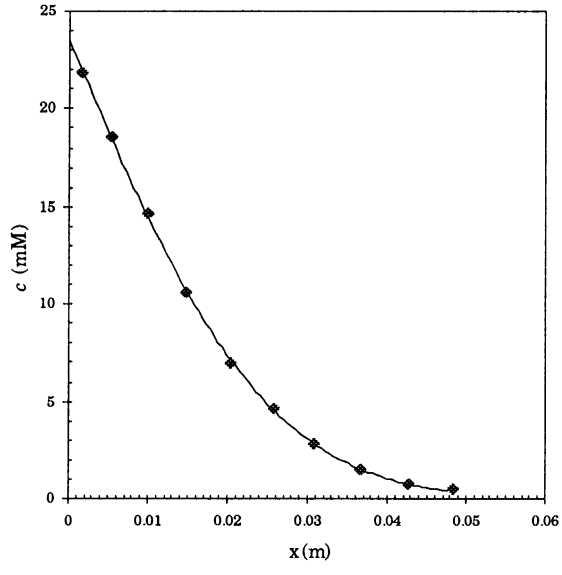



Fig. 2. A typical gel concentration profile (LidHCl). The curve represents the computer generated theoretical concentration profile according to Eq. (2). The dots are the experimentally observed concentrations.

Table 2
Molecular weights and experimentally determined diffusion coefficients for the drug solutes (for an initial concentration of 25 mM)[b]

| Solute | $M$ (g mol$^{-1}$) | $D \times 10^{10}$ (m$^2$ s$^{-1}$) | $\sigma$ (%)[a] | p$K_a$ | Number of samples |
|---|---|---|---|---|---|
| Bupivacaine HCl | 325.0 | 6.71 | 9.0 | 8.1 | 11 |
| Etidocaine HCl | 313.2 | 6.71 | 7.3 | 7.9 | 6 |
| Ropivacaine HCl | 310.9 | 6.39 | 4.4 | 8.1 | 12 |
| Mepivacaine HCl | 282.8 | 7.31 | 4.6 | 7.7 | 6 |
| Lidocaine HCl | 270.8 | 7.49 | 5.8 | 7.9 | 8 |
| Prilocaine HCl | 256.8 | 7.76 | 8.6 | 7.9 | 8 |

[a] $\sigma$ (%) is the relative standard deviation of the diffusion coefficient.
[b] All p$K_a$-values were obtained from Clarke's Isolation and Identification of Drugs, 2nd Edition, except for Ropivacaine (Niesel et al., 1990).

## 3. Results and conclusions

### 3.1. Evaluation of diffusion profiles

Table 2 shows molecular weights and diffusion coefficients for all six local anaesthetics. As mentioned above, the diffusion of low molecular weight substances in 1% agarose hydrogels does not differ significantly from the diffusion in water (Korsmeyer, 1991). The ionic radii of the solute molecules in the hydrogel (99% w/w water) are most probably equal to the corresponding radii in pure water as solvent. Hence it is assumed that the diffusive transport properties of the drug molecules in the 1% agarose hydrogel are similar to those in a pure aqueous system.

Regarding the solute molecules as sperical particles and the solvent medium as an ideal hydrodynamic continuum, the diffusion coefficent of the solute should, according to the Stokes–Einstein relationship, be inversely proportional to the radius of the solute molecule, cf. Robinson and Stokes (1965). Neglecting, tentatively, any variation in density and viscosity of the solution with the concentration of the drug, the diffusion coefficient, $D$, should depend linearly on $M^{-1/3}$, where $M$ is the molecular weight of the solute. A graph of this kind is shown in Fig. 3, where the straight line has been fitted to the experimental points according to the method of least squares. The correlation coefficient, $r = 0.94$, indicates that there might, in fact, exist a linear relationship of the kind suggested.

### 3.2. The diffusion coefficient of LidHCl according to the Nernst–Hartley relation

On the assumption above of negligible difference in diffusion properties between water and water containing 1% agarose as solvent media, a comparison between experimentally determined and theoretically calculated Nernst–Hartley diffusion coefficients for lidocaine hydrochloride (Lid

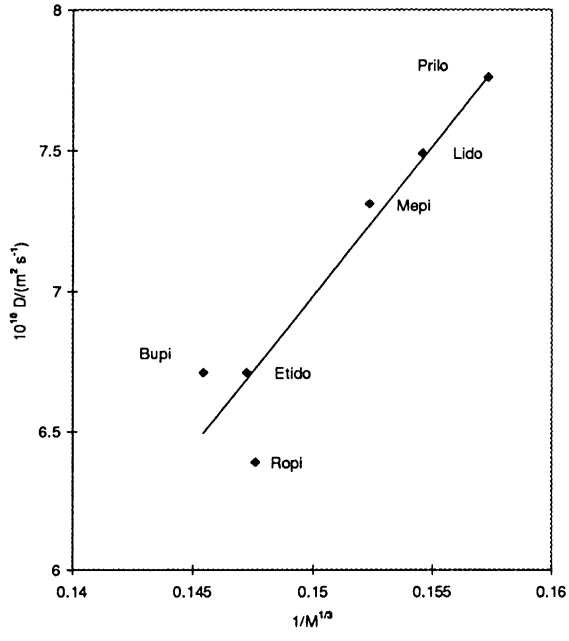



Fig. 3. Dependence of diffusion coefficients on molecular weight, $M$, of local anesthetics. The diffusion coefficients, $D$, in the graph are the mean values in Table 2.

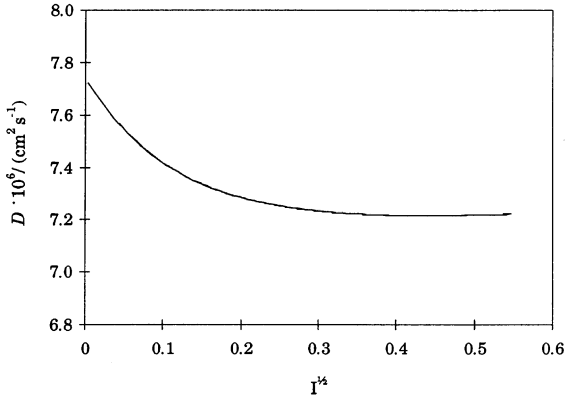



Fig. 4. The diffusion coefficient of LidHCl, according to the Nernst–Hartley equation, as a function of the square root of ionic strength (molarity scale).

HCl) will now be made. LidHCl was selected for such a comparison, because it is the only one of the systems here studied for which, according to the knowledge of the present authors, the limiting molar conductivity of the drug cation is available in the literature (Sjöberg et al., 1996).

In aqueous solution, the drug molecules here investigated are dissociated into the composite ionic species. However, electroneutrality of the solution is maintained throughout the diffusion process, and migration of one ionic species necessitates simultaneous movement of its counter-ions. In calculating the diffusion coefficient of an electrolyte, the Nernst–Hartley equation,

$$D = \frac{RT}{F^2}\frac{|z_1| + |z_2|}{|z_1|}\frac{\lambda_1^0\lambda_2^0}{\lambda_1^0 + \lambda_2^0}\left(1 + \frac{\mathrm{d}\ln\gamma_{\pm}}{\mathrm{d}\ln c}\right), \qquad (4)$$

may be employed whereby ionic interactions are taken into account. Although this relationship was originally constructed for small inorganic ions, we will here use it tentatively to make a crude comparison between experimentally and theoretically derived diffusion coefficients for a small organic drug molecule. For a more complete treatment of this matter, the reader is referred to the monograph of Robinson and Stokes (1965).

In Eq. (4) $R$ is the gas constant, $T$ the absolute temperature, $F$ Faraday's constant, $z_1$ and $z_2$ the ionic charges, $\lambda_1^0$ and $\lambda_2^0$ the limiting molar conductivities of the ions, ($LidH^+$ and $Cl^-$ for the system here discussed), $c$ the concentration, and $\gamma_{\pm}$ the mean molar ionic activity coefficient, which was calculated using the Debye–Hückel equation in the form,

$$\log\gamma_{\pm} = -\frac{A|z_1z_2|\sqrt{I}}{1 + Ba\sqrt{I}}, \qquad (5)$$

where the symbols have their ususal meaning.

The following values for limiting molar conductivities were used: $\lambda_0(LidH^+) = 17.87$ cm$^2$ S mol$^{-1}$ (Sjöberg et al., 1996), and $\lambda_0(Cl^-) = 76.35$ cm$^2$ S mol$^{-1}$ (Robinson and Stokes, 1965). The distance parameter, $a$, in Eq. (5) was set equal to the sum of the radii for $LidH^+$ and $Cl^-$, 5.2 and 1.8 Å, according to Sjöberg et al. (1996) and Robinson and Stokes (1965), respectively.

The dependence of the diffusion coefficient on ionic strength according to the Nernst–Hartley equation is shown in Fig. 4. The calculated diffusion coefficients at infinite dilution, at the average drug concentration in the gel (0.25 mM), and at 25 mM are $7.74 \times 10^{-10}$, $7.44 \times 10^{-10}$, and $7.33 \times 10^{-10}$ m$^2$ s$^{-1}$, respectively. These values differ from the experimental diffusion coefficient, $D = 7.49 \times 10^{-10}$ m$^2$ s$^{-1}$ in the 1% w/w agarose gel, by only $+3.3$, $-0.7$, and $-2.1$%, respectively.

Comparisons between experimental and theoretical Nernst–Hartley diffusion coefficients for the five other local anaesthetics here investigated has to await determinations of limiting molar conductivities of these drugs.

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