ISSN 1061-9348, Journal of Analytical Chemistry, 2009, Vol. 64, No. 2, pp. 195–200. © Pleiades Publishing, Ltd., 2009.

ARTICLES

A New Lidocaine-Selective Membrane Electrode Based on Its Sulfathiazole Ion-Pair[1]

M. Giahi[a], M. Pournaghdy[a], and R. Rakhshaee[b]

[a] *Department of Chemistry, Faculty of Science, Islamic Azad University, Lahijan Branch P. O. Box: 1616, Lahijan, Iran*

[b] *Department of Chemistry, Faculty of Science, Islamic Azad University, Rasht Branch P. O. Box: 41335–3516, Rasht, Iran*

e-mail: giahi_m@yahoo.com

Received May 16, 2007; in final form, December 20, 2007

Abstract—A novel lidocaine ion-selective electrode is prepared, characterized and used in pharmaceutical analysis. The electrode incorporates PVC-membrane with lidocaine-sulfathiazole ion pair complex. The influences of membrane composition, temperature, pH of the test solution, and foreign ions on the electrode performance were investigated. The electrode showed a Nernstian response over a lidocaine concentration range from 1.0×10^{-5} to 1.0×10^{-1} mol L^{-1} with a slope of 60.1 ± 0.2 mV per decade at 25°C and was found to be very selective, precise, and usable within the pH range 5–9.5. The standard electrode potentials, $E°$, were determined at 10, 15, 20, 25, 30, 35 and 40°C, and used to calculate the isothermal temperature coefficient ($dE°/dT$ = –0.0003 V $°C^{-1}$) of the electrode. However, the electrode performance is significantly decreased at temperatures higher than 45°C. The electrode was successfully used for potentiometric determination of lidocaine hydrochloride in pharmaceutical products.

DOI: 10.1134/S106193480902018X

In recent years, there has been a growing need for constructing chemical sensors for the fast and economical monitoring of pharmaceutical compounds [1–5]. However, poor chemical/physical stability of biomolecules prevents the use of biosensors in harsh environments such as acids, bases and at high temperatures. This led to the interest in chemical sensors by various researchers [6, 7]. We have been interested in constructing potentiometric ion-selective electrodes for monitoring of pharmaceutical compounds. Potentiometric methods are simple and rapid for pharmaceutical analysis when a suitable sensor is available, such as cation and anion selective electrodes [8–13]. In this paper, we report a simple plasticisized PVC potentiometric membrane sensor based on a lidocaine (N-diethylaminoacetyl-2,6-xylidine hydrochloride)—sulfathiazole (4-amino-N-thiazol-2-yl-benzenesulfonamide) ion-pair. This electrode exhibits useful analytical characteristics for the determination of protonated lidocaine either in pure form or in pharmaceuticals.

EXPERIMENTAL

Reagents. All reagents except lidocaine hydrochloride were of analytical reagent grade. Lidocaine hydrochloride was synthesized and purified in the laboratory of drug in Iran (Behdashtkar). Reagent grade dibutyl phthalate (DBP), acetophenone (AP), 2-nitrophenyloctyl-ether (2-NPOE), oleic acid (OA), sodium tetraphenylborate (NaTPB), tetrahydrofuran (THF) and high relative molecular weight PVC (all from Merck or Fluka) were used as received. Double distilled deionized water was used.

Preparation of ion-pair. A 10 mL volume of 10^{-1} M lidocaine hydochloride solution was mixed in a separating funnel with 10 ml of 10^{-1} M sulfathiazole solution (prepared by dissolution in dilute sodium carbonate on heating). Then the precipitate of lidocaine-sulfathiazole ion-pair was filtered, washed thoroughly with distilled water and dried under vacuum at 25°C for at least 24 h and grounded to fine powders.

Construction of electrodes. The general procedure used to prepare the PVC membrane was to mix thoroughly 30 mg of powdered PVC, 5 mg of ion-pair (lidocaine-sulfathiazole), 65 mg of plasticizer DBP until the PVC was wet [14]. The mixture was then dissolved in 3 ml of dry freshly distilled THF. The resulting clear mixture was transferred into a glass dish of 2 cm diameter. The solvent was evaporated slowly until an oily concentrated mixture was obtained. A Pyrex tube (5 mm o.d.) was dipped into the mixture for about 10 s so that a nontransparent membrane of about 0.3 mm thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for about 1 h. The tube was then filled with internal solution of 1.0×10^{-3} M lidocaine hydrochloride (Ld^+Cl^-). The electrode was finally conditioned for 4 h by soaking into a 1.0×10^{-2} M Ld^+ solution.

Emf measurements. The potential measurements were carried out with the following assembly: SCE/internal solution, 1.0×10^{-3} M Ld^+/PVC mem-

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Table 1. Optimization of the membrane ingredients

No.	Composition (%)				Slope (mV/decade)	Linear range (M)
	Ion-pair	PVC	Plasticizer*	Additive*		
1	–	30	65(2-NPOE)	5(OA)	24.2	1.0×10^{-4}–1.0×10^{-1}
2	3	30	67(DBP)	–	52.5	1.0×10^{-4}–1.0×10^{-1}
3	5	30	65(DBP)	–	60.1	1.0×10^{-4}–1.0×10^{-1}
4	5	30	60(2-NPOE)	5(OA)	57.7	1.0×10^{-4}–1.0×10^{-1}
5	5	30	62(2-NPOE)	3(NaTPB)	55.3	1.0×10^{-4}–1.0×10^{-1}
6	5	30	65(2-NPOE)	–	51.4	1.0×10^{-4}–1.0×10^{-1}
7	8	30	62(DBP)	–	54.3	4.0×10^{-4}–1.0×10^{-1}
8	5	30	58(2-NPOE)	7(OA)	56.0	1.0×10^{-4}–1.0×10^{-1}
9	3	30	62(DBP)	5(OA)	54.2	1.0×10^{-4}–1.0×10^{-1}
10	5	30	60(AP)	5(OA)	53.2	1.0×10^{-4}–1.0×10^{-1}

* 2-NPOE — 2-nitrophenyloctyl ether, DBP — di-*n*-butylphosphat, OA — *cis*-octadecanoic acid, NaTPB — sodium tetraphenylborate.

brane/test solution/SCE. A model 701 Orion ion analyzer pH/mV meter was used for the potential measurements at 25.0 ± 0.1°C. The external reference electrode was a standard calomel electrode (SCE) shielded by an intermediate salt bridge compartment containing the background electrolyte in order to prevent any transfer of potassium ions into the measuring solution.

RESULTS AND DISCUSSION

Membrane material. The influences of the membrane composition, nature and amount of plasticizer and amount of oleic acid as a lipophilic additive on the potential response of the Ld^+ sensor were investigated, and the results are summarized in Table 1. It is seen that the use of 65% DBP in the presence of 30% PVC, 5% ionophore (no. 3, Table 1) results in good electrode performance.

The potential response of the membrane at various concentrations of Ld^+ ion indicates a rectilinear range from 1.0×10^{-4} to 1.0×10^{-1} M. The slope of the calibration curve was 60.1 ± 0.2 mV/decade of Ld^+ concentration. The limit of detection, as determined from the intersection of the two extrapolated segments of the calibration graph, was 6.3×10^{-5} M. The standard deviation of 8 replicate measurements is ± 0.2 mV. The membrane sensors prepared could be used for more than 3.5 months without any measurable change in potential.

Effect of soaking. The performance characteristics of Ld^+ sensor were studied as a function of soaking time. For this purpose, the electrode was soaked in 10^{-2} M solution of lidocaine hydrochloride and the calibration graphs (E°_{elec}. versus pLd^+) were plotted after 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12, 24, and 48 h. The optimum soaking time was found to be 4.0–6.0 h, when the slopes of the calibration curves were 56.0–59.0 mV/pLd^+ decade at 25°C. Soaking for longer than 24 h is not recommended to avoid leaching of, although very little, the electroactive species into the external solution. The electrode should be kept dry in an opaque closed vessel while not in use.

Potentiometric selectivity. The selectivity coefficients of the proposed membrane selective electrode were determined against a number of interfering ions by using the two solution method (TSM) [15, 16] and the matched potential method (MPM) [17]. MPM is a recently recommended procedure by IUPAC, which gets rid of the limitations of the corresponding methods based on the Nicolski–Eisenman equation for the determination of potentiometric selectivity coefficients. These limitations include non-Nernstian behavior of interfering ions and inequality of charges of primary and interfering ions. The obtained results for the $K^{pot}_{Ld,\,M}$ of Ld^+ electrode are summarized in Table 2. There was no significant interference from most of the tested inorganic substances, with the exception of phenyl ephrine (PE^+) and phenyl propanol amine ions(PPA^+) ions in two methods because they mimic the structure of lidocaine hydrochloride. The proposed supported liquid membrane electrode seems to be reasonably selective towards lidocaine hydrochloride.

Response time. Dynamic response time is an important factor for an ion-selective electrode [18]. In this study, the practical response time was recorded by changing solution with different Ld^+ concentration from 1.0×10^{-4} to 1.0×10^{-2} M. The actual potential versus time traces is shown in Fig. 1 in which the electrode reaches the equilibrium response in a short time of <10 s.

Effect of pH. The pH dependence of membrane electrode was studied at 1.0×10^{-3} M Ld^+ ion concentration; the obtained results are shown in Fig. 2. The potential was found to remain constant from pH 5.0

to 9.5. This can be taken as the working pH range of the electrode. At pH values lower than 5.0, the pH of solution also influenced the potential response. This is because lidocaine-sulfathiazole ion pair complex in the membrane of electrode is unstable in this medium; the electrode becomes H^+-sensitive at this pH [19]. At higher pH, the lidocaine free base precipitates in the aqueous test solutions and, consequently, the concentration of deprotonated species gradually increases.

Reversibility of the electrode response. To evaluate the reversibility of the electrode, a similar procedure with opposite direction was adopted: the measurements were performed in the sequence of high-to-low (1.0×10^{-2} to 1.0×10^{-3} M) sample concentrations, and the results are shown in Fig. 3. It shows that the potentiometric responses of the sensor was reversible and had no memory effect, the time needed to reach equilibrium values was the same as low-to-high sample concentration [20].

Effect of temperature. Calibration graphs were constructed, as previously described, at test solution temperatures 10, 15, 20, 25, 30, 35, and 40°C are represented in Figs. 4a–4g, respectively. The slope, e.m.f. of the cell and electrode and linear concentration range of the electrode corresponding to each temperature are reported in Table 3. It is clear that the electrode gave a good Nernstian response over the temperature range of 10–40°C.

The standard cell potentials, (E_{cell}) were determined as the intercepts of the calibration graphs at $pLd^+ = 0$ and used to obtain the isothermal temperature coefficient ($dE°/dT$) of the cell with the aid of the following equation [21]:

$$E^\circ_{cell} = E^\circ_{cell(25°C)} + (dE°/dT)\ \text{cell}\ (t–25).$$

A plot of E°_{cell} versus (t–25) produced a straight line, as shown in Fig. 5. The slope of this line was taken as the isothermal temperature coefficient of the cell. It is equals to 0.00036 V/°C. The standard potential of the

Table 2. Potentiometric selectivity coefficients of various interfering cations (X^{n+})

M^{n+}	$K^{pot}_{Ld,M}$	
	TSM	MPM
Li^+	5.7×10^{-3}	3.0×10^{-3}
Na^+	2.2×10^{-3}	5.3×10^{-3}
K^+	2.2×10^{-3}	1.5×10^{-3}
Cs^+	2.3×10^{-3}	6.6×10^{-3}
NH_4^+	2.5×10^{-3}	8.2×10^{-3}
Mg^{2+}	2.0×10^{-3}	2.0×10^{-4}
Sr^{2+}	2.1×10^{-3}	1.8×10^{-2}
Fe^{2+}	6.5×10^{-3}	8.2×10^{-3}
Mn^{2+}	2.7×10^{-3}	1.9×10^{-4}
Cd^{2+}	2.4×10^{-3}	7.0×10^{-2}
[a]PE^+	1.0×10^{-1}	2.3×10^{-1}
[b]PPA^+	2.1×10^{-1}	1.8×10^{-1}

[a] Phenyl ephrine ion.
[b] Phenyl propanol ammonium ion.

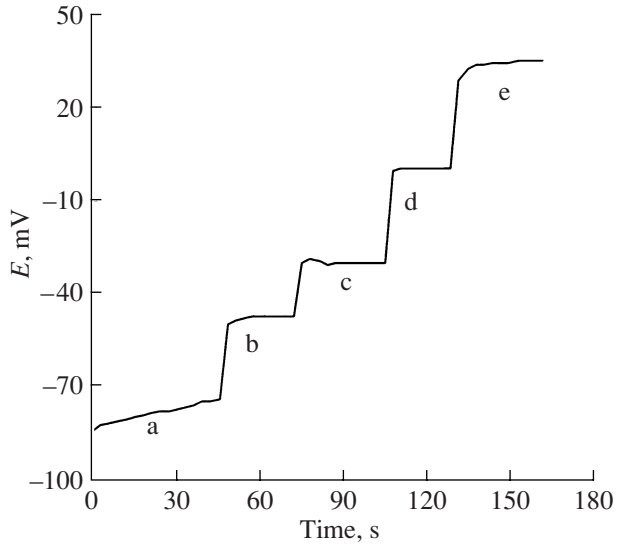

Fig. 1. Dynamic response time of the electrode for step change in concentration of Ld^+; (a) 1.0×10^{-4} M, (b) 5.0×10^{-4} M, (c) 1.0×10^{-3} M, (d) 5.0×10^{-3} M, (e) 1.0×10^{-2} M.

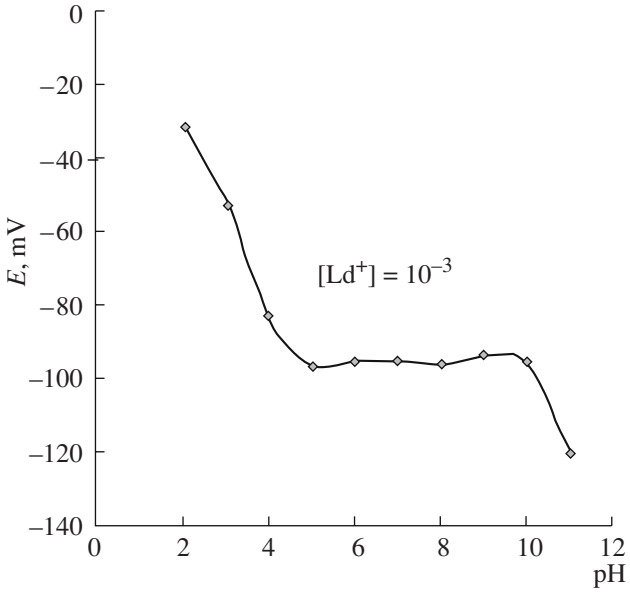

Fig. 2. Effect of pH of test solutions (1.0×10^{-3} M) on the potential response of the Ld^+ sensor.

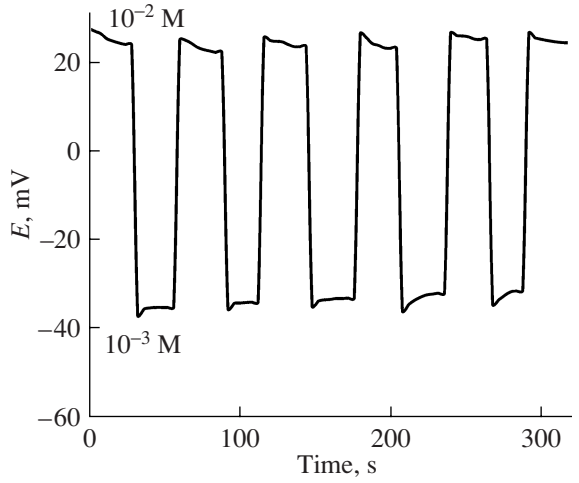

Fig. 3. Dynamic response characteristics of the Ld^+-electrode for several high-to-low sample cycles.

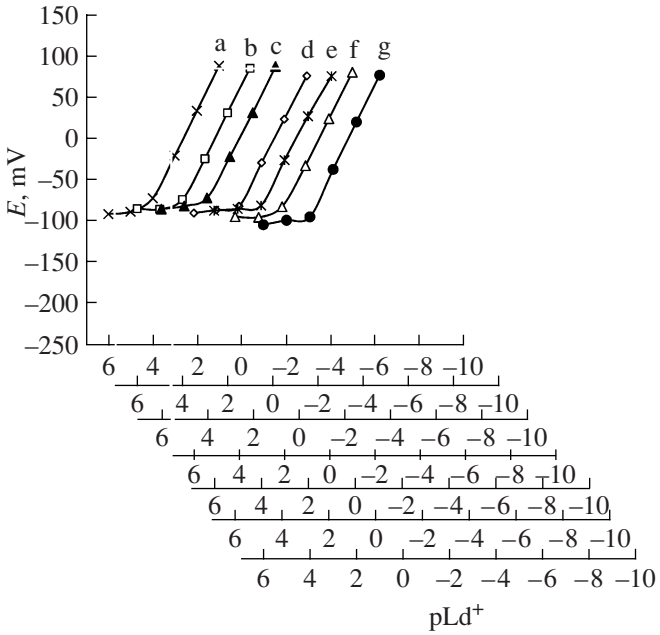

Fig. 4. Calibration graphs at (a) 10°C, (b) 15°C, (c) 20°C, (d) 25°C, (e) 30°C, (f) 35°C, and (g) 40°C using the Ld^+-electrode.

Hg/Hg_2Cl_2, KCl (sat'd) reference electrode was calculated using the following equation:

$$E^\circ_{Hg/Hg_2Cl_2} = 0.241 - 0.00066\,(t - 25).$$

The values of the standard potentials of Ld^+-electrode were calculated at the different temperatures from the following relation:

$$E^\circ_{cell} + E^\circ_{reference} = E^\circ_{electrode}.$$

A plot of $E^\circ_{electrode}$ versus (t–25) gave a straight line, as shown in Fig. 5. The slope of the line was taken as the isothermal temperature coefficient of the Ld^+-electrode. It is equals to –0.0003 V/°C. The small values of $(dE^\circ/dT)_{cell}$ and $(dE^\circ/dT)_{electrode}$ reveal the high thermal stability of the electrode within the investigated temperature range.

Analytical application. The proposed electrode was successfully applied to the determination of lidocaine hydrochloride in some real samples by standard addition. In this method, the potential of 10 mL of injection solution was measured as sample (E_u). Then 0.1 mL of 5.0×10^{-2} M, lidocaine hydrochloride standard solution was added into the testing solution and

Table 3. Performance characteristics of Ld^+ – electrode at different temperatures

Temperature (°C)	Slope (mV/decade)	E°_{cell} (mV)	E°_{elec} (mV)	Linear range (M)
10	53.4	140.1	391	4.0×10^{-5}–1.0×10^{-1}
15	54.0	142.8	390.4	6.3×10^{-5}–1.0×10^{-1}
20	54.9	145.5	389.8	7.9×10^{-5}–1.0×10^{-1}
25	56.1	146.7	387.7	1.0×10^{-4}–1.0×10^{-1}
30	56.6	148.4	386.1	1.0×10^{-4}–1.0×10^{-1}
35	57.5	149.3	383.7	1.0×10^{-4}–1.0×10^{-1}
40	59.7	151.6	382.7	1.0×10^{-4}–1.0×10^{-1}

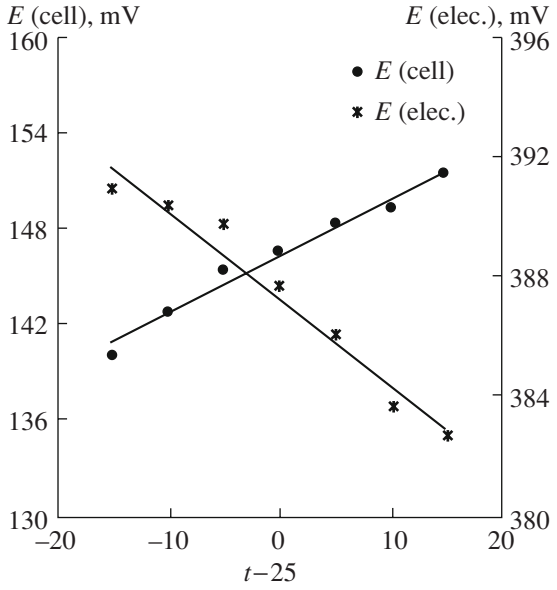

Fig. 5. Variation of standard potential of the cell and electrode with changes of test solution temperature.

the equilibrium potential (E_s) was obtained. From the potential change $\Delta E = E_u - E_s$ one can determine the concentration in the sample using the equation given below:

$$\mathbf{C_x} = \frac{\mathbf{C_s} \times \mathbf{V_s}}{(\mathbf{V_x} + \mathbf{V_s})10^{\mathbf{\Delta E/S}} - \mathbf{V_x}}.$$

Here $\mathbf{C_x}$ is lidocaine hydrochloride concentration in the sample, $\mathbf{C_s}$ the concentration of the standard, $\mathbf{V_x}$ and $\mathbf{V_s}$ the corresponding volumes, **S** the slope of the electrode response, and $\mathbf{\Delta E}$ the change in potential [22]. In the determination of lidocaine hydrochloride in injection solution, the electrode showed almost identical behavior. In all instances, the reproducibility was good and the relative standard deviation of the determinations was less than 2% (Table 4).

Table 4. Determination of lidocaine hydrochloride in aqueous injection solutions with a lidocaine-selective membrane electrode

Pharmaceutical product	Amount in the sample (mg)	Recovery (%) by standard addition method	RSD (%)
5% Lidocaine hydrochloride[a] injection solution (2 mL ampoule)	50	101.6	1.5 (n = 5)
2% Lidocaine hydrochloride[b] injection solution (10 mL ampoule)	100	97.8	1.8 (n = 5)
2% Lidocaine hydrochloride[c] injection B.P. (50 mL vial)	100	98.2	1.4 (n = 6)
2% Lidocaine hydrochloride[d] injection solution (50 mL vial)	100	97.8	1.7 (n = 5)

[a] Made in Switzerland.
[b] Made in Saudi Arabia.
[c] Made in United Kingdom.
[d] Made in Iran.

A new lidocaine-selective PVC membrane electrode based on the ion pair compound of lidocaine-sulfathiazole and DBP as plasticizer was developed. The lidocaine electrode which was designed in this work has many advantages including easy preparation, low cost, wide dynamic range, low detection limit, good selectivity and life time. The proposed electrode was successfully applied to the determination of lidocaine hydrochloride in pharmaceutical preparations. The proposed analytical method proved to be a simple, rapid and accurate.

ACKNOWLEDGMENTS

The authors gratefully thank the research counsil of Islamic Azad University–Lahidjan Branch for financial suppots.

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