JOURNAL OF THE Iranian Chemical Society

Potentiometric PVC Membrane Sensor for the Determination of Phenylephrine Hydrochloride in Some Pharmaceutical Products

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(Received 18 September 2008, Accepted 11 June 2009)

A new PVC membrane electrode for the determination of phenylephrine hydrochloride based on the formation of an ionassociation complex of phenylephrine hydrochloride with the phosphotungstate counter anion as an electroactive material dispersed in a PVC matrix is described. The sensor shows a fast, stable, near-Nernstian response for 1.0×10^{-5} to 1.0×10^{-1} M phenylephrine hydrochloride at 25 °C over the pH range of 3.5-8.0 with a cationic slope of 58.1 ± 0.6 mV decade⁻¹. The electrode was successfully used for potentiometric determination of phenylephrine hydrochloride in some pharmaceutical drugs.

Keywords: Ion-pair sensor, Phenylephrine hydrochloride, Potentiometry, PVC-membrane, Selectivity

INTRODUCTION

Phenylephrine or Neo-Synephrine is an α -adrenergic receptor agonist used primarily as a decongestant, an agent to dilate the pupil and to increase blood pressure. Phenylephrine has been recently marketed as a substitute for pseudoephedrine e.g. Pfizer's Sudafed original formulation. However, nowadays it has been claimed that oral phenylephrine may be no more effective as a decongestant than placebo. Therefore, compared with orally-taken pseudoephedrine, it has a reduced and variable bioavailability of only up to 38 percent and is thus less effective as a nasal decongestant than pseudoephedrine. Because phenylephrine is a direct selective α -adrenergic receptor agonist, it does not cause the release of endogenous noradrenaline as pseudoephedrine does. Therefore, phenylephrine is less likely to cause side-effects like central nervous system stimulation, insomnia, anxiety, irritability and restlessness. As a nasal spray, phenylephrine is available in 1% and 0.5%

concentrations. It suffers some rebound congestion effects, although to a lesser degree than oxymetazoline. Phenylephrine is used as an eye drop to dilate the pupil to facilitate visualization of the retina. It is often used in combination with tropicamide. Narrow angle glaucoma is a contra-indication to phenylephrine use. It is sometimes used as a vasopressor to increase the blood pressure in unstable patients with hypotension which is more common in anesthesia or critical care practices. It also has the advantage of not being inotropic or chronotropic which strictly elevates the blood pressure without increasing the heart rate [1].

The potentiometric membrane sensors have been widely used in pharmaceutical analysis [2-7]. Ion-selective membrane electrodes which are selective to a variety of ionic drugs have attracted increasing interest because of their potential use in pharmaceutical analysis [8-10].

The inherent advantages of ion-selective electrodes (ISEs) are simplicity, short measurement time, low cost, adequate precision and accuracy, adequate detection limits, wide analytical range, and particularly the ability to measure the activity of various drugs selectively, and in most cases, without

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solution/SCE.

prior separation of the drug of interest from the formulation matrix in colored or cloudy samples. These make ISE potentiometry very attractive for pharmaceutical analysis [11-13].

In this paper, we describe a simple potentiometric PVCmembrane sensor for the determination of phenylephrine in pharmaceutical preparations. The membrane used in this electrode was made from liquid-plasticized PVC and was based on a water-insoluble phenylephrine-phosphotungstate ion pair as an ion-exchanger.

EXPERIMENTAL

Reagents

All reagents except phenylephrine hydrochloride were of analytical reagent grade. Phenylephrine hydrochloride was synthesized and purified in a drug laboratory in Behdashtkar, grade dibutyl phthalate (DBP), Iran. Reagent phospohotungstic acid (PTA), sodium tetraphenylborate (NaTPB), acetophenone (AP), 2-nitro-phenyloctyl ether (2-NPOE), oleic acid (OA), tetrahydrofuran (THF) and high relative molecular weight PVC (all from Merck or Fulka) were used as received. Double distilled deionized water was used throughout.

Preparation of Membrane Electrode

Powdered PVC (30 mg), phospohotungstic acid (3 mg) and plasticizer DBP (67 mg) were thoroughly dissolved in 5 ml of THF. The resulting mixture was transferred into a glass dish of 2 cm diameter and the solvent was evaporated slowly until an oily concentrated mixture was obtained. A Pyrex tube of 3-5 mm internal diameter in top 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 (0.01 M phenylephrine hydrochloride). The electrode was finally conditioned for 4 h by soaking in a 0.05 M phenylephrine hydrochloride solution.

Emf Measurements

All emf measurements were carried out with the following assembly:

SCE/internal solution, 1.0×10^{-2} M PE⁺/PVC membrane/test

A model 654 Metrohm ion analyzer pH/mV meter was used for the potential measurements at 25.0 ± 0.2 °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 optimal percent membrane composition obtained was PVC:DBP:phospohotungstic acid ratio of 30:67:3 (No. 3, Table 1). The potential response of the membrane at varying concentrations of PE⁺ ion, indicates a rectilinear range from 1.0×10^{-5} to 1.0×10^{-1} M (Fig. 1). The slope of the calibration curve was 58.1 ± 0.6 mV decade⁻¹ of PE⁺ concentration. The limit of detection, as determined from the intersection of the two extrapolated segments of the calibration graph, was $8.9 \times$ 10^{-6} M. The electrode exhibited a day-to-day reproducibility of about ± 1.0 mV for at least 6 weeks after preparation, while stored in water.

Effect of Soaking

The performance characteristics of PE⁺ sensor were studied as a function of soaking time. For this purpose, the electrode was soaked in 10⁻² M solution of phenylephrine hydrochloride and the calibration graphs (\tilde{E}_{elec} , vs. pPE⁺) were plotted after 0.0, 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 h at room temperature.

Effect of pH

The pH dependence of the electrode potential for both 1.0 \times 10⁻³ and 1.0 \times 10⁻² M of phenylephrine hydrochloride was tested over a pH range of 2-11 whose results are depicted in Fig. 2. As it can be seen, the potential response remains almost constant over the pH range of 3.0-8.0 and 4.0-8.0 in 1.0×10^{-2} and 1.0×10^{-3} M PE⁺ ion, respectively. This can be taken as the working pH range of the electrode. At pH values lower than 3.0, the pH of solution affects the potential response, because the phenylephrine hydrochloride-phospohotungstate ion pair complex in the membrane of electrode is unstable in

No	Composition (%)				Slope	Linear range	
110.	РТА	PVC	Plasticizer	Additive	(mV decade ⁻¹)	[M]	
1	-	30	70(DBP)	-	11.2	1.0×10^{-5} - 1.0×10^{-1}	
2	1	34	65(DBP)	-	52.1	1.0×10^{-5} - 1.0×10^{-1}	
3	3	30	67(DBP)	-	58.1	1.0×10^{-5} - 1.0×10^{-1}	
4	3	30	67(2-NPOE)	-	49.4	1.0×10^{-5} - 1.0×10^{-1}	
5	3	30	67(AP)	-	23.9	1.0×10^{-5} - 1.0×10^{-2}	
6	5	30	65(DBP)		52.1	1.0×10^{-5} - 1.0×10^{-1}	
7	7	28	65(DBP)	-	55.1	1.0×10^{-5} - 1.0×10^{-1}	
8	10	30	67(DBP)		40.3	1.0×10^{-5} - 1.0×10^{-1}	
9	3	30	64(DBP)	3(OA)	55.3	1.0×10^{-5} - 1.0×10^{-1}	
10	3	30	64(2-NPOE)	3(NaTPB)	36.3	1.0×10^{-4} - 1.0×10^{-1}	
11	7	28	58(DBP)	7(OA)	35.2	1.0×10^{-4} - 1.0×10^{-1}	

Table 1. Optimization of the Membrane Ingredients







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

this medium [14]. At a higher pH, the potential response decreases drastically because of the decreasing of cationic form of phenylephrine concentration.

Response Time

Dynamic response time is an important factor for an ionselective electrode [15]. In this study, the practical response time was recorded by changing solution with different PE⁺ concentration from 1.0×10^{-4} to 1.0×10^{-2} M. The actual potential *vs.* time traces (Fig. 3) shows that the electrode reaches the equilibrium response in a short time of <12 s.

Potentiometric Selectivity

Potentiometric selectivity coefficients of the proposed membrane selective electrode were determined against a number of interfering ions by matched potential method (MPM) [16]. The obtained results for the $K_{PE,M}^{pot}$ of PE⁺ electrode are summarized in Table 2 which shows that, with the exception of LD⁺, DP⁺, BA⁺, TDTMA⁺ and PSE⁺ ions having similar structures with phenylephrine, the selectivity coefficients obtained for all other cations are in the order of 10^{-2} or smaller, indicating that they do not disturb the functioning of PE⁺ ion selective electrode significantly. The proposed membrane electrode seems to be reasonably selective towards phenylephrine hydrochloride.

Reversibility of the Electrode Response

To evaluate the reversibility of the electrode, the opposite direction was adopted. The measurements were performed in order of high-to-low $(1.0 \times 10^{-2} \text{ to } 1.0 \times 10^{-3} \text{ M})$ sample concentrations. The results are presented in Fig. 4 which shows that the potentiometric responses of the sensor were reversible and had no memory effect. The time needed to reach equilibrium values were the same as low-to-high sample concentration [17].

CONCLUSIONS

A new phenylephrine-selective PVC membrane electrode based on the ion pair compound of phenylephrine hydrochloride-phospohotungstate and DBP as plasticizer was developed. The phenylephrine hydrochloride electrode has many advantages including: easy preparation, low cost,



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

 Table 2. Potentiometric Selectivity Coefficient of Various

 Interfering Cations (Mⁿ⁺)

M^{n^+}	K_{PE-M}^{pot}	M^{n^+}	K_{PE-M}^{pot}
Na ⁺	9.0×10^{-3}	LD^{+a}	1.24
\mathbf{K}^+	2.2×10^{-2}	PSE^{+b}	$1.8 imes 10^{-1}$
Cs^+	9.0×10^{-2}	PPA^{+c}	$5.0 imes 10^{-3}$
$\mathrm{NH_4}^+$	1.8×10^{-2}	$\mathrm{DP}^{\mathrm{+d}}$	2.6×10^{-1}
Mg^{2+}	3.2×10^{-3}	BA^{+e}	$5.5 imes 10^{-1}$
Fe ³⁺	4.1×10^{-3}	$\mathrm{TDTMA}^{\mathrm{+f}}$	6.9×10^{-1}

^aLidocaine ion. ^bPseudoephedrine ion. ^cPhenyl propanol amine ion. ^dDiazepam ion. ^eBenzydamine ion. ^fTetra decyl tri methyl ammonium ion.

relatively wide dynamic range, low detection limit, good selectivity and lifetime. The proposed electrode was successfully applied to the determination of phenylephrine hydrochloride in pharmaceutical preparations.

Analytical Application

The proposed membrane sensor proved to be useful for the assay of phenylephrine hydrochloride (PEHCl) content of



Fig. 4. Dynamic response characteristics of the PE⁺-electrode for several high-to-low sample cycles.

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Table 3. Determination of Phenylephrir	ie Hydrochloride in Drop with a Phenylephrine-Selective Membrane
Electrode by Two Methods	0,

Methods	Amount of real sample (mg)	Amount of determination by sensor (mg)	R.S.D (%)
Standard addition method	10	9.5 ± 0.5	2.9 (n = 8)
Direct potentiometry	10	9.7 ± 0.2	2.5 (n = 8)

pharmaceutical preparations by using the two methods of standard addition method and direct potentiometry [18-21]. As the application of electrode, 2 ml of nasal drop of phenylephrine (0.5 g per 100 ml) was diluted up to 10 ml and then analyzed by the proposed electrode. The results obtained from eight replicate measurements were found to be 9.5 ± 0.5 mg by standard addition method and 9.7 ± 0.2 mg by direct potentiometry, which is in satisfactory agreement with the declared amount (Table 3).

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of this work by Islamic Azad University of Lahijan.

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