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Coated wire sensor for Potentiometric Determination of Duloxetine Hydrochloride in pure form and Pharmaceutical Formulations

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ABSTRACT

A coated wire duloxetine-selective electrode based on incorporation of duloxetine-tetraphenylborate ion pair in a poly (vinylchloride) coating membrane was constructed. The influences of membrane composition, pH of the test solution, and foreign ions on the electrode performance were investigated. The electrode showed a Nernstian response over a duloxetine concentration range from 1.0×10^{-5} to $1.0 \times 10^{-2}M$, at 25 °C, and was found to be very selective, precise, and usable within the pH range 4.0–9.0. The electrode was successfully used for potentiometric determination of duloxetine hydrochloride both in pure solutions and in pharmaceutical preparations.

KEYWORDS: Duloxetine hydrochloride (DLX) ; Ion-selective electrode; Pharmaceutical analysis.

INTRODUCTION

Duloxetine hydrochloride, ((+)-(S)-N-methyl-gamma- (1-naphthyloxy)-2-thiophenepropylamine hydrochloride), is a potent antidepressant which also acts as a central analgesic [1]. The chemical structure of duloxetine hydrochloride was depicted in Fig.1. A survey of literature showed that several analytical methods have been reported for determination of DLX in its pure form, pharmaceutical preparations and biological fluids, where DLX is not determined officially in any pharmacopoeia. These methods include high-performance liquid chromatography [2,3], liquid chromatography coupled with mass spectrometry [4-6], high performance thin layer chromatography [7], Spectrofluorimetry [8], spectrophotometry [9] and capillary zone electrophoresis [10]. Although, those methods are very sensitive, they are not adapted for in situ and real time detection of DLX as they are time consuming, involve expensive apparatus and require skilled technicians. Electrochemical techniques are of choice since they possess the advantages of simplicity, accuracy, and low cost without separation or pretreatment procedures [11].

The conventional Polyvinylchloride (PVC) membrane ion-selective electrodes have found a wide range of applications in pharmaceutical analysis; however they still have certain inherent limitations. Drawbacks in the use of PVC electrodes were arisen from the time consuming and inconsistent manual fabrication typically employed as well as short lifetime of these electrodes [12]. To overcome the aforementioned difficulties in PVC membrane electrodes, new kinds of all solid- state ones (without internal reference solution) allowing electrode miniaturization capability were introduced. Coated wire electrodes (CWEs) and coated graphite electrodes are examples of these sensors design; however the potential drift and the poor adhesion of the membrane to the metal substrate are main drawbacks of these electrodes [13].

The present work, thus, describes a new selective membrane electrode of the coated wire type, for determination of DLX in pure solutions and in pharmaceutical preparations. Fine copper wires coated with a solution mixture of liquid ion-pair complex of tetraphenylborate anion (TPB$^-$) and poly (vinyl chloride) in THF were used as anion-selective electrode for DLX$^+$ cation.
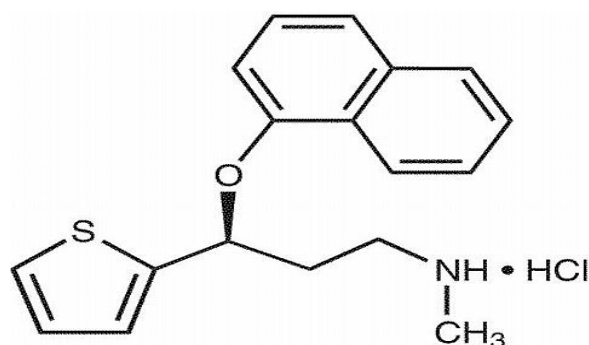
Figure 1. Chemical structure of duloxetine HCl.

EXPRIMENTAL

Reagents

All reagents were of analytical grade. Double distilled and deionized water was used throughout all experiments. The pharmaceutical preparations containing duloxetine HCl (Cymbalta®,60 mg DLX/capsules and Yentreve®, 20 mg DLX/capsules) were obtained from local drug stores. The DLX–TPB ion pair was prepared by a method similar to that described previously [14]. The agreement between calculated and found values was very good confirming the postulated stoichiometry; the 1 : 1 (DLX : TPB) molar ratio stoichiometry was also confirmed by elemental analysis.

Procedures

PreparationofDLX-TPB Ion-pair

Ion-pair compound of duloxetine HCl-tetraphenylborate (DLX-TPB): 1.0×10^{-2} M solution of duloxetine HCl was mixed with an equal volume 1.0×10^{-2} M solution of tetraphenylborate with continuous stirring. The resulting precipitate was left in contact with their mother liquor over night to assure complete coagulation, was filtered, washed thoroughly with distilled water until chloride free (tested using $AgNO_3$ solution) and dried at room temperature for 2 days.

Preparation of Electrode

The copper wires of 2.0 mm diameter and 12 cm length were tightly insulated by polyethylene tubes leaving 1.0 cm at one end of the coating and 0.5 cm at the other end for connection. The coating solutions were prepared by dissolving varying amounts of Polyvinylchloride (PVC), dioctylphthalate, DOP (plasticizer), and the DLX–TPB in the least amount of tetrahydrofuran possible (6 ml), Table 1. Prior to coating, the polished copper surface was washed with a detergent and water, thoroughly rinsed with de-ionized water, and dried with acetone.

Then the wire was rinsed with chloroform and allowed to dry. Afterwards, the copper wire was coated by quickly dipping it into the coating solutions, (a), (b), (c), (d) or (e) several times and allowing the film left on the wire to dry for about 2 min. The process was repeated several times until a plastic membrane of approximately 1.0 mm thickness was formed. The prepared electrodes were preconditioned by soaking them for 24 h in a 10^{-3} M of duloxetine hydrochloride solution.When not in use, the electrode was kept in a 1.0×10^{-3} M solution of the appropriate duloxetine hydrochloride.

Calibration Graph

Suitable increments of standard drug solution were add to 50 ml doubly distilled water so as to cover the concentration range from 1×10^{-6} - 1×10^{-2} M. In this solution the sensor and reference electrode were immersed and the e.m.f values were recorded after each addition. The electrode was washed with double distilled water and dried between measurements. The electrode potential was plotted versus negative logarithmic concentration of DLX, Slopes of the resulting calibration curves were calculated.The slope of the calibration graph was calculated using Nernestain equation:

$$E = E_{ISE}^{\circ} + 2.303 = \frac{RT}{ZF} \log[DLX] \textbf{eq. (1)}$$

Sensor Potential Measurement

Potentiometric measurements were carried out at 25 ± 0.1°C on a digital pH/millivolt meter (Jenway, Model 3510). The ectrochemicalsystem may be represented as follows:

Copper (wire)-PVC membrane | sample solution || Ag-AgCl, KC1 (satd.)

Selectivity of the electrode

Selectivity coefficients were determined by the separate solution method[15] , in which the following equation was applied.

$$Log \ K_{DLX, B^{z+}}^{pot.} = \left(E_2 - E_1\right) \Big/ S + \log \left[DLX\right] - \log \left[B^{z+}\right]^{1/z+} \textbf{ eq. (2)}$$

where E_1 and E_2 are the electrode potentials of solutions of the DLX and interfering cation, B^{z+}, respectively (both of the same concentration) and S is the slope of the calibration graph.

Conductimetric Determination of the Solubility Product of the Ion-pair

A series of solutions of different concentrations (c) was prepared for DLX, TPB. The conductances of these solutions were measured at 25°C, and the specific conductances (corrected for the effect of solvent) were calculated and used to obtain the equivalent conductances (λ) of the solutions. Straight-line plots of λ vs $\sqrt{c}$ were constructed, and λo for DLX, TPB were determined from the intercept of the respective line with the λ axis.

The activity coefficients of the ions employed were taken as unity because all the solutions were sufficiently dilute (1.0×10^{-5}- 1.0×10^{-2} M). The values of $\lambda_{DLX-.TPB}$, was calculated using Kohlrausch's law of independent migration of ions [16] .The solubility (S) and solubility product (K_{sp}) of a particular ion associate were calculated using the following equation :

$S = K_s \times 1000 / \lambda_{DLX-.TPB}$ **eq. (3)**

where K_s is the specific conductance of the saturated solution of the ion associate, determined at 25°C. The saturated solution was made by stirring a suspension of the solid precipitate in distilled water for 2 h at 25°C.

RESULTS and DISCUSSION

Influence of Membrane Composition

Five coating membrane compositions were investigated as given in Table1. The results show that on using membranes of optimum compositions (assigned by * in the table), slope of 59.0 mV/concentration decade over a relatively wide range of DLX concentration (1.0×10^{-5}- 1.0×10^{-2}). A typical calibration plot for electrode is shown in **Fig. 2**.Consequently; the electrode made by using coating solution (d) was selected for carrying out all the following studies.

Table 1. Composition of the coating membranes and slopes of the corresponding calibration graphs at 25°C.

No.	Composition % (w/w)			Slope	RSD[a]
	Ion Pair	DOP	PVC	nV/decade)	(%)
a	1.0	49.0	49.0	45.9	1.01
b	5.0	47.0	48.0	51.5	1.21
c	7.0	46.0	47.0	50.8	1.33
d	9.0*	45.0	46.0	59.0	1.12
e	15.0	40.0	45.0	49.0	1.34

[a] Relative standard deviation (five determinations)
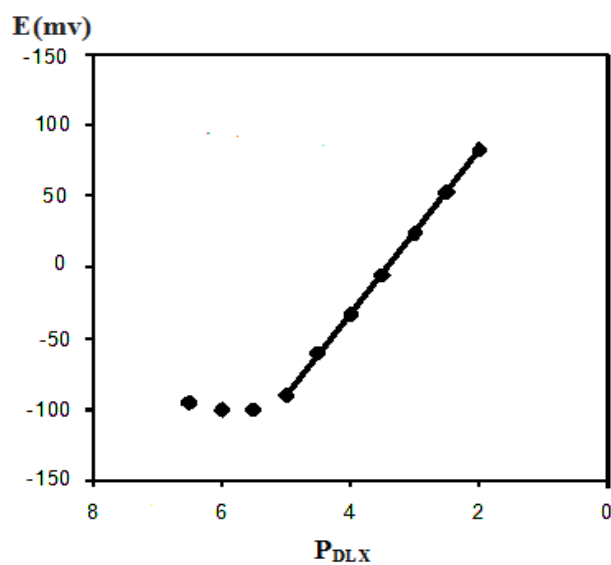*Optimum composition

Figure 2. Typical calibration graph of DLX wire coatedelectrode [membrane (d)] soaked for 24 h.

Dynamic Response Time

Dynamic response time is the required time for the electrode to achieve values within ±1 mV of the final equilibrium potential, after successive immersions in the sample solutions. Its calculation involved the variation and the recording of the DLX concentration in a series of standard solutions. This electrode exhibits a fast dynamic response of about 20 s.

Effect of pH

To examine the effect of pH on electrode response, the potential was measured at a specific concentrations of the DLX solution (1.0×10^{-3} M) from the pH value of 2.0 up to 12.0 (concentrated NaOH or HCl solutions were employed for the pH adjustment). The results showed that the potential remained constant despite the pH change in the range of 4.0 to 9.0, which indicates the applicability of this electrode in the specified pH range.

The fluctuations above the pH value of 9 might be justified by removing the positive charge on the drug molecule. Fluctuations below the pH value of 4.0 were caused by removal of the ion-pair in the membrane or analyte in the solution. During the operative life of the electrode (three months), nosignificant change in the potential–pH behaviour was observed.

Selectivity of the Electrode

The selectivity coefficients$K^{Pot}_{DLX, B^{Z+}}$ presented in Table (2) clearly showed that the proposed CWEelectrodeis highly selective towardDLX with respect to many common inorganic cations, sugars, and amino acids which are frequently present in biological fluids and pharmaceutical preparations.

Table2. Selectivity coefficients of DLX$^+$ CWE calculated by theseparate solution method (1.0×10^{-3}Mof both DLX$^+$ and the interferent) at25 °C

Interferent	$K^{pot}_{DLX, B^{Z+}}$	Interferent	$K^{pot}_{DLX, B^{Z+}}$
Na$^+$	3.8×10^{-5}	**Cr^{3+}**	8.5×10^{-3}
NH$_4^+$	2.3×10^{-3}	**Glucose**	4.3×10^{-4}
Cu^{2+}	7.3×10^{-3}	**Maltose**	2.5×10^{-5}
Co^2	1.6×10^{-5}	**Alanine**	2.7×10^{-4}
Fe^{3+}	7.0×10^{-5}	**Glycine**	8.4×10^{-5}

Conductometric Determination of the Solubility Product of DLX-TPB Ion-pair

The determination of the solubility product of a precipitate is important since its reciprocal is approximately equal to the equilibrium constant of the precipitation reaction leading to the ion-pair formation. This is related to the degree of hydrophobicity of the ion pair, so the leaching process of it, which is the main controlling factor of the electrode life time, is very slow.

The solubility product of the ion pair was found to be 5.43×10^{-7}. This value indicate that the solubility of the ion pair is very low (3.78×10^{-3}M). Consequently, the equilibrium constants of the reactions,

(DLX + Na-TPB = DLX-TPB + NaCl)
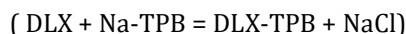
are 4.21×10^6, which reflects that the reaction is more than 99.9% complete. In the above equilibria, the solubilities of the undissociated ion pair in water (i.e. the intrinsic solubility) were omitted as they only have a negligible contribution to the total solubility.

Analytical Applications

Duloxetine HCl was determined potentiometrically using the investigated electrode by the standard addition method [17]. In the standard addition method, small increments of a standard duloxetine HCl solution 1.0×10^{-2}M were added to 50 mL aliquot samples of various drug concentrations. The change in potential reading at a constant temperature of 25 °C was recorded for each increment and used to calculate the concentration of the drug sample solution.

For analysis of DLX formulations ((Cymbalta, 60 mg DLX/capsules and Yentreve, 20 mg DLX/capsules),10 capsules were accurately weighed and powdered in a mortar; then, the required amount from the tablet powder was dissolved in about 30 mL distilled water and filtered in a 50 mL measuring flask. The residue was washed three times with double distilled water, and the pH of the solution was adjusted to 5 by 0.1M acetate buffer, and diluted to the mark with water. The contents of the measuring flask were transferred into a 100 mL beaker and the standard addition technique was applied as described above.

The recovery and the relative standard deviation values are summarized in Table 3. The data indicated that there was no interference from the excipients used in the formulations of the capsules.

Table 3. Potentiometric determination of DLX in aqueous solution and in pharmaceutical preparations with a DLX electrode by the standard addition method, at 25 °C

Sample	Taken (mg)	Recovery (%)	R. S. D.[a] (%)
Pure DLX solution	4.46-44.61	99.2±0.11	0.81
Cymbalta tablets	5.06- 29.74	100.0 ± 0.50	0.06
Xeristar tablets	5.65-53.53	99.4 ± 0.36	0.66

[a] RSD (three determination)

CONCLUSION

The Duloxetine HCl based on membrane electrode of the coated wire type exhibited the advantages of simple design and operation, reasonable selectivity and fast response. Further,the electrode can be used to determine duloxetine hydrochloride by direct potentiometry in pure form and in pharmaceutical preparations.

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