Potentiometric Determination of Duloxetine Hydrochloride Using Coated Wire Electrode in Pure and Pharmaceutical Preparations

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Abstract

Aim: An electrode of coated wire duloxetine-selective type was prepared and categorized in aqueous solution as a sensor for duloxetine hydrochloride (DLX) determination and in pharmaceutical preparations by the standard addition method, at 25°C. Materials and Methods: Local drug stores were the pharmaceutical preparations containing DLX (Cymbalta®, 60 mg DLX/capsules and Yentreve®, 20 mg DLX/capsules). Potentiometrically, DLX was determined by standard addition method utilizing the investigated electrode. Standard DLX solution in small increments $1.0 \times 10^{-2}$ M was added to 50 mL aliquot samples of various drug concentrations in the standard addition method. Variation in potential reading at a constant temperature of 25°C was documented for each increment and used to calculate the drug sample solution concentration. Results and Discussion: The electrode shows a linear response with slope of 59.0 mV per duloxetine concentration decade for optimum electrode 9.0% at 25°C ± 0.1°C when pH of test solution was in the range of 4.0–9.0 at with potentiometric responses were independent. In the presence of different inorganic cations, sugars and amino acids that electrode shown good selectivity for DLX. It was successfully used for potentiometric determination of DLX both in pure solutions and in pharmaceutical preparations. Conclusion: According to membrane electrode of the coated wire type, the DLX exhibited advantages of simple design and operation, reasonable selectivity, and fast response. Further, the electrode can be used by direct pure form potentiometry and in pharmaceutical preparations to DLX determination.

Key words: Duloxetine hydrochloride, ion-selective electrode, pharmaceutical analysis

INTRODUCTION

We can know duloxetine hydrochloride (DLX), (+)-(S)-N-methyl-gamma-(1-naphthyloxy)-2 thiophenepropylamine hydrochloride), as a potent antidepressant acts as a central analgesic.[1] In Figure 1, chemical structure of DLX was depicted. By literature survey, several analytical techniques have been stated for DLX determination in its pure form, pharmaceuticals and bio-fluids, where DLX is not specifically assigned to any pharmaceutical constitution. These techniques include high-performance liquid chromatography,[2,3] liquid chromatography joined with mass spectrometry,[4,6] high-performance thin-layer chromatography,[7] spectrofluorimetry,[8] spectrophotometry,[9] and capillary zone electrophoresis.[10] Although these techniques are very sensitive, and not adapted for in situ, and DLX real-time detection also takes a long time, involve expensive devices and skilled technicians are required. Our present research describes a new selective membrane electrode of the coated wire type, for DLX determination in both pure solutions and pharmaceutical preparations. Fine copper wires coated with 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.

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EXPERIMENTAL

Reagents

All reagents were of analytical grade. DD and DI water were used throughout all experiments. Local drug stores were the source of all pharmaceutical preparations containing DLX (Cymbalta®, 60 mg DLX/capsules and Yentreve®, 20 mg DLX/capsules). DLX–TPB ion pair was prepared likewise by a technique that described previously.[11] The assent between calculated and found values was approving very well the postulated stoichiometry; the 1:1 (DLX: TPB) molar ratio stoichiometry was also confirmed by elemental analysis.

Procedures

DLX-TPB ion-pair preparation

An equivalent volume $1.0 \times 10^{-2}$ M of ion-pair compound of duloxetine-tetraphenylborate (DLX-TPB) of DLX with tetraphenylborate solution was mixed and stirring continued. Leave the precipitate in contact with the mother liquor throughout the night to ensure full coagulation, then filtered, washed thoroughly with distilled water until chloride free (tested using AgNO₃ solution) and dried at room temperature for 2 days.

Construction of electrode

The copper wires in thin diameter of 2.0 mm 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. Varying amounts of polyvinylchloride (PVC), dioctyl phthalate, DOP (plasticizer), and the DLX–TPB in the least amount of tetrahydrofuran possible (6 ml), were dissolved to prepare coating solutions [Table 1]. Before coating, the surface of the polished copper was washed with a detergent and water, rinsed thoroughly with deionized water and dried with acetone. Then, rinse the wire with chloroform and allowed to dry. Afterward, the wire was coated by quickly dipping in coating solutions, (a), (b), (c), (d), or (e) several times and allowing the film to dry on the wire for about 2 min. This process was repeated several times to allow a plastic membrane of approximately 1.0 mm thickness formed. Soaked electrodes were determined in DLX solution $10^{-3}$ M for 24 h.

Calibration graph

Suitable increments of standard drug solution were add to 50 ml doubly distilled water so as to cover the concentration range from $1 \times 10^{-6}$ - $1 \times 10^{2}$ M. Both sensor and reference electrode immediately immersed then the e.m.f values were documented once addition takes place. Washed electrode with dd. Water then dried after any measurement. 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 slopes was calculated using Nernstian equation:

$$E = E_{ISE} + 2.303 \frac{RT}{ZF} \log[DLX]$$

Sensor potential measurement

Digital pH/millivoltmeter (Jenway, Model 3510) was used for potentiometric measurements at 25°C ± 0.1°C while conductance measurements were taken placed by Jenway 4330 conductivity meter.

emf measurements

Electrochemical system may be represented as follows:

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

Selectivity of the electrode

Separate solution method was the used method for the selectivity coefficients determination,[12] in which the following equation was applied (Equation 2).

$$\frac{1}{2} \log \frac{K_{DLX,B^+}}{K_{DLX,S}} = \frac{(E_2 - E_1)}{S} + \log[DLX] - \log[B^+]^{1/2}$$

Solutions electrode potentials of DLX represented by $E_1$, $E_2$ are referring to interfering cation, $B^+$, (both of the same concentration) and S is the slope of calibration graph.

Conductimetric determination of ion-pair solubility product

Several concentrations of solutions (c) were prepared for DLX, TPB. The conductance of these solutions should be measured at 25°C and the specific conductances (corrected for the effect of solvent) were taken till using for equivalent conductance reads ($\lambda$) of these solutions. Straight-line plots of $\lambda$ vs $\sqrt{c}$ were constructed, and $\lambda_0$ for DLX, TPB were determined from the intercept of the respective line with the $\lambda$ axis. The activity coefficients of the ions which employed may consider as a unit because all the solutions were sufficiently diluted ($1.0 \times 10^{-5}$–$1.0 \times 10^{-2}$ M).

Kohlrausch’s law has been utilized in values of $\lambda$, DLX, TPB calculating.[13] The solubility (S) and solubility product (Ksp) of a particular ion associate were calculated by the following equation:

$$S=K_s \times 1000/\lambda \text{ DLX, TPB}$$
When, $K_s$ 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**

In the present study, we have been studied five membrane coating combinations as shown in Table 1. The results show that, the slope of 59.0 mV/concentration decade over a somewhat wide range of DLX concentration ($1.0 \times 10^{-5}$–$1.0 \times 10^{-2}$). Therefore; the electrode made fundamentally by coating solution (d) was selected for carrying out all the following studies.

**Dynamic response time**

As it is known the dynamic response time is the time required for the electrode to realize values within ±1 mV of the final equilibrium potential, once immersions successive in the sample solutions. Its calculation involved the variation and the recording of the DLX concentration in a series of standard solutions. This electrode shows a rapid dynamic response of about 20 s.

**Effect of pH**

The potential was measured at a specific concentrations of the DLX solution ($1.0 \times 10^{-3}$M) with 2.0 up to 12.0 pH value (concentrated NaOH or HCl solutions were employed for the pH adjustment). The showed results explain that potential remained constant despite the pH change in the range of 4.0–9.0, which indicates the applicability of this electrode in the specified pH range. The above pH hesitancy value of 9 might be justified by positive charge eliminating on the drug molecule. Fluctuations below the pH value of 4.0 were caused by exclusion of the ion-pair in the membrane or solution analyte. During the operative life of the electrode (three months), no significant change in the potential–pH behavior was observed.

### Table 1: Composition of coating membranes and slopes of corresponding calibration graphs at 25°C

<table>
<thead>
<tr>
<th>No.</th>
<th>Composition % (w/w)</th>
<th>Slope (mV/decade)</th>
<th>RSD$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ion pair</td>
<td>DOP</td>
<td>PVC</td>
</tr>
<tr>
<td>A</td>
<td>1.0</td>
<td>49.0</td>
<td>49.0</td>
</tr>
<tr>
<td>B</td>
<td>5.0</td>
<td>47.0</td>
<td>48.0</td>
</tr>
<tr>
<td>C</td>
<td>7.0</td>
<td>46.0</td>
<td>47.0</td>
</tr>
<tr>
<td>D</td>
<td>9.0$^*$</td>
<td>45.0</td>
<td>46.0</td>
</tr>
<tr>
<td>E</td>
<td>15.0</td>
<td>40.0</td>
<td>45.0</td>
</tr>
</tbody>
</table>

$a$Relative standard deviation (five determinations). $^*$Optimum composition. PVC: Polyvinylchloride

**Selectivity of the Electrode**

The selectivity coefficients $K_{DLX, B}^{Pot}$ presented in Table 2 clearly showed that the proposed CWE electrode is highly selective toward DLX with respect to many common inorganic cations, sugars, and amino acids which are frequently present in biological fluids and pharmaceutical preparations.

**Conductimetric determination of DLX-TPB ion-pair solubility product**

The science of solubility product determination of a precipitate is considered significant since. The exchange is almost equal to the equilibrium balance in the reaction of precipitation leading to the formation of ion-pair. The degree of hydrophobicity of the ion pair is the very important factor, 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 $5.43 \times 10^{-7}$.

The solubility of the ion pair is very low ($3.78 \times 10^{-3}$M) that was indicated value. Consequently, the equilibrium constants of the reactions (DLX + Na-TPB = DLX-TPB + NaCl) were $4.21 \times 106$, which reflects that the reaction is almost done (more than 99.9% complete). Regarding the above equilibria, the undissociated ion-pair solubilities in water (i.e., the intrinsic solubility) were omitted as they only have a negligible contribution to the total solubility.

**Analytical applications**

By the standard addition method, DLX was determined potentiometrically utilizing the investigated electrode.$^{[14]}$ Small increments of a standard DLX solution $1.0 \times 10^2$ M in standard addition method were added to 50 mL aliquot samples of various drug concentrations. The potential reading variation at the same temperature 25°C has been documented for each one, and consequently, used to calculate the concentration of the drug sample solution.

DLX formulations analysis (Cymbalta, 60 mg DLX/capsules and Yentreve, 20 mg DLX/capsules), 10 capsules were
accurately weighed and grinded; then, the essential amount was dissolved in 30 mL d. Water and filtered poured in a 50 mL measuring flask. The residue was washed 3 times with dd. Water, and adjusted the pH to be 5 by 0.1 M acetate buffer, and diluted to the mark with water. Then, measuring flask contents were poured into a 100 mL beaker, and the standard addition technique was applied as styled previously.

In Table 3, both recovery and relative standard deviation values were summarized. No interference from the excipients used in the capsules formulations was indicated.

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**REFERENCES**


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