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Quantitative Determination of Duloxetine Hydrochloride in Pharmaceuticals and Urine Using Prepared Ion Selective Membrane Electrode

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A duloxetine ion selective membrane electrode is prepared. The electrode incorporates PVC membrane with duloxetine-silicomolybdate (DLX-SMA) ion pair complex with dioctylphthalate (DOP) as a plasticizer. The influence of membrane composition on the electrode response was studied. The electrode showed a fast, stable and Nernstian response over a wide duloxetine concentration range (1.0×10^{-5} to 1.0×10^{-2} M) with a slope of 59.40 mV dec^{-1} of concentration, a wide working pH range (4.3–8.4) and a fast response time (< 15 s). The electrode showed good selectivity towards duloxetine with respect to some metal ions, sugars and amino acids. The electrode has been applied to the determination of duloxetine hydrochloride in different pharmaceutical preparations and in urine.

Keywords: Duloxetine hydrochloride (DLX), Ion selective electrodes, Potentiometric determination, Pharmaceutical preparations.

1. INTRODUCTION

Duloxetine is the most recent serotonin and norepinephrine reuptake inhibitor (SSNRI) drug introduced for the therapy of depression[1]. Duloxetine HCl (DLX), Fig.1 is Chemically, 2(+)-(S)-N-methyl- (gamma) - (1-naphthyloxy)-2 thiophenepropylamine hydrochloride. A new dosing type duloxetine enteric-coated capsules, has been developed successfully, Administered in the form of capsules containing 20, 30 or 60 mg of DLX, the usual dose for all the approved indications is 60 $mgday^{-1}$, although a 40 mg day^{-1} initial treatment is recommended for the therapy of major depressive disorder. After oral administration, the drug is well absorbed, protein binding is relevant (96%) and the

mean elimination half-life is 12 h [2]. A review of the literature revealed that several analytical methods have been described for the determination of duloxetine in pharmaceuticals including UV spectrophotometric[3], spectrofluorometric[4], high performance thin layer chromatography [5] and Liquid chromatographic [6]. A few methods in literature were reported for the determination of duloxetine in biological fluids [7-9]. Ion-selective electrodes have been increasingly used for quantitative measurement of drugs. Potentiometric methods based on this technique are simple, rapid, low cost, low detection limit, good accuracy, wide concentration range, applicability to coloured and turbid solutions and offer enough selectivity towards the drugs in the presence of various pharmaceutical excipients [10, 11].The present investigation describes a simple, rapid and selective duloxetine membrane electrode. The electrode is based on the incorporation of duloxetine-silicomolybdate [DLX-SMA] ion pair in poly (vinyl chloride) (PVC) membranes plasticized with dioctylphthalate (DOP). The prepared electrode has been used for the determination of the duloxetine pharmaceutical formulations without any prior separation and humane urine sample. The effects of membranes compositions, response time, selectivity and other factors have been investigated on electrodes performance are described.

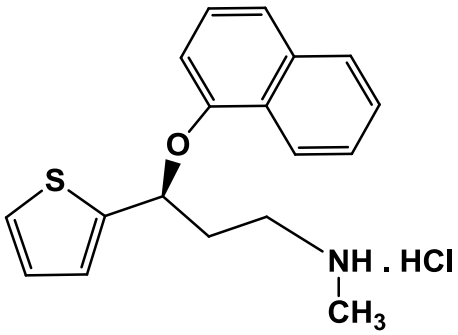

Figure 1. Chemical structure of duloxetine HCl.

2. EXPERIMENTAL

2.2. Apparatus and Reagents

Potentiometric measurements were carried out at 25±0.1^{o}C on a digital pH/millivoltmeter (Jenway, Model 3510). A (WTW) packed saturated calomel electrode (SCE) was used as an external reference electrode. The electrochemical system may be represented as follows:

Ag/ AgCl /internal solution/PVC membrane/ test solution / SCE (sat. KCl).

All chemicals used in this study were of the highest purity available and were used without any further purification. Doubly distilled deionized water was used throughout. Duloxetine HCl (DLX) was purchased from jai radhe sales (India).The pharmaceutical preparations (capsules) containing

duloxetine HCl (Cymbalta®,60 mg DLX/capsules and Yentreve®, 20 mg DLX/capsules) were purchased from local pharmacy. Membrane components silicomolybdic acid (SMA) $H_4SiO_4.12MoO_3.H_2O$ and Dioctylphthalate (DOP) $C_{24}H_{38}O_4$ were obtained from Sigma-Aldrich. High molecular weight poly(vinyl chloride) (PVC), used as the electrode membrane material, freshly distilled tetrahydrofuran (THF), used as a solvent for the membrane components, were obtained from Fluka.

A stock duloxetine hydrochloride solutions (1.0×10^{-2} M) was prepared by dissolving the accurately weighed amount in doubly distilled water. Working solutions of the drug (1.0×10^{-7} to 1×10^{-3} M) were prepared by suitable dilution from the stock solution with water while keeping pH constant at a value of 5.0 by 0.1M acetate buffer. The stock solution and the dilutions were kept in dark bottles in the refrigerator.

To investigate the selectivity of the proposed electrode towards inorganic cations, amino acids and sugars, 1.0×10^{-2} M solution of each of the following ions were prepared : Na^+, NH_4^+, Cu^{2+}, Co^{2+} and Cr^{3+}. Also 1.0×10^{-2} M solution of glucose, histidine and cysteine were prepared.

2.2. Preparation of DLX-SMA ion- pair complex

Duloxetine solution 1.0×10^{-2} M was mixed with an equal volume 1.0×10^{-2} M silico molybdic acid (SMA) solution 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. Elemental analyses were carried out to study the formation DLX-SMA ion- pair complex. The agreement between calculated and found values was very good confirming the postulated stoichiometry; the 4:1 (DLX-SMA) molar ratio stoichiometry.

2.3. Electrode fabrication

The general procedure to prepare the PVC membrane was as follow: different amounts of the ion-pair along with appropriate amounts of PVC, plasticizer and additive were dissolved in tetrahydrofuran (THF), Table1, and the solution was mixed well. The resulting mixture was transferred into a glass dish of 5 cm diameter. The solvent was evaporated slowly until an oily concentrated mixture was obtained (about 2 days). The thickness of the membrane was about 0.2 mm.

In each case, prepared membrane and glued using PVC-THF paste to the end of a glass tube (17 mm in diameter).

The electrode body was then filled with a mixture containing equal volumes of 1.0×10^{-3} M duloxetine HCl and 1.0×10^{-1} M NaCl (as internal reference solution) in which the Ag/AgCl reference electrode was dipped.

The electrode was finally conditioned for 3*h* by soaking in a 1.0×10^{-3} M duloxetine HCl solution. When not in use the sensor was kept stored in a refrigerator, showed a good preservation of the slope values and response properties extending to several months.

2.4. Construction of the calibration graphs

The electrodes were calibrated by separately transferring 50 mL aliquots of solutions (1×10^{-7} to 1×10^{-2} M) of DLX into a series of 100 mL beakers, while keeping pH constant at a value of 5.0. The Prepared electrode in conjunction with the reference electrode were immersed in the above test solutions and allowed to equilibrate while stirring. The potential was recorded after stabilizing to ± 1 mV.

The electrode was washed with double distilled water and dried between measurements. The electrode was washed with double distilled water and dried between measurements. The electrode potential was plotted versus negative logarithmic concentration of DLX (P_{DLX}), Slopes of the resulting calibration curves were calculated.

2.5. Selectivity of the electrode

The selectivity coefficient values for the proposed electrode were evaluated by the modified form of the Matched Potential Method (MPM).[12] According to MPM, the selectivity coefficient is defined as the activity ratio of the primary ion and interfering ion that gives the same potential change in a reference solution.

Thus, the change in potential upon changing the primary ion activity is measured. Then the interfering ion is added to an identical reference solution until the same potential change is obtained. The selectivity coefficient, $K_{A,B}^{pot.}$ is determined as

$$K_{A,B}^{pot.} = \frac{\Delta a_A}{a_B} = \frac{a'_A - a_A}{a_B}$$

In this method, the specified activity of the primary ion ($a_A = 1.0\times10^{-3}$M of drug) is added to reference solution ($a'_A = 1.0 \times 10^{-4}$M) of drug, and the potential is measured.

In a separate experiment interfering ion concentrations ($a_B = 1.0\times10^{-2}$M) were added to an identical reference solution, until the measured potential matched that obtained before the addition of the primary ions. The selectivity coefficients were then given by the resulting primary to interfering ion activity ratio.

2.6. Response time

The response time is the time which elapses between the instant when an ion-selective electrode and a reference electrode (ISE cell) are brought into contact with a sample solution. The response time were obtained from the dynamic potential response corresponding to duloxetine concentration steps between 1.0×10^{-5} M and 1.0×10^{-3}M

2.7. Effect of pH on the electrode potential

The effect of pH of the Duloxetine HCl solutions (1.0×10^{-3}, 1.0×10^{-4} and 1.0×10^{-5} M DLX) on the electrode potential was investigated. Aliquots of duloxetine HCl drug (50 mL) were transferred to 100 mL beaker and the tested ion-selective electrode in conjugation with a saturated calomel electrode and a combined glass electrode were immersed in the same solution. The solutions were acidified by the addition of very small volumes of 0.1 M HCl acid then the pH value was increased gradually using NaOH (0.1 or 1.0 M) for each pH value, the potential readings corresponding to different pH values were recorded and thus the potential-pH curves were plotted.

2.8. Potentiometric Determination of DLX

The standard addition method [13] was applied, in which small increments of the standard solution 1.0×10^{-2} M of duloxetine HCl were added to 50 mL aliquot samples of various concentrations from pure drug . The change in potential reading was recorded for each increment at a constant temperature of 25±1˚C and used to calculate the concentration

$$C_x = C_s\left(\frac{V_s}{V_s+V_s}\right)\left(10^{n\left(\Delta E/S\right)}-\frac{V_x}{V_x+V_s}\right)^{-1}$$

where C_x and V_x are the concentration and volume of the unknown, respectively, C_s and V_s are the concentration and volume of the standard, respectively, S is the slope of the calibration graph, and ΔE is the change in potential due to the addition of the standards.

2.9. Application to pharmaceutical

The contents of 10 capsules were accurately weighed and powdered in a mortar; then, the required amount from the capsule 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 5.0, 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 subjected to potentiometric determination of DLX.

2.10. Application to spiked urine samples

Urine samples containing different duloxetine concentrations (1.0×10^{-5} to 1.0×10^{-3}M) were prepared by adding known amounts of duloxetine to 25 mL aliquots of blank urine sample, the duloxetine selective and reference electrodes were immersed and the duloxetine concentration was determined by direct potentiometry using the standard additions technique.

2.11. Potentiometric titration of DLX

An aliquot of DLX (1.0×10^{-3}M – 1.0×10^{-5} M) was transferred into a 100 mL beaker, then titrated against a 1.0×10^{-3} M SMA using the investigated electrodes as indicator electrodes. The same method was applied for the determination of DLX in the pharmaceutical preparations and urine.

3. RESULTS AND DISCUSSION

3.1. Composition of the membranes

Five membrane compositions were prepared by varying the percentages of the ion pair, while keeping the percentages of the PVC and the plasticizer equal 1:1 (table 1) The results showed that the electrode made of membrane with 10% DLX-SMA ion pair exhibits the best performance characteristics [slope 59.40 mV concentration decade^{-1} at 25±0.1 °C , the highest value of the correlation coefficient, usable concentration range (1.0×10^{-5} to 1.0×10^{-2} M and detection limit 6.31×10^{-6} M DLX]. A typical calibration plot for electrode is shown in Fig. 2. The limit of detection, as determined from the intersection of the two extrapolated segments of the calibration graph.

Table 1. Composition of different DLX-SMA membranes and slopes of the corresponding calibration graphs at 25.0 °C.

Composition % (w/w)			Slope	Correlation	RSD[a]
Ion Pair	PVC	DOP	mV/decade	Coefficient	(%)
1.00	49.50	49.50	52.40	99.30×10^{-2}	0.02
3.00	48.50	48.50	55.60	99.00×10^{-2}	0.06
5.00	47.50	47.50	54.77	99.10×10^{-2}	0.08
7.00	46.50	46.50	52.98	99.60×10^{-2}	0.03
10.00[b]	45.00	45.00	59.40	99.70×10^{-2}	0.04

[a]Relative standard deviation(three determinations),
[b]Optimum composition.

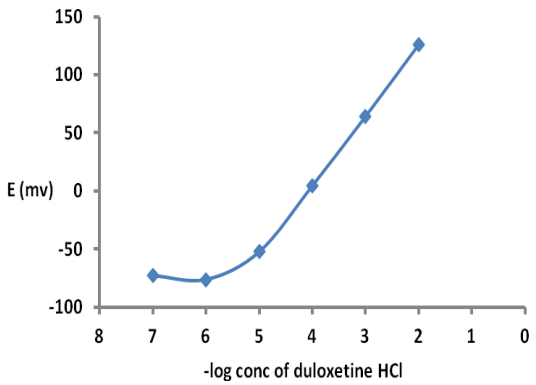

Figure 2. Typical calibration graph of duloxetine-silicomolybdate–PVC membrane electrode

3.1.1. Effect of Soaking and Lifetime of the Electrodes

Freshly prepared electrode must be soaked to activate the surface of the membrane to form an infinitesimally thin gel layer at which ion exchange occurs. This preconditioning process requires different times depending on diffusion and equilibration at the electrode test solution interface; a fast establishment of equilibrium is certainly a condition for a fast potential response. [14]

The effect of soaking time on the performance of the electrode was studied by measuring the slope of the calibration graphs for variable intervals of time starting from 0.5 h reaching to 24 h. The slope of the calibration graph for the DLX-SMA electrode remained near Nernstian for about 5*h* and was found to be 55.1 mV/concentration decade, before decreasing gradually to reach about 49.3 mV/concentration decade after 10 h. The optimum soaking time was found 0.5 *h* at pH 5.0, which the slope of the calibration curve was 59.1 mV per pDLX decade, at 25±0.1 for electrode. Soaking for longer than 10 h is not recommended to avoid leaching, though very little, of the electro active species into the bathing solution. The decrease in the efficiency of the electrode was due to a diminished DLX^+ ion exchange rate on the membrane gel layer test solution interface, which was responsible for the membrane potential. The electrodes should be stored in a refrigerator when not in use.

The electrode lifetime was obtained by periodically performing calibration graphs for DLX and calculating the response slopes. The duloxetine selective electrode worked for at least 30 – 40 days, during which time no appreciable change in the calibration characteristics or response time was observed, while at higher times the slopes of the electrode started to decrease.

3.1.2. Selectivity of the electrode

The selectivity behavior is obviously one of the most important characteristics of an ion-selective electrode, determining whether a reliable measurement can be obtained by the electrode proposed and the selectivity coefficient of an electrode is defined by its relative response for the primary ion over the other ions present in the solution.

The selectivity of an ion-pair based membrane electrode depends on the physico-chemical characteristics of the ion-exchange process at the membrane. For example, sample solution interface, mobility of the respective ions in the matrix of the membrane and on the hydrophobic interactions between the primary ions and the PVC membrane[15].

The selectivity of the duloxetine membrane electrode is related to the free energy of transfer of the duloxetine cation between aqueous and membrane phases. the potential response was investigated in the presence of many common inorganic cations, sugars, and amino acids which are frequently present in biological fluids and pharmaceutical preparations using the matched potential method (MPM)[12] .

The resulting values are listed in Table 2. As is evident, the results of the selectivity coefficients are smaller than (1.0) which means that the proposed electrode is highly selective toward DLX .The inorganic cations did not interfere owing to the differences in ionic size and consequently in their mobilities and permeabilites as compared with DLX^+. In the case of glucose and histidine, the high selectivity may be attributed to the difference in polarity and to the lipophilic nature of their

molecules relative to DLX cation. The mechanism of the selectivity is mainly based on the electrostatic environment and its dependant on how good the fit between the locations of the lipophilic sites in the two competing species in the bathing solution side and those present in the receptor of the ion exchanger[16]

Table 2. Selectivity coefficients $K^{pot}_{DLX^+,B}$ for the proposed electrode at 25.0℃

Interfering ions (B)	$K^{pot}_{DLX^+,B}$	Interfering ions (B)	$K^{pot}_{DLX^+,B}$
Na^+	4.94×10^{-2}	Cr^{3+}	6.50×10^{-2}
NH_4^+	3.65×10^{-2}	Glucose	-
Co^{2+}	13.6×10^{-3}	Histidine	-
Cu^{2+}	1.60×10^{-3}	Cysteine	8.00×10^{-3}

- Negligible interference.

3.1.3. Response time

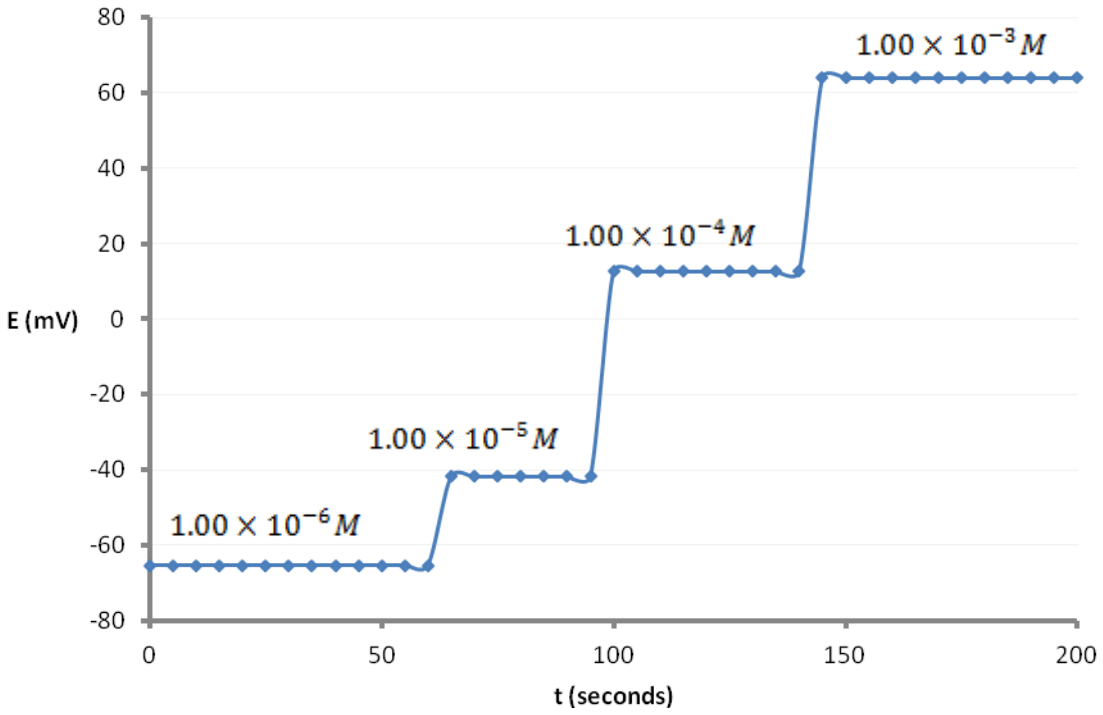

Figure 4.The potentiometric dynamic response time of the DLX-SMA membrane electrode.

The response time is defined as the time between the addition of analyte to the sample solution and the time when a steady-state potential with less than 0.1 mV/min change has been achieved. The dynamic response time [17] of proposed electrode was tested by measuring the time required to achieve a steady-state potential (within ±1 mV) after successive immersions of the electrode in a series

of drug solutions, each having a 10-fold increase in concentration (from 1.0×10^{-3} to 1.0×10^{-6} M). The electrode yielded steady potential within 15 s. The potential readings stayed constant, to within ±1 mV for at 40 s, Fig. 2. This is most probably due to the fast exchange kinetics of association–dissociation of duloxetine ion with the ionophores at the solution–membrane interface.

3.1.4. Effect of pH

The influence of pH on the response of the prepared DLX electrodes for (1.00×10^{-5}, 1.00×10^{-4}, 1.00×10^{-3} M) Duloxetine HCl solutions, was evaluated over a pH range of 2.0 to 12.0, and the results show that in the pH range 4.30–8.35, the potential had a negligible change with changing pH, and thus in this range the electrodes can safely be used for duloxetine HCl determination. At pH less than 4.30, potential displayed by the electrode increased due to increasing the acid nature of the drug or interferences by hydrogen ion. At pH higher than 8.35 , the potential displayed by the electrode sharply decreases due to formation of non-protonated duloxetine. The *pKa* value of duloxetine is reported to be 9.34. However, below and above this pH range, the potential response changes drastically [18, 19] . And the potential-pH curves for three duloxetine HCl concentrations were constructed as shown in Fig. 4.

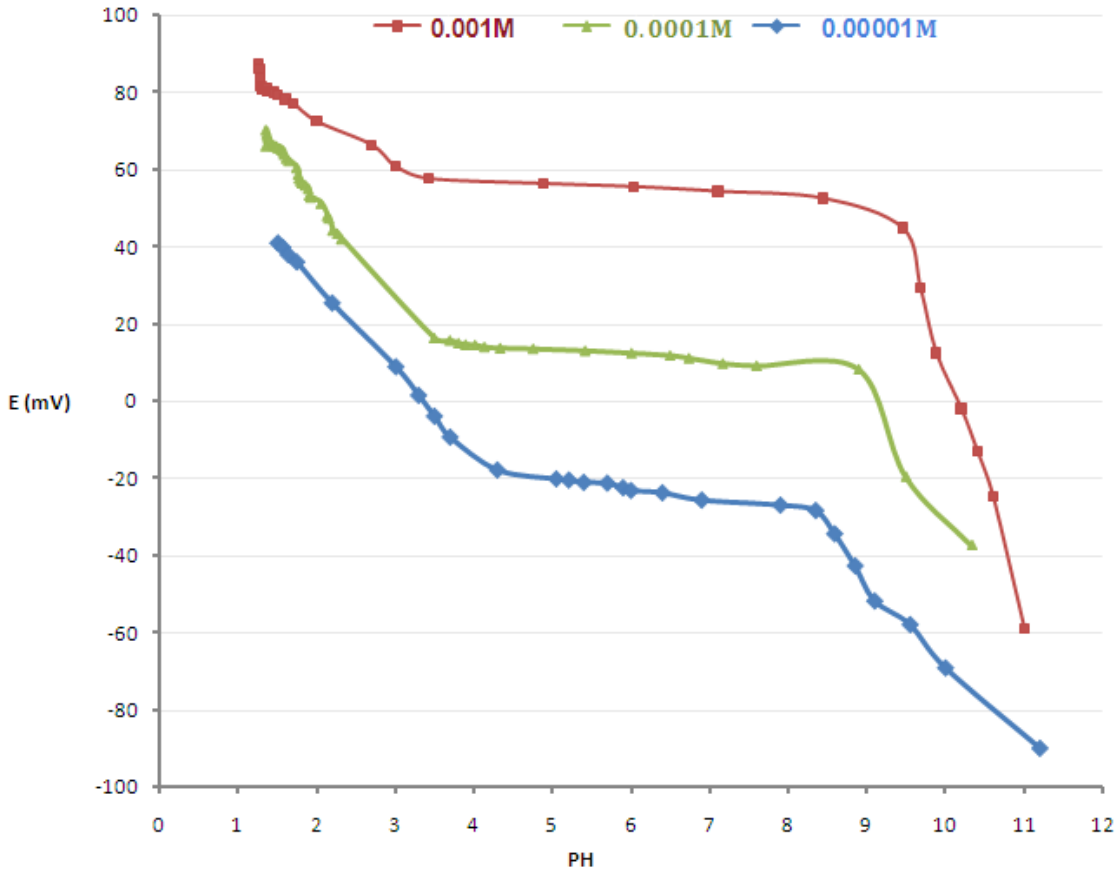

Figure 4. Effect of pH on electrode potential/mV duloxetine- silicomolybdate–PVC membrane electrode.

4. ANALYTICAL APPLICATIONS.

Table 3. Application of proposed electrode for the determination of duloxetine hydrochloride in pure solutions.

	Proposed methods					Reference method
		Standard addition		Potentiometric titration		
	Amount taken (M)	Recovery %	RSD*	Recovery %	RSD*	
	1×10^{-5}	100.90	1.50	99.70	0.77	100.26 ± 0.899
	1×10^{-4}	101.67	1.60	100.50	0.32	
	1×10^{-3}	101.19	1.20	101.10	0.20	
Mean		101.25	1.40	100.58	0.43	
Mean ± SD		101.25 ± 1.4		100.58± 0.43		
F value (19.9) [a]		2.43		4.37		
Student *t* test (4.303) [b]		1.24		.049		

***** RSD (three determination)
[a] Theoretical value of *F*-value.
[b] Theoretical value of *t*-test.

Table 4. Application of proposed electrode for the determination of duloxetine hydrochloride in pharmaceutical preparations.

	Proposed methods					Reference method
		Standard addition		Potentiometric titration		
	Amount taken (M)	Recovery %	RSD*	Recovery %	RSD*	
Cymbalta® Capsules (60mg DLX/capsules)	1×10^{-5}	102.80	1.70	101.10	0.55	99.5 ± 1.053
	1×10^{-4}	101.27	0.77	100.06	1.39	
	1×10^{-3}	101.90	0.84	100.55	0.79	
Mean		101.99	1.10	100.57	0.91	
Mean ± SD		101.99± 1.1		100.57± 0.91		
F value (19.9) [a]		1.09		1.34		
Student *t* test (4.303) [b]		3.15		1.41		
Yentreve® Capsules (20mg DLX/capsules)	1×10^{-5}	99.5	0.69	101.5	0.37	99.5 ± 1.053
	1×10^{-4}	101.1	0.88	100.8	1.42	
	1×10^{-3}	99.8	1.02	100.2	0.51	
Mean		100.13	0.86	100.83	0.77	
Mean ± SD		100.13± 0.86		100.83± 0.77		
F value (19.9) [a]		1.49		1.87		
Student *t* test (4.303) [b]		0.83		1.81		

***** RSD (three determination)
[a] Theoretical value of *F*-value.
[b] Theoretical value of *t*-test.

Table 5. Application of proposed electrode for the determination of duloxetine hydrochloride in Urine.

Sample		Potentiometric titration		Standard addition	
	Amount taken (M)	Recovery %	RSD*	Recovery %	RSD*
Human urine	1 x10^{-5}	98.9	0.52	99.2	0.71
	1 x10^{-4}	100.02	0.39	100.5	0.45
	1 x10^{-3}	99.1	0.81	100.4	0.24

***** RSD (three determination)

The duloxetine selective electrode was satisfactorily applied to the potentiometric determination of duloxetine in pure solution, pharmaceutical preparations and in the urine by the standard additions method and potentiometric titration.The result are shown in Tables 3,4 and 5. These results revealed that the duloxetine can be accurately determined using the proposed electrode.

The results of the pure solutions and the pharmaceutical preparations were compared (Tables 3 and 4) with the reference method [20] at 95% confidence level. The results are in good agreement with those obtained from the reference method. Student's *t* test and *F* test were applied [21] . The results showed that the calculated *t*- and *F* values did not exceed the theoretical values.

5. CONCLUSION

The proposed electrode is sufficiently simple and selective for the determination of DLX in pure form, pharmaceutical preparations and in urine. The use of the proposed electrode offers the advantage of fast response, elimination of drug pre-treatment or separation steps and accuracy over wide concentration range. They can therefore be used for the routine analysis of the drug in quality control laboratories.

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