Research Article

A New Atomoxetine Hydrochloride Selective Electrode and Its Pharmaceuticals Application

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ABSTRACT

The fabrication and electrochemical response characteristics of a poly(vinyl chloride) (PVC) membrane selective electrode for the determination of atomoxetine HCl (ATO) are described. The electrode incorporates PVC membrane with atomoxetine-tetraphenyl borate (ATO-TPB) 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 atomoxetine concentration range ($1.0x10^{-5}$M-$1x10^{-2}$ M) with a slope of 58.0 mV dec^{-1} of concentration, a detection limit of $2.2x10^{-5}$M, and was found to be very selective, and usable within the pH range 3-7.8. These characteristics of the electrode enable it to be used successfully for the determination of atomoxetine hydrochloride in pure form and in pharmaceutical preparations.

Keywords: Atomoxetine hydrochloride (ATO), Ion selective electrodes, Pharmaceuticals application.

INTRODUCTION

Atomoxetine hydrochloride (ATO) is the first non-stimulant choice drug for symptomatic treatment of attention-deficit hyperactivity disorder (ADHD). It is a selective norepinephrine reuptake inhibitor (NRI). It is chemically known as (*R*)-*N*-methyl-3-phenyl-3-(o-tolyloxy) propan-1-amine hydrochloride base (1:1)[1,2]. Atomoxetine hydrochloride was determined by other methods mainly HPLC[3-8], LC-MS-MS[9], HPTLC[10], Chemiluminescence[11] and UV[12-13] have been reported for its determination in plasma and capsule dosage forms. However, some of these methods have less selectivity and/or need expensive equipment. Ion selective electrodes have found widespread applications in pharmaceutical analysis. This is mainly due to simple design, low cost, adequate selectivity, low detection limit, high accuracy, wide linear dynamic range and applicability of the selective electrodes to colored and turbid solutions. The chemical structure of atomoxetine hydrochloride was depicted in Fig. 1.

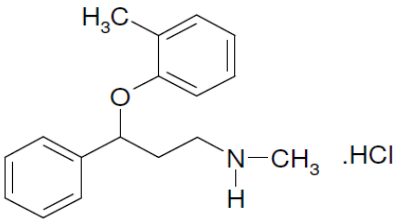

Figure 1: Chemical Structure of Atomoxetine Hydrochloride.

The aim of the present work, describes a sensitive and reasonably selective poly (vinyl chloride) membrane electrode based on the use of atomoxetine-tetraphenyl borate as a novel electroactive material. The electrode exhibit useful analytical characteristics for the direct determination of atomoxetine HCl in pure form and in pharmaceutical preparations.

MATERIALS AND METHODS

Materials and reagents

All chemicals were of analytical grade, and double distilled water was used throughout the experiments. Pure grade atomoxetine HCl (ATM), Poly (vinyl chloride) (PVC) of high relative molecular weight and tetraphenyl borate (TPB) were obtained from Sigma-Aldrich. Dioctylphthalate (DOP) was purchased from Merck. Tetrahydrofuran (THF) was obtained from (Fluka). The pharmaceutical preparations containing atomoxetine HCl (Axepta®, 40mg/tablet and Attentrol®, 25mg/capsule) was purchased from local drug stores. Stock duloxetine hydrochloride solution (1.0×10^{-2} M) was prepared daily by dissolving an appropriate amount of the drug in double distilled water. More dilute solutions were prepared by appropriate dilutions.

Preparation of ATO-TPB ion pair

The ion-pair was prepared by mixing 50 ml aliquots of 1.0×10^{-2} M atomoxetine HCl and sodium tetraphenyl borate. 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 two days.

Construction of electrode

For preparation of PVC membrane, different amounts of ion-pair along with appropriate amounts of PVC, plasticizer and additive were dissolved in tetrahydrofuran (THF), and the solution was mixed well into a glass dish of

5 cm diameter. Then THF was evaporated slowly until an oily concentrated mixture was obtained. A plastic tube (about 3 mm o.d.) was dipped into the mixture for about 10 s so a transparent membrane of about 0.3 mm in thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for about 10 h. Afterwards, the tube was filled with an internal filling solution (1.0×10^{-3} M of atomoxetine. HCl solution). The electrode was finally conditioned for 24 h by soaking in the same solution[14-17].

Apparatus

Potentiometric measurements were carried out at 25±0.1°C on a digital pH/millivoltmeter (Jenway, Model 3510). A (WTW) packed saturated calomel electrode (SCE) was used as an external reference electrode. Jenway 4330 conductivity meter was used for conductance measurements.

emf Measurements

Following cell assembly for emf (electromotive force) measurements were used:

Ag-AgCl// internal solution / membrane/ sample solution || Ag-AgCl, KC1 (satd.)

Electrode calibration

Ten ml aliquots of 1.0×10^{-7} M to 1.0×10^{-2} M standard atomoxetine HCl solution were transferred into 50 ml beaker and the sensor in conjunction with Ag/AgCl reference electrode were immersed in the solution. The electrode was washed with double distilled water and dried between measurements. The electrode potential was plotted versus negative logarithmic concentration of ATO, Slopes of the resulting calibration curves were calculated. The slope of the calibration graph was calculated using Nernestain equation:

$$E = E^{\circ}_{ISE} + 2.303 = \frac{RT}{ZF} log[ATO] \qquad \text{eq. (1)}$$

Selectivity of the electrode

Selectivity coefficients were determined by the separate solution method[18], in which the following equation was applied.

$$\log K^{pot.}_{ATO,B^{z+}} = \frac{(E_2 - E_1)}{S} + \log[ATO] - \log\left[B^{z+}\right]^{1/z+} \qquad \text{eq. (2)}$$

where E_1 and E_2 are the electrode potentials of solutions of the ATO and interfering cation, B^{z+}, respectively (both of the same concentration) and S is the slope of the calibration graph. The selectivity of the electrode towards sugars, amino acids, and certain cations was studied.

Conductimetric determination of ATO

A volume containing 9-100 mg of ATO was transferred to a 50.0 ml volumetric flask and made up to the mark with double distilled water. The contents of the volumetric flask were transferred to a beaker, and the conductivity cell was immersed. Then 10^{-2} M NaTPB was added, and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring. The conductance reading after each addition was corrected for dilution[19] by means of the following equation, assuming that conductivity was a linear function of dilution:

$$\Omega_{corr} = \Omega_{obs}\left[\nu_1 + \nu_2 / \nu_1\right] \qquad \text{eq. (3)}$$

where Ω is electrolytic conductivity, ν_1 is the initial volume and ν_2 is the volume of the added reagent (corr.= corrected and obs.= observed). A graph of corrected conductivity *vs.* volume of the added titrant was constructed, and the end point was determined.

Potentiometric determination of ATO

Atomoxetine hydrochloride was determined potentiometrically using the investigated electrode by the standard addition method[20]. In the standard addition method, Small increments of a standard atomoxetine hydrochloride 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 ±1°C was recorded for each increment and used to calculate the concentration of the drug sample solution using the following equation:

$$C_x = C_s\left(\frac{V_s}{V_s + V_s}\right)\left(10^{n(\Delta E/S)} - \frac{V_x}{V_x + V_s}\right)^{-1} \qquad \text{eq. (4)}$$

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.

Determination of ATO in pharmaceutical preparations

Sample preparation of ATO in tablet dosage form

The contents of ten tablets were accurately weighed and powdered in a mortar; then, the required amount from the tablet powder was dissolved in about 30.0 ml distilled water and filtered in a 50.0 ml measuring flask. The residue was washed three times with double distilled water, and the volume was completed to the mark with distilled water. The contents of the measuring flask were transferred in to a 100.0 ml beaker and subjected to potentiometric determination of ATO.

Sample preparation of ATO in capsule dosage form

Twenty capsules were opened. Powder was taken and weighed. Sample solution was prepared as per the procedure described for sample preparation of atomoxetine hydrochloride h tablet.

Potentiometric titration of ATO

An aliquot of ATO 1.0×10^{-3} M was transferred into a 100 mL beaker, then titrated against a 1.0×10^{-3} M TPB using

the investigated electrodes as indicator electrodes. The same method was applied for the determination of ATO in the pharmaceutical preparations.

RESULTS AND DISCUSSION

A number of characteristics are required for a sensor to be considered as a suitable sensor for determination of a substance, including selectivity, response time, response range, and sensitivity.

Influence of membrane composition

The behavior of ion-selective electrodes with solid-state membranes depends on the composition of membrane material used and the condition of the membrane surface in contact with the solution in which the activity of sensed ion is monitored. Preliminary experiments were carried out to obtain an optimum membrane composition. The optimized membrane was used to test the performance of the membrane characteristics. Six 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 10.0% ATO-TPB ion pair exhibits the best performance characteristics [slope 58.0 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 2.2×10^{-5} M ATO)]. The limit of detection, as determined from the intersection of the two extrapolated segments of the calibration graph. A typical calibration plot for electrode is shown in Fig. 2.

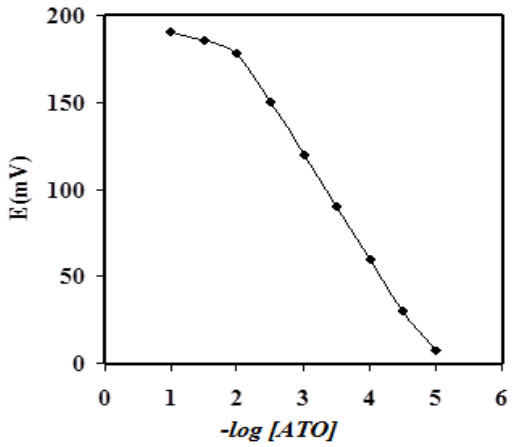

Figure 2: Typical calibration graph of ATO-selective electrode.

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[21]. For this purpose the electrode was soaked in 1×10^{-3} M of drug solution and the calibration graphs (-log[ATO] *vs.* *E*elec, mV) were plotted after 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 and 6 h. The optimum soaking time was found to be 0.5-3 hr, at which the slopes of the calibration curves were 54.0-58.0 mV per concentration decade, at 25 °C. Soaking for longer than 8 h is not recommended to avoid leaching, though very little, of the electroactive species into the bathing solution. The electrode should be kept dry in an opaque closed vessel and stored in a refrigerator while not in use. The reproducibility of five repeated measurements on the same solution was ± 1 mV. 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.

Response time

The dynamic response time is an important factor with selective electrodes. The average time required for the ATO selective electrode to reach a value of ±1 mV from the final equilibrium potential in the same day after successive immersion in different ATO concentration solutions (from 1.0×10^{-3} to 1.0×10^{-6} M) were measured. The static response time for the proposed sensor was less than 15s over all linear concentration ranges. In addition, the potentials displayed by the electrode in the linear concentration range of ATO in the same day do not vary by more than ±0.5 mV. The stability of the potential reading for the ATO-based electrodes is within ±2 mV during the lifetime (40 days) of the electrodes.

Effect of pH

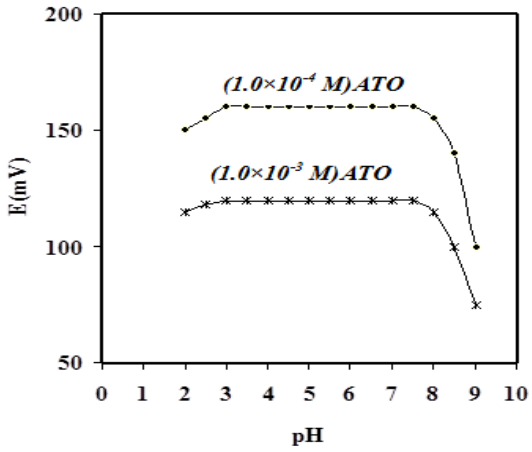

Figure 3: Effect of pH on the potential response of ATO-selective electrode

The pH dependence of the electrode potential was studied for the two concentrations of (1.0×10^{-3} M and 1.0×10^{-4} M) ATO over the pH range of 2–9. The pH was adjusted with NaOH or HCl solution (0.5 M). The potential was recorded and thus the potential-pH curves for two ATO concentrations were constructed as shown in Fig.3, indicates that the pH has a negligible effect within the pH range of 3.0-7.8. In this range the electrode can be safely used for ATO determination. The decrease in the potential reading with pH above the mentioned range can

be attributed to the formation of the free base of the drug and disappearance of the protonated species[22].

Selectivity of the electrode

The influence of some possible interfering inorganic cations, sugars and amino acids on the ATO-electrode was investigated. The resulting selectivity coefficients are summarized in **Table 2**. The selectivity coefficients revealed that the proposed electrode are highly selective. The inorganic cations did not interfere due to the differences in their ionic size, mobility and permeability. Also, the smaller the energy of hydration of the cation facilitated a greater response of the membrane. In the case of sugar and amino acid, the high selectivity is mainly attributed to the difference in polarity and lipophilic nature of their molecules relative to atomoxetine hydrochloride.

Conductimetric Studies of Pure Solution of Drug

Conductance measurements have been used successfully in quantitative conductimetric titration of system in which the conductance of the solution varies before and after the equivalence point. The system under investigation showed a regular rise in conductance up to the equivalence point where a sudden change in the slope occurred. The results of the drug determination (**Table 3**) showed that good recoveries and low standard deviations were obtained. The optimum concentration ranges for ATO determination were 10.73–98.22 mg with mean recovery value of 99.78 with coefficients of variation of 0.16–0.40, at which sharp inflections and stable conductance readings were obtained.

Table 1: Composition of different ATO-TPB membranes and slopes of the corresponding calibration graphs at 25.0 °C.

Composition % (w/w)			Slope	Linear range	Detection limit	RSD[a] (%)
Ion Pair	DBP	PVC	(mV\decade)			
1.0%	49.5%	49.5%	45.0	1.3×10^{-4}–1.0×10^{-2}	8.2×10^{-5}	1.21
5.0%	47.5%	47.5%	49.0	2.4×10^{-4}–1.0×10^{-2}	7.2×10^{-5}	1.34
8.0%	45.0%	45.0%	52.0	7.5×10^{-5}-1.0×10^{-2}	3.9×10^{-5}	0.88
10.0%**	49.5%	49.5%	58.0	1.0×10^{-5}–1.0×10^{-2}	2.2×10^{-5}	0.76
13.0%	43.5%	43.5%	54.0	5.3×10^{-4}–1.0×10^{-2}	2.40×10^{-5}	0.31
15.0%	42.50%	42.50%	43.0	4.4×10^{-4}–1.0×10^{-2}	9.4×10^{-5}	1.40

[a]Relative standard deviation (four preparations); **Optimum composition.

Table 2: Selectivity coefficients of the ATO-selective electrode calculated by the separate solution method (1×10^{-3} M of both atomoxetine and the interferent) at 25°C.

Interferent	$K^{pot}_{ATO,\ B^{Z+}}$	Interferent	$K^{pot}_{ATO,\ B^{Z+}}$
Na^{+}	3.1×10^{-2}	Glucose	$7.\ 8\times10^{-4}$
NH_4^{+}	9.0×10^{-3}	Lactose	8.2×10^{-3}
Cu^{2+}	4.5×10^{-4}	Starch	1.8×10^{-4}
Ni^{2+}	6.0×10^{-3}	Glycine	2.4×10^{-2}
Co^{2+}	$7.\ 1\times10^{-3}$	Aspargine	3.7×10^{-2}
Mg^{2+}	$4.\ 4\times10^{-3}$	Alanine	1.5×10^{-3}
Cr^{3+}	1.9×10^{-4}	Methonine	6.9×10^{-2}
Al^{3+}	6.8×10^{-2}	Histidine	5.2×10^{-2}
Fe^{3+}	6.4×10^{-3}	Cysteine	8.3×10^{-2}

Table 3: Conductimetric Determination of atomoxetine HCl in pure Solution.

Atomoxetine HCl			
Taken (mg)	Found (mg)	Recovery (%)	R.S.D. (%)
10.73	10.65	99.54	0.40
22.55	22.35	99.87	0.16
51.49	51.32	99.82	0.33
72.73	72.65	99.91	0.26
98.22	97.75	99.78	0.34

Table 4: Determination of atomoxetine HCl in pure form and in pharmaceutical preparations using ATO-selective electrode.

	Pure Solution		pharmaceutical preparations			
			Tablet (Axepta)		Capsule (Attentrol)	
	Standard addition	Potentiometric titration	Standard addition	Potentiometric titration	Standard addition	Potentiometric titration
Taken (M)	1.0×10^{-3}	3.0×10^{-3}	1.0×10^{-3}	3.0×10^{-3}	1.0×10^{-3}	3.0×10^{-3}
	3.0×10^{-3}	5.0×10^{-3}	3.0×10^{-3}	5.0×10^{-3}	3.0×10^{-3}	5.0×10^{-3}
	5.0×10^{-3}	7.0×10^{-3}	5.0×10^{-3}	7.0×10^{-3}	5.0×10^{-3}	7.0×10^{-3}
Recovery (%)	99.40	97.54	98.68	96.54	97.60	96.62
	97.21	99.11	97.55	101.65	98.42	96.22
	98.50	98.20	97.90	98.32	97.50	97.21
R.S.D.** (%)	0.19	0.95	0.97	0.50	0.60	0.12
	1.12	0.73	1.12	0.42	0.52	0.24
	0.56	0.33	0.91	0.88	0.39	0.48

**Relative standard deviation (five determinations)

Analytical Applications

The investigated electrodes were found to be useful in the potentiometric determination of ATO in pure solutions and in the pharmaceutical preparations. The mean recovery and the relative standard deviation values are summarized in Table 4. The data indicated that there was no interference from the excipients used in the formulations of the tablets and capsules.

CONCLUSION

A New atomoxetine Hydrochloride ion-selective electrode based on PVC membrane was constructed and used for determining atomoxetine HCl in pure form, and pharmaceutical preparations. The proposed ion-selective electrode has shown good performance characteristics with time stability up to six weeks. This electrode is sensitive and accurate to be a privilege for applications in atomoxetine HCl determination and its quality control.

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