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All Solid Sate Potentiometric Sensors for the Measurement of Paroxetine in Pharmaceutical Formulation

Farnoush Faridbod[1,2,*], *Nazila Davarkhah*[1], *Sanaz Karamdoust*[1]

[1] Center of Excellence in Electrochemistry, Faculty of Chemistry, University of Tehran, Tehran, Iran
[2] Biosensor Research Center, Endocrinology & Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[*]E-mail: faridbodf@khayam.ut.ac.ir

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One of the selective serotonin reuptake inhibitors (SSRIs) is Paroxetine which is used as an antidepressant compound. A PVC membrane electrode (PME), as a symmetric potentiometric sensor and all solid state polymeric membrane electrode (ASS-PME) as an asymmetric sensor were made and used for determination of Paroxetine in pharmaceutical tablets. The sensing element of two kinds of sensor was an ion-pair compound. The finest membrane was composed of 7% PAX-tetrakis (p-chlorophenyl) borate as sensing element, 59% dibutyl sebacate as a solvent mediator, 30% poly(vinyl chloride) as polymeric matrix, 2% ionic liquid and 2% KpClTPB as an ionic additive. The all solid state electrode is made of a conductive composite of graphite, MWCNTs, and epoxy resin on a copper wire. A thin layer of PVC membrane is then coated on the surface of the new conducting transducer. The Nernstian behavior (slope of 57.8±0.3 mV/decade in case of PME and 58.6±0.3 mV/decade) can be seen in a wide concentration range of 7.5×10^{-6} to 1.0×10^{-1} mol L^{-1} for PME, 8.0×10^{-8} to 1.0×10^{-3} mol L^{-1} for ASSME. Method validation parameters were calculated and can be used in quality control analysis of Paroxetine hydrochloride in pharmaceutical formulations. The sensors were successfully used for measurement of the active ingredient of Paroxetine tablets.

Keywords: Paroxetine, Polymeric membrane, All solid state, Potentiometry, Pharmaceutical formulation

1. INTRODUCTION

Paroxetine, (3s-trans)-3-[(1,3-benzodioxol-5-yl-oxy)methyl]-4-(4-fluorophenyl) piperidine, also known as a trade name, Paxil (PAX) (Fig. 1), is placed in the group of drugs act as potent selective serotonin re-uptake inhibitors (SSRIs) in the central nervous system [1]. They generally act as the antidepressant compounds [2] and safely is prescribed for panic fits, obsessive-compulsive

disorder, posttraumatic stress and social phobia [3]. Due to the significant effects of the antidepressant drugs on human body, their determination is of great importance. Having a sensitive, fast and cheap analysis method for paroxetine determination can be required for studying the presence of paroxetine in pharmaceutical formulations.

Some analytical methods have been used for the analysis of Paroxetine in some pharmaceutical and biological samples such as spectrophotometry [4], spectrofluorimetry [5] high performance liquid chromatography (HPLC) [6], potentiometry [7], and voltammetry [8].

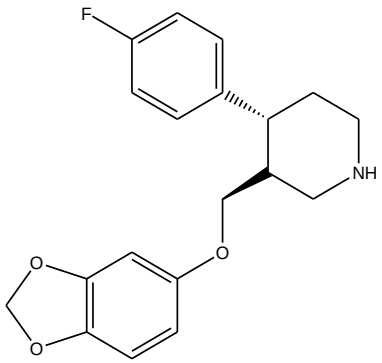
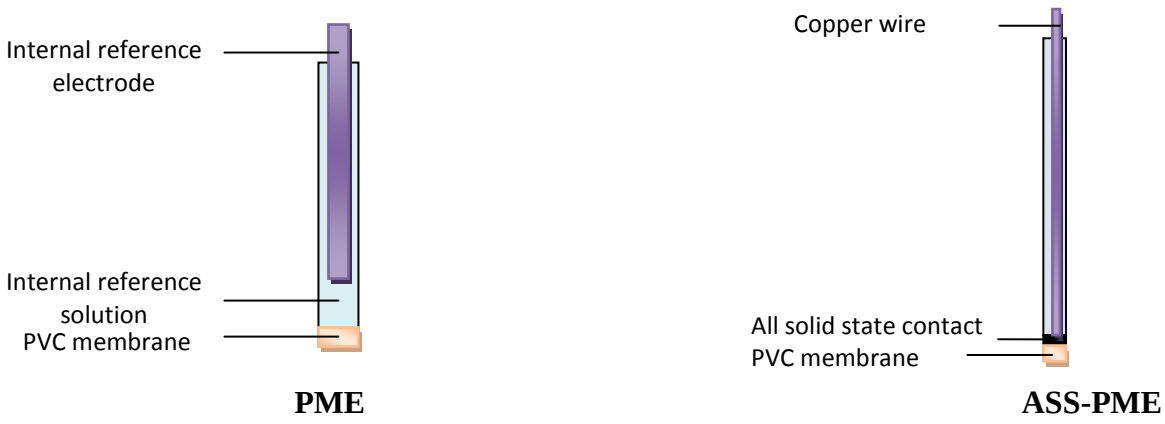


Figure 1. Chemical structure of Paroxetine



Scheme 1. Schematic illustration of PME and ASS-PME as symmetric and asymmetric sensors

Although instrumental analytical techniques have high sensitivity and low detection limits, potentiometric methods also offer some superiorities such as simplicity of the methodology, short time of analysis, wide linear range, and acceptable selectivity. Furthermore, they are inexpensive methods which can be easily portable. Thus, potentiometric sensors are used in determination of the active ingredients of some pharmaceutical formulations [9-13].

Potentiometric ion-selective electrodes (ISEs) are a wide class of electrochemical sensors [14-25]. PVC membrane electrodes (PME), coated wire electrodes (CWE), carbon paste electrodes (CPE), all solid state electrodes (ASS) and field effective transistors (FET) are various kinds of designed ISEs.

These types of ISEs, based on the way which PVC membrane is placed on the transducer, can be divided in to two categories; symmetric and asymmetric electrodes (Scheme 1). In first type like general PVC membrane ISEs, the membrane is located between the internal and external solutions while in second one, one side of the membrane is in contact with the solution and the other side is in contact with a solid state transducer. A symmetric electrodes can easily remove during the long time treatments. In addition, detection limits of these kinds of sensor are not too low (10^{-5} to 10^{-7} mol L^{-1}). While detection limits in CWEs, as asymmetric electrodes without internal filling solutions, were improved somewhat (10^{-8} mol L^{-1}).

All-solid-state polymeric membrane electrodes (ASS-PME) [26-30] (Scheme 1) are one of the classes of asymmetric electrodes [31-34]. In this type, a conductive polymeric composite of graphite mixed with epoxy resin is applied as an internal contact to transduce the chemical signal. A layer of general PVC membrane is then coated on the surface of the conductive composite. Solid-contact ion-selective electrodes can provide very low detection limits. Moreover, they do not require an optimization of the inner filling solution, and have a good mechanical stability and simplicity of preparation.

In this work, PME and ASS-PME were made and applied for determination of Paroxetine in pharmaceutical formulations. The linear ranges of PME and ASS-PME cover each other to provide a wide linear range of concentrations for analysis of PAX and hence, enhance the performance of the potentiometric determinations. Both sensors responded based on ion-exchange mechanism. An ion-pair compound which is synthesized and incorporated in a polymeric matrix was responsible of the exchanging. The proposed method was validated and finally used in analysis of Paroxetine hydrochloride active ingredients of some tablets successfully.

2. EXPERIMENTAL SECTION

2.1. Apparatus and measurements

PME or ASS-PME, as indicator electrodes, and a reference electrode (Ag/AgCl; Azar-Elelectrode Co., Iran) were connected to an ion analyzer (with a 250 pH/mV meter with ±0.1 mV precision). The below cell assembly were applied for potentiometric measurements:

In case of PME:

Ag-AgCl || internal solution, 1×10^{-3} mol L^{-1} PAX hydrochloride solution | PVC membrane | sample solution || Ag-AgCl, KC1 (satd.)

And in case of ASS-PME:

Cu wire | ASS layer | PVC membrane | sample solution || Ag-AgCl, KC1 (satd.)

All measurements were performed by calibration method using several standard solutions.

2.2. Materials and Reagents

The chemicals used in this work of analytical reagent grade with highest available purity from Merck Co. and were sodium tetraphenyl borate (NaTPB), potassium tetrakis (p-chlorophenyl) borate (KTPClPB), dibutyl phthalate (DBP), nitrobenzene (NB), dibutyl sebacate (DBS), benzyl acetate (BA), *o*-nitrophenyloctylether (*o*-NPOE), room temperature ionic liquids, 1-n-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4), 1-n-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), tetrahydrofuran (THF), all solvents, all salts (nitrate or chloride form) and graphite powder with a 1–2 μm particle size were taken from Merck Co. The high-molecular weight polyvinylchloride (PVC) was from Fluka Co. The multi-walled carbon nanotubes (MWCNTs) with 10-40 nm diameters, 1-25 μm length, core diameter: 5-10 nm, SBET: 40-600 m^2/g, V_{total}: 0.9 cm3/g, bulk density 0.1 g/cm^3, true density 2.1 g/cm^3 and with 95% purity were purchased from a local company (Research Institute of the Petroleum Industry, Iran). Epoxy (macroplast Su 2227) from Henkel (Germany) and hardener (desmodur RFE) were from Bayer Ag (Germany). PAX hydrochloride was obtained from Sigma-Aldrich. The pharmaceutical formulations were gotton from a local pharmacy (Tehran, Iran).

2.3. ion-pair synthesis

The ion-pair complex was synthesized through mixing a solution f PAX-HCl and a solution of a suitable organic salt (i.e. sodium tetraphenyl borate or potassium tetrakis (p-chlorophenyl) borate). Sodium tetraphenyl borate (NaTPB) and potassium tetrakis (p-chlorophenyl) borate are suitable organic salts which have hydrophobic large anions and small inorganic cations as shown in Fig. 2. These kind of salts are usually applied as a precipitating reagent in inorganic or organometallic studies [9-12].

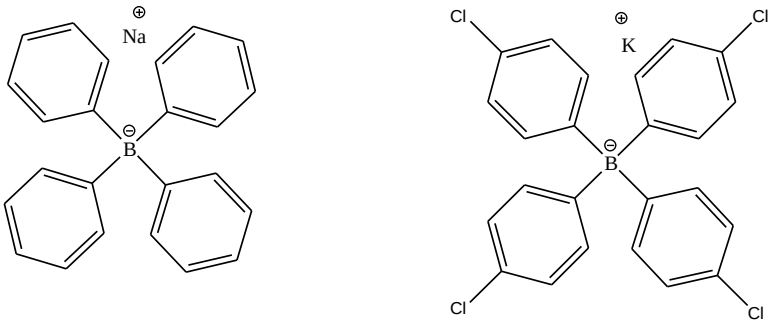


Figure 2. Chemical structure of ionic additives

Ion-pair complex was synthesized by adding of the organic salt solution (40 mg in 5 mL distilled water) to PAX.HCl solution (40 mg in 15 mL distilled water). The formed precipitate was filtered, and washed with distilled water, then dried in room temperature.

2.4. Constructions of the sensors

For construction of both sensors, a polymeric membrane is required. The membrane was made by mixing certain amount of ion-pair compound , and appropriate amount of PVC, plasticizer and ionic additive in tetrahydrofuran (THF). into a glass dish of 2 cm diameter. Then, by slowly heating of the solution, THF was evaporated and an oily concentrated solution was formed.

In case of PME, a plastic tube (with ~3 mm o.d.) was dipped into the oily solution for about 10 s to form a transparent membrane with thickness of about 0.3 mm . The tube was then pulled out and kept at room temperature for 5 h. Next, the plastic tube was filled by an internal filling solution (1.0×10^{-3} mol L^{-1} of PAX HCl solution) and conditioned the same solution for 15 h [35-40].

In case of ASS-PME, at first, a conductive polymeric composite made of MWCNTs-incorporated epoxy resin was placed on the surface of a copper wire, as internal contact and transducer. Graphite powder, MWCNTs, epoxy, and hardener were mixed in various amounts. The best all solid-state contact material was prepared by mixing 0.30 g (30% w/w) of epoxy resin, 0.15 (15% w/w) of hardener, 0.05 g (5% w/w) of MWCNTs and 0.50 g (50% w/w) of graphite powder in THF solvent and after mixing, the solution was left to stand about 20-30 min in air for aging. The epoxy resin mixture is used to bind the graphite. After a viscose mixture was obtained, the surface of a shielded copper wire (0.5 mm diameter and 15 cm length) was polished well and dipped in to the solution for about 10 times. Thus, the wire was covered with the black mixture, and then let it dried for about 10 h. The solid-state contact material was then immersed into the polymeric membrane solution as described above for 3 times and then allowed to dry in air for 24 h. Next, prepared ASS-PME was conditioned in a 10^{-3} mol L^{-1} solution of PAX.HCl.

2.5. Preparation of Paroxetine solutions

Since PAX.HCl is a soluble compound in water, a solution of 0.1 mol L^{-1} of the drug was prepared in distilled water and used as stock solution. Then, by appropriate dilution of this solution, working standard solutions from 1×10^{-9} to 1×10^{-2} mol L^{-1} were prepared. The solutions were kept in refrigerator (4°C) when not in use.

For real sample analysis, 20 tablets of PAX.HCl were powdered. Amounts equivalent to the weight of 5 tablets (each tablet contain 20 mg Paroxetine) were weighed carefully and transferred into a 100-mL volumetric flask, shaken thoroughly and diluted with acetate buffer (0.1 mol L^{-1}; pH=4). Suitable amounts of this solution were filtered through a Millipore filter (0.45 mm). This solution was used as a stock solution.

3. RESULTS AND DISCUSSION

Design and construction of membrane sensors can be a new attitude in rapid, simple and inexpensive analysis of some drugs. However, it should be noted that they are not as sensitive as complex instrumental methods. Here, the most important part of PME and ASS-PME is polymeric

membrane which the sensing material should be incorporated in it. The constituents used in the membrane can directly affect the performance of the sensor.

3.1. Optimization of Polymeric Membrane Composition

The ingredients of a membrane are a sensing material, a plasticizer, a polymeric matrix and sometimes a suitable ionic additive. The type, amount and their ratio of each components should be optimized to achieve a best sensor performance. Table 1 lists the various membrane compositions tested to find the best one. PVC is used as polymeric matrix. The ratio of the plasticizer to the polymer is normally something between 2 to 2.2 [40-46]. Here, 30%wt. PVC was used for all the membranes presented in Table 1.

Table 1. Compositions of the membranes used in preparation of PAX sensor

No	Composition of the membrane			Characterization of PME			
	Plasticizer	Ion-pair	Ionic Additive	Slope mV/decade	LR (mol L^{-1})	DL (mol L^{-1})	Response time
1	DBS,67	3	-	14.1±0.8*	3.2×10^{-4}-1.0×10^{-3}	3.0×10^{-4}	1.3 min
2	DBS,65	5	-	32.7±0.5	1.0×10^{-4}-1.0×10^{-3}	8.0×10^{-5}	1 min
3	DBS,63	7	-	49.9±0.6	5.0×10^{-5}-5.0×10^{-3}	4.0×10^{-5}	55 s
4	DBS,61	9	-	45.2±0.7	5.0×10^{-5}-5.0×10^{-3}	5.0×10^{-5}	60 s
5	DBP,63	7	-	44.5±0.6	3.2×10^{-5}-5.0×10^{-3}	2.0×10^{-5}	57 s
6	NPOE,63	7	-	30.7±0.5	5.0×10^{-5}-1.0×10^{-3}	5.0×10^{-5}	1 min
7	BA,63	7	-	38.5±0.7	5.0×10^{-5}-1.0×10^{-3}	5.0×10^{-5}	58 s
8	NB,63	7	-	27.5±0.8	8.0×10^{-5}-1.0×10^{-3}	7.0×10^{-5}	1 min
9	DBS,63	7	2 KpClTPB	51.3±0.5	1.0×10^{-5}-1.0×10^{-2}	9.0×10^{-6}	40 s
10	DBS,63	7	2 NaTPB	49.5±0.5	1.0×10^{-5}-5.0×10^{-2}	1.0×10^{-5}	41 s
11	DBS,62	7	1 $[bmim]PF_6$	51.4±0.4	1.0×10^{-5}-1.0×10^{-2}	8.0×10^{-6}	36 s
12	DBS,62	7	1 $[bmim]BF_4$	50.5±0.5	1.0×10^{-5}-1.0×10^{-2}	1.0×10^{-58}	45 s
13	DBS,61	7	2 $[bmim]BF_4$	52.3±0.5	1.0×10^{-5}-1.0×10^{-2}	8.5×10^{-6}	41 s
14	DBS,61	7	2 $[bmim]PF_6$	54.1±0.4	8.0×10^{-6}-8.0×10^{-2}	7.5×10^{-6}	29 s
15	DBS,60	7	3 $[bmim]PF_6$	53.2±0.6	9.0×10^{-6}-7.0×10^{-2}	8.0×10^{-6}	32 s
16	DBS,59	7	2 KpClTPB, 2 $[bmim]PF_6$	57.8±0.3	7.5×10^{-6}-1.0×10^{-1}	5.0×10^{-6}	15 s
17	DBS,60	7	1 KpClTPB, 2 $[bmim]PF_6$	55.6±0.4	8.0×10^{-6}-1.0×10^{-1}	8.0×10^{-6}	17 s
18	DBS,68	0	2 KpClTPB, 2 $[bmim]PF_6$	3.3±0.8	5.0×10^{-4}-1.0×10^{-3}	5.0×10^{-4}	1.5 min

*standard deviation of five repeated measurements

Solvent mediator called plasticizer is a component which is used to plasticize the membrane. It is an organic solvent which is water-immiscible solvent having low vapor-pressure. The mobility of the sensing material in the membrane can be affected by the nature of the plasticizer [9,12]. The

plasticizer should be compatible with PVC and has no functional groups to protonate during the interactions. Variety of plasticizers having different dielectric constants can be used in the membrane. Dibutyl sebacate (DBS;DC: 4.5), dibutyl phthalate (DBP; DC: 6.4), nitrophenyloctyl ether (*o*-NPOE; DC: 24), nitrobenzene (NB; DC: 35.7) and benzylacetate (BA; DC: 5.7) were used. From the results shown in Table 1, membrane no. 5 to 8, DBS had the better performance in the membrane. PAX cation is a hydrophobic species, thus, plasticizer with lower DC helps the better extraction of organic cations in the membrane. Ionic additives are components of the membrane can be used to reduce the Ohmic resistance of the membrane. They should be used as small amounts if higher amounts are added to the membrane, it may acts as ion-exchanger to and lower the limit of detection of the sensor. Room temperature ionic liquids (RTILs) are recently applied as ionic additive. They can help the ion-exchanging and lower the detection limits. Among the tested RTILs, [bmim]PF_6 as can be seen in Table 1(membranes no. 11 to 15) achieved the best results. Here, using the combination of RTIL with a common cationic additive in the membrane, makes the sensor responses Nernstian (membrane no. 16).

As seen from data in Table 1, a membrane which has no sensing material, has no response (membrane no. 18).Hence, membrane no. 16 with 7% ion-pair, 59% DBS, 30% PVC, and 2% KpClTPB-2% [bmim]PF_6 shows the Nernstian behavior with slope of 57.8±0.3 mV per decade. The membrane no. 16 was used for next studies and also in case of ASS-PME construction.

3.2. Calibration curves

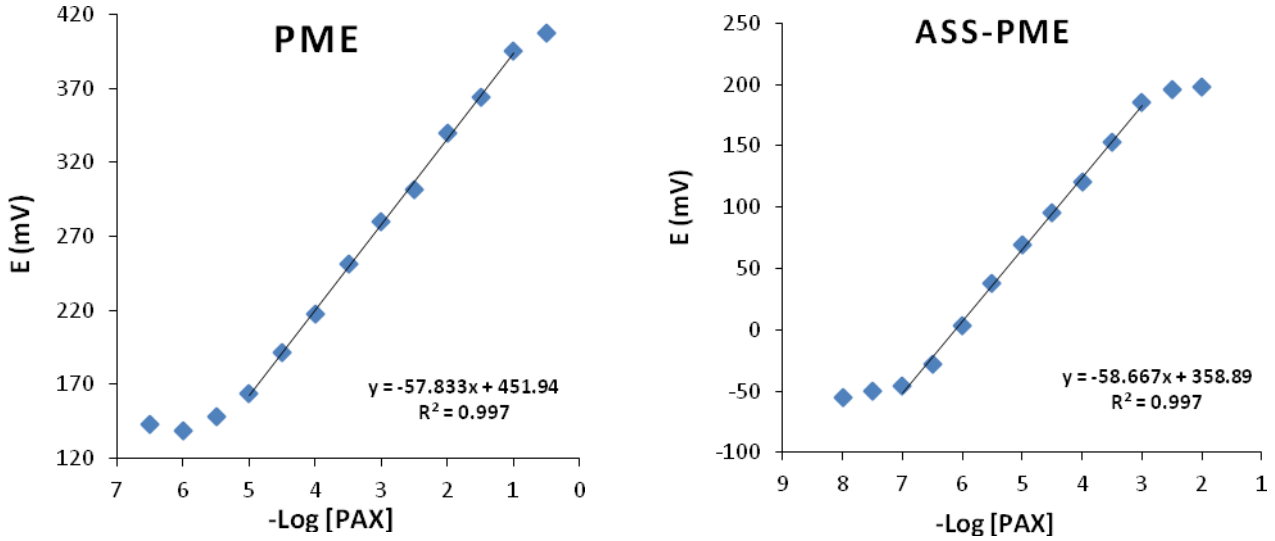


Figure 3. Calibration curves of PAX potentiometric sensors; each points are averaged of five replicate measurements.

Different concentrations of the PAX HCl (one decade difference in concentration) was measured by the proposed sensors. Based on the Nernst equation, E *vs.* –log [PAX] was drawn (Figure

3). The linear section of the curves is the linear range (LR) of the sensor response. Most of the PME sensors for pharmaceutical compounds have a linear range of 10^{-2} to 10^{-5} mol L^{-1} [37-45]. Here, in case of PME, the linear range of the sensor was 7.5×10^{-6}-1.0×10^{-1} mol L^{-1} of the PAX concentration with a Nernstian slope of 57.8±0.3 mV per decade. In case of ASS-PME, which is an asymmetric sensor as explained in introduction, a LR of 8.0×10^{-8} to 1.0×10^{-3} mol L^{-1} with slope of 58.6±0.3 mV per decade. Through extrapolating two sections of the calibration curves, DL of the polymeric membrane sensors were calculated 5.0×10^{-6} mol L^{-1} and for PME and 5.0×10^{-8} mol L^{-1} for ASS-PME.

3.3. Response Time

Response time of a potentiometric sensor is the time takes to reach the ±1 mV of the final potential. It can be obtained after successive immersions of the sensors in the analyte solutions [40-49]. Here, the PAX concentration was changed from 1.0×10^{-5} to 1.0×10^{-2} mol L^{-1} continuously and the times were recorded Sensor was able to quickly reach its equilibrium response in the whole concentration range. The response time was about 15 s in case of PME and about 10 s about PME-ASS.

3.4. pH Effect on the potential response of the sensors

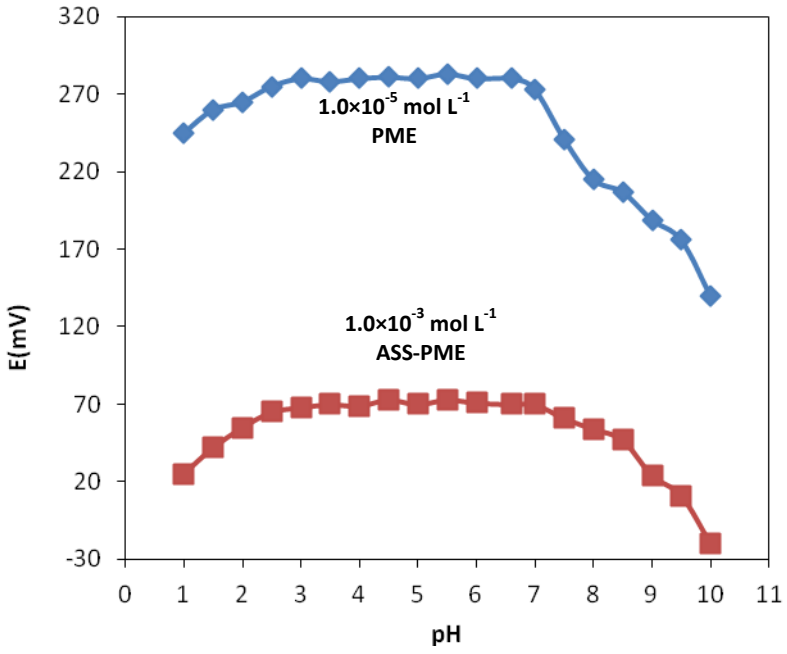


Figure 4. pH range of the electrodes performance in the solutions of 1.0×10^{-3}, and 1.0×10^{-5} mol L^{-1} for PME and ASS-PME

pH effect on the potential responses of the sensors was tested in the PAX solution (1.0×10^{-3}, and 1.0×10^{-5} mol L^{-1}) when the pH was changed from 1.0 to 10.0 (adjusted by concentrated NaOH or HCl solutions). As can be seen in Fig. 4, potentials stayed constant upon pH changes in the range

of 2.5 to 7.0, in both types of sensor which shows the applicability of these electrodes in the this pH range.

Changes in the potential above and below the pH ranges can be due to the removing the positive charge on the cations of the drug molecule and lessening the solubility of the drug in the solution and by removing of the membrane components or the analyte in the solution, respectively.

3.5. Life-time

Lifetime of a potentiometric sensor can be evaluated using the Nernstian slope and detection limit. For this purpose, three electrodes were used for 1 hour per day within 10 weeks. The common lifetime of the reported potentiometric sensors is in the range of 4–10 weeks [44-49]. The results have been summarized in Table 3.

As it can be seen, after 7 weeks usage of the sensor, the slope gradually decreased and the detection limit were increased in case of PME. ASS-PME shows a longer life-time than PME. The changes can be seen after 9 weeks. In general the mechanical stability of the PME are too less than ASS-PME. Losing of the membrane ingredients into the solution by several times of usage, causes such limitation of the sensors.

Table 3. Lifetime of PME and ASS-PME

Week	PME		ASS-PME	
	Slope (mV per decade)	DL (mol L^{-1})	Slope (mV per decade)	DL (mol L^{-1})
First	57.8±0.3	5.0×10^{-6}	58.6±0.3	5.0×10^{-8}
Second	57.6±0.4	5.0×10^{-6}	58.5±0.3	5.2×10^{-8}
Third	57.4±0.4	5.5×10^{-6}	58.3±0.4	6.5×10^{-8}
Fourth	57.3±0.5	7.5×10^{-6}	58.1±0.3	8.0×10^{-8}
Fifth	56.9±0.3	8.0×10^{-6}	57.8±0.4	9.5×10^{-8}
Sixth	56.5±0.4	9.0×10^{-5}	57.5±0.3	1.5×10^{-7}
Seventh	56.2±0.5	1.5×10^{-5}	57.4±0.6	3.0×10^{-7}
Eighth	37.7±0.5	1.0×10^{-4}	57.2±0.4	4.0×10^{-7}
Ninth	21.6±0.6	2.5×10^{-4}	57.0±0.4	7.5×10^{-7}
Tenth	18.9±0.7	5.0×10^{-4}	40.7±0.6	1.0×10^{-5}

3.6. Analytical characterization of the sensors

To show the analytical applicability of the prepared sensors, they were used in the determination of PAX in pure solution and in pharmaceutical tablets. There are some parameters which should be applied for validation a sensor including linear range, detection limit, selectivity, precision, accuracy,

and ruggedness/robustness.

The proposed sensors were used in analysis of PAX in some tablets (Table 4). Calibration method was used to determine PAX content of tablets. There is no significant difference among the results of the proposed method and labeled amounts and HPLC standard method.

One of the most important parameter of each sensor is its selectivity. The selectivity of an ion-selective electrode is tendency of the sensing element to the analyte in the presence of interfering species. The selectivity is stated as selectivity coefficient in potentiometric sensors. Various methods has been reported for determination of the selectivity coefficients. Here, they were calculated by the matched potential method (MPM) [48,49]. The obtained selectivity coefficients are presented in Table 5. According to the resulted data, the interferences from ionic and non-ionic species in PAX determination are not significant.

Table 4. Measurement of PAX.HClin pharmaceutical formulations by the proposed sensors and standard methods

Sample	**Labeled amount (mg/tab.)**	**Found by the PME* (mg/tab.) n=5**	**Found by the ASS-PME* (mg/tab.) n=5**	**Standard method n=5**	**t-test (p-value: 0.05; $t_{theoritical}$: 2.31)**
Sample 1	20	18.75±0.47	19.11±0.57	19.00±0.27	PME: $t_{experimental}$= 2.07 ASS-PME: $t_{experimental}$= 0.91
Sample 2	20	21.23±0.55	21.03±0.45	20.95±0.34	PME: $t_{experimental}$= 1.84 ASS-PME: $t_{experimental}$= 0.53
Sample 3	20	22.17±0.63	22.10±0.45	21.85±0.35	PME: $t_{experimental}$= 2.04 ASS-PME: $t_{experimental}$= 1.60

* Averages of five repeated measurements

Table 5. Selectivity coefficients obtained for PAX sensors

Interfering species	PME	ASS-PME
	Log (K_{MPM})	Log (K_{MPM})
Na^+	-3.7	-3.8
K^+	-3.4	-3.2
NH_4^+	-2.5	-2.8
Ca^{2+}	-3.4	-3.3
Mg^{2+}	-3.6	-3.7
Cl^-	-3.5	-3.5
NO_3^-	-4.2	-4.2
Lactose	-4.7	-4.8
Glucose	-4.4	-4.4

Repeatability of the sensors was calculated using three standard synthetic samples. The samples were measured repeatedly. RSD% obtained for PME was 3.64 and for ASS-PME 3.25%. Ruggedness of the method was performed by comparing the results of the experiments which done by two analysts intra- and inter-day in the same laboratory. RSD% calculated for two analysis did not exceed 4.3% for PME and 3.8% for ASS-PME. Robustness was obtained while the important parameters (i.e. pH of the solution and the laboratory temperature) changed slightly. PAX recovery% were good under most conditions, and show no significant change when the critical parameters were changed.

4. CONCLUSIONS

Paroxetine which is a selective serotonin reuptake inhibitors (SSRIs) prescribed as an antidepressant compound was measured by a PVC membrane electrode (PME), and all solid state polymeric membrane electrode (ASS-PME). An ion-pair based polymeric membrane was used in construction of the both sensors and the best membrane composition was obtained by a liquid membrane composed of 6% PAX-tetrakis (p-chlorophenyl) borate, 62% dibutyl sebacate, 30% poly(vinyl chloride), and 2% ionic liquid. The all solid state electrode is made based on a conductive composite of graphite, MWCNTs, and epoxy resin on a copper wire. A thin layer of PVC membrane is then coated on the surface of the new conducting transducer. The Nernstian behavior (slope of 57.8±0.3 mV/decade in case of PME and 58.6±0.3 mV/decade) can be seen in a wide concentration range of 7.5×10^{-6} to 1.0×10^{-1} mol L^{-1} for PME, 8.0×10^{-8} to 1.0×10^{-3} mol L^{-1} for ASSME. Validation of the method was done and showed applicability of the sensors for the quality control analysis of Paroxetine hydrochloride in pharmaceutical formulation.

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