Scientific paper

Determination of Atomoxetine Hydrochloride in Biological Fluids Using Potentiometric Carbon Paste Electrode Modified by TiO_2 Nanoparticles

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Abstract

Endeavors to improve the limit of detection for atomoxetine-selective electrode were documented. Simple potentiometric carbon paste electrodes (CPEs) based on atomoxetine-derivatized with tetraphenylborate (ATM-TPB) or phosphotungstic acid (ATM-PTA) as ion-pairs decorated with TiO_2 nanoparticles and sodium tetraphenylborate (Na-TPB) as additives were most useful. Parameters affecting the performance of the electrodes were investigated, such as paste composition, type of plasticizers, kind of electroactive materials and interfering species. The electrodes were notable for bringing down the detection limit to 8.0×10^{-7} M and 9.2×10^{-7} M, wide linear ranges 1.1×10^{-6}–1.0×10^{-2} M and 1.75×10^{-6}–1.00×10^{-2} M, slope 58.7 ± 0.5 mV/decade and 67.2 ± 0.8 mV/decade, respectively. Importantly, the potential reading became more stable and rapidly attained in the presence of additives. The selectivity for the drug over other species such as inorganic and organic cations, as well as different excipients that are likely incorporated in pharmaceutical preparations was high making their effect negligible on the response of the electrodes. The sensors, as indicator electrodes, were successfully applied for determination of the drug in pharmaceutical preparation, urine and serum with good accuracy, excellent recovery and efficiency.

Keywords: Atomoxetine-ion selective electrodes; carbon paste electrode; nanoparticles; ion-pairs

1. Introduction

Determination of drug species in real samples such as biological and pharmaceutical samples is an important branch of analytical chemistry for clinical, quality production control and other applications.[1–4] Atomoxetine hydrochloride (Fig. 1), is designated chemically as (-)-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)-propylamine hydrochloride. Atomoxetine is a white solid that exists as a granular powder inside the capsule along with pregelatinized starch and dimethicone.[5–7] Atomoxetine is the first non-stimulant drug approved for the treatment of attention-deficit hyperactivity disorder (ADHD) with no associated side effects. However, cases of chronic overdose and acute and lethal poisoning by atomoxetine were registered.[8,9]

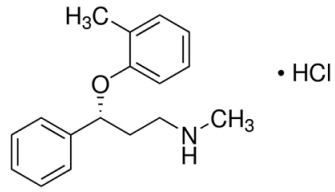

Fig 1. The chemical structure of atomoxetine hydrochloride

Therefore, estimation of trace amounts of atomoxetine in various media is necessary.

Literature survey showed different methods for determination of atomoxetine that are mainly chromato-

graphic utilizing various means of detection such as: UV, colorimetric, fluorometric, mass spectrometric,[10–13] RP-HPLC,[14,15] spectrophotometry,[16,17] and potentiometric method.[18]

Comparatively, most of these methods require sample manipulations giving ways to various interferences. Moreover, they are not applicable for colored and turbid solutions. Even more, they are more expensive for they require large infrastructure backup and qualified personnel. Thus, the development of selective, sensitive, accurate and inexpensive tool for the determination of this drug is of utmost need.

Potentiometric sensors (ion-selective electrodes, ISEs) are taken as one of the simplest and oldest electrochemical techniques being attractive for numerous analyses due to the low cost and ease of implementation.[19–21] They have other interesting properties such as short response times, high selectivity and very low detection limits. In addition, ISEs allow nondestructive, on line monitoring of particular ions in a small volume of sample without any pretreatment. Considering these merits, ISEs are getting more attention as routine tools of chemical analysis in industry, clinical and environmental analyses.[22–26]

Coated-wire ion-selective electrodes that were employed to overcome the problems associated with conventional ISE's[27,28] still suffer some shortcomings such as giving unreliable measurements due to the fluctuation of the electric potential.[29] New measures must be introduced to the working electrodes to alleviate or eliminate these effects and carbon-paste electrodes (CPE's)[30] appear to be suitable alternatives.

Carbon paste electrodes (CPEs), one type of ISEs, combine a carbon powder with a pasting liquid (an organic binder). CPEs are superior to other types of ISEs for their favorable characteristics and advantages such as stable response, easy renewal of surface and no requirement of internal solution, and were utilized in various applications.[31–35] Moreover, CPEs are nontoxic and environmentally friendly making their use soaring. Modification of CPEs with nanoparticles having unique electrochemical properties showed interesting affinity toward various ions and biological molecules. The morphological structure of nanoparticles may improve diffusion of the electroactive species and improve sensitivity thus enhancing a fast response.[36,37]

Careful review of the literature found no reports on potentiometric determination of atomoxetine based on the carbon paste electrode modified with additives such as Na-TPB and the nanoparticles of TiO_2. In the present work, carbon paste and nano-composite carbon paste electrodes were utilized for determination of atomoxetine drug in pharmaceutical preparations, as well as spiked urine and serum samples with notable selectivity, accuracy and precision. The electrodes exhibit a near-Nernstian slope, wide concentration range, low detection limit and short response time. The lowering of detection limit, wider concentration range and stability of the response are apparently due to the incorporated nanoparticles.

2. Materials and Methods

2. 1. Reagents

All reagents used were of chemically pure grade. Doubly distilled water was used throughout all experiments. Atomoxetine hydrochloride was obtained from (Multi apex pharma, Cairo, Egypt) and its pharmaceutical preparations (capsules 10, 25, 40 mg and tablets 10, 25, 40 mg) were obtained from local drug stores. Silicomolybdic acid (SMA) $H_4[SiMo_{12}O_{40}]$ M = 1823 Da, silicotungstic acid (STA) $H_4[SiW_{12}O_{40}]$ M = 2878 Da, phosphomolybdic acid (PMA) $H_3[PMo_{12}O_{40}]$ M = 1825 Da, phosphotungstic acid (PTA) $H_3[PW_{12}O_{40}]$ M = 2880 Da, and sodium tetraphenylborate (Na-TPB) $Na[C_{24}H_{20}B]$ M = 342 Da, were purchased from Sigma-Aldrich. Pure graphite powder and the plasticizers: dibutyl phthalate (DBP), dioctyl phthalate (DOP), dioctyl sebacate (DOS), tris(2-ethylhexyl) phosphate (TEPh), and bis(2-ethylhexyl) adipate (DOA) were obtained from Aldrich chemical company. In addition, ranitidine hydrochloride, tramadol hydrochloride, ephedrine hydrochloride, diclofenac potassium, glucose, galactose, fructose, sucrose, ceftriaxone sodium, gentamycin sulfate, lasix, vardenafil hydrochloride, lidocaine hydrochloride, hydralazine hydrochloride, pethidine hydrochloride, dopamine hydrochloride, dexamethasone hydrochloride, midazolam hydrochloride, tranexamic acid, furosemide, amoxicillin, and paracetamol were commercially available. Salts of inorganic cations were used in their soluble forms such as chloride or sulfate.

Titanium(IV) oxide nanopowder, 21 nm primary particle size, was obtained from Aldrich and used as received.

2. 2. Apparatus

Potentiometric and pH measurements were performed using a Pocket pH/mV meters, (pH315i) from Wissenschaftlich-Technische Werkstatten GmbH (WTW), Weilheim, Germany. A saturated calomel electrode (SCE) was used as reference electrode and was obtained from Sigma–Aldrich Co. (St Louis, MO, USA). Electromotive force measurements with CPE were carried out with the following cell assemblies: Hg, $Hg_2Cl_{2(s)}$, KCl(sat.) || sample solution || carbon paste electrode.

Solutions having concentrations 1.0×10^{-7}–10×1.0^{-2} M were made and used to investigate performance of the electrodes with continuous stirring by recording the potential and plotting as a logarithmic function of ATM ion activities.

2. 3. Preparation of the Ion-Pairs

An ion-pair was made from atomoxetine hydrochloride and one of the following substances: STA, SMA, PTA, PMA and Na-TPB according to a reported method[38] as detailed below. The ion-pairs, (ATM_4-ST), (ATM_4-SM), (ATM_3-PT), (ATM_3-PM), and (ATM-TPB), were pre-

pared by addition of 20 mL of 0.01 M ATMCl solution to 20 mL of 0.0025 M of STA, 0.0025 M of SMA, 0.0033 M of PTA, 0.0033 M of PMA, and 0.01 M of Na-TPB. The resulting precipitates were left overnight to assure complete coagulation. The products were then filtered and washed thoroughly with copious amounts of distilled water, dried at room temperature and ground to fine powders and applied as the modifiers for constructing the electrodes of atomoxetine hydrochloride.

2. 4. Fabrication of the Electrodes

Modified electrodes were made by mixing 0.001–0.03 g ion-exchangers, 0.0005–0.002 g Na-TPB, 0.003–0.009 g TiO_2 nanoparticles, and 0.260–320 g high purity graphite. These components were mixed and 0.260–0.320 g of a plasticizer was added. Thorough homogenization was then assured by careful mixing with a spatula in an agate mortar and pressing with a pestle. The produced paste was then packed in the tip of a polypropylene syringe (3 mm i.d., 0.5 mL). A copper wire conducted the current to the paste. This paste was polished by pressing on a weighing paper to a shining surface before use for potentiometric measurements without pre-soaking. It is best for such sensors to be stored in a dry and cold place until use.

2. 5. Effect of Interfering ions

The separate solution method (SSM)[39] and the modified separate solution method (MSSM)[40] were applied to evaluate the potentiometric selectivity factors of the electrode. In the SSM, the potential of a cell constructed from a working electrode containing the drug ions, E_D and a reference electrode containing the interferent ions (E_J) is measured one solution at a time. The measured potentials were used to calculate the selectivity coefficient from the following equation:

$$\log K_{D\,J^{z+}}^{pot} = \frac{E_J - E_D}{S} + \left(1 - \frac{Z_D}{Z_I}\right) log\, a_D$$

where E_J and S is the slope of the calibration graph, Z_D and Z_J are the charge of ATM and interfering species, respectively.

In the modified separate solution method (MSSM), the potentiometric calibration curves are measured for the drug ions (D) and interfering ions (J). A plot of the measured potentials at various concentrations of the measured species is made and used to find the potential corresponding to 1.0 M concentration by extrapolation. The selectivity coefficients are calculated from the equation:

$$\log K_{D\,J}^{pot} = \frac{E_J^o - E_D^o}{S_D}$$

where $\log K_{DJ}^{pot}$ is selectivity coefficient; E_j^o and E_D^o are values from the extrapolation of calibration curves to log(a) = 0 for various interfering species and drug, for the studied electrode, respectively; S_D is the slope of the drug electrode.

2. 6. Effect of pH on the Electrode Potential

The effect of pH of the test solution on the potential values of the electrode system in solutions of different concentrations (1.0×10^{-4} M and 1.0×10^{-5} M) of the ATM solution was studied. Aliquots of the drug (50 mL) were transferred to a 100-mL titration cell and the tested ISE in conjunction with the SCE, and a combined glass electrode were immersed in the same solution. The pH of the solution was varied over the range of 2.0–9.0 by addition of very small volumes of (0.1 or 1.0 M) HCl and/or NaOH solution. The potential readings were plotted against the pH-values for the different analyte solutions.

2. 7. Determination of Atomoxetine Hydrochloride in Miscellaneous Samples

2. 7. 1. Potentiometric Titration Method

Real samples containing 1.5–60 mg (5×10^{-3}–2×10^{-1} mmol) of atomoxetine hydrochloride were potentiometrically titrated with 0.01 M Na-TPB. The end point was determined from s-shaped plot of potential versus volume of titrant.

2. 7. 2. Calibration Graph Method

This method involves addition of the required amounts of drug to the test solution to make 50 mL-solutions with concentrations in the range 2.0×10^{-7} M–1.0×10^{-2} M of the drug and the measured potential was recorded using the present sensors. A plot of the potential versus logarithm of the ATM^+ activity was used for determination of unknown drug concentration.

2. 7. 3. Analysis of the Drug in Tablets and Capsules

A few tablets were powdered, (20 capsules were emptied and mixed) then an equivalent amount of 10^{-4} to 10^{-6} M were dissolved and filtered. The measured potential of each solution was used to calculate the concentration of the solution from the calibration plot constructed as detailed above.

2. 7. 4. Determination of Atomoxetine in Spiked Human Serum and Urine Samples

Different amounts of atomoxetine and 0.5 mL plasma or 1.0 mL urine were transferred to a 50-mL volumetric flask and diluted to volume. The solution was transferred to a 100-mL beaker and subjected to the calibration curve method for determination of atomoxetine hydrochloride.

3. Results and Discussion

Titanium dioxide nanoparticles and sodium tetraphenylborate as a lipophilic additive were incorporated in the atomoxetine-sensitive electrodes to utilize their electrochemical properties in improving the performance of the present electrode, namely, the detection limit, the linear range and slope of the electrodes which is shown in the results obtained from the present electrodes. These effects add up to those of the other components that exemplify the basic parts in the sensors, namely the ion-pairs, the plasticizers and carbon paste whose properties made the back bone for the response of shown in Table 1.

Table 1. Response characteristics of ATM-TPB and ATM-PTA electrodes at 0.90 g/p ratio.

No.	Composition%				Slope	C.R. (M)	LOD (M)	R(s)
	I.P	g	(TEPh)		(mV/decade)			
Effect of different ion pair								
ATM-TPB electrode at 0.17% Na-TPB								
1	–	47.50	52.50		27.7 ± 0.6	3.00×10^{-5}–1.00×10^{-2}	1.50×10^{-5}	13
2	0.20	47.23	52.40		52.1 ± 1.0	8.00×10^{-6}–1.00×10^{-2}	7.30×10^{-6}	10
3	0.50	47.13	52.20		59.2 ± 0.7	3.00×10^{-6}–1.00×10^{-2}	2.80×10^{-6}	10
4	1.00	46.90	52.10		44.2 ± 0.4	3.50×10^{-6}–1.00×10^{-2}	3.10×10^{-6}	8
5	1.00	46.83	52.00		57.9 ± 0.3	2.70×10^{-6}–1.00×10^{-2}	2.30×10^{-6}	5
6	2.00	46.43	51.40		53.3 ± 0.5	5.40×10^{-6}–1.00×10^{-2}	4.40×10^{-6}	7
7	3.00	45.83	51.00		52.8 ± 0.6	5.70×10^{-6}–1.00×10^{-2}	4.60×10^{-6}	10
8	5.00	44.83	50.00		50.7 ± 1.1	4.20×10^{-5}–1.00×10^{-2}	2.50×10^{-5}	10
ATM-PTA electrode at 0.11% Na-TPB								
9	0.20	47.29	52.40		53.9 ± 0.8	7.70×10^{-6}–1.00×10^{-2}	6.20×10^{-6}	12
10	0.35	47.20	52.34		55.5 ± 0.7	1.00×10^{-5}–1.00×10^{-2}	9.20×10^{-6}	11
11	0.50	47.20	52.30		39.7 ± 0.4	5.30×10^{-6}–1.00×10^{-2}	3.90×10^{-6}	9
12	0.50	47.19	52.20		64.4 ± 0.6	3.60×10^{-6}–1.00×10^{-2}	2.80×10^{-6}	5
13	1.00	46.89	52.00		73.4 ± 0.5	5.00×10^{-5}–1.00×10^{-2}	4.20×10^{-5}	10
14	2.00	46.49	51.40		83.2 ± 0.4	8.00×10^{-5}–1.00×10^{-2}	6.50×10^{-5}	11
15	3.00	45.89	51.00		66.8 ± 0.9	1.50×10^{-5}–1.00×10^{-2}	9.10×10^{-6}	10
16	5.00	44.89	50.00		66.5 ± 1.2	1.10×10^{-5}–1.00×10^{-2}	8.20×10^{-6}	13
Effect of amount TiO_2 additive ATM-TPB electrode								
				TiO_2				
17	1.00	46.33	51.50	1.0	70.0 ± 1.0	3.30×10^{-6}–1.00×10^{-2}	2.60×10^{-6}	05
18*	1.00	45.83	51.00	2.0	58.7 ± 0.5	1.10×10^{-6}–1.00×10^{-2}	8.00×10^{-7}	03
19	1.00	45.33	50.50	3.0	71.1 ± 0.8	8.00×10^{-6}–1.00×10^{-2}	7.10×10^{-6}	06
Effect of amount TiO_2 additive ATM-PTA electrode								
20	0.50	46.69	51.70	1.0	63.0 ± 0.4	8.00×10^{-6}–1.00×10^{-2}	7.30×10^{-6}	09
21*	0.50	45.19	51.20	2.0	67.2 ± 0.8	1.75×10^{-6}–1.00×10^{-2}	9.20×10^{-7}	05
22	0.50	45.69	50.70	3.0	70.1 ± 0.9	6.30×10^{-6}–1.00×10^{-2}	5.90×10^{-6}	08

I.P: ion-pair, g: graphite, p: plasticizer, S: slope (mV/decade), C.R.: concentration range, LOD: limit of detection, R(s): response time(s), * selected composition.

3. 1. Effect of the Ion-Pair

The ion-pair renders selectivity to the paste by strongly bonding the target ion thus it can transport the ion across the paste of the electrode, an effect which stems from the physico-chemical properties of the composite parts of the ion-pair intentionally incorporated for their properties. More specifically, they affect solubility, exchange kinetics and formation constants in the paste, as well as leaching and interference with existing ions. Each ion-pair is a complex of atomoxetine drug associated with STA, SMA, PMA, PTA, and Na-TPB which are high-molecular weight anions with different lipophilicities and stabilities. A few pastes with different compositions were fabricated and tested, out of which sensors ATM-TPB and ATM-PTA gave the best results. On examination of the results collected in Table 1, it is noticed that the electrodes containing zero percent modifier complexes (electrode #1) have lower sensitivity and selectivity with poor repeatability toward atomoxetine cations. Electrodes comprising various amounts of the ion-pairs, namely 0.2%, 0.5%, 1.0%, 2.0%, 3.0%, and 5.0% (*w*/*w*), were made and tested to figure out the composition of the electrode that provides the best results for use in the rest of the study. Two electrodes showed the best characteristics: one composed of 1.0% ATM-TPB, made in the stoichiometry of 1:1 (sensor #5), and the other 0.5% ATM-PTA, made in the stoichiometry of 3:1 (sensor #12). However, increase of the

amount of the modifier complex hampered the sensitivity and the working range as excess modifier changes the ratio of the ionic sites to the ionophore in the paste and possible saturation of the membrane leading to sub-Nernstian slopes.

3. 2. Plasticizer Selection

A plasticizer influences the detection limit, selectivity and sensitivity of the electrode. The partition coefficients of chemical species are strongly dependent on the solvation properties of the organic phase[41] which are mainly determined by the polarity of the plasticizer used in the electrode. In addition, the nature of the plasticizer affects both the dielectric constant of the paste and the mobility of the ionophore and its complex.[42] The desirable properties of a plasticizer used in the preparation of the ion-selective electrodes are: compatibility with the polymer, low volatility and low solubility in aqueous solution, low viscosity, low cost and low toxicity.[43,44] The plasticizers viz. DOS, DOP, DBP, TEPh, and DOA with different physical parameters, such as dielectric constant, lipophilicity, viscosity, and molecular weight (M)[45,46] were employed to study the effect on the electrochemical behavior of the electrodes (Fig. 2) to select the plasticizer that provides the best improvement of the electrode response. Comparatively, tris(2-ethylhexyl) phosphate (TEPh), with relatively high lipophilicity and similarity to that of the ion pair, produced the best improvement to the response, an effect that stems from its direct effect on solubility in the paste which is in line with the rule of the thumb "like dissolve like". Therefore, it was incorporated in all mixtures utilized in characterization of the present electrode.

3. 3. The Graphite/Plasticizer (g/p) Ratio Study

The sensitivity and selectivity of the electrode depend on graphite/plasticizer ratio used.[47] Pastes comprising graphite/plasticizer ratios of 0.75–1.35 were examined. It is interesting to note that the ratio of ca. 0.90 was the best combination as it showed the optimum response as the outcome of the physical properties of the constituents that enabled high mobilities of the inherent constituents.[48] Pastes with g/p ratio >1.35 are crumbly and those with g/p <0.75 are not sticky enough to be workable.

3. 4. The Influence of Na-TPB as Anionic Additives

It is intended to improve the sensitivity of the electrode by incorporation of selected components based on their physicochemical properties that show up in the response of the sensor. As for the additives to the ingredients of the paste, it is the hydrophobicity that marks this additive and makes it compatible with other components.[20] Sodium tetraphenyl borate, namely, was found notably effective for this purpose. This behavior is due to tetraphenyl borate anions that repel diffusion of anions from the analyte solution, this diffusion results in a decrease of the number of the cation-anion sites in the bilayer at the membrane-analyte interphase making a smaller difference in the concentrations of this cation-anion combination at the two sides of the membrane, that consequently reduces the measured potential. These additives reduce ohmic resistance and improve response behavior and selectivity. In addition, they may catalyze the exchange kinetics at the sam-

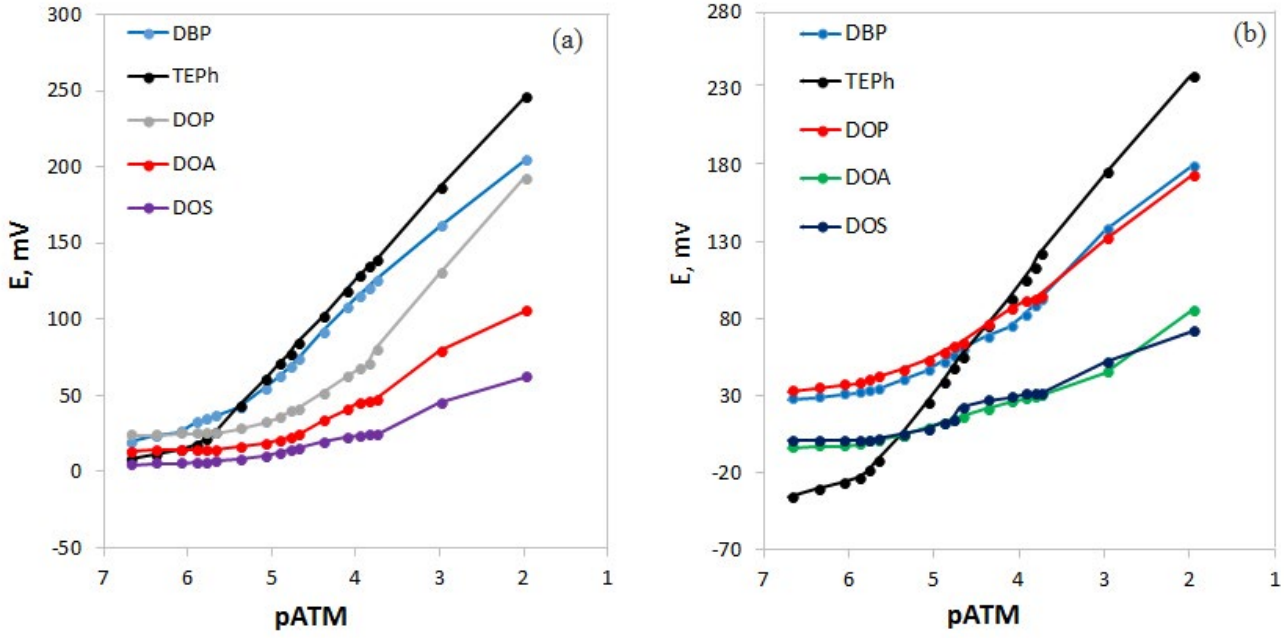

Fig 2. Effect of different plasticizers on the response of (a) ATM-TPB and (b) ATM-PTA electrodes.

ple-electrode interface.[49] The results collected on the present electrodes, as well as reports in the literature[50,51] are in line with this explanation. Electrodes containing various amounts, namely, 0.11, 0.17, and 0.33% (*w/w*) of Na-TPB were tested among which electrode ATM-TPB and electrode ATM-PTA containing no additive showed slopes of 44.2 and 39.7 mV per decade that were improved to 57.9 and 64.4 mV per decade on incorporation of 0.17 and 0.11% of Na-TPB to these electrodes, respectively.

3. 5. The Effect of TiO_2 Nanoparticles

Nanoparticles, as solid matrices, are important for their special properties which are currently utilized in development of the characteristics of ISEs toward stronger signals, increased sensitivity, decreased detection limit, and better reproducibility. For example, TiO_2 nanoparticles are non-toxic, stable, mechanically strong and biocompatible. In addition, they have large surface area and thus can act as an effective electron transfer agent. With these properties, they attracted interest of researchers around the globe for implementation in ISEs in endeavors to develop better electrodes for various purposes.[36,52,53] In the present work, pastes containing different amounts of TiO_2 nanoparticles (as given in Table 1) were incorporated in studying the effect of composition on the performance of the electrode. A lowering of the detection limit and stabilization of the potential reading was observed with the two electrodes containing 2.0% of TiO_2 nanoparticles as shown in Figure 3.[54]

3. 6. Effect of Diverse Ions

The selectivity coefficients are the foremost important characteristics of ISEs, informing about the ability of the sensing membrane for discrimination of the primary ion against other ions of the same charge.[55] The response of the electrode to the analyte must surpass that to other substances in a way that the electrode exhibits Nernstian dependence on concentration of the primary ion over a wide concentration range. The selectivity of the electrode stems from the selectivity of the ion-exchange process at the phase boundary and the mobilities of the relevant ions in the matrix of the sensor. It is desired that an electrode has as low as possible response to all species other than that for which it was fabricated to measure. The selectivity coefficients of these electrodes toward a variety of chemical species and excipients, likely incorporated in pharmaceutical preparations, or found in biological fluids, and some of the tested species are normally taken with the prescribed drug, were evaluated by the separate solution method SSM and the modified separate solution method, MSSM. The results collected for the two methods, listed in Table 2, are clearly different and those obtained by MSSM are much better and are in line with expectations as MSSM is unbiased.[56,57] That entails use of an alternative approach, the modified separate solution method as described by Bakker et al.[40] Consequently, the results (less than 1.0) in Table 2 indicate that the effects of the interfering ions on the response of the electrodes are small which means that the inorganic cations do not interfere for they have different ionic size resulting in different mobility and permeability. Overall, similarity in the composition of the paste to that of drug ion leads to better compatibility and improved response. The results indicate that the constructed sensor displays high selectivity for ATM over common drugs.

3. 7. Response Time and Reversibility of the Electrodes

The time between addition of the analyte to the sample solution and the time when a limiting potential was

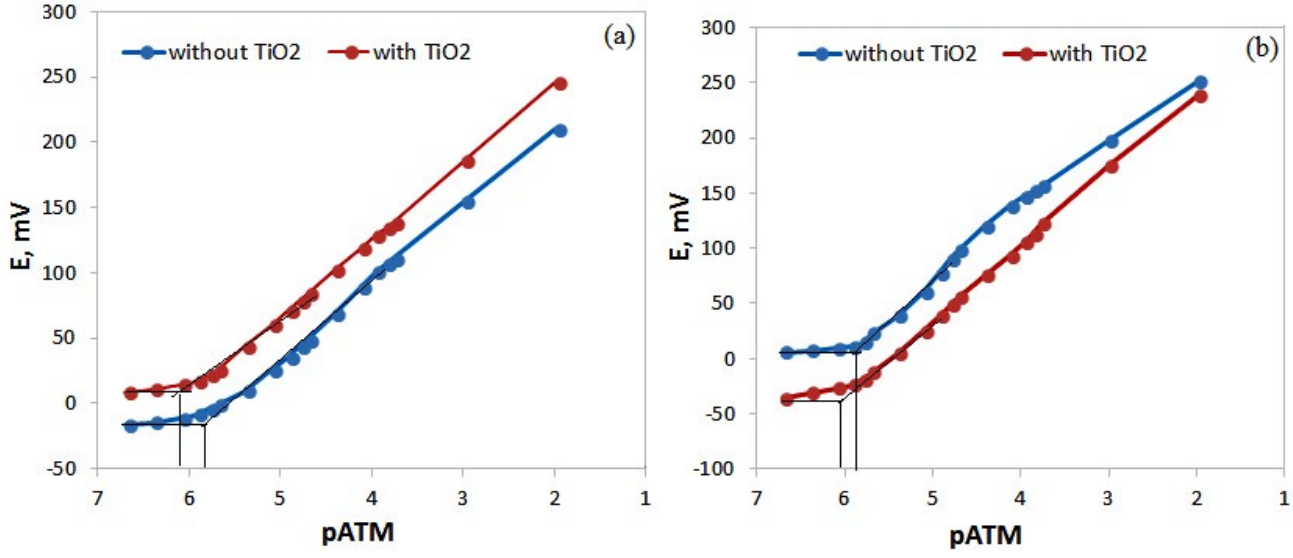

Fig. 3. Calibration graph and limit of detection of (a) ATM-TPB and (b) ATM-PTA electrodes with and without TiO_2 nanoparticles.

Table 2. Selectivity coefficients of various interfering ions for sensor ATM-TPB and sensor ATM-PTA.

Interfering species	SSM		MSSM	
	ATM-TPB	ATM-PTA	ATM-TPB	ATM-PTA
Ca(II)	–4.23	–3.45	–5.28	–4.71
Mg(II)	–4.08	–3.89	–4.33	–4.13
Cu(II)	–2.92	–2.13	–5.30	–4.32
Na(I)	–3.99	–3.36	–5.81	–4.83
K(I)	–4.04	–3.38	–5.91	–4.89
maltose	–	–	–6.29	–5.03
L-ascorbic acid	–	–	–6.35	–5.10
galactose	–	–	–6.27	–5.06
glucose	–	–	–6.07	–5.03
sucrose	–	–	–6.10	–5.00
asparagine	–	–	–6.15	–4.91
histidine	–	–	–6.28	–5.07
glycine	–	–	–6.30	–5.05
lactose	–	–	–6.32	–4.98
arginine	–	–	–5.98	–5.06
midazolam hydrochloride	–3.94	–3.48	–5.64	–5.09
dexamethasone hydrochloride	–3.92	–3.45	–5.72	–4.98
tramadol hydrochloride	–1.45	–2.08	–1.64	–2.38
tranexamic acid	–3.97	–3.48	–5.82	–5.03
pethidine hydrochloride	–1.70	–1.93	–2.06	–2.23
ranitidine hydrochloride	–3.15	–3.16	–3.25	–4.46
dopamine hydrochloride	–3.66	–3.12	–5.12	–4.46
furosemide	–4.00	–3.42	–5.88	–5.03
ephedrine hydrochloride	–2.39	–2.23	–2.57	–2.46
hydralazine hydrochloride	–2.47	–1.89	–2.74	–2.01
lidocaine hydrochloride	–1.53	–1.84	–1.90	–1.79
diclofenac potassium	–3.83	–3.31	–5.67	–4.84
vardenafil hydrochloride	–3.66	–3.45	–5.18	–5.06
amoxicillin	–3.83	–3.44	–5.36	–5.03
paracetamol	–3.90	–3.40	–5.81	–4.98
gentamycin sulfate	–2.63	–2.19	–4.04	–3.93
lasix	–2.46	–2.23	–2.66	–2.73
ceftriaxone sodium	–2.05	–1.86	–2.26	–2.31

attained, known as the response time,[58] was measured in accordance with the IUPAC recommendations with all relevant measurements made under the same experimental conditions. As it depends on the membrane type and the interferents, measurements of the response time are related to how quickly the layer of sample adhering to the ISE membrane can be exchanged for a new layer since potentiometric responses require ion movement over nanometers at the phase boundary of the analyte and the ion-selective membrane.[59] In the present contribution, 1.0×10^{-6} M to 1.0×10^{-2} M solutions were used for measurement of the response time of the electrode which reached equilibrium in ~ 5 s as evident in Fig. 4a. The electrode has a long term stability as the response remains practically constant and stable for 35–40 min and starts to drop slightly following this period. The response of each electrode was checked for reversibility. The electrode potentials of 1.0×10^{-4} M and 1.0×10^{-5} M atomoxetine hydrochloride solutions were estimated alternately in the same solution after making the proper treatment. The results, shown in Figure 4b, indicate reversibility in potentiometric responses of the sensors.

3. 8. Surface-Renewal and Reproducibility of the Electrode

Modified electrodes are attractive for possibility of surface renewal after every use. The slope of the calibration graph constructed for the present electrodes decreased slightly after three consequent uses which may be attributed to memory effect caused by accumulating surface contamination. Fortunately, a fresh surface of the modified electrodes can be exposed by squeezing a little carbon paste out of the tube and smoothing on a piece of weighing paper whenever needed. Accordingly, a paste of optimum composition and suitable mass (~2.0 g) can be used for several months to get dependable response of the electrode. The reproducibility of the new layer of the paste was

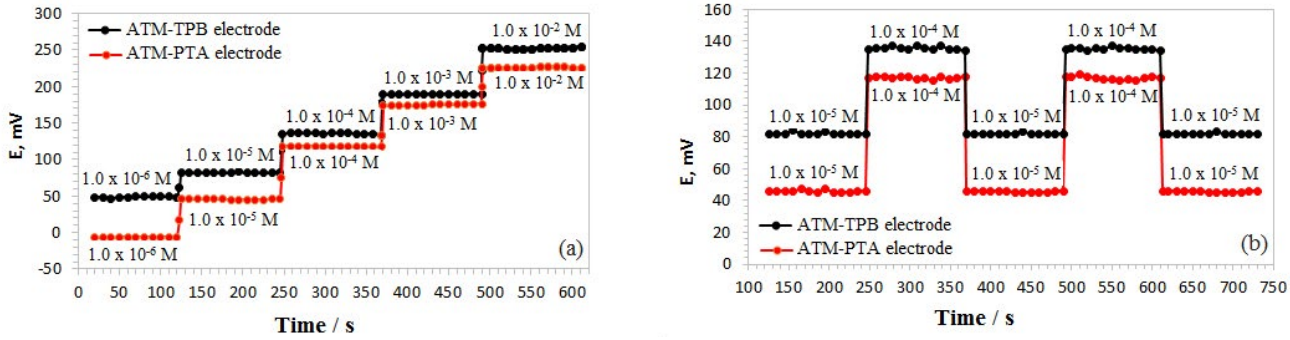

Fig. 4. (a) Typical potential-time plot for response of ATM-TPB and ATM-PTA electrodes (b) Dynamic response of the ATM-TPB and ATM-PTA electrodes for several high-to-low respective measurements.

checked by 10 successive measurements on the same surface giving a lower relative standard deviation. This indicates excellent repeatability of the potential response of the electrodes.

3. 9. pH Dependence

It is relevant to state that atomoxetine is a primary amine which is basic and has a pH around 9. The drug is a hydrochloride salt of the primary amine and the pH of the drug in solution lies in the range 4–5. The effect of the acidity of the solution on the response of the ATM-TPB and ATM-PTA electrodes was studied for 1.0×10^{-4} M and 1.0×10^{-5} M atomoxetine hydrochloride in the pH range of 2.0–9.0. The pH was adjusted with 0.2 M solutions of hydrochloric acid or sodium hydroxide. It is noted from Fig. 5a and Fig. 5b that the sensors can be dependently used in the pH range 4.0–7.5 providing acceptable results which clearly shows that they are not affected by slight changes of the pH of the solution in this range. PTA and TPB are components of the electrode which are not normally affected by changes of pH in this range as they are in salt forms and moreover they are components of practically insoluble ingredients of the electrode. Nevertheless, at pH 4.0 a nonlinear response was seen with slight increase in the potential. This is reasonably linked to the effect of the accumulating hydronium ion on the electrode behavior. At high pH the OH^- ions penetrate the paste and react with counter ions of the drug anions of the polyprotic acid. Therefore, the equilibrium is hampered and shifted to the right by consumption of some drug anions on formation of the insoluble drug in the paste with the effect of slow decrease of the ion-exchanger and a decrease in the concentration of the active species of the sensor, a similar explanation to a few recently reported sensors.[60]

3. 10. Effect of Temperature

To study the thermal stability of the electrodes, calibration curves (E_{cell} vs. log [drug]) were constructed at various temperatures covering the range 20–60 °C where it is noticed that the slopes of the calibration graphs remained in the Nernstian range up to 50 °C of the test solution over almost the same linear concentration ranges of the electrodes. These measurements ensure that the present electrodes are usable up to 50 °C without noticeable deviation from the Nernstian behavior, i.e. provide dependable results. However, temperatures higher than 50 °C cause significant deviations from the theoretical values. This effect is likely due to the damage of the electrode surface and probable leaching of the plasticizer due to decreasing viscosity as temperature is raised, a collective effect that shows up in lower response of the electrode.

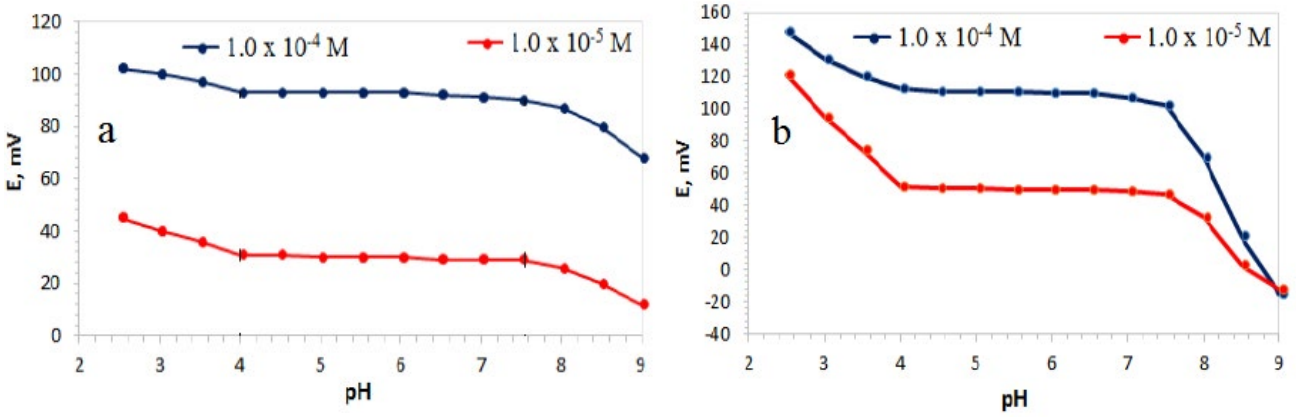

Fig. 5. Effect of pH of the test solution on the potential response of a) ATM-TPB and b) ATM-PTA.

3. 11. Analytical Performance

It is important to check the applicability of the present electrode for determination of atomoxetine drug in biological fluids and pharmaceutical preparations. This goal was achieved by using the calibration curve and potentiometric titration methods.

3. 11. 1. Determination of Atomoxetine Drug in Tablets and Capsules

The calibration curve method was employed for determination of the drug in pharmaceutical products (tablets and capsules). The results, collected in Table 3, with the relative standard deviation of the results were calculated and found to range between 0.94% and 1.86% which is an indication of precision of the results. Moreover, percentage recovery of all the experiments was in the range 97.2% to 103% which is an indication of accuracy of the results. These results indicate dependable and successful use of the presently fabricated electrodes for the intended determinations of atomoxetine hydrochloride.

3. 11. 2. Determination of Drug Ions in Urine and Serum

Atomoxetine has high aqueous solubility and biological membrane permeability that facilitates its rapid and complete absorption after oral administration. Absolute oral bioavailability ranges from 63% to 94%, which is governed by the extent of its first-pass metabolism.[61] A small fraction (<3%) of the dose is excreted as unchanged drug in the urine indicating minor role of renal excretion of the drug.[62] Calculation shows that the concentration of the drug in the blood and the urine is within the range covered

Table 3: Recovery of atomoxetine hydrochloride from pharmaceutical preparations and spiked biological fluids samples by ATM-TPB and ATM-PTA electrodes.

Samples	Taken (M)	Found (M)	X%	R.S.D %	F-value	t-values
ATM-TPB electrode						
Capsules						
	1.00×10^{-6}	1.01×10^{-6}	101	1.11	2.51	1.22
	1.00×10^{-5}	9.96×10^{-6}	99.6	1.05	2.13	1.56
	1.00×10^{-4}	9.79×10^{-5}	97.9	0.94	1.85	1.40
Tablet						
	1.00×10^{-6}	1.03×10^{-6}	103	1.41	1.98	1.38
	1.00×10^{-5}	9.89×10^{-6}	98.9	1.08	1.56	1.87
	1.00×10^{-4}	9.72×10^{-5}	97.2	1.45	2.18	2.31
Urine						
	1.00×10^{-6}	1.05×10^{-6}	105	1.76	2.08	2.14
	1.00×10^{-5}	1.02×10^{-5}	102	1.48	2.39	1.98
	1.00×10^{-4}	9.91×10^{-5}	99.1	1.64	3.76	2.39
Serum						
	1.00×10^{-6}	1.06×10^{-6}	106	1.38	4.15	3.17
	1.00×10^{-5}	1.04×10^{-5}	104	1.67	3.62	2.87
	1.00×10^{-4}	1.01×10^{-4}	101	1.44	5.98	3.28
ATM-PTA electrode						
Capsules						
	1.00×10^{-6}	9.86×10^{-7}	98.6	1.28	1.25	1.30
	1.00×10^{-5}	9.91×10^{-6}	99.1	1.02	1.58	1.52
	1.00×10^{-4}	9.87×10^{-5}	98.7	1.86	1.98	2.23
Tablet						
	1.00×10^{-6}	1.01×10^{-6}	101	1.07	1.77	2.45
	1.00×10^{-5}	9.94×10^{-6}	99.4	1.39	1.23	2.13
	1.00×10^{-4}	9.81×10^{-5}	98.1	1.26	2.24	1.95
Urine						
	1.00×10^{-6}	1.03×10^{-6}	103	1.12	3.21	2.58
	1.00×10^{-5}	1.01×10^{-5}	101	1.18	2.58	2.84
	1.00×10^{-4}	9.97×10^{-5}	99.7	1.51	3.79	3.11
Serum						
	1.00×10^{-6}	1.07×10^{-6}	107	1.22	4.52	3.29
	1.00×10^{-5}	9.73×10^{-6}	97.3	1.42	4.76	3.44
	1.00×10^{-4}	9.91×10^{-5}	99.1	1.36	3.95	3.08

X: recovery, M: the molar concentration of atomoxetine samples (taken), RSD relative standard deviation, the number of replicate measurements = 3. The critical value of F = 9.28 and the critical value of t = 3.707.

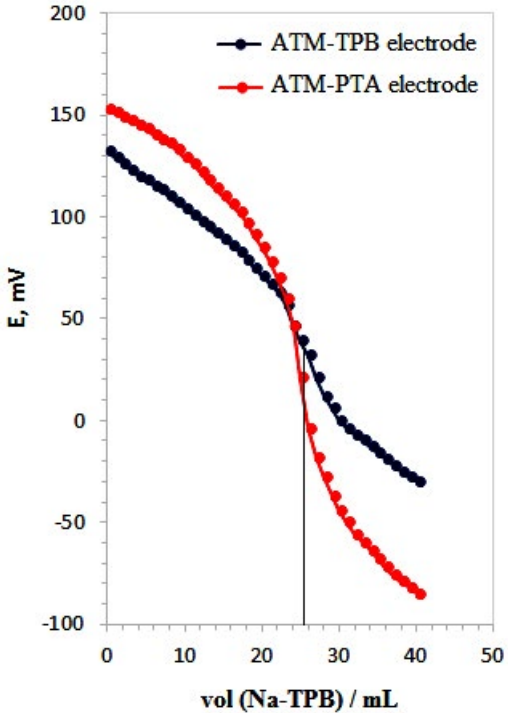

Fig. 6. Potentiometric titration curve of 25.0 mL 1.0×10^{-3} M atomoxetine hydrochloride solution with 1.0×10^{-3} M Na-TPB standard solution using ATM-TPB and ATM-PTA electrodes.

by the present electrodes suggesting that they will be useful tools to assess the drug in biological samples. Experiments were conducted by spiking urine and serum samples with appropriate amounts of ATM ions. Low volume urine (1.0 mL) and serum (0.5 mL) samples gave results with best recovery suitable for low interference. The measured potentials were used to calculate the corresponding concentrations using the calibration curve. As can be seen in Table 3, the results were acceptable and reproducible with quantitative recovery of atomoxetine showing that the proposed sensors can be employed for quantification of the drug in biological fluids.

3. 11. 3. Titration of Atomoxetine Hydrochloride Solution with Na-TPB Solution

Potentiometric titrations involve detection of the end-point at a drastic change in the concentrations of the reactants causing a big shift in the electrode potential. 25.0 mL-samples of 1.0×10^{-3} M of atomoxetine hydrochloride solution were titrated successfully against 1.0×10^{-3} M Na-TPB standard solution using the present electrodes ATM-TPB and ATM-PTA. The data, plot in Fig. 6, clearly show a steep potential jump at the end point indicating completeness of the titration. Na-TPB reacts with the drug forming an ion-pair complex and causes its gradual depletion in solution and concomitant drop in the corresponding measured potential. ATM-PTA sensor provided a better response (a steeper titration curve with sharper end point), a reasonable result for having a higher molar mass and less solubility in the test solution. In brief, the present electrodes can be dependently used as indicators in determination of atomoxetine drug in solutions.

3. 11. 4 Statistical Treatment of Results

The results obtained for the above method were compared with the values obtained from the values from the published method.[63] F-test was used for comparing the precision of the two methods and t-test for comparing the accuracy.[64] The estimated F and t-test values in Table 3 were less than the critical (tabulated) ones. Therefore, there is no significant difference between the precisions or the accuracies of the methods at 95% confidence levels and the obtained results indicated a reasonably fair agreement of the present and official methods.

4. Conclusions

Two carbon paste atomoxetine-sensitive electrodes were fabricated that employ the various desired characteristics of the composite materials. Their properties comprise lower detection limits 8.0×10^{-7} M and 9.2×10^{-7} M, wider concentration ranges 1.2×10^{-6}–1.0×10^{-2} M and 2.7×10^{-6}–1.0×10^{-2} M, less interferences, and better selectivity. Importantly, these electrodes utilize small particle size, large surface and better conductivity, the favorable characteristics of TiO_2 nanoparticles to effectively improve the electrode response. These electrodes effectively join the characteristics of the composite materials to fulfil the intended target, fabrication of atomoxetine-sensitive electrodes that were successfully used for determination of atomoxetine in pharmaceutical and biological samples.

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Povzetek

Opisujemo raziskavo za izboljšanje mej zaznave pri elektrodi, selektivni za atomoksetin. Najbolje sta se izkazali preprosti potenciometrični elektrodi z ogljikovo pasto (CPE), osnovani na atomoksetinu, derivatiziranem z tetrafenilboratom (ATM-TPB) ali s fosfovolframovo kislino (ATM-PTA) kot ionskima paroma, z dodanimi nanodelci TiO_2 in z natrijevim tetrafenilboratom (Na-TPB) kot aditivom. Raziskali smo parametre, ki vplivajo na odgovor electrod, kot so: sestava paste, vrsta plastifikatorja, vrsta elektroaktivnega materiala in moteče zvrsti. Elektrodi sta imeli dobre karakteristike, saj so se meje zaznave spustile do $8{,}0 \times 10^{-7}$ M in $9{,}2 \times 10^{-7}$ M, imeli sta široko linearno območje $1{,}1 \times 10^{-6}$–$1{,}0 \times 10^{-2}$ M in $1{,}75 \times 10^{-6}$–$1{,}00 \times 10^{-2}$ M, naklon 58,7 ± 0,5 mV/dekado in 67,2 ±0 ,8 mV/dekado. Pomembno je tudi, da je odčitek potenciala postal bolj stabilen in je bil hitreje dosežen v prisotnosti aditivov. Selektivnost za učinkovino nasproti drugim zvrstem, kot so anorganski in organski kationi, pa tudi različne pomožne snovi, ki so lahko prisotne v farmacevtskih pripravkih, je bila visoka in njihov učinek na odgovor elektrod je bil zanemarljiv. Senzorja smo kot indikatorski elektrodi uspešno uporabili za določitev učinkovine v farmacevtskih pripravkih, urinu in serumu z dobro točnostjo, izvrstnim izkoristkom in učinkovitostjo.