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Full Paper

Novel Validated Potentiometric Methods for the Determination of Torasemide in Bulk Drug, in Formulations and in Plasma

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Abstract- Three novel techniques for the selective determination of torasemide (TOS) in bulk powder, in formulations and in plasma were described. The three techniques were the construction and electrochemical response characteristics of novel poly (vinyl chloride) matrix membrane sensors for torasemide cation based on the use of the ion-association complexes of this cation with tetraphenyl borate, phosphotungestic acid and ammonium reineckate counter anions as ion exchange sites in a plasticized PVC matrix, either as ion selective membranes, microcoated wire or as microsized graphite selective sensors. All these sensors were prepared and fully characterized in terms of composition, life span, usable pH range, response time and temperature. The electrodes were selectively applied for the potentiometric determination of torasemide in pure form, pharmaceutical preparations and in plasma. These sensors showed near Nernstian responses with slopes of 28.3, 28.9, 27.9, 28.0, 30.0, 27.7, 28.5, 29.2 and 27.5 mv over the concentration ranges of 1.0×10^{-6}-1.0×10^{-2} M for all sensors. The electrodes exhibit good selectivity for (TOS) with respect to a large number of inorganic cations, organic cations, sugars and amino acids. The proposed electrodes offer the advantages of simplicity, accuracy and applicability to turbid and colored samples. The behavior of the three sensors in presence of human plasma was also studied and reasonable results were obtained. All the fabricated sensors were validated according to the International Conference on Harmonization (ICH) guidelines and successfully applied for the determination of the studied drug in pure form, pharmaceutical preparations and in plasma without any interference.

Keywords- Torasemide, Sodium Tetraphenyl Borate (NaTPB), Phosphotungestic Acid (PTA), Ammonium Reineckate (ARNC), Potentiometry and Plasma

1. INTRODUCTION

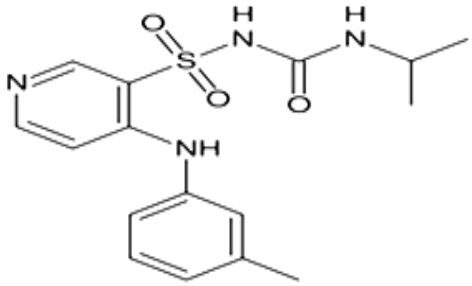

Fig. 1. Structural formula of Torasemide (TOS)

Torsemide (TOS) [1-2] is loop diuretic and is chemically known as 3-pyridine sulfonamide N-[[(1-methylethyl) amino] - carbonyl]-4-[(3-methylphenyl) amino], whose structure is given in Fig. 1. It acts by inhibiting the Na^+/ K^+/ $2Cl^-$ carrier system (via interference of the chloride binding site) in the lumen of the thick ascending portion of the loop of Henle, resulting in the decrease in reabsorption of sodium and chloride. It's mainly used at low doses for the management of hypertension, where in large doses used for management of oedema associated with congestive heart failure [3]. Literature survey reveals that, several methods have been reported for the determination of (TOS), including colorimetry [4], differential–pulse adsorptive stripping voltammetry [5], capillary zone electrophoresis (CZE) [6-7], gas chromatography [8], micellar liquid chromatography [9], and High-performance liquid chromatography (HPLC) [10-18] either alone or in combination. Few chromatographic methods [3-6] have been reported for the estimation of TOS in human plasma and urine. To the best of our knowledge, there is no work in the literature reported about the potentiometric method for the analysis of TOS either in biological fluids, in pharmaceutical formulations or in plasma.

Hence the author has made an attempt to develop precise and sensitive sensors for the estimation of TOS in pure drug, in pharmaceutical formulations and in plasma without previous treatment.

2. EXPERIMENTAL

2.1. Instrument

- Jenway digital ion analyser model 3330 (UK) with Ag/AgCl double junction reference electrode No. 924017-LO-Q11C containing 10% (W/V) KNO_3 solution in the outer compartment
- Jenway (UK), No. 924005-BO3-Q11C glass electrode
- Bandelin sonorox, Rx 510 S, magnetic stirrer (Hungarian)

- Thermostatic shaker Schutzart DIN 40050-IP 20, 1 Nenn temp: 100 ºC, Type: WB 14

2.2. Materials

2.2.1. Reference samples

Torasemide was kindly provided by Apex Pharma-Egypt and certified to contain 99.75%.

2.2.2. Pharmaceutical preparations

Examide® (5, 10 and 20 mg) tablets: batch numbers: MT2480710, MT0420112 and MT3411010 manufactured Apex Pharma-Egypt, Egypt Company. Each tablet was labeled to contain 5, 10 and 20 mg; respectively of torasemide.

2.3. Reagents

All chemicals were of analytical-reagent grade unless otherwise stated and bidistilled deionized water was used throughout.

- Dioctyl phthalate (DOP); Sigma
- Dioctylsebacate (DOS); Sigma
- Poly (vinyl chloride) (PVC) of high molecular weight; Fluka Chemie GmbH, Germany
- Sodium hydroxide, 1 M aqueous solution; Prolabo
- Hydrochloric acid, 1 M aqueous solution; Prolabo
- Tricresyl phosphate (TCP); Aldrich
- Tetrahydro furan (THF); BDH
- Graphite rod
- Sodium tetraphenyl borate (NaTPB), phosphotungestic acid and ammonium reineckate $NH_4[Cr(NH_3)_2(SCN)_4]$ in concentration of 1.0×10^{-2} M were prepared from material of analytical Grade purity
- Frozen human plasma was obtained from VACCERA

2.4. Standard solutions

2.4.1. Torasemide stock solution (1×10^{-1} M)

It was freshly prepared daily by transferring 3.48 g of TOS into 100 ml volumetric flask, dissolving in distilled water and tightly closed.

2.4.2. Torasemide working solutions (1×10^{-7} to 1×10^{-2} M)

They were freshly prepared by suitable serial dilution from their stock solution of (1.0×10^{-2} M) using distilled water.

2.5. Procedures

2.5.1. Sensors preparation and calibration

A 50 ml aliquot of 1.0×10^{-2} M aqueous torasemide solutions was mixed with 50 ml of aqueous 1.0×10^{-2} M aqueous NaTPB, aqueous phosphotungestic acid (PTA) and aqueous ammonium rhenickate (Amm. RNC), respectively and continuously stirred. Each ion exchanger complex was precipitated, filtered off through a G4 sintered glass crucible, washed thoroughly with bi-distilled water, dried at room temperature and ground to a fine powder. Elemental analysis of the formed complex confirmed the formation of drug: ion exchanger in a ratio of 1:2 .

A 10 mg of torasemide ion exchanger was mixed with 350 mg of DOP plasticizer and 190 mg of PVC powder and dissolved in 5 ml of THF. The solution was poured into Petri dishes (5 cm diameter) and then the following procedure was followed:

2.5.1. A. Fabrication and calibration of sensors 1, 1`and 1 ``

The solvent in the previously prepared solutions was left to evaporate slowly at room temperature. The membrane formed was used for sensor construction as described in Moody et al procedure [19]. A master membrane of 0.1 mm thickness was obtained. From the master membrane, a disk (about 8 mm diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of the electrode glass body. A solution containing equal volume of 1.0×10^{-2} M potassium chloride and 1.0×10^{-2} M torasemide was used as an internal reference solution. Ag/AgCl wire (1 mm diameter) was immersed in the internal reference solution as an internal reference electrode. The sensors was preconditioned by soaking overnight in a 1.0×10^{-2} M torasemide solution before use and stored in distilled water between measurements. The electrochemical cell for potential measurements was: Ag/AgCl (internal reference electrode)/1.0×10^{-2} M torasemide, 1.0×10^{-2} M KCl (internal reference solution)//PVC membrane//test solution (pH 3-5)//Ag/AgCl double junction reference electrode. The membrane sensors were calibrated by immersion in 1.0×10^{-2}-1×10^{-7} M torasemide solution and allowed to equilibrate with constant stirring in conjunction with a reference electrode. The sensors were stored in bidistilled deionized water between measurements. The electrode potential was recorded as a function of torasemide concentration. The calibration plot obtained was used for subsequent measurements of unknown torasemide concentrations.

2.5.1. B. Procedure for Preparation of microcoated wire sensors (sensor 2,2`,2 `')

The Petri dishes prepared under 2.5.1.A. were covered with filter paper and left to stand for one hour to allow slow evaporation of the solvent, producing the master thick PVC solution.

The covers were removed for a length of about one cm at both ends of an insulated platinum wire. One end of the wire was immersed in the previously prepared PVC solution and left to stand for 10 min. to allow complete air drying, forming a thin membrane around the wire end.

Immersing and air drying of the wire were repeated until a globular membrane of about 3 mm diameter around the wire end was formed. The resultant dry coated wire membrane sensors had to be conditioned by soaking in 1.0×10^{-2} M drug solution for 3 h and had to be stored in the same solution when not in use. The electrochemical cell for potential measurements was: Platinium wire//PVC membrane//test solution (pH 3-5)//Ag/AgCl double junction reference electrode.

The potential readings of stirred 1.0×10^{-2}-1.0×10^{-7} M torasemide solution were measured at 25±1^{o}C and recorded after stabilization to ±0.2 mv. A calibration graphs were constructed and used for subsequent measurements of unknown torasemide test solutions.

2.5.1. C. Procedure for Preparation of microsized graphite sensors (sensor 3, 3`and 3``)

A graphite rod (5 mm in diameter and 15 mm long) was inserted in a polyethylene tube, such that its tip is exposed (5 mm diameter & 0.3 mm length) from the other end of the protruded rod served as a measuring surface. This end of the rod was washed with acetone, dried in air for 3 h, and dipped rapidly into the previously prepared master thick PVC solution (2.5.1B). The solvent was allowed to evaporate in air after each dipping, and the dipping process was repeated 4-6 times to produce a uniform membrane on the surface of the graphite rod. Drops of mercury were added in the polyethylene tube to ensure electrical contact with the connection cable. The coated graphite rod was conditioned by soaking in a 10^{-2} M torasemide solution for 2 h, the sensors stored in the same solution when not in use. The electrochemical cell for potential measurements was: Metallic mercury//graphite rod//PVC membrane//test solution (pH 3-5) Ag/AgCl double junction reference electrode.

Solutions were measured at 25±1^{o}C and recorded after stabilization to ±0.2 mv. A calibration graphs were constructed and used for subsequent measurements of unknown torasemide test solutions.

2.5.2. Direct determination of Torasemide in its pure powdered sample

The prepared electrodes in conjunction with the double junction Ag/AgCl reference electrode were immersed in 50 ml aliquots of solutions of torasemide covering the concentration range of (1×10^{-7}-1×10^{-2} M) into a series of 100 ml beakers. They were allowed to equilibrate while stirring using a magnetic stirrer and the emfs were recorded within ±1 mV. The membrane sensors were washed with double distilled water between measurements. Calibration graphs were plotted relating the recorded potentials *vs*. –log drug concentrations. These calibration graphs or the computed regression equations were used for subsequent measurements of unknown concentrations of torasemide.

2.5.3. Direct potentiometric determination of Torasemide in its pharmaceutical formulations

The content of 10 tablets were powdered and an accurately weighed, portion equivalent to 34.84 mg were transferred to a 100 ml volumetric flask and diluted to volume with distilled water to prepare 1×10^{-3} M aqueous solution of TOS. Suitable dilutions were performed using distilled water to obtain serial of 10^{-6} to 10^{-4} M TOS. Procedure was then completed as under Section 2.5.2. The potential were measured using the three different sensors and the concentration was determined using their corresponding calibration plots.

2.5.4. Direct potentiometric determination of Torasemide in spiked human plasma sample

Nine ml of human plasma were placed into three stoppered shaking tubes (10 ml), and then 1 ml of 10^{-2}, 10^{-3} and 10^{-4} M torasemide was added separately and shaked. The membrane sensors were immersed in conjunction with the Ag/AgCl reference electrode in these solutions. The membrane sensors were washed with water between measurements. The potentials readings produced by immersing the prepared electrodes in conjunction with the double junction Ag/AgCl reference electrode in the prepared solutions were recorded and compared with the calibration plots.

3. RESULTS AND DISCUSSION

Selective membranes in ion selective electrodes (ISEs) have shown both ion exchange and perm-selectivity of the sensor ions [20].

The present study originates from the fact that torasemide behaves as cationic in acidic medium. This fact suggests the use of anionic type of ion exchangers, sodium tetraphenyl borate, phosphotungestic acid and ammonioum renickate with their low solubility products and suitable grain size. The PVC was used as a polymer matrix in fabrication of the nine sensors. Torasemide was found to form 1:2 ion association complexes with NaTPB, PTA and ARNC, as proved by IR data and elemental analysis.

3.1. Sensors fabrication

The nine proposed sensors were prepared and electrochemically TOS behavior evaluated as prospective sensors for TOS according to the IUPAC guidelines [21] (Table 1).

PVC act as regular support matrices for the membrane and reproducible traps for the ions sensed, but its use creates a need for a plasticizer [19]. The influence of the plasticizer type and concentration on the characteristics of the torasemide sensors were investigated by using four different plasticizers with different polarities including: DBP, DOS, TCP and DOP, the use of DOP results in a Nernstian linear plot over a wide concentration range. Also it was found to be the optimum available mediator for the PVC membrane sensors. It plasticizes the membrane, dissolves the ion-association complexes and adjusts both of the membranes

permittivity and ion-exchanger sites mobility to give the highest possible selectivity and sensitivity. The concentration of DOP as a plasticizer for all the proposed sensors was optimized. In recent years, molecular recognition at the surface of solid materials has attracted the interest of researchers who are trying to realize functional materials for chemical sensors. Although, the investigated coated wire sensors consists of membrane of PVC/sensing system/mediator in ratios 34:2:64 without an internal reference system, there is a confident view that the coated wire sensors have an inbuilt reference system which is attributed to the permeability of PVC to both water and oxygen and, thus, setting up an oxygen electrode at the wire membrane interface to function as an internal reference system [19].

3.2. Sensors calibration and response time

Table (1) shows the slopes of lines, response times, detection limits and intervals of linearity over a period of one month for nine different assemblies of each sensor at optimal pH using the recommendations of IUPAC [21-22].

The sensors displayed constant potential readings within 1 mv from day-to-day and the calibration slopes did not change by more than 1 mv per decade over a period of one month for the nine sensors. The slopes of the calibration plots were 28.3, 28.9, 27.9, 28.0, 30.0, 27.7, 28.5, 29.2 and 27.5 mv for the investigated sensors (Fig. 2A, 2B & 2C). Slopes values of the nine electrodes were about 30 mV; the typical value of divalent substances as TOS behaves as divalent anion in the studied experimental pH value. Deviation from the ideal Nernstian slope (30 mV) for these sensors stems from the fact that the electrode responds to the activities of drug anion rather than its concentration. The investigated electrodes exhibit fast response time (5–60 s) and fair stability (7–15 days). The response characteristics of the nine electrodes are summarized in Table 1. The proposed method was compared with a reported one [6], no significant difference was observed.

3.3. Sensors temperature and pH

For quantitative measurements with ISEs, studies were carried out to reach the optimum experimental conditions.

In measurements with the investigated sensors, the experimental conditions were studied to reach the optimum. The potential response displayed by each investigated electrode was monitored as a function of the temperature and the drug concentration in the range of 20-40^{o}C. The suggested electrodes exhibited slight increase in their potentials as the temperature increased, however the calibration graphs obtained at different temperature were parallel .The limit of detection, slop and response time did not significantly vary with variation of temperature, indicating reasonable thermal stability up to 40 ^{o}C. A pH value within the range of 3-5 was found optimum from the point of view of sensor function. Fig. (3A, 3B & 3C) show the potential-pH profiles for 10^{-4} M drug solutions using sensors

1-9, respectively. It's apparent that the sensor responses were fairly constant at pH 3-5. Above pH 5, drug precipitation occurs, while in highly acidic solutions, less than pH 2.5 less Nernestian responses were displayed by sensors.

Table 1. Response characteristics for Torasemide by the proposed sensors

Parameter	***Sensor 1***	***Sensor 1`***	***Sensor 1``***	***Sensor 2***	***Sensor 2`***	***Sensor 2``***	***Sensor 3***	***Sensor 3`***	***Sensor 3``***
Validation of the regression equations									
Slope(mV per decade)	27.8	29.9	28.9	26.9	29.9	28.1	27.4	29.9	28.0
Intercept (mV)	249.1	262.7	256.2	246.4	246.4	262.1	251.8	273.5	262.4
Correlation coefficient (r)	0.9999	1	0.9999	0.9999	0.9999	0.9999	1	1	1
Validation of the responses									
***Response time* (Sec.)**	30	30	30	30	30	30	30	30	30
Working pH range	3-5	3-5	3-5	3-5	3-5	3-5	3-5	3-5	3-5
Conc. range (M)	1×10^{-7}-1×10^{-3}	1×10^{7}-1×10^{-3}	1×10^{7}-1×10^{-3}	1×10^{7}-1×10^{-3}	1×10^{7}-1×10^{-3}	1×10^{7}-1×10^{-3}	1×10^{-7}-1×10^{-3}	1×10^{7}-1×10^{-3}	1×10^{-7}-1×10^{-3}
LOD (M) [a]	3.50×10^{-8}	5.50×10^{-8}	4.50×10^{-8}	6.50×10^{-8}	7.50×10^{-8}	3.50×10^{-8}	5.50×10^{-8}	5.50×10^{-8}	4.50×10^{-8}
Life time (weeks)	6	6	6	6	6	6	6	6	6
Average recovery (%)	98.34	99.15	98.55	98.88	99.36	99.20	98.40	98.52	98.62
R.S.D [b]	0.9	0.9	0.8	0.8	0.9	0.9	0.9	0.8	0.9
Precision									
Repeatability % [c]	100.01 ±0.24	99.92± 0.51	100.00 ±0.33	100.90 ±0.31	99.40± 0.73	100.91 ±0.11	99.39± 0.93	98.99± 0.62	100.71 ±0.38
Intermediate precision %[d]	99.35± 0.40	99.26± 0.17	99.99± 0.29	98.99± 0.50	98.83± 0.58	99.79± 0.09	101.05 ±0.12	101.11 ±0.48	99.95± 0.22

[a] Limit of Detection (LOD) defined as drug concentration obtained at the intersection of the extrapolated high concentration (linear segment) with the low concentration (zero slope segment) of the calibration plot

[b] Results of five determinations .

[c] n=3×3(1×10^{-2}, 1×10^{-3}, 1×10^{-4} M)

[d] n=3×3(1×10^{-2}, 1×10^{-3}, 1×10^{-4} M)

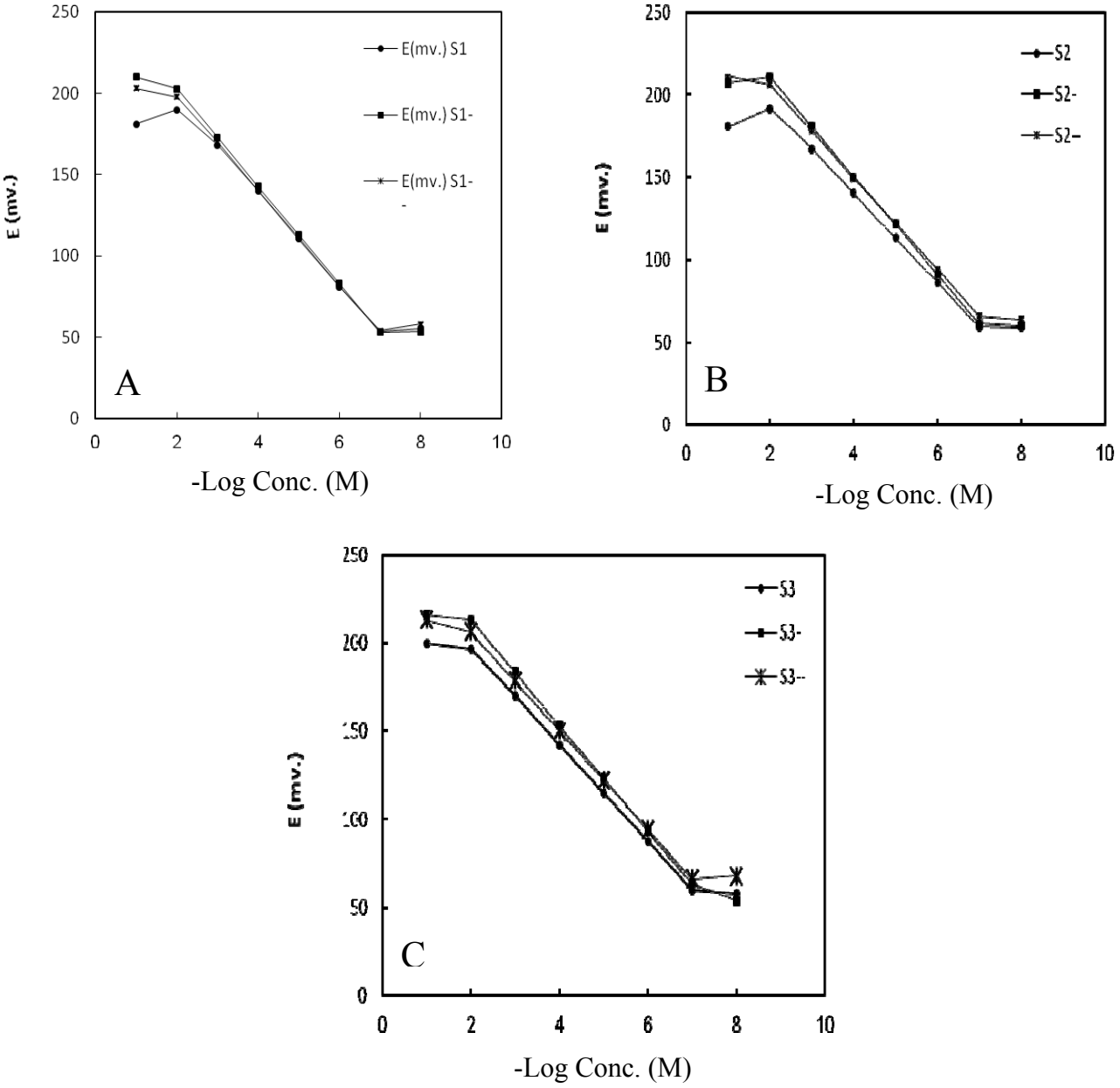

Fig. 2. A) Profile of the potential in mV. To the –Log concentration of Torasemide sensors 1, 1`and 1¨ , B) Profile of the potential in mV. To the –Log concentration of Torasemide sensors 2, 2`and 2`` C) Profile of the potential in mV. To the –Log concentration of Torasemide sensors 3, 3`and 3``

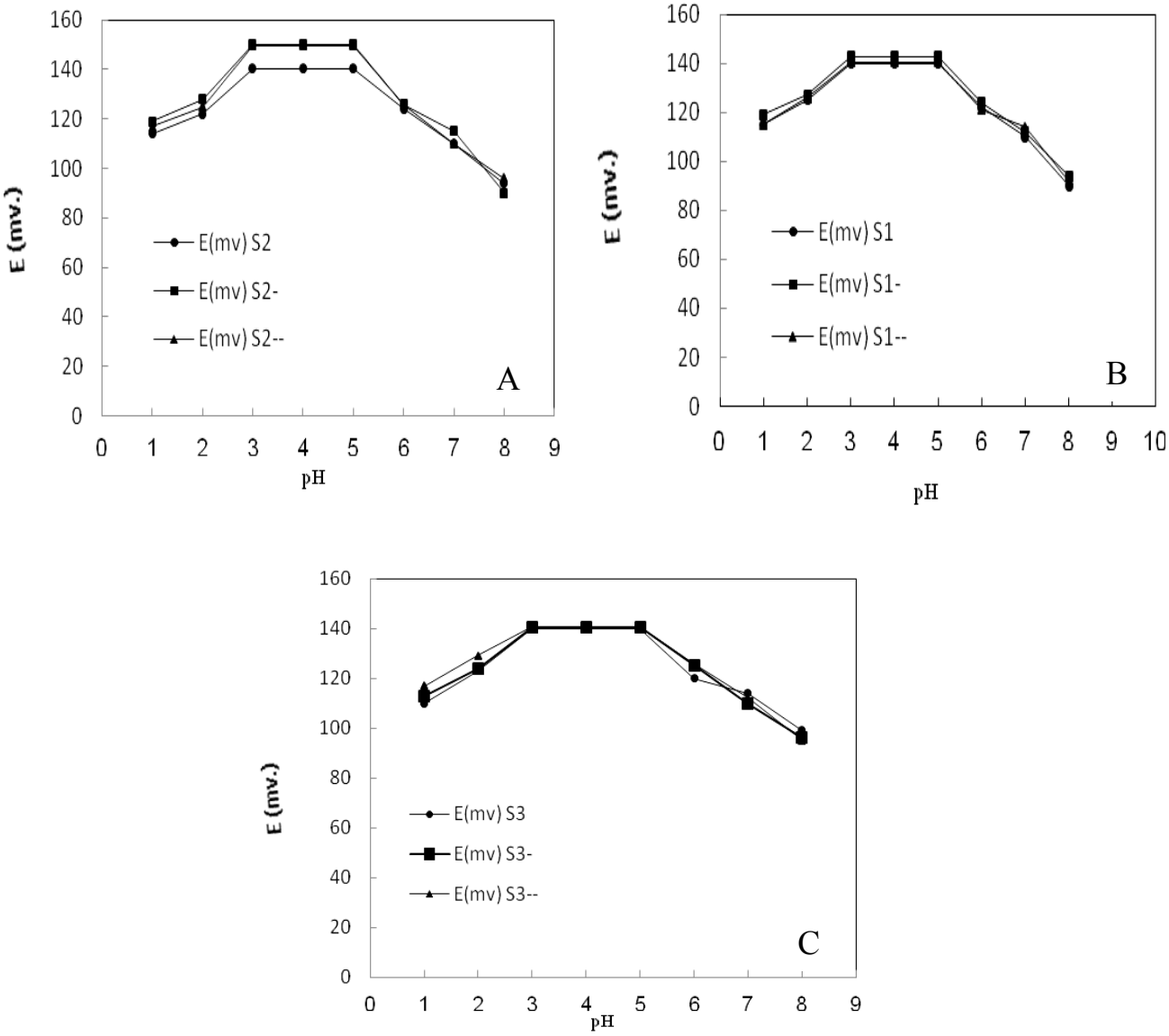

Fig. 3. A) Effect of pH on the response of the studied sensors upon using 10^{-4} M Torasemide (S_1, S_1`, S_1``), B) Effect of pH on the response of the studied sensors upon using $10^{-4}$ M Torasemide ($S_2$, $S_2$`, $S_2$``), C) Effect of pH on the response of the studied sensors upon using 10^{-4} M Torasemide (S_3, S_3`, S_3``)

3.4. Sensors selectivity

The effect of interfering substances upon the performance of the sensors was studied by separate solution method (SSM) (20) using the following equation [21]:

$$-\log\left(K^{Pot}_{Primary\ ion,interferent}\right) = \frac{(ETOS-EM)}{\left[2.303\frac{RT}{ZTOSF}\right]+\left[1+\frac{ZTOS}{ZM}\right]log[TOS]}$$

Where E_{Tos} is the potential measured in 10^{-4} M TOS solution, E_M the potential measured in 10^{-4} M interferent solution, Z_{TOS} and Z_M are the charges of TOS and interfering ion, respectively, and $2.303RT/Z_{TOS}F$ represents the slope of the investigated sensor (mV/concentration decade).

Furthermore, the potentiometric selectivity coefficients of the proposed sensors were calculated in the presence of other related organic and inorganic substances using separate solution method (SSM) [20]. The results revealed that the proposed sensors have reasonable selectivity, (Table 2).

Table 2. Potentiometric selectivity coefficients (average of five measurements) (−log KPot.Torasemide, interferent (of the nine proposed sensors by separate selectivity method (SSM) [20]

Interferent[a]	***Sensor 1***	***Sensor 1`***	***Sensor 1``***	***Sensor 2***	***Sensor 2`***	***Sensor 2``***	***Sensor 3***	***Sensor 3`***	***Sensor 3``***
Lactose	2.2×10^{-3}	3.1×10^{-3}	3.8×10^{-3}	2.5×10^{-3}	4.1×10^{-3}	4.4×10^{-3}	3.2×10^{-3}	2.1×10^{-3}	2.6×10^{-3}
Glucose	3.1×10^{-3}	4.5×10^{-3}	3.9×10^{-3}	3.6×10^{-3}	3.0×10^{-3}	4.0×10^{-3}	3.1×10^{-3}	3.5×10^{-3}	3.9×10^{-3}
Mannitol	1.9×10^{-3}	1.1×10^{-3}	1.4×10^{-3}	2.2×10^{-3}	1.6×10^{-3}	2.1×10^{-3}	2.0×10^{-3}	2.4×10^{-3}	1.4×10^{-3}
Sodium chloride	3.3×10^{-3}	3.2×10^{-3}	2.9×10^{-3}	2.0×10^{-3}	2.4×10^{-3}	2.6×10^{-3}	3.7×10^{-3}	3.5×10^{-3}	3.1×10^{-3}
Potassium chloride	3.3×10^{-3}	3.5×10^{-3}	2.9×10^{-3}	3.0×10^{-3}	2.8×10^{-3}	2.5×10^{-3}	3.3×10^{-3}	3.5×10^{-3}	2.9×10^{-3}
Ammonium chloride	3.8×10^{-3}	4.1×10^{-3}	3.7×10^{-3}	3.7×10^{-3}	3.2×10^{-3}	3.3×10^{-3}	3.0×10^{-3}	2.1×10^{-3}	2.7×10^{-3}
Hydroxypropyl cellulose	2.5×10^{-3}	3.0×10^{-3}	1.9×10^{-3}	2.1×10^{-3}	2.0×10^{-3}	2.4×10^{-3}	2.5×10^{-3}	3.0×10^{-3}	1.9×10^{-3}
Polyethylene glycol	2.2×10^{-3}	2.1×10^{-3}	2.7×10^{-3}	2.6×10^{-3}	2.1×10^{-3}	2.1×10^{-3}	2.2×10^{-3}	2.1×10^{-3}	2.7×10^{-3}
Methylparaben	2.6×10^{-2}	2.5×10^{-2}	2.4×10^{-2}	2.3×10^{-2}	2.4×10^{-2}	2.6×10^{-2}	2.8×10^{-2}	3.0×10^{-2}	2.9×10^{-2}

[a] All interferents above were in the form of 10^{-3} M, aqueous solutions

Table (3) shows the results obtained for the determination of torasemide in pharmaceutical formulations that proves the applicability of the method, as demonstrated by the accurate and precise percentage recovery. Placebo experiments contain all additives in the

same ratio as that used in pharmaceutical formulations were investigated. Thus, analysis was carried out without prior treatment or extraction. The proposed TOS-selective sensors have shown excellent selectivity.

On application to human plasma, It is found that high accuracy (recovery) and precision (RSD) were given by the studied sensors. Furthermore no adverse effect on the responses of the electrodes was observed when the drug was spiked with the human plasma samples without prior removal of the protein as shown in Table (3).

As for robustness, determining 10^{-5}, 10^{-4} and 10^{-3} M solutions of TOS for the nine studied electrodes preparing the membrane using oNPPE as plasticizer instead of DOP was studied; the methods demonstrated efficient stability. To study the methods, ruggedness, 10^{-5}, 10^{-4} and 10^{-3}M solutions of TOS were analyzed by the nine studied electrodes using Jenway 3310 digital ion analyzer instead of 3330 Model; proved stability of the methods upon change of the instrument.

Table 3. Determination of Torasemide in its pharmaceutical preparation the proposed sensors Conclusions

	Drug Recovery [a] %									**HPLC[(6)]**
	Sensor 1	**Sensor 1`**	**Sensor 1``**	**Sensor 2**	**Sensor 2`**	**Sensor 2``**	**Sensor 3**	**Sensor 3`**	**Sensor 3``**	
Examide 5 mg(B.N.M T 2480710)	100.20± 0.18	99.57±0 .22	100.50 ±0.23	99.47 ±0.21	98.77± 0.35	99.09±0 .20	100.21 ±0.26	98.28±0 .27	100.28± 0.31	100.00±0 .33
Examide 10 mg (B.N.MT 3411010)	99.27±0 .38	99.48±0 .28	99.98± 0.23	100.0 0±0.3 0	100.14 ±0.36	98.59 ±0.34	99.24± 0.29	99.26±0 .35	99.96±0 .48	
Examide 20 mg (B.N.MT 0420112)	100.12± 0.14	100.31± 0.51	99.51± 0.28	99.62 ±0.16	98.99± 0.35	100.09± 0.11	98.52± 0.53	98.52±0 .53	99.66±0 .57	

[a] All interferents above were in the form of 10^{-3} M, aqueous solutions

4. CONCLUSIONS

The described novel sensors are sufficiently simple, cheap and selective for the quantitative determination of torasemide in pure form, plasma and pharmaceutical

formulations. The use of the proposed sensors offers advantages of fast response and elimination of drug pretreatment or separation steps. They can therefore, be used for routine analysis of torasemide in quality control laboratories.

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