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Ion Selective Membrane Electrodes for Stability-Indicating Determination of Amisulpride

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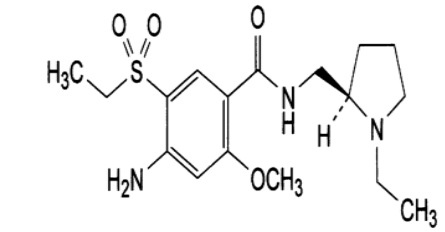
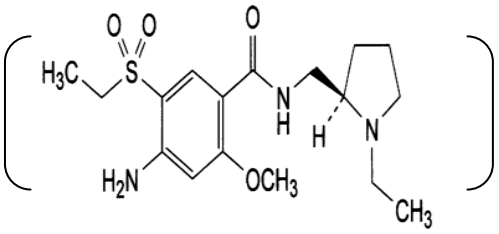
Abstract- This work describes the construction and electrochemical response characteristics for three different polyvinyl chloride (PVC) membrane sensors for determination of amisulpride in presence of its degradation products and commonly used excipients. The first two sensors are based on the ion association complexes of amisulpride cation with sodium tetraphenyl borate (TPB) [sensor 1] or ammonium reineckate (R) [sensor 2] counter anions as ion exchange sites in PVC matrix. β-cyclodextrin (β-CD)-based technique with TPB as a fixed anionic site in PVC matrix was used for fabrication of the third membrane sensor [sensor 3]. The performance characteristics, sensitivity and selectivity of these electrodes in presence of amisulpride degradation products were evaluated according to IUPAC recommendations. Fast, stable and linear response was obtained for amisulpride over the concentration range 1×10^{-6}-1×10^{-2} M for sensors 1 and 3 while for sensor 2 it was found to be 1×10^{-5}-1×10^{-2} M. The proposed sensors showed stable Nernstian responses of 29.1, 28.2 and 31.1 mV per concentration decade with sensors 1, 2 and 3, respectively. These sensors exhibit fast response time (10-20 s) and good stability (4-6 weeks). The direct potentiometric determination of amisulpride in its pure form using the proposed sensors gave average recoveries of 99.93±0.72, 100.01±0.93 and 99.94±0.87 for sensors 1, 2 and 3, respectively. The sensors were used for determination of amisulpride, in pure form, in presence of its degradation products, in tablets and in plasma. Validation of the method shows suitability of the proposed sensors for use in the quality control assessment of amisulpride and for routine analysis as stability indicating method. The developed method was found to be simple, accurate and precise when compared with a reported RP-HPLC method.

Key words- Amisulpride, Ion Selective Electrodes, Potentiometry, Pharmaceutical Analysis, Stability Indicating Methods

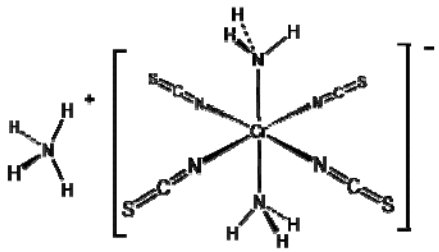
1. INTRODUCTION

Amisulpride (Fig. 1) is a substituted benzamide chemically designated as 4-Amino-N-[[(2RS)-1-ethylpyrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-methoxybenzamide [1,2]. It is classified as a second generation (atypical) antipsychotic which is mainly used in management of behavioral disorders and for ttreatment of schizophrenia. It is claimed to exert its antipsychotic action via a selective blockade of central dopamine D2/D3 receptors [3].

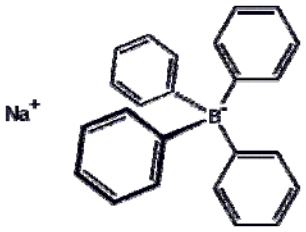




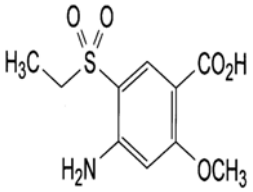
2TPB$^-$
Or
2R$^-$



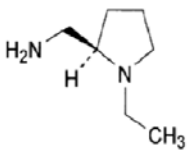
Ammouium Reineckate



Sodium tetraphenyl borate



Degradate I
(M.Wt. 259)



Degradate II
(M.Wt. 128)

Fig. 1. Chemical Structure of amisulpride, its complexes either with sodium tetrapheyl borate or ammonium reineckate and its induced hydrolytic degradates

Various analytical procedures have been reported for determination of amisulpride including nonaqueous [1], HPLC [4-16], also amisulpride was estimated in pharmaceutical preparations utilizing different spectrophotometric techniques [17]. Furthermore capillary electrophoretic methods were developed for analysis of amisulpride [18,19]. From the literature review, it was found that none of these methods analyzed amisulpride in presence of its degradation products. Additionally, most of these methods as HPLC and CE involve time-consuming procedures and use sophisticated instruments.

Tetraphenyl borate and ammonium reinickate were reported as ion exchanges for basic drugs [20,21]. They have been used in the formation of many sensors [22]. Cyclodextrins are optically active oligosaccharides that form inclusion compounds in the aqueous and in solid state with organic molecules. By alkylation of the hydroxyl groups in the 2-, 3- and 6-positions, cyclodextrins become lipophilic. This enables their incorporation in plasticized PVC membranes and use as ionophores in ion-selective electrodes [23-25]. They were previously applied as sensor ionophores to potentiometric ISEs for the determination of drugs [26,27].

In this work, it has been found that amisulpride reacts with tetraphenyl borate or ammonium reinickate to form water insoluble ion association complex. The high lipophilicity and remarkable stability of these complexes suggested their selective use as electroactive materials in PVC matrix membrane sensors for the determination of the studied drug in the presence of degradates and related substances either in pure form, pharmaceutical preparation and spiked human plasma.

2. EXPERIMENTAL

2.1. Apparatus

Potentiometric measurements were made at 25±1^{o}C with a Jenway digital ion analyzer model 3330 (Essex UK) with Ag/AgCl double junction reference electrode No. Z113107-1EAPW (Aldrich Chemical Co.). A Jenway pH glass electrode No. 924005-BO3-Q11C, (Jenway, Essex, UK) was used for pH measurements. A magnetic stirrer, Bandelin Sonorex model Rx510S (Budapest, Hungary) was used.

2.2. Reagents and Solvents

All chemicals were of analytical grade and bidistilled water was used. Tetrahydrofuran (THF) 99% (Lab scan), high molecular weight (10000) polyvinylchloride (PVC) powder (Aldrich), sodium tetraphenyl borate (Na TPB) (Aldrich), ammonium reineckate (R) and dibutylsebathete (DBS) were obtained from Sigma, phosphate buffer pH 4.5 was prepared [1] and plasma was supplied by VACSERA (Giza, Egypt). (2-Hydroxy propyl) β-cyclodextrin

from Fluka (Steinhein,Germany). Sodium hydroxide, HCl and potassium chloride were purchased from Prolabo (Pennsylvania, USA).

2.3. Materials

2.3.1. Pure Samples

Amisulpride (Batch No. 20107) was kindly supplied by Al-Andalus Medical Company, Cairo-Egypt. Its purity was found to be 99.79 according to the reported HPLC method [16].

2.3.2. Market Samples

Amipride tablets (Batch No.90989 and), labeled to contain 50 mg amisulpride/tablet (Al-Andalus), were used.

2.4. Standard Solutions

2.4.1. Amisulpride Stock Solutions

(1×10^{-1} M) in either water or phosphate buffer pH 4.5±0.1 were prepared by transforming 3.695 g of amisulpride powder into 100 mL measuring flask, 1 mL 0.1 M HCl and 49 mL of either water or phosphate buffer pH 4.5 were added, shaken and completed to volume with same solvent.

Working Standard Solutions; Amisulpride working solution (1×10^{-7}-1×10^{-2} M) were prepared by suitable dilution from its stock solution using phosphate buffer pH 4.5.

2.5. Preparation of Pure Degraded Sample

Stock solution of degradation products (1×10^{-2} M) was prepared from complete degradation of 10 mL of 1×10^{-1} M standard solution of amisulpride in 4 M HCl, refluxed for 4 h the degraded sample was neutralized by 4 M NaOH to pH 7 and then transferred quantitatively into 100 mL measuring flask and completed to volume with the phosphate buffer.

2.5.1. Laboratory prepared mixtures

Different aliquots of amisulpride working solution (1×10^{-4} M) were mixed with its complementary aliquots from the corresponding degradation products solution (1×10^{-4} M) to prepare mixtures containing different ratios of amisulpride and its degradation products.

2.6. Procedures

2.6.1. Preparation of the membrane sensors

For sensor 1, 10 mL of 1×10^{-2} M amisulpride aqueous solution was mixed with 10 mL of a saturated aqueous solution of TPB. The resulting precipitate was filtered, washed with cold water, allowed to dry at room temperature then grounded to fine powder. Elemental analysis for carbon, hydrogen and nitrogen was carried to study the formation of the complex. In a

glass Petri dish (5 cm diameter), 10 mg of the previously prepared ion association complex was mixed thoroughly with 0.35 mL of (DBS) then 0.19 g PVC was added. This mixture was dissolved in 5 mL (THF). For sensor 2, the same procedure described was followed using saturated aqueous solution of R instead of TPB. While sensor 3 was prepared by mixing 0.04 g β-CD with 0.35 mL DBS and 0.01 g TPB in a glass petri dish (5 cm diameter). PVC, 0.18 g, previously dissolved in 6 mL THF was added and the contents were mixed thoroughly. The three petri dishes were covered with a filter paper and left to stand overnight to allow solvent evaporation at room temperature. A Master membrane with thickness of 0.1 mm was obtained and used for the construction of the electrodes.

2.6.2. Preparation of the electrode assembly

From the prepared master membranes (sensors), a disk (≈5mm diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of the glassy electrode body. Equal volumes of 1×10^{-2} M amisulpride and 1×10^{-2} M KCl was mixed and this solution was used as internal solution for the three electrodes. Ag/AgCl wire (1mm diameter) was immersed in the internal reference solution as an internal reference electrode. The electrochemical cell arrangement was Ag–AgCl/internal solution, 10^{-2} M amisulpride, 10^{-2} M KCl/PVC membrane sensor/test solution/Ag–AgCl, KC1(saturated). The prepared sensors were conditioned by soaking for 24 h into 1×10^{-2} M aqueous drug solution and stored in the same solution when not in use.

2.6.3. Sensors Calibration

The prepared electrodes were immersed in conjugation with the double junction Ag/AgCl reference electrode in phosphate buffer pH 4.5±0.1 solution of amisulpride in the range of 1×10^{-7} to 1×10^{-2} M. They were allowed to equilibrate whilst stirring and recording the emf readings within ±1 mv. The membrane sensors were washed between measurements with water. The mV-concentration profiles were plotted. The regression equations for the linear part of the curves were computed and used for subsequent determination of unknown amisulpride concentrations.

2.6.4. Selectivity Measurements

Potentiometry selectivity coefficient (K^{Pot}_{Ami}) were evaluated according to IUPAC guidelines using the separate solutions method [28] in which the potential of cell compromising the membrane electrode and a reference electrode is measured with two separate solutions, A and B where A (Amisulpride ions) and B (interfering ion) at the same activity $a_A=a_B$. The emf for A and B are measured values, respectively. Different interfering anions at a concentration of 1×10^{-3} M at a suitable pH (phosphate buffer) were utilized and the results were obtained using the equation:

$$-LogK_{AB}^{Pot} = \frac{E_1 - E_2}{2.303RT/ZAF}K + \frac{1 - Z_A}{Z_B}Loga_A$$

Where K^{Pot}_{AB} is the potentiometric selectivity coefficient, E_1 is the potential measured in 1×10^{-3} M amisulpride solution, E_2 is the potential measured in 1×10^{-3} M interferent solution, 2.303RT/ZAF represents the slope of the investigated sensors, a_A the activity of amisulpride and Z_A and Z_B are charges on amisulpride and interfering ion, respectively.

2.6.5. Application to Pharmaceutical Preparation

Ten tablets of amipride tablets were weighed and powdered. An amount of the powdered tablets equivalent to 18.475 mg amisulpride was accurately transferred into a 50 mL volumetric flask and the volume was completed to the mark with phosphate buffer (pH 4.5) to prepare a 1×10^{-3} M solution of amisulpride. The emf produced by immersing the prepared electrodes in conjunction with double junction Ag/AgCl reference electrode in the prepared solution was determined then the concentration of amisulpride was calculated from the regression equation of the corresponding electrode.

2.6.6. Application to Laboratory Prepared Mixtures

The emf produced when immersing the suggested electrode and the reference electrode in the lab prepared mixtures was measured and the concentration of amisulpride was determined from the corresponding regression equation.

2.6.7. Application to Plasma Sample

Nine mL of spiked human plasma were placed into two stoppered tubes, and then 1 mL of 1×10^{-2} and 1×10^{-3}M amisulpride were added separately and shaken. The membrane sensor was immersed in conjunction with the double junction Ag/AgCl reference electrode in this solution and complete as previous section.

3. RESULTS AND DISCUSSION

Sensors for basic drugs are based on the use of the ion association complexes of these species with one of anionic compounds forming ion-association complexes embedded in PVC matrix membrane with suitable solvent and mediators [29].

In the present work amisulpride behaves as a cation in acidic medium, due to presence of the amino groups. This fact suggests the use of anionic type of ion exchangers, sodium tetraphenyl borate and ammonium reineckate. The PVC was used as a polymer matrix in fabrication of membrane sensors. The drug was found to form 1:2 ion association complexes with each TPB and R as proved by elemental analysis. Calculated results were agreed with the found ones, also the Nernstian response of the suggested sensors was about 30 mV; which

is the typical value for divalent drugs [28]. The suggested structural formulae are shown in Fig. 1. The PVC acts as a regular support matrix for the membrane but its use creates a need for a plasticizer [30]. In the present investigation, dibutylsebacate was found to be the optimum available plasticizer for the PVC membrane sensors. It plasticizes the membrane, dissolves the ion-association complexes and adjusts both of the membrane permittivity and ion-exchanger sites mobility to give highest possible selectivity and sensitivity [20]. Other plasticizers such as nitrophenyl phenyl ether, tricresyl phosphate and castor oil failed in dissolving the ion association complexes and thus gave noisy response. β-CD- based technique was used in the preparation of sensor 3 where amisulpride is extracted into the membrane via inclusion into the β-CD cavities through inclusion-complex formation [31].

Electrochemical performance characteristics of the proposed sensors were systematically evaluated according to IUPAC standards [28].

Table 1. Response Characteristics for Amisulpride, PVC Membranes

Parameters	**Sensors**		
	Sensor I	**Sensor II**	**Sensor III**
Slope (mV/decade)	29.1	28.16	31.1
Intercept (mV)	187.6	140.26	211.4
Correlation coefficient	0.9998	0.9996	0.9999
Response time (s)	10-20	10-20	10-20
Working pH range	3-7	3-6	4-7
Concentration range (M)	10^{-6} - 10^{-2}	10^{-5} - 10^{-2}	10^{-6} - 10^{-2}
Life time (weeks)	4-6	4-6	4-6
Average recovery (%)	99.93	100.01	99.94
RSD[(a)]	0.72	0.93	0.87
Repeatability[(b)]	0.83	0.96	0.85
Intermediate precision[(c)]	1.13	1.27	0.91
Ruggedness[(d)]	98.49	99.13	100.38

(a) Results of five determinations

(b) Average of three different concentrations repeated three times within the day (n=9)

(c) Average of three concentrations repeated three times in three successive days

(d) Average recovery percent of determining 1×10^{-4} and 1×10^{-3} M of amisulpride for the studied electrodes using a Jenway 3310 digital ion analyzer instead of 3330

Table 1 shows the slopes of lines, response times and intervals of linearity over a period of 6 weeks for 3 different assemblies of each sensor at optimal pH and temperature at 25±1^{o}C

using the recommendations of IUPAC [28]. The sensors displayed constant potential readings within 1 mV from day to day and the calibration slopes did not change by more than 2 mV per decade over a period of about 1 month for PVC sensors.

Table 2. Potentiometric Selectivity Coefficients (K_{pot}) of Amisulpride PVC Membrane Based Sensors

Interferent[(a)]	**Selectivity coefficient**[(b)]		
	Sensor I	**Sensor II**	**Sensor III**
Degradate I	9.52×10^{-3}	9.85×10^{-3}	8.71×10^{-3}
Degradate II	6.52×10^{-3}	7.27×10^{-3}	9.48×10^{-3}
NH_4Cl	2.77×10^{-3}	2.96×10^{-3}	1.94×10^{-3}
NaCl	13.9×10^{-3}	15.19×10^{-3}	6.61×10^{-3}
KCl	2.64×10^{-3}	3.85×10^{-3}	7.05×10^{-3}
$CaCl_2$	11.74×10^{-3}	12.74×10^{-3}	4.72×10^{-3}
Glucose	8.55×10^{-3}	10.49×10^{-3}	7.39×10^{-3}
Lactose	3.91×10^{-3}	5.07×10^{-3}	3.32×10^{-3}
Starch	4.49×10^{-3}	6.33×10^{-3}	4.17×10^{-3}
Talc	5.29×10^{-3}	8.16×10^{-3}	1.89×10^{-3}
Urea	0.41×10^{-3}	1.06×10^{-3}	3.95×10^{-3}
Veralipride	7.85×10^{-3}	9.52×10^{-3}	8.56×10^{-3}

(a) All interferents were in the form of 1×10^{-3} M

(b) Each value is the average of three determinations

In measurements with the investigated sensors the experimental conditions were studied to reach the optimum ones. A pH value within the range of 3-7 for sensor 1, 3-6 for sensor 2 and 4-7 for sensor 3 was found optimum. Figs. 2 and 3 show the potential-pH profiles for 1×10^{-3} and 1×10^{-4} M drug solutions using the investigated sensors. It is apparent that the sensor responses are fairly constant in phosphate buffer solution of pH 4.5. Above pH 8, drug precipitation occurs while in highly acidic solution less than pH 3 unstable nernestian responses were displayed by the sensors. At pH range of 3-7, drug cations are dissociated and therefore they become sensible. The response time of the electrodes was tested for concentrations of the drug from 1×10^{-7} to 1×10^{-2} M. The measurements were characterized by a fast stable response within 10-20 s. Long terms potential stability of the proposed sensors was fairly good as it was practically unchanged over a period of 4-6 weeks. The potentiometric response of the three studied electrodes at the optimum pH was linear with constant slopes over a drug concentration range 1×10^{-6}- 1×10^{-2} M for sensors 1 and 3 and 1×10^{-5}- 1×10^{-2} M for sensor 2. The suggested electrodes exhibited a Nernstian slope of 29.1,

28.16 and 31.1 mV per concentration decade with sensors 1, 2 and 3, respectively as shown in Fig. 4. The accuracy and precision of the proposed membrane sensors for the quantitation of blind samples of amisulpride was assessed by using the proposed sensors. The results showed average recoveries of 99.93±0.72, 100.01±0.93 and 99.94±0.87 for sensors 1, 2 and 3, respectively, as declared in Table 1. The performance of the studied sensors in the presence of some nitrogenous compounds such as degradation products I or II, veralipride, amines, and some inorganic cations, was assessed by measuring and comparing the potentiometic

Selectivity coefficient values (K^{pot}_{Ami}). The separate solution method with a fixed concentration of the interferent (1×10^{-3} M) was used for evaluation of the selectivity. The results obtained by the developed sensors, Table 2, showed reasonable selectivity for the sensors for amisulpride in presence of any of the mentioned interferents.

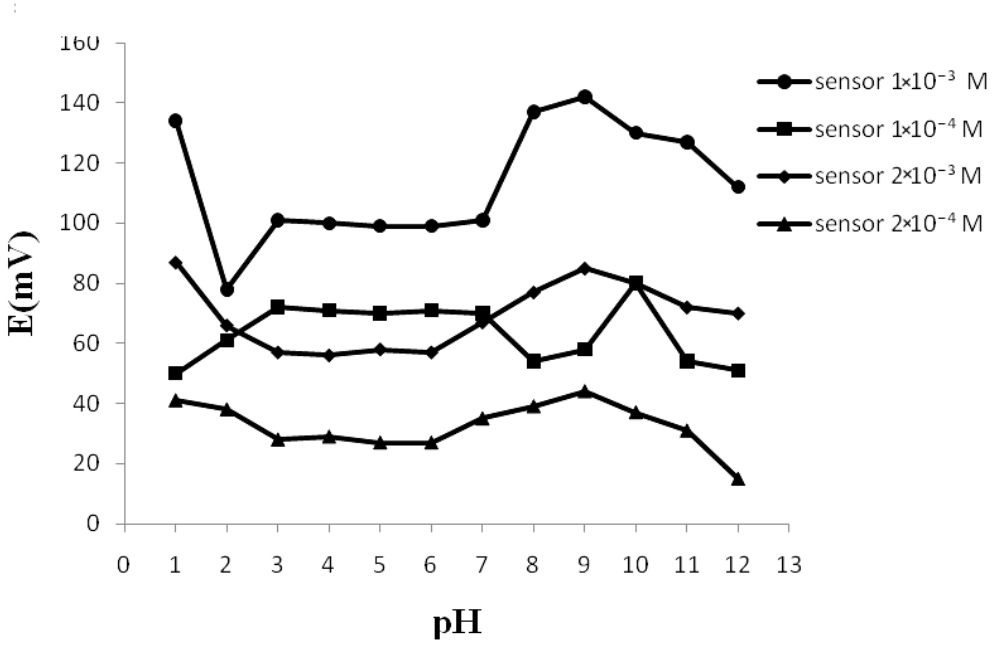


Fig. 2. Effect of pH on the response of sensors 1 and 2

To study the method's ruggedness, 1×10^{-4} and 1×10^{-3} M solutions of amisulpride were analyzed by the suggested electrode using Jenway 3310 digital ion analyzer instead of 3330 Model. Results proved the stability of the method upon changing the instrument (Table 1). Pharmaceutical additives, diluents and ingredients commonly used in drug formulations such as lactase, sucrose, starch and talc did not show any interference, (Table 2). Thus, analysis was carried out without prior treatment or extraction. The investigated sensors were successfully used for the determination of amisulpride in amipride tablets as shown in Table 3.

In the British pharmacopeia [1] degradates I and II were mentioned to be present as impurities. Improper storage conditions can cause degradation which may decrease the

potency of the drug. This fact motivated us to determine the intact drug in the presence of its degradation products.

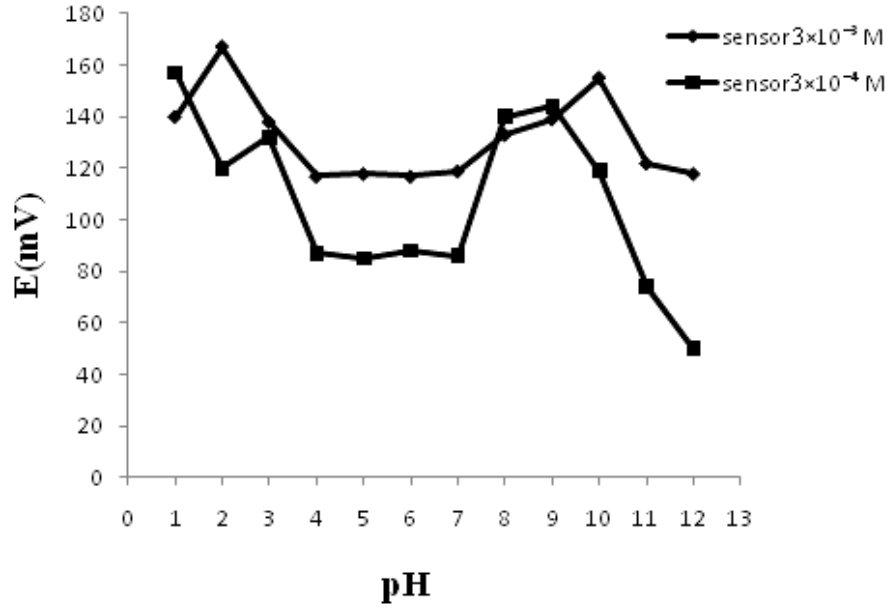


Fig. 3. Effect of pH on the response of sensors 3

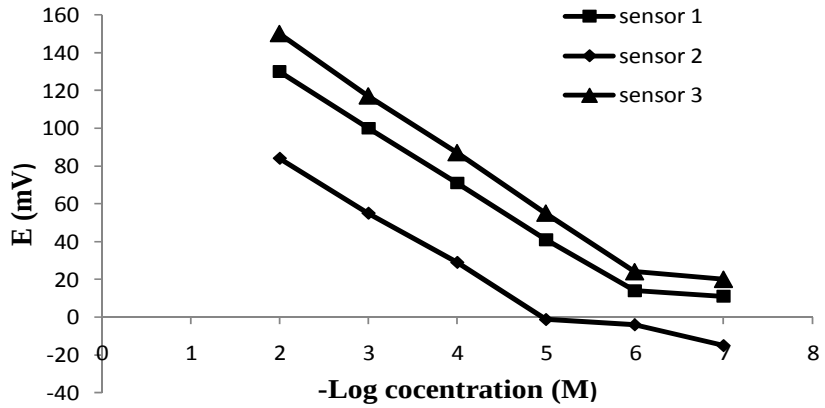


Fig. 4. Potentiometric profile of sensor 1,2 and 3

Table 3. Determination of Amisulpride in its pharmaceutical formulation by the three p roposed sensors and the reported HPLC method

Pharmaceutical formulation	Recovery % ± RSD[(a)]			
	Sensor I	Sensor II	Sensor III	Reported HPLC method[16]
Amipride tablets (Batch No. 90989)	100.75± 0.87	99.03±1.03	99.72±0.62	100.15±0.88
Student's t test (1.860)	1.084	1.851	0.893	-----
F- value (6.39)	1.023	1.369	2.015	-----
Amipride tablets (Batch No. 12498)	101.46±0.84	100.93±0.75	101.71±0.96	100.87±0.67
Student's t test (1.860)	1.228	0.112	1.606	-----
F- value (6.39)	1.572	1.253	2.053	-----

(a)Average of five determinations for either the proposed sensors or the reported HPLC method

(b)The values between parentheses are the corresponding theoretical values of t and F at the 95% confidence level

Table 4. Determination of Amisulpride in lab prepared mixtures containing different ratios of Amisulpride and its induced hydrolytic degradation products by the proposed sensors

Ratio%	Drug recovery % ± RSD[(a)]		
Amisulpride : degradates	**Sensor I**	**Sensor II**	**Sensor III**
90:10	98.51±0.98	100.05±0.49	100.13±0.45
80:20	99.17±0.73	98.86±0.69	99.94±0.73
70:30	100.64±0.91	99.77±0.78	101.64±0.58
60:40	100.87±1.01	100.63±1.06	100.89±0.33
50:50	101.53±0.86	100.83±0.94	100.68±21
40:60	103.89±1.12	104.89±0.88	99.07±0.60
30:70	108.37±0.84	117.07±0.58	100.77±0.71
20:80	120.41±0.59	147.48±0.75	102.52±0.75
10:90	123.81±0.51	156.99±0.93	110.72±0.64

(a) Average of three determinations

Table 4 shows the results obtained upon analysis of synthetic mixtures of intact drug and its hydrolytic degradation products. It is obvious from the results in Table 4 that sensor 1 and 2 suffer from high interference when degradation products concentration reaches about 50%.

Sensor 3 can be successfully used for selective determination of intact drug in the presence of up to 80% of its degradation products in spite of their closely related structures with amisulpride. This can be attributed to the preferential interaction between amisulpride cation and very polar OH- groups present in β-CD. Therefore sensor 3 is recommended for use in stability indicating methods.

On application to plasma, it has been found that the three electrodes gave stable results as revealed by high precision and accuracy of recoveries of the spiked human plasma samples without interference from any components in the plasma which represent the main advantage of ion selective electrode method (Table 5).

Table 5. Determination of Amisulpride in Spiked Human Plasma by the Proposed Sensors

Concentration	**Recovery % ± RSD[(a)]**		
(M)	**Sensor I**	**Sensor II**	**Sensor III**
1×10^{-3}	100.45±0.67	98.73±0.80	99.04±0.62
1×10^{-4}	99.9±0.41	100.68±0.56	100.75±0.59

(a)Average of three determinations

Statistical evaluation of the results of analysis of pure amisulpride by the proposed electrodes and the reported HPLC method [16] showed that there is no significant difference between the proposed and the reported method in term of accuracy and precision (Table 6).

Table 6. Statistical analysis of the results obtained by the proposed and the reported HPLC methods for the analysis of amisulpride in pure powder form

Parameter	**Sensor I**	**Sensor II**	**Sensor III**	**Reported HPLC method[16]**
Mean	99.93	100.01	99.94	100.30
RSD	0.72	0.93	0.87	1.42
Student's t-test (1.833)	0.593	0.428	0.545	-
F – test (6.16)	3.89	2.33	2.66	-

The values between parentheses are the corresponding theoretical values of t and F at the 95% confidence level

4. CONCLUSION

Three new sensors were described for the determination of amisulpride. The described sensors are sufficiently simple and selective for the quantitative determination of amisulpride in pure form and pharmaceutical formulation. The use of 2-hydroxy propyl-β-cyclodextrin as ionophore increased the membrane sensitivity and selectivity as in sensors 3 in comparison with sensors 1 and 2. The proposed sensors offer advantages of fast response and elimination of drug pre-treatment or separation steps. They can therefore be used for routine analysis of amisulpride in quality-control laboratories.

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