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Potentiometric Membrane Sensors for the Selective Determination of Memantine Hydrochloride in Pharmaceutical Preparations

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Three potentiometric sensors responsive to Memantine HCl (MEM) drug are described, characterized, compared and used for drug assessment. The sensors are based on the use of the ion-association complex of (MEM) cation with Flavianate (FA), 5-Nitro-barbiturate (NBA) and phosphomolybdate (PMA) anions as electroactive materials in plasticized poly(vinyl chloride) membranes. The sensors demonstrate fast near-Nernstian response for MEM with lower limits of quantification of: $4.76x10^{-6}$, $5.22x10^{-5}$ and $9.08x10^{-6}$ M with detection limits of $1.74x10^{-6}$, $9.17x10^{-6}$ and $2.93\ x10^{-6}$ M , with slopes of 55.45, 45.84 and 54.58 mV/concentration decade over a pH range of 2.66-9.54, 4.64-8.51 and 4.60-9.07 for Flavianate (FA), 5-Nitro-barbiturate (NBA) and phosphomolybdate (PMA), respectively. The three sensors showed good selectivity for MEM drug over several inorganic cations, nitrogeneous excipients and diluents commonly used in drug formulations. The dissolution profile was also plotted using the proposed sensor at optimum electrode conditions.

Keywords: Potentiometric sensors, Memantine, Flow injection analysis (FIA), dissolution test, drug analysis.

1. INTRODUCTION

Memantine (1-amino-3,5-dimethyladamantane) is a tricyclic amine structurally and pharmacologically related to the antiviral amantadine. The drug is used to treat Parkinson's disease, movement disorders and dementia syndrome. Memantine (MEM) acts as a non-competitive inhibitor

of the N-methyl-D-aspartate (NMDA) receptor complex. MEM was first synthesized in the 1960s and was found in the 1970s to affect the CNS. In 1989 MEM was found to inhibit NMDARs with an IC50 of approximately 1 μM (which corresponds well with its therapeutic concentration range). The principal mechanism of action of memantine is believed to be the blockade of current through channels of N-methyl-D-aspartate (NMDA) receptors, a glutamate receptor subfamily broadly involved in brain function [1], (Fig. 1).

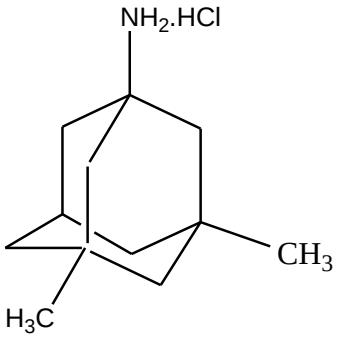

Figure 1. Structure of memantine hydrochloride.

MEM is well absorbed with peak plasma concentrations (C_{max}) ranging from 22 to 46 ng/mL following a single dose of 20 mg; the time to achieve maximum plasma concentration (T_{max}) following single doses of 10–40 mg ranges from 3 to 8 h. Methods including high performance liquid chromatography (HPLC) [2, 3] and gas chromatography coupled to mass spectrometry [4] (GC–MS) and LC–MS [5, 6] are previously reported in literature. Potentiometric membrane sensors are playing an important role in pharmaceutical analysis [7-10] because of their simplicity, rapidity and accuracy over other analytical methods such as spectrophotometry and HPLC which are elaborate, time-consuming and involve sophisticated equipment that might not be available in most analytical laboratories. Computational chemistry and molecular modeling play an important role in modern drug discovery and electrochemical science [11-17]. The interaction of memantine with ion-pair reagents was studied by theoretical and calculative methods. According to the obtained results, a memantine ion-selective potentiometric membrane electrode was developed based on the ion-pair compound of memantine-tetraphenylbroate (MEM-TPB) as the electroactive substance. The proposed electrode was successfully applied for the determination of Memantine in pharmaceutical formulations and urine samples [18].

The present work describes preparation, characterization and application of three potentiometric membrane sensors for determination of memantine in pharmaceutical preparations. These sensors incorporate ion-association complexes of memantine–flavianate (MEM–FA), memantine–nitrobarbiturate (MEM–NBA) and memantine–phosphomolybdate (MEM–PMA) embedded in plasticized PVC matrix membranes. Performance characteristics of these sensors, low detection limit, linear range, pH range, response time were investigated and the best performance was found to be attained using memantine–flavianate (MEM–FA) ion-association. Application for accurate determination of memantine in pharmaceutical preparations under static and hydrodynamic (FIA)

modes of operation for MEM-FA ion pair electrode was also investigated. The dissolution profile of memantine was followed up using the designed sensor.

2. EXPERIMENTAL

2.1. Reagents and chemicals

All chemicals were of analytical-reagent grade and doubly-distilled water was used throughout the whole work. Pure grade (MEM) was provided by Eva pharma, Egypt. The pharmaceutical preparations: Mantine® tablets (10 mg/tab.), Ebixa® tablets (10 mg/tab.), were obtained from local market. Phosphomolybdic acid (PMA), dioctyl phthalate (DOP) and polyvinyl chloride (PVC) were purchased from Fluka, Switzerland. Tetrahydrofuran (THF) was obtained from Sigma (St. Louis, USA). A stock solution of $1x10^{-1}$ M was prepared by dissolving 2.158 g of the memantine HCl in 100 ml H_2O. Lower concentrations ($1x10^{-2}$, $1x10^{-3}$ and $1x10^{-4}$ M) were freshly prepared by diluting the stock solution with doubly distilled water.

2.2. Apparatus

All potential measurements were made at 25±1°C with an Orion (Cambridge, MA, USA) Model 720 SA pH/mV meter using an Orion Ag/AgCl double-junction reference electrode (Orion 90-02). An Orion Ross pH electrode (Model 80-02) was used for pH adjustment. The components of the FI system were similar to those previously described [19]. The flow injection analysis (FIA) system manifold (Fig. 2) consisted of a two channel Ismatec MS-REGLO model peristaltic pump with polyethylene tubing (0.71'' i.d.) and an Omnifit injection valve (Omnifit, Cambridge, UK) with sample loop of 500 µl volume. Cell potentials were measured using eight-channel electrode-computer interface (Nico2000 Ltd., London, UK) controlled by Nico-2000 software using an Orion Ag/AgCl double-junction reference electrode (Orion 90-02).

Tablet dissolution measurements were made according to the method provided by the company (Pfizer®) using an Erwika dissolution device, Germany (USP-type apparatus).

2.3. Sensor construction

Memantine–flavianate (MEM–FA), memantine–nitrobarbiturate (MEM–NBA) and memantine–phosphomolybdate (MEM–PMA) complexes were prepared by mixing of equimolar concentration of flavianic, 5-nitro barbituric or phosphomolybdic acid solutions with MEM drug. A 2 mg portion of the formed ion-association (MEM–FA), (MEM–NBA) or (MEM-PMA) was mixed with 133 mg of DOP, 66 mg of PVC and 4 ml THF in a glass Petri dish (2.2 cm diameter) covered with filter paper and left to stand overnight to allow slow evaporation of THF at room temperature. The master membrane was sectioned with a cork borer (10 mm diameter) and glued to a PVC tubing

(~3 cm length, 8 mm; id) using THF. Elemental analysis for MEM–FA revealed the formation of 1:1 drug-reagent ion-pair complex. A tubular detector was constructed as described previously [20].

The coating solution was prepared by dissolving 66 mg of PVC in 7 ml THF followed by addition of 133 mg of DOP and 2 mg of MEM-FA ion association complex. The solution was deposited, using a micro dropper, 3–4 times in a hole (3 mm wide-1cm length) made in the middle of a 15 cm Tygon tube (ALKEM, P/N A003494 green/green 1.85 mm i.d). The tube was inserted and sealed with Araldite in 100 µl pipette tip (7 cm long, 0.4 cm diameter). The tubular detector was inserted into the flow injection system as schematically shown in Fig. 2.

The internal filling solution was $1x10^{-2}$ M MEM. Ag/AgCl as internal reference electrode (1.0 mm diameter). The sensors were conditioned by soaking in $1x10^{-2}$ M MEM solution for 2hrs and stored dry when not in use in case of the three ion-pairs. Each sensor was calibrated by transferring 1.0 ml aliquots of $1x10^{-4}$–$1x10^{-1}$ M, 0.5 ml at each addition, to a beaker containing 10 ml of $1x10^{-2}$ M acetate buffer of pH 4.7, i.e. from $9.1x10^{-6}$-$7.9x10^{-3}$ M, under static mode and from $1x10^{-5}$-$1x10^{-1}$ M under hydrodynamic mode of operation using the one of optimum performance.

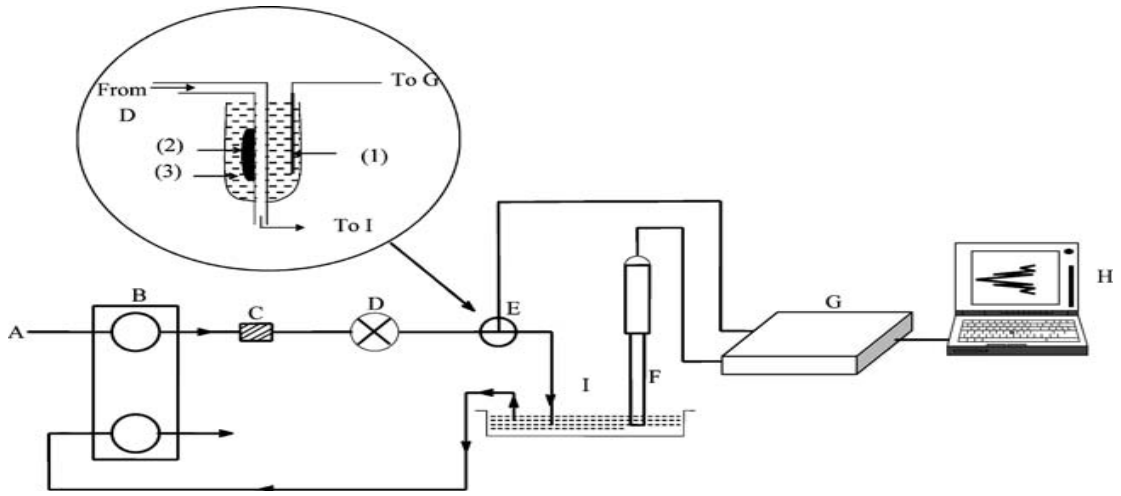

Figure 2. Manifold for the two channel FIA set up used for the determination of Memantine. A, carrier $1x10^{-2}$ M acetate buffer, pH=4.7; B, peristaltic pump; C, pulse damper; D, sample injection valve; E, flow injection detector; [(1) Ag/AgCl internal reference electrode, (2) membrane; (3) internal reference solution]; F, reference electrode; G, data aquisition; H, pc computer; I, beaker.

The sensor was immersed in the solution in conjunction with a double junction Ag/AgCl reference electrode. The potential readings were recorded after stabilization to ±0.2 mV and the e.m.f. was plotted as a function of logarithm MEM concentration. The calibration graphs were used for subsequent determination of unknown MEM concentrations. For FIA, $1x10^{-2}$ M acetate buffer of pH=4.7 was used as a carrier solution at flow rate 5 ml min^{-1} for (MEM-FA) ion-pair electrode. All injection tubes were green/green 1.85 mm i.d). The detector was calibrated at 25 $^{\circ}$C under hydrodynamic mode of operation by injection of MEM samples through a valve loop of 500 µl in the

carrier stream. After a steady-state, the baseline was reached, the potential signals were recorded using an Orion (Cambridge, MA, USA) Model 720 SA pH/mV meter using an Orion Ag/AgCl double-junction reference electrode (Orion 90-02) connected to a PC using eight-channel electrode-computer interface (Nico2000 Ltd., London, UK) controlled by Nico-2000 software.

An Orion Ag/AgCl double junction reference electrode was placed in a beaker down stream from the indicator sensor just before the solution went to waste (Fig. 2). Successive 500 µl aliquots of the standard memantine were injected into the flowing stream. The corresponding potential change was measured and recorded vs. time using the tubular sensor. Calibration plot was made and used to determine memantine using the (MEM–FA) ion-pair tubular sensor. Also the % recovery was calculated for Mantine® and Ebixa®.

Tablet dissolution measurements were made according to the method provided by the company (Pfizer®) using an Erwika dissolution device, Germany (USP-type apparatus).

2.4. Preparation of the forced degradation products of MEM

To accurately weighed 0.50 g of memantine hydrochloride, 10 mL of 5.0 N HCl; 2.0 N NaOH or 30% H_2O_2 were added and the solutions were then refluxed at 80 °C for 12 hrs in the acidic degradation and for 6 hrs in case of alkaline and oxidative degradation. The solutions were then cooled in dry air, neutralized and then diluted with methanol. The degradation process completeness was tested using TLC (mobile phase n-butanol: acetic acid: water: 4:1:1) to assure complete degradation. The memantine ring was so stable towards the degradation process releasing unchanged IR, ^{1}HNMR and mass spectra revealing the persistence of the memantine drug towards degradation process.

2.5. Determination of Memantine HCl in pharmaceutical preparations:

For sampling of tablets (Mantine® or Ebixa® tablets (10 mg/tab.), 20 tablets were ground and appropriate weights were taken as samples and dissolved in distilled water up to 10 ml. The contents of the measuring flask were subjected to potentiometric determination of MEM using batch and continuous measurements (FIA), in a flow stream of $1x10^{-2}$ M acetate buffer of pH 4.7 carrier solution. In FIA, successive 500 µl aliquots were injected in triplicate at flow rate of 5 ml min^{-1} and the average potential reading was compared with the calibration plot. The corresponding potential change was measured and recorded vs. time. A typical calibration plot was made and used to determine the concentration of the unknown samples. For batch assessment, the drug sensor and reference electrode were immersed in the solution, and the potential readings were recorded after reaching the equilibrium response (10–15 s). The concentration of MEM was calculated using a calibration graph.

2.6. Dissolution test

Tablet dissolution measurements were made using Type I basket, Erwika dissolution device, Germany, (USP-type apparatus). One tablet of Memantcare® (10 mg/tablet) was placed in the

dissolution medium, analyzed using USP Type 1 apparatus in 500 ml of 0.1 M HCl solution and the temperature was maintained at 37.0±0.5^{o}C. The basket was rotated at 100 r.p.m and comprised the MEM-FA-electrode and the apparatus was operated for 1 hr in conjunction with a saturated calomel reference electrode dipped in the solution for the continuous recording of the potential. At different time intervals, the potential values were recorded until the potential reached the plateau then the dissolution profile was constructed and the amount of the drug released was determined from the calibration curve.

A calibration curve, to be used for translating the measured potential into MEM concentration and % dissolved was constructed by adding, appropriate weights of the standard drug (2.0-12 mg) to the dissolution medium and the potential developed using the designed electrode was plotted against the negative logarithmic value of the drug concentration (pdrug). The data for this plot were obtained under the same experimental conditions as the dissolution curves. The only difference is that instead of the MEM tablets, subsequent MEM standard additions were performed yielding a 12 mg/500 ml end concentration in the dissolution medium. After each addition, the potential was recorded when it reaches a plateau [21].

3. RESULTS AND DISCUSSION

3.1. Performance Characteristics of the sensors

3.1.1. Composition of the membranes

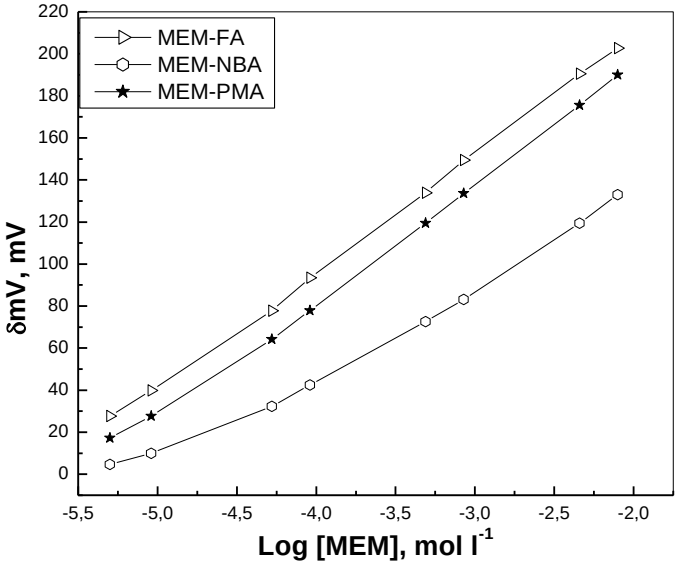

Figure 3. Potential response of MEM-FA, MEM-NBA and MEM-PMA ion-pairs, DOP plasticized, PVC membrane sensors under static (batch) mode of operation using 1x10^{-2} M acetate buffer of pH=4.7 for MEM analyte.

Three membranes were prepared using the optimum standard casting solution of the composition 2:33:66 wt.% ion associate, PVC and plasticizer (DOP), respectively [22]. Results from duplicate studies using (MEM–FA), (MEM–NBA) and (MEM–PMA) ion-pairs plasticized with DOP gave near-Nernstian slopes of 55.45; 45.84 and 54.58 mV decade^{-1} with a lower limit of quantification of : 4.76x10^{-6}, 5.22x10^{-5} and 9.08x10^{-6} M with detection limits of 1.74x10^{-6}, 9.17x10^{-6} and 2.93x10^{-6} M for (MEM–FA), (MEM–NBA) and (MEM–PMA) ion-pairs plasticized with DOP based membrane sensors, respectively, Fig.(3).

The response characteristics of the sensor was systematically evaluated according to IUPAC recommendations with membrane incorporating the ion associate under static conditions [23]. Calibrations were made in 1x10^{-2} M acetate buffer solution of pH 4.7 as a background in case of batch and continuous monitoring.

3.1.2. Response time

The dynamic response time of the (MEM–FA), (MEM–NBA) and (MEM–PMA) ion-pairs were examined by recording the potential readings at time intervals of 10 s over 2 min. The relation between potential reading and response time was plotted for 9.1x10^{-6}-7.9x10^{-3} M MEM. The time required to attain 95% of the equilibrium by the sensors was less than 10 s as shown in Fig. (4). These results indicate that the sensors are amenable for use with automated systems.

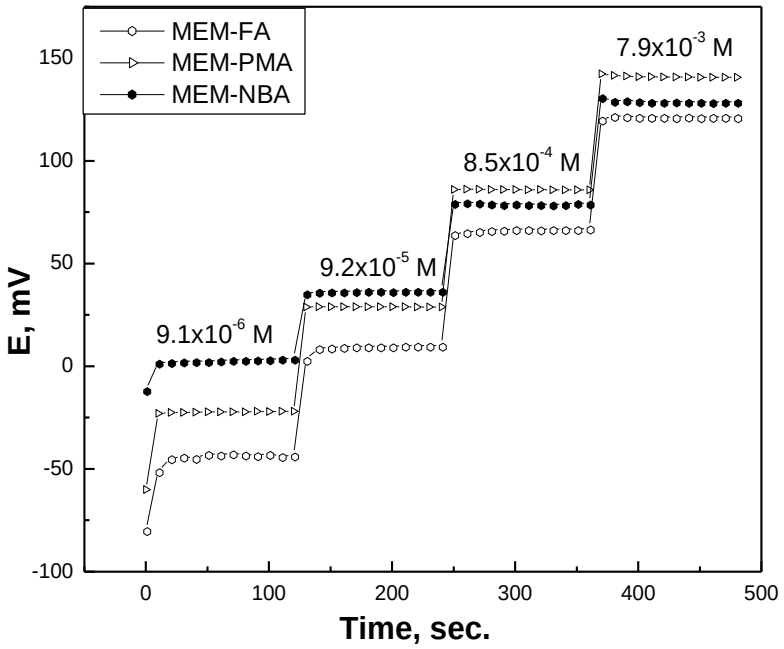

Figure 4. Response time for MEM-FA, MEM-NBA and MEM-PMA electrodes using 1x10^{-2} M acetate buffer of pH=4.7as a background, in the concentration range of 9.1x10^{-6}-7.9x10^{-3} M MEM.

3.1.3. Effect of pH

The influence of pH on the potentiometric response of (MEM–FA), (MEM–NBA) and (MEM–PMA) based membrane sensors were examined with standard $1x10^{-4}$ and $1x10^{-3}$ M MEM solutions over a pH range of 2-10.8. The pH of the solution was adjusted with either hydrochloric acid and/or sodium hydroxide solutions. The results represented in Fig. (5) using $1x10^{-3}$ M MEM indicate that the variation of solution pH over the ranges 2.66-9.54; 4.64-8.51 and 4.60-9.07 have no significant effect on the sensors response for (MEM–FA), (MEM–NBA) and (MEM–PMA) ion-pairs, respectively. The potentials of sensors considerably declined with negative drift at higher pH values due to progressive precipitation of the free memantine base. At pH<3, the sensor responses are severely influenced by H_3O^+.

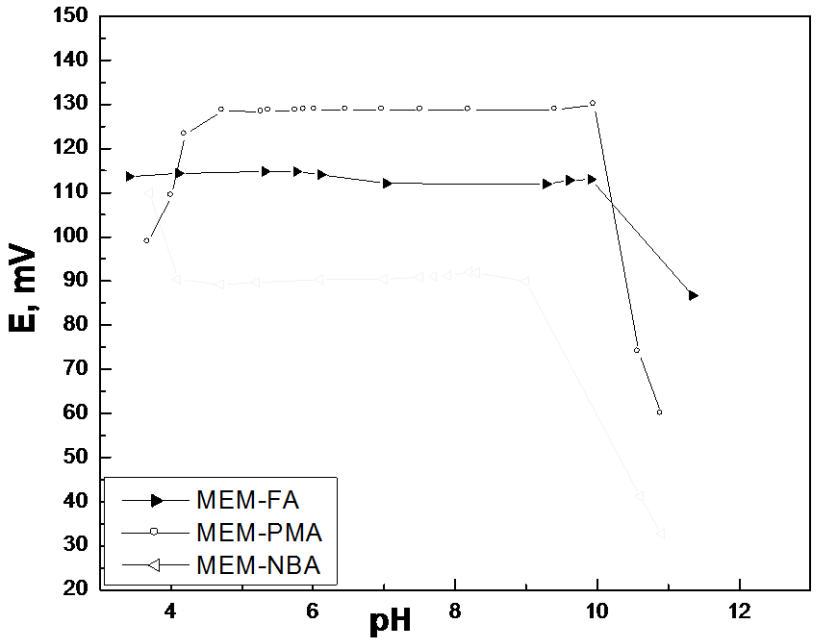

Figure 5. Effect of pH on MEM-FA, MEM-NBA and MEM-PMA electrodes using $1.0x10^{-3}$ M MEM.

3.1.4. Sensor selectivity

The matched solution method was applied to determine the selectivity coefficients log $K^{POT}_{MEM,\ B}$ of the electrode where a calibration curve for each interfering ion was constructed using $1x10^{-2}$ M acetate buffer pH=4.7 as the background covering the concentration range of $4.76x10^{-6}$-$8.54x10^{-4}$ M for each interferant, Figs.(6).

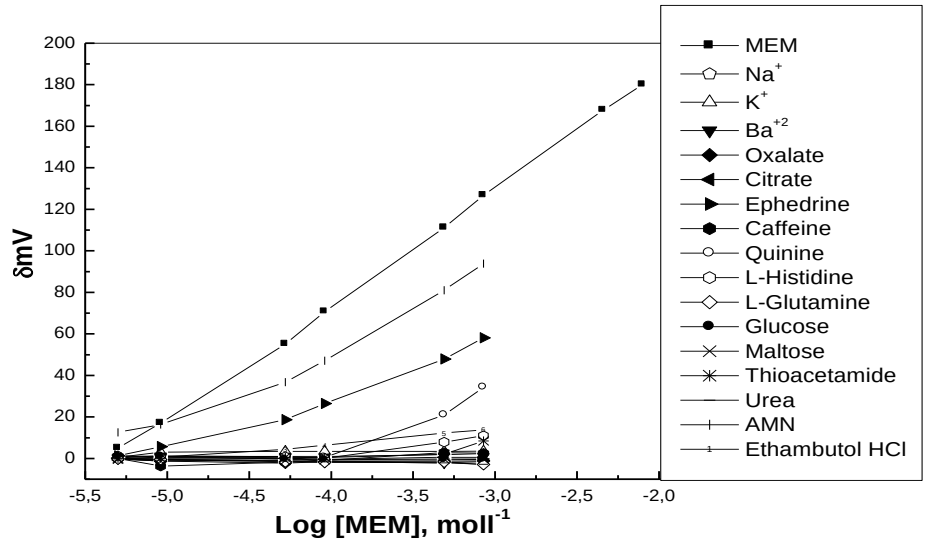

Figure 6. Potentiometric response of MEM-FA-PVC membrane sensor plasticized with DOP in $1x10^{-2}$M acetate buffer pH=4.7 for various interferes.

The selectivity coefficients were determined using the following equation:

$$\log K^{POT}_{MEM,\,B} = a_A/(a_B)^{ZA/ZB}$$

Where a_A and a_B activities of MEM and interfering ion, respectively and Z_A, Z_B are the charges of MEM and interfering ion. Then, the activities that correspond to the same electrode potential value are used to determine the log $K^{POT}_{MEM,\,B}$ value [20].

Potentiometric selectivities of the proposed sensors are related to the preferential interaction of the membrane electroactive materials with (MEM) over various drugs, inorganic cations, and additives commonly used in the drug formulations. The mechanism of selectivity is mainly based on the stereo-specificity and electrostatic environment and it is dependent on how much fitting is present between the locations of the lipophilicity sites in the two competing species in the bathing solution side and those present in the receptor of the ion-exchanger. The selectivity coefficients ranged from -1.859 to -0.504, -1.296 to -0.642 and -2.055 to -0.319 for MEM–FA, MEM–NBA and MEM–PMA electrodes, respectively. Selectivity coefficients of based membrane sensors are shown in Table (1).

3.2. Determination of Memantine HCl in pharmaceutical preparations

Potentiometric determinations of memantine HCl in drug formulations under static mode of operation was done three times for three different concentrations, in $1.0x10^{-2}$ M acetate buffer pH=4.7 as given in table 2. The average recovery ± mean standard deviation was 97.04±1.90 and 98.43±2.31for Mantine® and Ebexia® tablets (10 mg/tab.,each), respectively, for MEM-FA electrode. These data were compared with results obtained by the manufacturer procedures supplied by Adwia Co. for chemicals & pharmaceuticals, Egypt, by personal communication using non-aqueous titration

(0.200g MEM in 5 ml mercuric acetate and 50 ml glacial acetic acid), with 0.1 M perchloric acid as titrant and crystal violet as indicator (1 ml of 0.1 M perchloric acid is equivalent to 21.58 mg MEM) [24].

Table 1. Selectivity coefficients and tolerance values for MEM-FA, MEM-PMA and MEM-NBA sensors.

	$-\log K^{POT}_{MEM, B}$		
Interferent	MEM-FA	MEM-NBA	MEM- PMA
Na^+	1.77	1.09	2.04
K^+	1.75	1.09	1.99
Ba^{2+}	1.86	0.94	1.93
Oxalate	1.82	1.29	1.91
Citrate	1.79	1.26	1.95
Ephedrine HCl	1.08	0.89	1.16
Caffeine	1.78	1.16	1.97
L-Histidine	1.71	0.91	2.05
L-Glutamine	1.86	1.16	1.99
Glucose	1.82	0.96	2.03
Maltose	1.80	1.04	2.04
Thioacetamide	1.79	1.12	2.06
Urea	1.85	1.10	2.04
Amantadine HCl	0.50	0.73	0.32
Ethambutol HCl	1.63	1.15	1.93
Quinine	1.53	0.64	1.31

3.3. Continuous monitoring flow injection analysis (FIA) of Mantine® and Ebixa®:

Continuous injection of 500 µl MEM standard solution at a flow rate of 5.0 ml min^{-1} was applied to MEM-FA-electrode, Fig (7). The slope of the calibration plot was Nernestian (58.59 mV $decade^{-1}$) with an LOD of $1.0x10^{-5}$ M.

Table 2. Determination of MEM in pharmaceutical preparations on using MEM-FA sensor under Static and FIA conditions.

	Batch			FIA		
Sample	Taken (mg ml^{-1})	Found (mg ml^{-1})	(%) Recovery ± (%)RSD [a]	Taken (mg ml^{-1})	Found (mg ml^{-1})	(%) Recovery ± (%)RSD [a]
Mantine® tablets (10 mg/tablet)	2.50	2.36	94.4 ± 2.64	5.00	4.65	93.0±1.65
	5.00	4.87	97.8 ± 1.74	10.0	9.58	95.8±2.15
	10.0	9.89	98.9± 1.32	15.0	14.8	98.5±1.20
Ebixia®tablets (10 mg/tablet)	2.50	2.43	97.2 ± 4.41	5.00	0.89	95.6±1.60
	5.00	4.92	98.5 ± 1.56	10.0	9.79	97.9±1.13
	10.0	9.96	99.6 ± 0.97	15.0	15.1	100.7±0.56

[a] RSD represents the average of three different determinations

A linear relationship between MEM concentrations and FIA signals was obtained over the range $1x10^{-5}$-$1x10^{-1}$ M of standard MEM. The peak heights of series of solutions of different concentrations from the tablets was and the obtained peak heights were then compared to those obtained from injecting standard solutions of the same concentrations prepared from pure drug and the recovery % can then be calculated as the ratio of the peak heights of the preparations to that of the equivalent concentration of the standard.

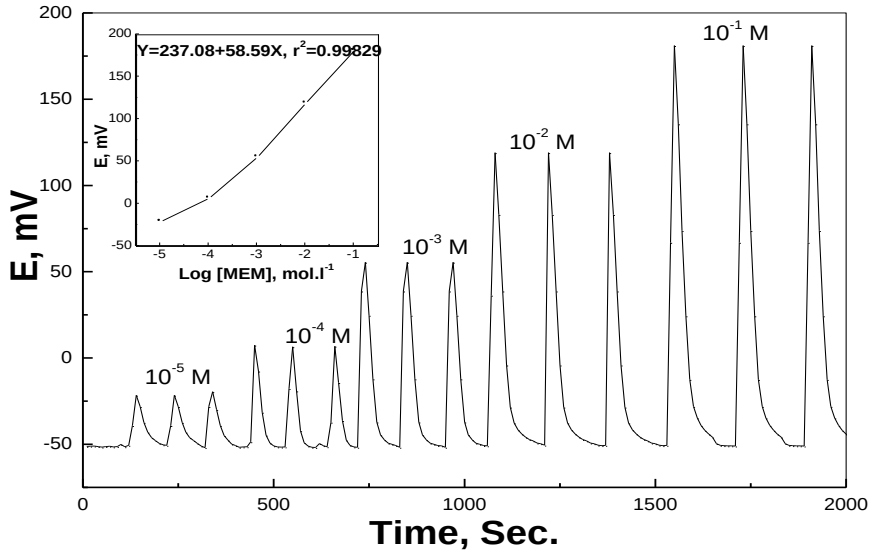

Figure 7. The recordings of FIA of MEM and their corresponding calibration curve on using MEM-FA electrode in $1x10^{-2}$ M acetate buffer, pH=4.7at flow rate 5 ml min^{-1}.

3.4. Dissolution Test

Drug absorption from a solid dosage form after oral administration is a very important factor to study in drug administration and quality control and it depends on the release of the drug substance from the drug product, the dissolution or the drug under physiological conditions, and the permeability across the gastro-intestinal tract. In vitro dissolution testing is usually relevant to predict the in vivo performance.

In Vitro dissolution testing can be used to: assess the batch-to-batch consistency and to signal potential problems with in vivo bioavailability of a drug product; and ensure continuing product quality and performance after certain changes, such as changes in the formulation during the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process and finally, help in suggesting new formulations that might have faster or slower release according to the use of the pharmaceutical compound.

The proposed electrode was applied to follow the dissolution profile of MEM in Memantcare® tablet. It was found that the released amount of MEM increase with time till a plateau is reached after 30 min., MEM-FA detects the release of 96 % of the drug; this result meets the specifications of the

Pharmaceutical Company (Pfizer) which states that not less than 95% of the labeled amount of MEM is dissolved after 45 minutes.

In this work, the ISE and the Calomel reference electrode were dipped inside the vessel for an hr. to measure the potential continuously without any need to take a sample from the dissolution medium at each time interval and measuring it spectro-photometrically (UV) or using HPLC and without the need for any complicated logarithmic volume correction procedure followed commonly in these two techniques. ISE is not affected by turbidity due to excipients, there was no need to centrifuge the sample before measuring it and this is another advantage of the ion-selective electrode procedure. Thus, the suggested method in this study, not only offers a dissolution profile in agreement with the spectrophotometric method but also minimizes error, and consumes less time and effort. Dissolution profile and the used calibration curve for MEM in Memantcare® tablet on using MEM-FA electrode is presented in Fig. (8).

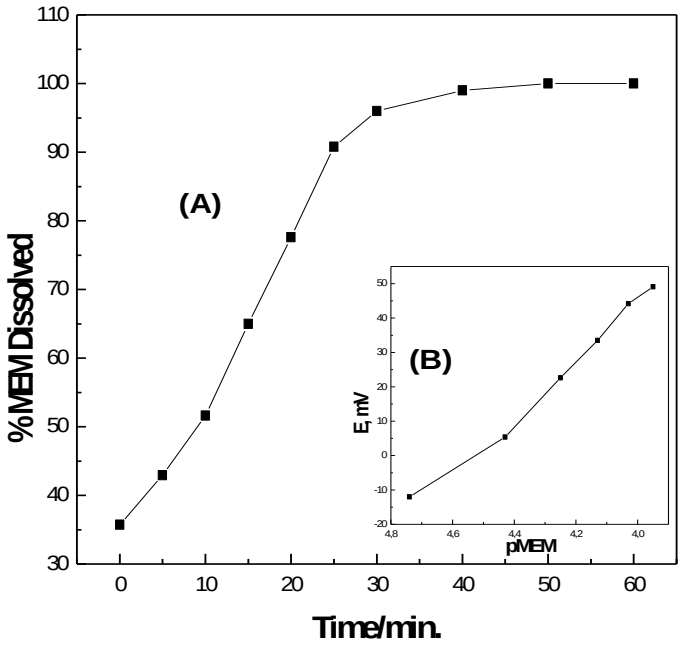

Figure 8. Dissolution profile of MEM in Memantcarel® tablet on using MEM-FA electrode (A) and the calibration curve used in dissolution testing to convert the resulting potentials into concentrations (M) of drug and consequently into % dissolved.

3.5. Statistical analysis and validity of the proposed method

3.5.1. Precision and accuracy of the method

The precision and accuracy of the method are expressed as RSD and % of deviation of the measured concentration (recovery %), also reproducibility (day to day) were investigated. Also the relative standard deviation for (MEM–FA), (MEM–NBA) and (MEM–PMA) were obtained [25, 26]. The limit of detection of the studied sensor (LOD) was calculated, defined as the MEM concentration

corresponding to the intersection of the extrapolation of the linear part of the calibration curve; were $1.74x10^{-6}$, $9.174x10^{-6}$ and $2.93x10^{-6}$ M for (MEM–FA), (MEM–NBA) and (MEM–PMA) electrodes, respectively [27].

3.5.2. Ruggedness

The ruggedness of the potentiometric method was evaluated by carrying out the analysis using two different instruments on different days. The RSD of less than 1.0 % were observed for repetitive measurements in three different day time periods using two different instruments. The results indicate that the method is capable of producing results with high precision [25].

3.5.3. Robustness

Robustness is the quality of being able to withstand stresses, pressures, or changes in procedure or circumstance. A system, organism or design may be said to be "robust" if it is capable of coping well with variations (sometimes unpredictable variations) in its operating environment with minimal damage, alteration or loss of functionality. The robustness of the method was explained by the evaluation of the influence of small variation of the most important procedure variables including pH, potential range and measuring time. The results showed that the method is fairly robust, results are stable, but in the pH range around 2.66-9.54; 4.64-8.51 and 4.60-9.07 for (MEM–FA), (MEM–NBA) and (MEM–PMA) under batch conditions [25].

In order to know if the investigated sensors exhibit any fixed or proportional bias, a simple linear regression for the observed drug concentrations against expected values (4 points) was performed using a computer program (Excel 5). The slopes of the regression lines are near to those of the ideal value of unity. While the intercepts were very small indicating that there is no systematic difference between determined and expected concentrations within the investigated range using the presented method.

Table (3) presents the statistical treatment of data obtained for the determination of MEM using MEM-FA sensor, in comparison the in-house specification method prescribed [24].

The comparison of the results of the presented sensors to those in literature show that the sensors proposed in this study show a wide range of selectivity with respect to a large number of inorganic cations, drugs, urea and sugars, when compared to the other method. The MEM-FA sensor exhibits long life span (more than 60 days) in dry conditions, and have stable pH range under both batch and FIA conditions.

So, it can be used for routine analysis and verification in quality assurance during manufacture of memantine HCl and related pharmaceuticals. In addition, FIA conditions shorten the time needed for the determination and allow using little amounts of sample for the detection of the drug in both parent and related pharmaceutical preparations.

Table 3. Statistical treatment of data obtained for the determination of MEM HCl using MEM-FA sensor, in comparison with specified method [24].

Item	Mantine ® tablets		Ebixia ® tablets		Specified
	Batch	FIA	Batch	FIA	method [24]
Mean±SD	97.04±1.90	95.78±1.67	98.43±2.31	98.07±1.09	99.60±2.45
F test	1.67	2.15	1.12	5.04	-
Student t test	0.43	0.68	0.17	0.31	-
Probability	>0.05	>0.05	>0.05	>0.05	-

Table 4. Comparison of performance characteristics of MEM sensors.

Parameter	MEM Ion-pairs		
Ion-pair	MEM-FA	MEM-NBA	MEM-PMA
Intercept, mV	238.25	220.75	244.03
Slope [mV/log C]	55.45	45.84	54.58
LOD [M])	$1.74x10^{-6}$	$9.17x10^{-6}$	$2.93x10^{-6}$
Lower limit of Linear range[M]	$4.76x10^{-6}$	$5.22x10^{-5}$	$9.08x10^{-6}$
Response time, Sec.	10-15 s		
SD	2.16	2.45	3.26
R^2	0.99953	0.99852	0.99891
Working range, pH	2.66-9.54	4.64-8.51	4.60-9.07
Flow Injection analysis	Applied	---	---
Dissolution Test	Applied	---	---
Degradation	Applied	---	---

Table (4) represents the response characteristics of the new electrodes using different ion-associations. From the results given in Table (4), it is clear that the (MEM–FA) ion-pair plasticized with DOP has the lowest LOD and highest slope in comparison with the other two electrodes and consequently was the one chosen for all the consecutive assays and determinations of the drug. It demonstrated an advanced performance with a fast response time (~10-15 s), lower detection limit of $1.74x10^{-6}$ mol L^{-1} and pH independent potential responses across the range of 2.66-9.54. Also, it has a wide range of selectivity with respect to a large number of inorganic cations, neutral molecules and even in presence of its degradation products. Accordingly it is used for the analysis of memantine in pure form and in its pharmaceutical formulations. Also it can be used under batch and FIA conditions as well as for constructing its dissolution profile. The sensor can be used within temperature range.

Also, the advantages of the proposed method compared to HPLC are low cost, ease of fabrication, tolerance of a less purified measurement medium (may be turbid or colored), and no need for a derivatization process.

4. CONCLUSIONS

In this study it is observed that types of interactions exist between drugs and ligands. After a series of experiments involving the use of (MEM–FA), (MEM–NBA) and (MEM–PMA) ion-pair complexes along with DOP plasticizer in the membrane design, it was concluded that the Memantine-Flavianate sensor exhibited excellent analytical performance characteristics.

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