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Development of Membrane Electrodes for the Specific Determination of Moexipril Hydrochloride in Dosage Forms and Biological Fluids

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Abstract

Three polyvinylchloride (PVC) membrane sensors for the determination of moexipril hydrochloride were prepared and characterized. The sensors are based on the use of the ion association complexes of moexipril cation with either ammonium reineckate (sensor 1) or tetraphenyl borate (sensor 2) or phosphotungistic acid (sensor 3) counter anions as ion exchange sites in the PVC matrix. The performance characteristics of these sensors were evaluated according to IUPAC recommendations, which reveal a fast, stable and linear response for moexipril over the concentration range of 10^{-6} to 10^{-2} M for the three sensors with cationic slopes of 29.1, 30.1 and 30.2 mV per concentration decade for the three sensors, respectively. The direct potentiometric determination of moexipril hydrochloride using the proposed sensors gave recoveries % of 99.64 ± 0.34, 99.34 ± 0.56 and 99.68 ± 0.42 for the three sensors, respectively. The sensors were used for determination of moexipril hydrochloride in pharmaceutical formulations and in plasma. Validation of the method shows suitability of the proposed sensors for use in quality control assessment of moexipril hydrochloride. The obtained results were in a good agreement with those obtained using the reported spectrophotometric method.

Keywords: moexipril hydrochloride, ion selective electrodes, PVC membranes, ammonium reneickate, tetraphenyl borate, phosphotungistic acid.

Introduction

Moexipril hydrochloride (MOEX), (3S)-2-[(2S)-2-[[(1S)-1-(Ethoxycarbonyl) -3-phenylpropyl] amino] -1- oxopropyl] -1-2, 3, 4- tetrahydro-6, 7-dimethoxy-3-

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isoquinoline carboxylic acid hydrochloride (Fig. 1) is a new potent orally active non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor which is used for the treatment of hypertension and congestive heart failure. MOEX is administered alone or together with other antihypertensives or diuretics [1, 2].

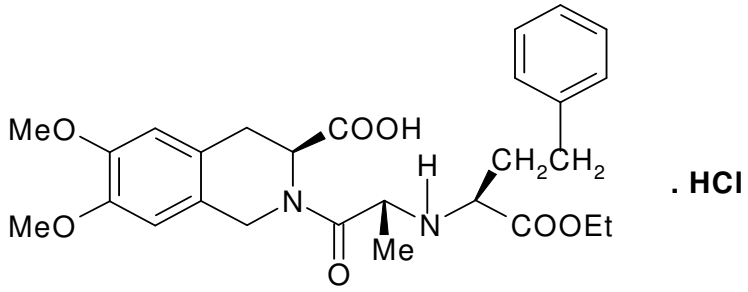


Figure 1. Chemical structure of moexipril hydrochloride [8].

A few analytical methods have been developed for the determination of MOEX, including derivative spectrophotometric [3] which has been reported for the simultaneous determination of MOEX and hydrochlorothiazide (HCTZ) in its Co-formulated form. Also, three simple spectrophotometric methods were described for the assay of MOEX either in bulk form or in presence of its degradation products. The methods are based on ion pair complex formation between MOEX and bromocresol purple (BCP), bromophenol blue (BPB) and bromothymol blue (BTB) [4]. An isocratic RP-HPLC method has been developed for the simultaneous determination of MOEX and HCTZ [3]. A stability-indicating RP-HPLC method was developed for the determination of MOEX [5]. Also, another HPLC- Electrospray Ionization MS method was established for the determination of MOEX in presence of its degradation product in biological samples [6]. A gas chromatographic-mass spectrometric method [7] has been developed for MOEX and its active metabolite moexiprilate in human plasma.

In the last three decades, being commercially important and not expensive, ion selective electrodes have become an item of general equipment for analytical work. This result happens because ion selective electrodes have rapid, simple, lower cost and give accurate measurements of ionic species.

The key to constructing such an electrode is to produce a sensitive and selective membrane that responds to a particular drug. Such membrane is usually prepared by incorporating an appropriate ion-exchanger and solvent mediator into a polyvinyl chloride (PVC) matrix.

The present work originates from the fact that moexipril hydrochloride (MOEX) behaves as cation, as it contains two nitrogen atoms, one in the form of secondary amino group, while other in the form of amide group. This fact suggests the use of anionic type of ion-exchangers, forming water insoluble ion association complexes. Three types of anionic exchangers, namely, ammonium reineckate, tetraphenyl borate and phosphotungistic acid were used for construction of water insoluble complexes with MOEX. The high lipophilicity and remarkable stability of these complexes suggested their selective use as

electro-active materials in PVC matrix membrane sensors for the determination of MOEX. These sensors showed no interference either from the alkaline-induced degradation product or from co-administered drugs, such as verapamil or from Co-formulated drugs like hydrochlorothiazide.

Experimental

Instrument

Potentiometric measurements were made at 25 ± 1 ºC with a Hanna (Model 211) pH / mV meter. A single junction calomel reference electrode (Model HI 5412) was used in conjunction with the drug sensor. A WPA pH combined glass electrode (Model CD 740) was used for pH measurements. Bandelin sonorex, RK 510 S, magnetic stirrer and a silver wire (3 mm diameter) immersed in the internal solutions were also applied.

Reagents

All chemicals used were of analytical grade and bi-distilled water was used. Tetrahydrofuran (THF) 99% (Lab Scan), high molecular weight (10.000) polyvinyl chloride (PVC) powder were obtained from Aldrich, (Steinheium, Switzerland). Dibutylsebathete (DBS), ammonium reneickate (R), tetraphenyl borate (TPB) and phosphotungistic acid (PTA) were obtained from Sigma, (St. Louis, USA). Phosphate buffers of pH 2 and 3 were prepared [9].

Materials

Pure sample

Moexipril hydrochloride was kindly supplied by (MinaPharm Company for Pharmaceutical Industries), Cairo, Egypt. Its purity was found to be (99.78 ± 0.45)%, according to the reported spectrophotometric procedure [3].

Pharmaceutical dosage form

Primox tablets (Mina Pharm. Ind., Cairo, Egypt) batch no. 7EE0881 and SKE1587. Each tablet is claimed to contain 7.5 and 15 mg of moexipril hydrochloride, respectively.

Plasma

Fresh human plasma was obtained from (VACSERA) and kept frozen until use after gentle thawing.

Prepared solutions

Preparation of degradation product stock solution

0.25 gm of pure MOEX were weighed accurately, transferred into a conical flask and dissolved in 5.0 mL methanol. 20.0 mL of 2 M sodium hydroxide were added and the solution was refluxed for 2 hours. The solution was cooled and neutralized by 2 M hydrochloric acid. The obtained precipitate was filtered, washed, transferred quantitatively into a 50-mL measuring flask and dissolved in

least amount of methanol. The volume was then completed to 50 mL with water to give a solution of final concentration of 1 x 10^{-2} M.

Stock standard solutions
MOEX stock solution (10^{-2} M) in either water or phosphate buffer of pH 2 (in case of sensors 2 and 3) or pH 3 (in case of sensor 1) were prepared by transferring 0.535 g of MOEX into three separate 100-mL measuring flasks. Fifty milliliters of either water or phosphate buffer pH 2 or 3 were added, shaken for few minutes and completed to volume with the same solvent.

Working standard solutions
MOEX working solutions (10^{-6} – 10^{-2} M) were prepared by suitable dilution from its stock solution using either water or phosphate buffer pH 2 (in case of sensors 2 and 3) or pH 3 (in case of sensor 1).

Procedures
Precipitation-based technique for the preparation of the three sensors
Ten milliliters of 10^{-2} M MOEX aqueous solution were mixed with 10.0 mL of either saturated aqueous solution of ammonium reineckate (sensor 1), or tetraphenyl borate (sensor 2), or phosphotungistic acid (sensor 3). The resulting precipitates were filtered, washed with cold water, allowed to dry at room temperature and grounded to fine powder. Elemental analysis for carbon, hydrogen and nitrogen were carried out to study the ratio of each element.
In three Petri dishes (5 cm diameter), 10.0 mg of previously prepared ion association complexes were mixed thoroughly with 0.35 gm of DBS, then 0.19 g of polyvinyl chloride (PVC) were added. These mixtures were dissolved in 5 mL of tetrahydrofuran (THF). The dishes were covered with a filter paper and left to stand overnight to allow slow evaporation of the solvent at room temperature, forming master membrane with a 0.1 mm thickness.
Sensors were assembled using a disk of an appropriate diameter (about 8.0 mm) were cut from the previously prepared master membranes and cemented to the flat end of PVC tubing with THF. A mixed solution consisting of equal volumes of 10^{-2} M MOEX and 10^{-2} M potassium chloride was used as an internal reference solution. Ag / AgCl coated wire (3.0 mm diameter) was employed as an internal reference electrode. The sensors were conditioned by soaking for 24 hours in a solution of 10^{-2} M of drug and stored in the same solution when not in use.

Study of the experimental conditions
Determination of slope, response time and life time of the studied electrodes
The electrochemical performance characteristics of the three studied MOEX-selective electrodes (sensors 1-3) were evaluated according to IUPAC Standards [10]. Sensors calibration was carried out by measuring the potential of 10^{-6} - 10^{-2} M drug solutions starting from low to high concentrations. The potentials were plotted as a function of drug concentrations. Operative life of the studied electrodes was evaluated by determining replicate calibration graphs for each

electrode over a period of six to eight weeks. During this period, the electrodes were stored and conditioned in 1 x 10^{-2} M MOEX solution. It was found that the electrodes remain stable without any color change of their surfaces. The detection limit was taken at the point of intersection of the extrapolated linear segment of the drug calibration graph.
The dynamic response times of the electrodes were tested for the concentrations of 10^{-6} - 10^{-2} M MOEX solutions. It was found that the membranes gave rapid response with a stable potential. The sequence of measurements was from low to high concentrations. The time required for the electrodes to reach values within ± 2 mV from the final equilibrium potential after increasing MOEX concentration level by ten folds was measured.

Effect of pH on the electrode response
The effect of pH on the potential values of the three electrode systems was studied over pH range 1-11 at 1-pH unit interval. Each electrode was immersed in 10^{-3} and 10^{-4} M MOEX solutions. The pH values were recorded while aliquots of diluted sodium hydroxide or hydrochloric acid solutions were added.

Effect of temperature on the electrode response
The potential response displayed by the investigated electrode was monitored as a function of temperature in the range of 25 – 40 ºC for 5 minutes at 5 ºC degree interval using MOEX concentrations of 10^{-3} and 10^{-4} M.

Effect of foreign compounds on the electrode selectivity
The response of the three studied electrodes was also examined in the presence of a number of other related substances. The potentiometric selectivity coefficients (K^{pot}_{AB}) were evaluated according to IUPAC guidelines using the separate solutions method [10, 11] 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 (MOEX ions) and B (interfering ion) have the same activity aA = aB. Selectivity coefficients were calculated using the separate solutions method where potentials were measured for 10^{-3} M MOEX solution and then for 10^{-3} M interfering solution, separately, then potentiometric selectivity coefficients were calculated using the following equation:

$$\log K^{pot}_{A,B} = \frac{(EB - EA)}{S} + \frac{(1 - ZA)}{ZB} \log aA \qquad (1)$$

where $K^{pot}_{A,B}$ is the potentiometric selectivity coefficient, S the slope of calibration plot, aA the activity of MOEX and ZA and ZB are the charges on MOEX and interfering ion, respectively.

Construction of calibration graphs
The sensors were conditioned by soaking in 10^{-2} M MOEX solution for 24 h. Storage was in the same solution when not in use. The conditioned electrodes were immersed in conjunction with the single junction calomel reference electrode in solutions of MOEX in the range of 10^{-6} - 10^{-2} M. They were allowed

to equilibrate whilst stirring and recording the e.m.f 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 concentrations of MOEX.

Application to pharmaceutical dosage forms

The content of ten primox tablets was mixed. An amount of this powder equivalent to 53.50 mg MOEX was accurately transferred separately to a 50-mL volumetric flask, and the volume was completed to the mark with phosphate buffer of pH 3 for (sensor 1) and pH 2 for (sensor 2 and 3) to prepare 10^{-3} M of MOEX. The emf produced by immersing the prepared electrodes in conjunction with calomel reference electrode in the prepared solutions was determined, then the concentration of MOEX was calculated from the regression equation of the corresponding electrode.

Application to spiked plasma samples

4.5 mL plasma were placed into two stoppered shaking tubes, then 0.5 mL of 10^{-3} and 10^{-4} M MOEX were added separately and shaked. Each membrane sensor was immersed in conjunction with calomel reference electrode in spiked plasma solutions. The emf produced for each solution was measured by one of the three proposed electrodes, then the concentration of MOEX was determined from the corresponding regression equations.

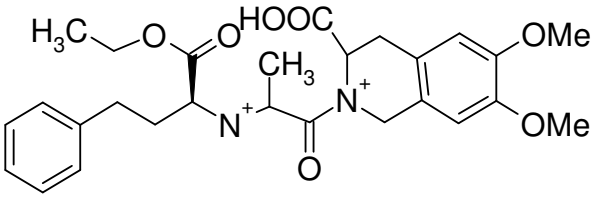
Results and discussion

The development and application of ion-selective electrodes (ISEs) continue to be of interest for pharmaceutical analysis because these sensors offer the advantages of simple design and operation, fast response, reasonable selectivity, low detection limit, high accuracy, wide concentration range applicability to colored and turbid solutions and possible interfacing with automated and computerized systems [11].

Moexipril hydrochloride contains an ester linkage in its structure, so it is liable to hydrolysis. It was found that refluxing of the drug with 2 M sodium hydroxide for 2 hours led to complete degradation of ester bond. This was confirmed by TLC and further assessed by mass spectral analysis, so that the aim of this work is to develop a specific method for the determination of MOEX without any interference either from its degradation products or from any Co-formulated drugs.

The most common anionic exchangers that react with cationic drugs are ammonium reineckate, tetraphenyl borate and phosphotungistic acid. Ammonium reineckate was used for development of selective electrodes for many drugs, like hyoscine butylbromide [12], drotaverine hydrochloride [13], pethidine [14], atropine [15] and cinnarizine [16]. Tetraphenyl borate was incorporated in many selective electrodes of drugs like bromhexine [17], hydralazine [18], metformin [19], thiamine [20] and nalbuphine [21]. Also, phosphotungistic acid was utilized

in several selective electrodes like amoxicillin [22], ampicillin [23], trimethoprim [24], etilefrine [25] and clozapine [26].
MOEX reacts with ammonium reineckate, tetraphenyl borate and phosphotungistic acid to form stable 1: 2 water insoluble ion association complexes, with low solubility product and suitable grain size precipitates, having the following suggested composition:



2R-($C_4H_{10}CrN_7S_4$)

2TPB($C_{24}H_{20}BNa$)

2PTA- ($24WO_3.2H_3PO_4.48H_2O$)

This ratio was confirmed by the elemental analysis data (Table 1) and by the Nernstian response of the suggested sensors, which was about 30 mV, the typical value for divalent drugs [10].

Table 1. Elemental analysis of MOEX-R, MOEX-TPB and MOEX-PTA complexes.

Parameters	Analysis %								
	Sensor 1			Sensor 2			Sensor 3		
	C	H	N	C	H	N	C	H	N
Calculated %*	33.76	4.42	18.00	73.80	6.15	2.30	14.12	4.44	1.22
Found %	34.00	4.50	17.80	74.00	6.22	2.40	14.20	4.50	1.15

* Calculated according to 1: 2 ratio.

The introduction of high molecular weight PVC, as regular support matrix and traps for the sensed ions, creates a need for a plasticizer [27]. In the present investigation, dibutylsebathete (DBS) was chosen from diesters of di-carboxylic acids. With PVC, it plasticizes the membrane, dissolves the ion association complex and adjusts both permeability of the final organic membrane and mobility of the ion exchange sites. Such adjustments influence the partition coefficient of the studied drug with subsequent effect on electrode selectivity.
The electrochemical cell of the suggested membrane electrodes for the determination of MOEX can be illustrated diagrammatically as follows:

Single Junction		MOEX association	internal reference	Ag / AgCl internal
Calomel	test	complex	solution 10^{-2}M	reference
Reference	solution	incorporated in	KCl + 10^{-2}M	wire
Electrode		PVC membrane	drug in 1:1 ratio	

Electrochemical performance characteristics of the proposed sensors were evaluated according to the IUPAC recommendations data [10]. It was found that

the electrodes displayed constant and stable potential readings within 2 mV from day to day and the calibration slopes did not change by more than 2 mV per decade over a period of 1 month for the three sensors.

The response time of the electrodes were tested for concentrations of the drug from 10^{-6} – 10^{-2} M. The measurements were characterized by a fast stable response within 20 – 30 seconds for concentrations less than 10^{-4} M and 10 – 20 seconds for concentrations more than 10^{-4} M.

The effect of pH on the electrode potential was investigated and it was observed that the electrodes had a stable pH range from 1-3 for sensors (2, 3) and pH 2 – 4 for sensor (1) (Figs. 2, 3). Above and below this pH range, the potentials displayed by the electrodes were noisy.

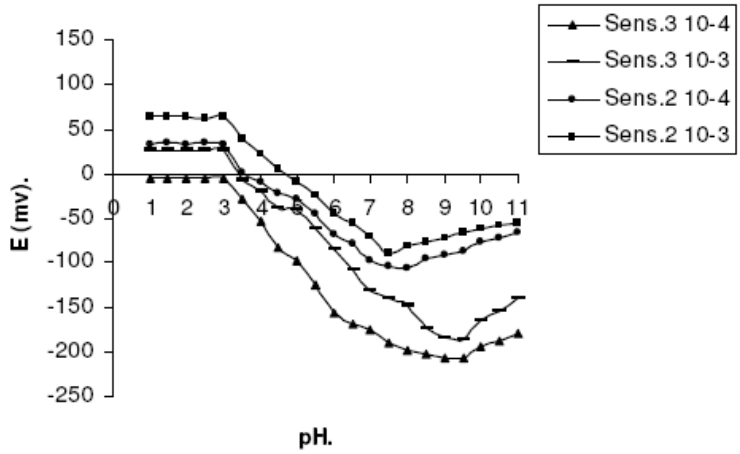


Figure 2. Effect of pH on the response of sensors 2 and 3.

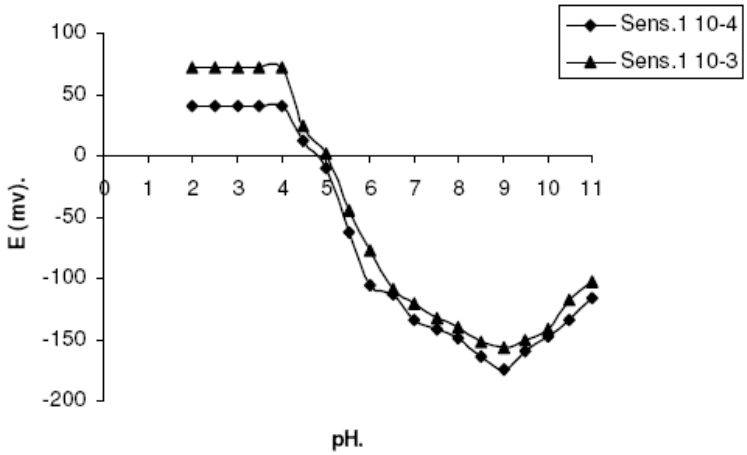


Figure 3. Effect of pH on the response of sensor 1.

The performance of each electrode was studied at temperature range of 25 – 40 ºC at 5 ºC interval using MOEX concentrations of 10^{-3} and 10^{-4} M. It was observed that the potential increased with temperature; however, the calibration graphs obtained at different temperatures were parallel, the limit of detection,

slope and response time did not significantly vary with temperature, indicating reasonable thermal stability of the prepared PVC membranes up to 40 ºC (Fig. 4).

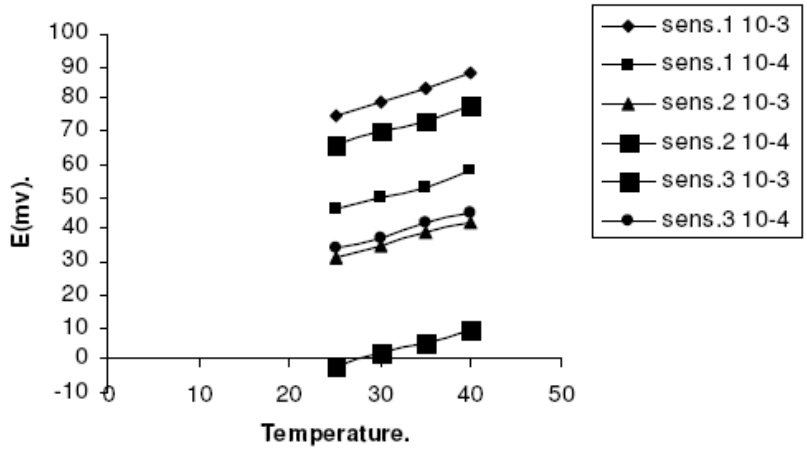


Figure 4. Effect of temperature on the response of the studied sensors.

The potentiometric response of the three studied electrodes at the optimum pH was linear with constant slopes over a drug concentration range 10^{-6} – 10^{-2} M for the three studied sensors (Fig. 5).

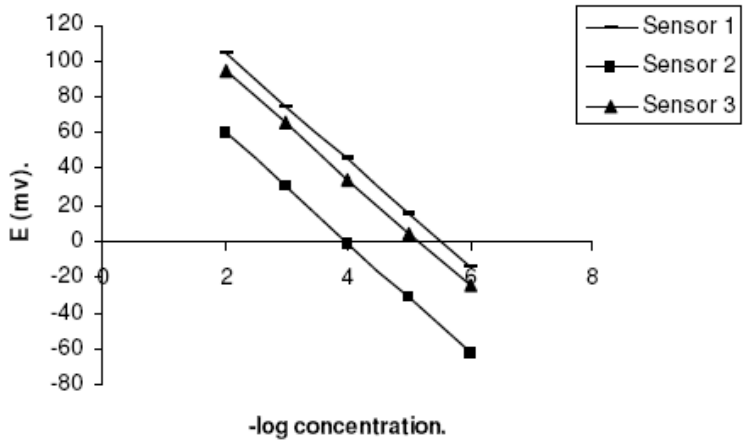


Figure 5. Profile of the potential in mV to – log concentration of sensors 1-3.

The linear regression equations were computed and found to be:

E = -29.75 X + 164.1 r = 0.9998 (for sensor 1)
E = -30.6 X + 121.6 r = 0.9997 (for sensor 2)
E = -30.2 X + 155.6 r = 0.9997 (for sensor 3)

where E is the potential in mV, X is the concentration in M and r is the correlation coefficient.

The accuracy of the proposed membrane sensors for the quantification of blind samples of MOEX was assessed by using the three sensors. The results showed average percentage recoveries of 99.34 ± 0.56, 100.04 ± 0.32 and 99.68 ± 0.42 for sensor 1, 2 and 3, respectively.

The performance of the three electrodes in the presence of some related interfering substances was assessed. Selectivity coefficient values ($K^{pot}_{MOEX,I}$) were measured using a fixed concentration of the interfering ion (10^{-3} M). The results obtained by the developed sensors (Table 2) showed reasonable selectivity of the three sensors for MOEX. Co-administered drugs such as verapamil and Co-formulated drugs such as hydrochlorothiazide were also tested for potential interference in biological fluids. The results in (Table 3) show no interference was encountered from them and the drug.

Table 2. Response characteristics and method validation for the three investigated MOEX electrodes.

Parameter	Sensor 1	Sensor 2	Sensor 3
Slope(mV/ decade)	-29.75	-30.6	-30.2
Intercept (mV)	164.1	121.6	155.6
Correlation coefficient	0.9998	0.9997	0.9997
LOD (M)	1.5×10^{-7}	2.3×10^{-7}	1.8×10^{-7}
Response time (sec)	20-30	20-30	20-30
Working pH range	2-4	1-3	1-3
Concentration range (M)	10^{-6}-10^{-2}	10^{-6}-10^{-2}	10^{-6}-10^{-2}
Life span (weeks)	6-8	6-8	6-8
Mean ± S.D.*	99.64 ± 0.34	99.34 ± 0.56	99.68 ± 0.42
Repeatability **	99.45 ± 0.61	99.53 ± 0.70	99.26 ± 0.39
Intermediate Precision***	99.58 ± 0.82	99.14 ± 0.49	98.78 ± 0.52

* Results of three determinations; ** The intra-day variability of MOEX concentrations of 10^{-3} and 10^{-4} (n =5); *** The inter-day variability of MOEX concentration of 10^{-3} and 10^{-4} (n =5).

Table 3. Potentiometric selectivity coefficient ($K^{pot}_{A,B}$) for the three proposed electrodes.

Interfering substance**	Selectivity coefficient*		
	Sensor 1	Sensor 2	Sensor 3
Na^+	4.14×10^{-3}	1.19×10^{-3}	1.48×10^{-3}
K^+	2.1×10^{-3}	4.2×10^{-3}	1.93×10^{-3}
Mg^{+2}	1.77×10^{-3}	2.5×10^{-3}	1.62×10^{-3}
NH_4^+	1.15×10^{-3}	2.2×10^{-3}	1.32×10^{-3}
Lactose	6.8×10^{-3}	5.3×10^{-3}	2.08×10^{-3}
Urea	5.4×10^{-3}	4.8×10^{-3}	3.8×10^{-3}
L-phenyl alanine	4.5×10^{-3}	5.1×10^{-3}	2.24×10^{-3}
Degradation product	2.84×10^{-3}	3.14×10^{-3}	1.73×10^{-3}
Hydrochlorothiazide***	3.74×10^{-3}	4.34×10^{-3}	3.32×10^{-3}
Verapamil****	4.22×10^{-3}	3.92×10^{-3}	3.13×10^{-3}

* Average of three determinations; ** All interferents are in the form of 1×10^{-3} M solution; *** Co-formulated drug;**** Co-administered drug.

Pharmaceutical additives did not show any interference. Thus, analysis was carried out without prior treatment or extraction. The three sensors were successfully used for the determination of MOEX in primox tablets (Table 4).
On application to the biological fluids, plasma electrolytes did not show any interference. It has been found that three electrodes gave stable results as

revealed by high precision and accuracy of recoveries of the spiked plasma samples (Table 5).

Table 4. Determination of MOEX in primox tablets by the proposed electrodes.

Dosage form	Recovery % *		
	Sensor 1	Sensor 2	Sensor 3
Primox tablets 7.5 mg (batch no. 7EE0881)	100.27 ± 0.23	100.54 ± 0.15	99.96 ± 0.34
Primox tablets 15 mg (batch no. 5KE1587)	99.73 ± 0.54	100.17 ± 0.38	99.44 ± 0.63

* Average of three determinations.

Table 5. Determination of MOEX in spiked human plasma by the proposed electrodes.

Concentration (M)	Recovery % *		
	Sensor 1	Sensor 2	Sensor 3
1×10^{-5}	99.43 ± 0.75	99.25 ± 0.51	100.08 ± 0.27
1×10^{-6}	99.19 ± 0.63	98.89 ± 0.42	99.15 ± 0.57

* Average of three determinations.

Statistical evaluation of the results obtained from analysis of pure MOEX by the proposed electrodes and the reported method showed that there is no significant difference between the proposed and reported method in terms of accuracy and precision (Table 6). The reported method is a second derivative spectrophotometric method which was based on measuring the peak amplitudes at 215 nm for the second derivative spectra of MOEX in a concentration range of 0.5-12.0 $\mu g.mL^{-1}$.

Table 6. Statistical analysis of the results obtained by applying the proposed electrodes and the reported method for the analysis of MOEX in pure powder form.

Item	Sensor 1	Sensor 2	Sensor 3	Reported method [3]**
Mean	99.64	99.34	99.68	99.86
S.D	0.34	0.56	0.42	0.66
N	5	5	5	10
Variance	0.12	0.31	0.18	0.44
t (2.16)*	0.85	1.60	0.64	…….
F test (6.00)*	3.67	1.42	2.44	…….

* The values between parentheses are the corresponding theoretical values of t and F at 95% Conf. level
** Second derivative spectrophotometric method.

Validation of the proposed potentiometric methods for determining MOEX was made by measuring the range, lower limit of detection (LOD), lower limit of quantification (LOQ), accuracy, precision, repeatability (inter-and intra-day variability), linearity and sensitivity. Results obtained on three batches are depicted in Table 2.

Conclusion

The use of the proposed sensors offers the advantages of fast response, elimination of drug pretreatment or separation steps, low detection limits and

direct determination of drug in turbid or colored solutions. They can therefore be used for routine analysis of the MOEX in quality control laboratories.

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