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Electrometric Assay for the Determination of Moexipril HCl Using Sensitive Sensors Based on Carbon Paste and PVC Membrane Electrodes.

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Carbon paste (CPE) and PVC membrane ion selective electrodes have been described for determination of moexipril HCl (MOEX.HCl) in pure form and primox tablet. The method based on the ion-pair formation between MOEX.HCl with sodium tetraphenylborate. The two types of electrodes were prepared using five types of plasticizers with each type of electrode. The electrodes showed a linear response with a good Nernstian slope of 58.82±0.53 and 58.57±0.98 mV decade^{-1} over the concentration range from 10^{-7} to 10^{-2} mol L^{-1} for CPE and PVC membrane electrodes, respectively. The standard electrode potentials, $E°$, were determined at 10, 20, 30, 40 and 50 °C and the isothermal temperature coefficient ($dE°/dT$) of the electrodes was calculated. The electrodes proved high selectivity with selectivity coefficients ranging from 2.23×10^{-6} to 39.9×10^{-3} and 5.9×10^{-4} to 8.3×10^{-3} mol L^{-1} for CPE and PVC membrane potentiometric sensors, respectively. The detection limits (signal/noise [S/N] = 3) were found to be $6.73\text{x}10^{-8}$ and 5.38 x10^{-8} mol L^{-1} for CPE and PVC membrane potentiometric sensors, respectively. The practical applications of these electrodes were demonstrated by determining the concentrations of MOEX.HCl in pure solutions and pharmaceutical primox tablet with satisfactory results (percentage recovery was 98.94-99.59 and 98.44-99.25 % for CPE and PVC membrane electrodes, respectively). The reliability and stability of the electrodes gave a good possibility for applying the technique in routine analysis.

Keywords: Moexipril HCl, pharmaceutical analysis, potentiometry, tetraphenylborate, CPE, PVC.

1. INTRODUCTION

Meoxipril (Figure 1) is angiotensin-converting-enzyme inhibitor and used in the treatment of hypertension and heart failure [1]. Meoxipril is (3*S*)-2-[(2*S*)-2-{[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-

yl]amino}propanoyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

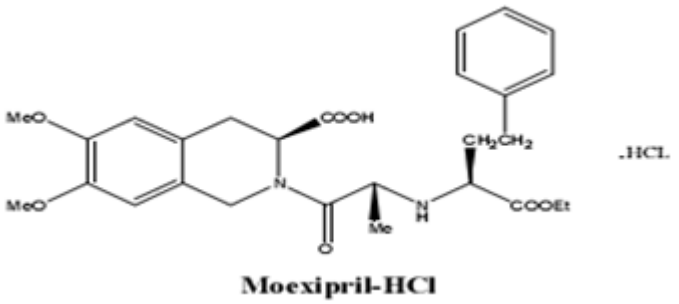


Figure 1. Structure formula of moexipril hydrochloride

Meoxipril was determined by gas chromatography [2] and electroanalytical [3, 4] techniques. Simultaneous determination of meoxipril and hydrochlorothiazide in tablets by derivative spectrophotometric and high performance liquid chromatographic methods were also done [5-8].

In the present work, carbon paste (CPE) and plastic membrane electrodes of the conventional type (PVC) have been constructed and their performance characteristics were studied. The electrodes were based on the interaction of the sodium tetraphenylborate (Na^+TPB^-) with the meoxipril drug [$MOEX^+$] to form the ion-pair which utilized to study the life time of the above-mentioned electrodes by observing the changes that appear on their voltage until they lose their sensitivity and all effects such as pH, temperature, selectivity, etc were studied. The electrodes were used successfully as sensors to determine MOEX.HCl in pure form and pharmaceutical preparation. Method validation parameters were evaluated in order to measure to what extent this method can be applied for routine analysis measurements of MOEX.HCl.

2. EXPERIMENTAL

2.1. Materials

All chemicals and reagents used were of analytical reagent grade and some of them were used as such without any further purification. Distilled water was used throughout all experiments. MOEX.HCl was provided by Mina Pharm Company for Pharmaceutical Industry, Egypt. Glucose, sucrose, starch, maltose, lactose, fructose, glycine, sodium fluoride, lead nitrate and chloride salts of calcium, mercury, nickel, potassium, ammonium, zinc, cadmium and cobalt were used as interfering materials.

For making ISE membrane the following reagents were used: *o*-nitrophenyloctylether (*o*-NPOE) was supplied from Fluka, while di-n-octyl phthalate (DOP), dibutylphthalate (DBP) and dioctyl sebacate (DOS) were supplied from BDH. In addition, tricresylphosphate (TCP),

polyvinylchloride (PVC relative high molecular weight) and graphite powder (synthetic 1 – 2μm) were supplied from Aldrich.

Sodium tetraphenylborate (NaTPB, Sigma-Aldrich, Germany), phosphotungstic acid (PTA, Fluka, Switzerland), phosphomolybdic acid (PMA, Fluka, Switzerland) and ammonium reineckate (RN, Fluka, Switzerland) were used for precipitation of different ion pairs. Cyclohexanone and acetone were supplied from Fluka (Switzerland).

MOEX.HCl pharmaceutical preparation (Primox tablet, 15 mg/tablet) was purchased from Mina Pharm, Egypt.

2.2. Apparatus

Elemental analysis (C, H, N) were determined at the Microanalytical Center at Cairo University using CHNS-932 (LECO) Vario Elemental analyzers. Laboratory potential measurements were performed using a Jenway potentiometer model 3505. Silver-silver chloride double-junction reference electrode (Metrohm 6.0222.100) in conjugation with different drug ion selective electrodes was used. pH measurements were done using HANNA, model 211, Romania.

2.3. Standard solutions

2.3.1. Meoxipril HCl solution

Stock MOEX.HCl solution (1.0×10^{-2} mol L^{-1}) was prepared by dissolving the proper weight of the drug (535.04 mg) into smaller amount of distilled water, heated with stirring till the drug completely dissolved. The resulting solution was then made up to 100 mL with distilled water in a measuring flask.

To compare the sensitivity of the electrodes with the drug once and with the pharmaceutical preparation, Primox (15 mg MOEX.HCl) used, take 18 tablets and ground them well then calculate the right weight to prepare 10^{-2} mol L^{-1}. The weighed amount was dissolved in smaller amount of distilled water, heated with stirring then filtered using filter paper to get rid of insoluble materials and transferred quantitatively to 100 mL volumetric flask. Then the content was estimated via potentiometric titration with NaTPB using CPE and PVC (plasticized with TCP) as sensing electrodes. The method was repeated several times to check the accuracy and reproducibility of the proposed method.

2.3.2. Tetraphenylborate solution (TPB^-)

1×10^{-2} mol L^{-1} NaTPB solution was prepared by dissolving 1811 mg into 500 mL distilled water, adjusted to pH = 9 by adding sodium hydroxide and completed to the desired volume with water. The resulting solution was standardized potentiometrically against standard (1×10^{-2} mol L^{-1}) thallium (I) acetate solution [9].

2.3.3. Interfering ions solutions

A 10^{-3} mol L^{-1} solution each of glycine, glucose, sucrose, starch, fructose, maltose, lactose, sodium fluoride, lead nitrate, chloride salts of calcium, mercury, zinc, ammonium, nickel, potassium, cadmium and cobalt were prepared by dissolving the proper weights into 100 mL bidistilled water.

2.4. Electrodes preparation

2.4.1. Carbon paste electrode preparation

The sensing electrodes were prepared by intimate mixing accurately weighed amount of highly pure graphite powder (500 mg) and plasticizer (0.2 mL of DOP, TCP, DBP, DOS or *o*-NPOE). This matrix was thoroughly mixed in the mortar and the resulted past was used to fill the electrode body [10, 11]. A fresh surface was obtained by gently pushing the stainless-steel screw forward and polishing the new carbon-paste surface with filter paper to obtain a shiny new surface.

2.4.2. PVC membrane preparation

For PVC electrode, five membranes were prepared using the cocktail consisting of 240 mg plasticizer "DOP, DBP, TCP, DOS and *o*-NPOE", 240 mg PVC and 6 mL THF. The cocktail was stirred for 5 min and poured into Petri dish "5 cm" diameter. After 24 h of slow evaporation of solvent, a master membrane with 0.11 mm thickness was obtained which was mounted on the softened end of the PVC tubing with the help of adhesive solution prepared by dissolving PVC in tetrahydrofuran (THF). The PVC closed tube with the membrane was filled with 0.25 mL of 1 mol L^{-1} KCl and completed to 25 mL with 0.01 mol L^{-1} MOEX.HCl drug solution under investigation using Ag/AgCl as internal reference electrode.

2.5. Procedures

2.5.1. Study of the experimental conditions

2.5.1.1. Identification of slope of the studied electrodes:

The electrochemical performance characteristics of the two studied MOEX.HCl-selective electrodes were evaluated according to IUPAC guidelines [12].

Sensors calibration was carried out by measuring the potential of 10^{-7}–10^{-2} mol L^{-1} drug solutions starting from low to high concentrations. The potentials were plotted as a function of drug concentrations. Sensors life spans were examined by repeated monitoring of the change in the potential break and total potential jump of the drug titration periodically. 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 (PVC membrane and CPE) were tested within the concentration range of 10^{-7}–10^{-2} mol L^{-1} MOEX.HCl solutions. The sequence of measurements was from low to high concentrations. The time required for the electrodes to reach value within ±2 mV from the final equilibrium potential after increasing MOEX.HCl concentration level by ten folds was measured.

2.5.1.2. Effect of pH on the electrodes response

The effect of pH on the potential values of the two electrodes was studied over the pH range of 1–10 at 1-pH interval by immersing electrodes in 10^{-2} and 10^{-4} mol L^{-1} MOEX.HCl solutions. The pH was gradually increased or decreased by adding aliquots of diluted sodium hydroxide or hydrochloric acid solutions, respectively. The potential obtained at each pH was recorded.

2.5.1.3. Effect of temperature

The effect of temperature on the performance of the potentiometric electrodes was evaluated in a thermostat at different temperatures ranged from 10 to 60 °C.

2.5.1.4. Effect of titrants

3 mL of 10^{-2} mol L^{-1} MOEX.HCl drug solution was potentiometrically titrated against different titrants including NaTPB, RN, PTA and PMA using CPE and PVC (plasticized with TCP) as sensing electrodes where the total potential change and the potential break for each titrant were calculated at the end point.

2.5.1.5. Effect of foreign compounds on the electrodes selectivity

The selectivity coefficients of many compounds such as starch, sugars, glycine and some cations of different valences were obtained by the matched method which is totally independent of the Nicolsky equation. To determine the selectivity coefficients by the matched method, a known activity ($a_{D'}$) of the primary ion solution is added into a reference solution that contains a fixed activity (a_D) of primary ions, and the corresponding potential change (ΔE) is recorded. Next, a solution of interfering specie is added to the reference solution until the same potential change (ΔE) is reached and the activity of interfering (a_B) is recorded. The change in potential produced at the constant background of the primary ion must be the same in both cases. Also, the potentiometric selectivity coefficients ($K^{Pot}_{MOEX.HCl,I}$) were evaluated according to IUPAC guidelines using the separate solution method [13,14] 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.HCl ions) and B (interfering ion) at the same activity $a_A = a_B$. Selectivity coefficients were calculated by the separate solutions method,

where potentials were measured for 10^{-3} mol L^{-1} MOEX.HCl solution and 10^{-3} mol L^{-1} interfering solution, separately, and then potentiometric selectivity coefficients were calculated [13, 14].

2.5.1.6. Studying the effect of soaking time using the proposed sensors

Freshly prepared electrodes must be soaked to activate the surface to form an infinitesimally thin gel layer at which ion exchange occurs. Storage was in the distilled water when not in use.

2.6. Potentiometric determination of MOEX.HCl in pharmaceutical preparations

MOEX.HCl was determined in pure solution and pharmaceutical preparations using the developed electrodes under both batch conditions (by standard addition and potentiometric titration). In standard addition method, known increments of 10^{-2} mol L^{-1} standard MOEX.HCl solution were added to 25 mL aliquot of sample solution where the change in the potential readings was recorded for each increment and used to calculate the concentration of MOEX.HCl in sample solution. For potentiometric titration, aliquots of the sample solutions containing 3.5-16.05 mg mL^{-1} MOEX.HCl were titrated against standard NaTPB solution. The titration process was monitored using MOEX.HCl sensors in conjugation with the conventional Ag/AgCl reference electrode and the potential values were plotted against the titrant volume to estimate the end point.

3. RESULTS AND DISCUSSION

The development and application of ion-selective electrodes (ISEs) is of interest for pharmaceutical analysis. This can be attributed to the fact that these sensors offer the advantages of simple design and operation, fast response time, reasonable selectivity for the drug under investigation, low detection limit, high accuracy, wide concentration range applicability to coloured and turbid solutions, and possible interfacing with automated and computerized systems. MOEX.HCl reacted with sodium tetraphenylborate to form stable 1:1 water insoluble ion association complex, with low solubility product and suitable grain size precipitate, having the following suggested composition: $C_{51}H_{63}BN_2O_7$ with elemental analysis data: Found: %C = 74.50, %H = 7.44 and %N = 3.42, Calculated: %C = 74.10, %H = 7.60, %N = 3.39. This data are nearly similar to the previously reported [4] which confirm that the assumption 1:2 [MOEX]:[TPB] is incorrect. Also, 1:1 [MOEX]:[TPB] is confirmed by titration of different drug solutions with sodium tetraphenyl borate.

3.1. Electrochemical behaviour of moexipril hydrochloride with utilized electrodes

To obtain the electrochemical behaviour of the electrodes under study, calibration was carried out by immersing the electrodes in conjunction with the double junction Ag/AgCl reference electrode in solutions of MOEX.HCl in the concentration range of 10^{-7}–10^{-2} mol L^{-1}. They were allowed to

equilibrate whilst stirring and recording the electromotive force readings (e.m.f.). The electrodes showed a linear response over the concentration range 10^{-7}–10^{-2} mol L^{-1} with Nernstian slope of 58.82±0.53 and 58.57±0.98 mV $decade^{-1}$ for CPE and PVC potentiometric sensors, respectively (Table 1). The E (mV)–p[MOEX] profile was plotted as shown in Figure (2). The previously reported data [4] reveals a lower concentration range (10^{-5} -10^{-2} mol L^{-1}), if it is compared with the data reported in our work.

Table 1. Response characteristics of the investigated MOEX.HCl electrodes.

Parameters	CPE	PVC
Slope (mV $decade^{-1}$)	58.82±0.53	58.57±0.98
Intercept (mV)	39.26	38.00
Correlation coefficient	0.988	0.992
Detection limit (mol L^{-1})	$6.73x10^{-8}$	$5.38x10^{-8}$
Limit of quantitation (mol L^{-1})	$2.24x10^{-7}$	$1.79x10^{-7}$
Working pH range	2-4	2-4
Concentration range, mol L^{-1}	10^{-7}-10^{-2}	10^{-7}-10^{-2}
Life span (weeks)	10-15	2-3
Average recovery (%)	98.94-99.59	98.44-99.25
RSD%[a]	0.83	0.66
Between day variability (CV[b] %)	0.78	0.65
Robustness[b]	99.02±1.02	98.45±1.11
Ruggedness[c]	98.88±0.62	98.22±1.05

[a] Average of four determinations.
[b] Variation in method parameters such as pH of buffer.
[c] Comparing the results by those obtained by using HANNA 211.

3.2. Effect of soaking time on the electrode performance

Table 2. Effect of soaking time on the CPE and PVC performance in the potentiometric titration of 3 mL of 10^{-2} mol L^{-1} MOEX with 10^{-2} mol L^{-1} NaTPB.

Time of soaking	CPE		PVC	
	Potential break at the end point, mV	ΔE/ΔV (mV/mL)	Potential break at the end point, mV	ΔE/ΔV (mV/mL)
With out	80	202.5	172	450
5 min	150	382.5	40	120
15 min	230	587.5	60	170
30 min	99	250	35	107.5
1 hr	93	235	30	95
2 hr	84	212.5	25	82.5
12 hr	88	192.5	20	70
24 hr	30	77.5	20	70

The effect of soaking time on the performance of the electrodes was studied and the data obtained are listed in Table (2). The electrodes were soaked in MOEX-TPB ion-pair suspended solution and the titration curves were plotted from which the total potential changes are recorded after different time intervals. The optimum time was found to be 1 hr soaking, as indicated by the values of total potential change (293 and 192 mV mL^{-1} for CPE and PVC membrane electrodes plasticized with TCP, respectively) and potential break at the end point (230 and 172 mV for CPE and PVC membrane electrodes, respectively).

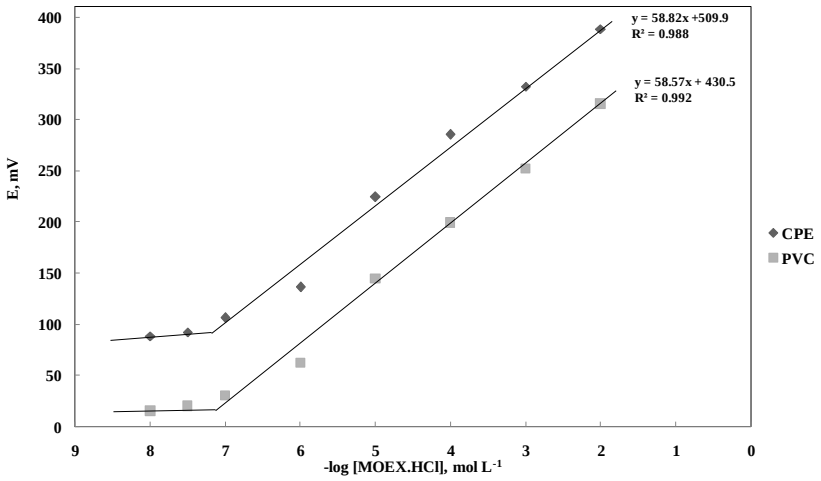
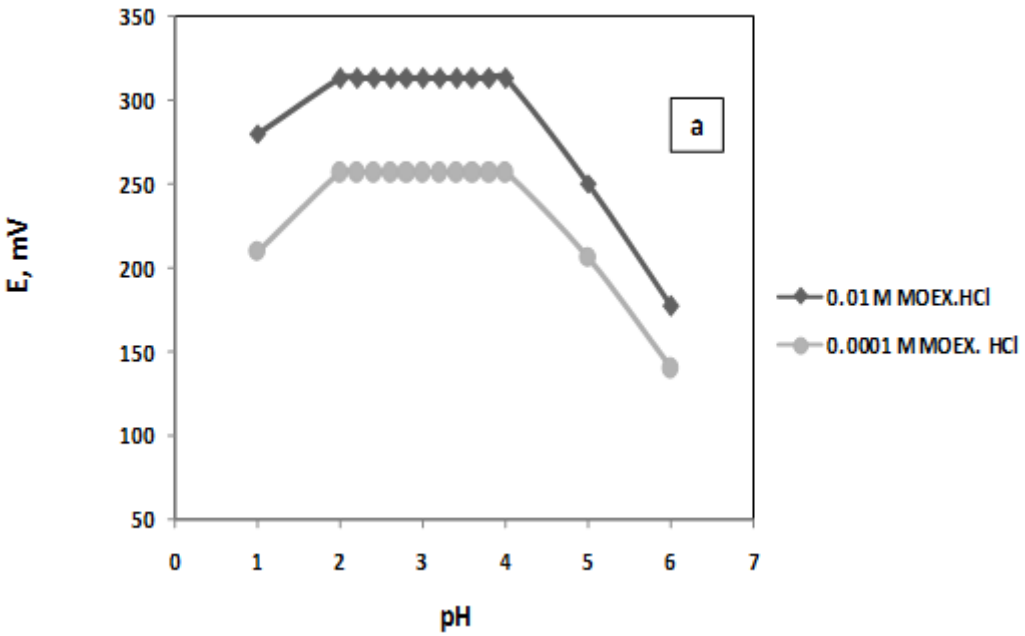


Figure 2. Nernstian slope using CPE and PVC membrane potentiometric sensors.

3.3. pH effect



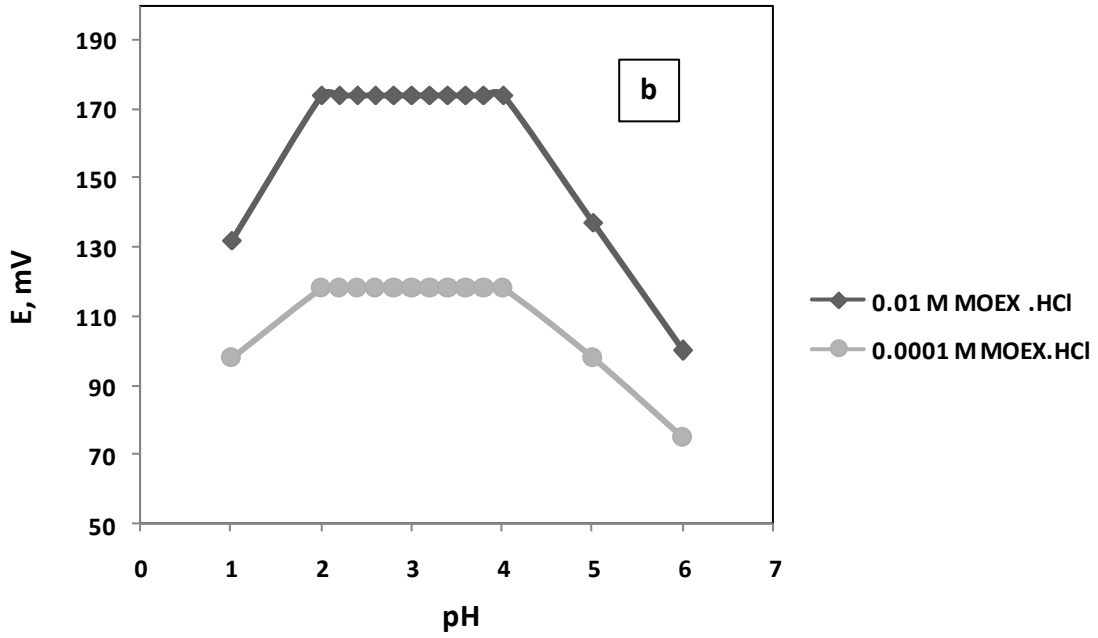


Figure 3. Effect of pH on the electrodes performance using (a) CPE and (b) PVC membrane potentiometric sensors.

The influence of the hydrogen ion towards the e.m.f. of the electrodes was tested at 1.0×10^{-2} and 1.0×10^{-4} mol L^{-1} of the drug solution by varying the pH from 1.0 to 10.0 with diluted HCl or NaOH. It is clear from Figure (3) that the electrodes have stable readings in the pH range 2-4 for CPE and PVC membrane electrodes. The change at higher pHs could be the result of hydroxide precipitate formation, while in the low pH range, competitive proton binding is probably behind the decreased potential values [15].

3.4. Selectivity coefficients

Potentiometric selectivity coefficients can be measured with different methods that fall into two main groups, namely (1) mixed solution methods, and (2) separate solution methods, Selectivity coefficient (K_{ij}) for every interfering secondary ion was determined by the separate solutions method [13, 14, 16]. Separate drug primary ion (i) and interfering secondary ion (j) solutions were prepared having equal concentrations (1.0×10^{-3} mol L^{-1}). Their potentials E_i and E_j were measured using CPE and PVC electrodes plasticized with TCP. Selectivity coefficients were calculated using the following equations:

$$\log K_{ij} = (E_j - E_i) / S \quad (1)$$

$$\log K_{ij} = [(E_j - E_i) / S] + [1 - (Z_j / Z_i)] \log[i] \quad (2)$$

Equation (1) is used for monovalent secondary ions whereas equation (2) is used for divalent or higher ones. Z_i and Z_j are the charges on the primary and secondary ions, respectively.

While the selectivity coefficients of many nitrogenous compounds such as starch, sugars and glycine were obtained by the matched method [17] which is totally independent of the Nicolsky equation. The following equation is applied:

$$\log K^{pot}_{D,B} = (a_D' - a_D) / a_B$$

The influence of some inorganic cations, sugars and glycine on the MOEX.HCl-electrodes was investigated (Table 3).

Table 3. Potentiometric selectivity coefficients of the MOEX sensors.

Interfering ions (B)	$K^{pot}_{D,B}$			
	CPE		PVC	
	SSM	MPM	SSM	MPM
Glucose	-------	9.68×10^{-3}	-------	2.7×10^{-3}
Lactose	-------	1.9×10^{-3}	-------	5.9×10^{-4}
Fructose	-------	39.9×10^{-3}	-------	5.12×10^{-4}
Maltose	-------	26.8×10^{-3}	-------	1.3×10^{-2}
Starch	-------	18.9×10^{-3}	-------	5.8×10^{-4}
Sucrose	-------	8.6×10^{-3}	-------	4.7×10^{-2}
Glycine	-------	15×10^{-3}	-------	8.3×10^{-3}
Co^{2+}	6.13×10^{-4}	-------	4.5×10^{-3}	-------
Ni^{2+}	2.23×10^{-6}	-------	3.7×10^{-4}	-------
Ca^{2+}	2.15×10^{-3}	-------	4.20×10^{-4}	-------
NH_4^+	1.34×10^{-3}	-------	5.6×10^{-3}	-------
K^+	1.29×10^{-3}	-------	2.7×10^{-3}	-------
Na^+	2.15×10^{-3}	-------	3.4×10^{-3}	-------
Cd^{2+}	3.52×10^{-5}	-------	1.45×10^{-5}	-------
Pb^{2+}	7.7×10^{-5}	-------	5.26×10^{-5}	-------
Hg^{2+}	5.25×10^{-5}	-------	6.2×10^{-3}	-------
Zn^{2+}	4.63×10^{-5}	-------	2.34×10^{-5}	-------
Fe^{+3}	4.10×10^{-4}	-------	4.65×10^{-4}	-------
Al^{+3}	5.05×10^{-4}	-------	5.15×10^{-4}	-------
Cr^{+3}	6.23×10^{-4}	-------	6.03×10^{-4}	-------

The selectivity coefficients values of the modified CPE and PVC membrane electrodes reflect a very high selectivity of the investigated electrodes for the moexipril cation ($MOEX^+$). The inorganic cations do not interfere owing to the differences in ionic size, and consequently their mobilities and permeability, as compared with those of $MOEX^+$ (Table 3). Also, the smaller the energy of hydration of the cation, the greater the response of the membrane, in case of sugars and glycine, the high selectivity is mainly attributed to the difference in polarity and lipophilic character of their molecules relative to MOEX.HCl. The selectivity coefficient values are more or less close to those previously reported [4].

3.5 Lifetime

The aim of this test was to compare lifetime of different electrodes related to their preparation mode. In overall, lifetime taken into account (CPE and PVC membrane electrodes plasticized with TCP) shows relatively good performance. After this time the total potential change and the potential break at the end point of the sensors will decrease where the electrodes were used extensively (twenty times per day). It is well established that the loss of plasticizer, carrier, or ionic site from the polymeric film due to leaching into the sample is a primary reason for limited lifetimes of the sensors [10, 11].

3.6. Effect of titrants

Table 4. Potentiometric titration of 3 mL of 10^{-2} mol L^{-1} MOEX.HCl with different titrants: a) 1×10^{-2} mol L^{-1} NaTPB, b) 1×10^{-2} mol L^{-1} RN, c) 3.3×10^{-3} mol L^{-1} PMA, d) 3.3×10^{-3} mol L^{-1} PTM, using CPE and PVC membrane electrodes.

Titrant	Total potential change, mV		Potential break at the end point, mV		ΔE/ΔV, (mV/mL)	
	CPE	PVC	CPE	PVC	CPE	PVC
NaTPB	261	180	230	153	587.5	400
RN	146	117	115	90	300	242.5
PMA	101	78	70	51	187.5	145
PTA	61	71	30	44	87.5	127.5

Table (4) shows the total potential change and the abrupt change in the potential at the end point obtained for the titration of MOEX with different titrants using modified CPE and PVC membrane electrode. It is obvious from these data that NaTPB is the most suitable titrant on the performance of electrodes as it gives the highest potential jumb and potential break at the end point.

3.7. Effect of temperature

The effect of temperature on the response of electrodes utilized was studied. The potential of 1.0×10^{-6} - 1.0×10^{-2} mol L^{-1} MOEX.HCl solutions were determined the temperatures in (10, 20, 30, 40, 50 and 60 °C) and the calibration graph was constructed. The standard electrode potentials ($E°_{elec.}$)

(obtained from the calibration plots) corresponding to each temperature were recorded. It is obvious that the electrodes gave a good Nernstian response in the temperature range 10–50 °C. For the determination of the isothermal coefficient ($dE°/dT$) of the electrodes, the standard electrode potential ($E°_{elec.}$) at different temperatures was plotted vs. (t – 25), where t is the temperature of the test solution. A straight-line plot was obtained according to the following equation [17]:

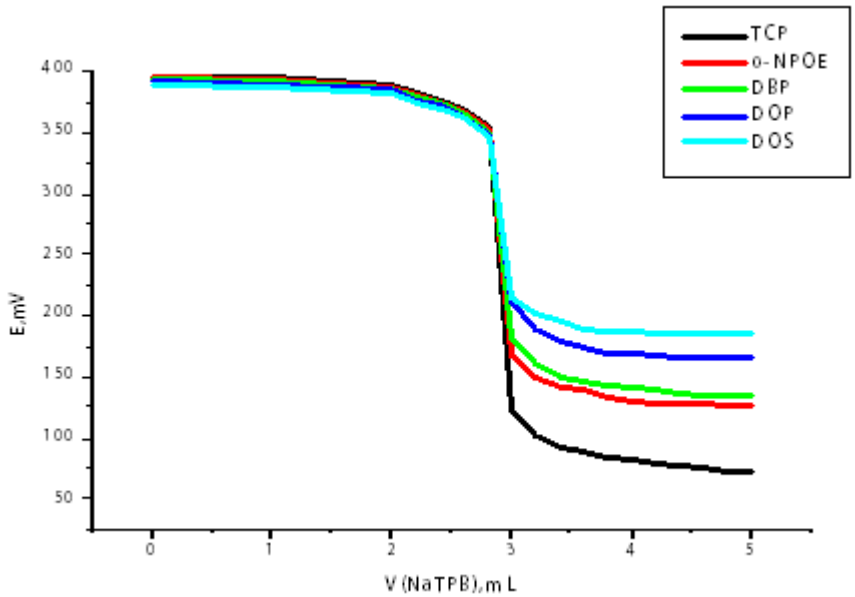
$$E° = E°_{(25)} + (dE° / dT)(t - 25)$$

Isothermal coefficients are found to be 0.050 and 0.054 mV/C° for CPE and PVC membrane electrodes, respectively. There is no significant variation in the slope and response time of both modified electrodes with variation in temperature indicating the thermal stability of the electrodes up to 50 ºC.

3.8. Effect of plasticizer type:

The role of plasticizer may be considered analogous to that of the organic solvent in liquid membrane electrodes and it influences both the selectivity and sensitivity of the electrodes. When these electrodes are used to monitor the potentiometric titration based on ion pair formation, the magnitude of both the potential break and sharpness at the inflexion point of the titration curve is predetermined by the plasticizer polarity (dielecterical constants, ε) as a result of higher extractability of the ion pair into the plasticizer [18].

The influence of the plasticizer choice on the electrode performances has been studied as the electrode plasticized with *o*-NPOE is compared with those plasticized with DBP, DOP, DOS, or TCP (Figure 5) for CPE and PVC membrane. From the all tested plasticizers, TCP shows the highest total potential change (293 and 192 mV) and the highest potential break at the end point (230 and 172 mV) for CPE and PVC membrane potentiometric sensors, respectively (Figure 5).



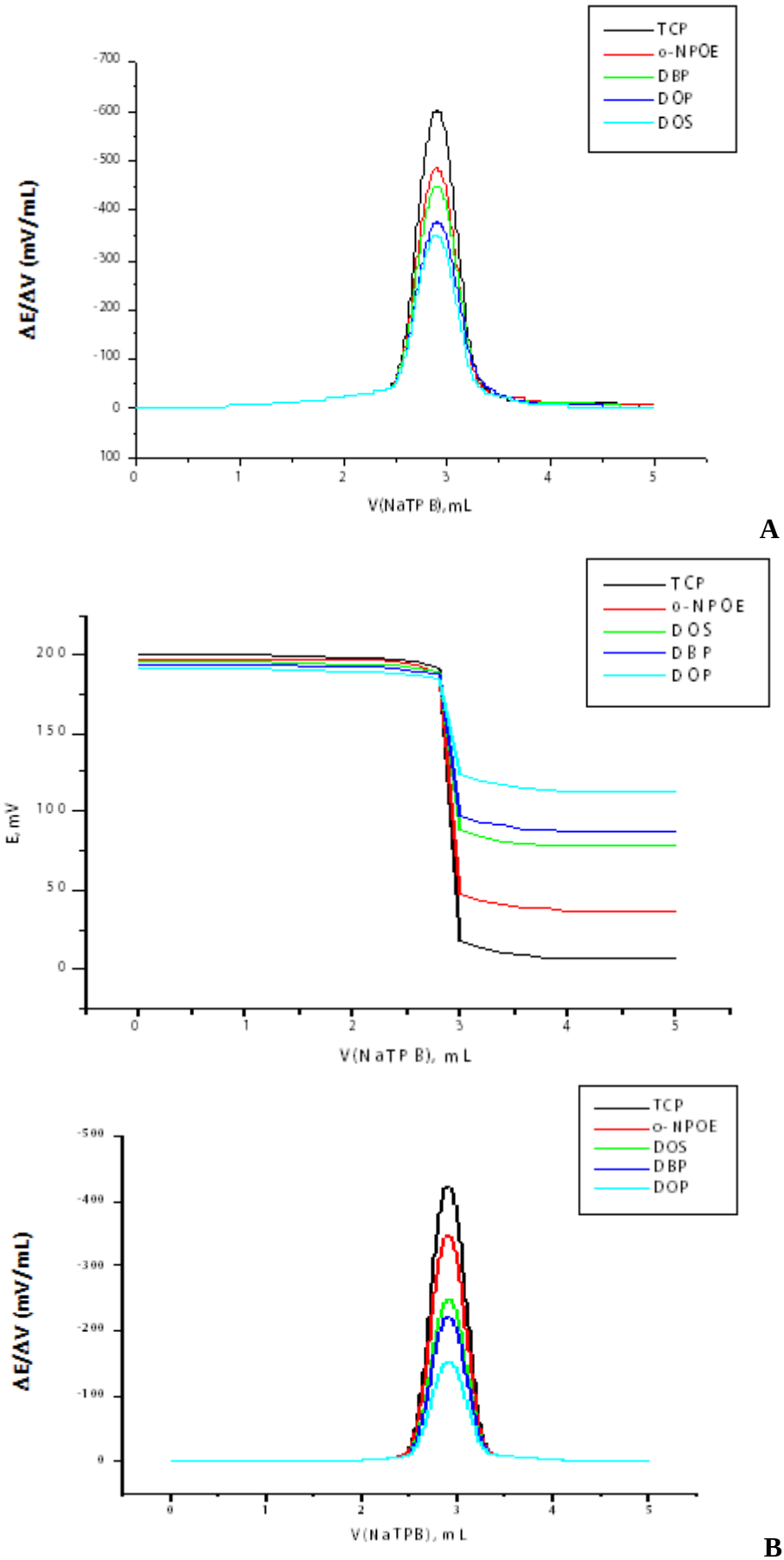


Figure 4. The effect of plasticizer type using: a) CPE and b) PVC membrane electrodes.

No electrode preconditioning is needed before applying in the potentiometric titration and excellent titration curves can be achieved from the second titration process, while electrodes fabricated using other plasticizers need either to operate the titration process at least 5-7 times or to soak the electrode in the aqueous solution of the ion pair for more than one hour before using these electrodes in the titration process. Also the electrode plasticized with DBP showed the shortest response time compared with other electrodes plasticized with the rest of plasticizers which is reflected on the total time required to achieve stable potential readings and the titration time.

3.9. Application on pharmaceuticals and official method:

Table 5. Determination of moexipril hydrochloride in pharmaceutical preparation applying the proposed and official methods.

Electrode	Sample	Proposed [Drug] mg mL^{-1}		Official [Drug] µg mL^{-1}		% Recovery		SD^{*} (RSD^{*} (%))	SD^{**} (RSD^{**} (%))
		Taken	Found	Taken	Found	Proposed	Official		
CPE (TCP)	Primox	3.50 10.20 16.05	3.47 10.16 15.88	10.00	10. 05	99.14 99.60 98.90	100.50	0.14(0.62) 0.12(0.58) 0.13(0.79)	0.36(0.83)
PVC (TCP)		3.50 10.20 16.05	3.45 10.17 15.80			98.57 99.70 98.40		0.15(0.72) 0.11(0.59) 0.17(0.63)	

* Proposed method ** Official method

The designed sensors were utilized to determine MOEX.HCl in pharmaceutical preparations (Primox tablet) using the proposed potentiometric method. The results obtained were compared to the official method [6, 7] and the data obtained are summarized in Table (5). There were no significant differences between the calculated and comparative values indicating that the electrodes can be used for potentiometric determinations of MOEX.HCl in such samples. Statistical evaluation of the results of analysis of pure MOEX.HCl by the proposed electrodes and the official method [6, 7] showed that there is no significant difference between the proposed and reported method in terms of accuracy and precision (Table 5).

4. METHOD VALIDATION:

The analytical method was validated according to the international conference for harmonization (ICH) guidelines under the optimized experimental conditions: linearity, accuracy, precision, specificity and stability.

4.1. Linearity

The linearity was evaluated by linear regression analysis, which was calculated by the least squares regression method and the data obtained are summarized in Table (1).

4.2. Limit of detection (LOD) and quantification (LOQ)

The limit of detection and quantification were calculated by LOD = 3δ/S and LOQ = 10δ/S, respectively, where S is the slope of the calibration curve and δ is the standard deviation of the response of the blank or the standard deviation of the intercepts of regression lines[19,20]. The values listed previously in Table 1, indicate that the proposed modified CPE and PVC membrane sensors are sensitive to detection of low concentrations of MOEX.HCl. These electrodes show a lower detection limit values ($6.73x\ 10^{-8}$ and $5.38x\ 10^{-8}$ mol L^{-1}) of MOEX.HCl using CPE and PVC membrane sensors, respectively if it is compared with the previously reported data ($1.5x10^{-7}$- $2.3x10^{-7}$ mol L^{-1}) of MOEX. HCl [4].

4.3. Accuracy

The accuracy of the proposed CPE and PVC membrane sensors for the determination of MOEX.HCl is investigated by using standard addition and potentiometric titration methods. MOEX.HCl is determined in primox samples prepared from serial concentrations of MOEX.HCl reference standards.

Table 6. Intra- and Inter-days precision of the determination of MOEX.HCl using the three types of electrodes with determination of pure and pharmaceutical tablet.

Drug	Electrode type (plasticizer used)	Taken, mg mL^{-1}	Intra day				Inter day			
			Found, mg mL^{-1}	Recovery %	SD	RSD%	Found, mg mL^{-1}	Recovery %	SD	RSD%
Pure form	CPE (TCP)	6.05	5.94	99.31	0.120	0.68	5.89	99.00	0.140	0.58
		9.65	9.61	99.59	0.150	0.82	9.59	99.38	0.210	0.87
		16.75	16.59	99.40	0.260	1.56	16.55	99.25	0.320	1.16
	PVC (o-NPOE)	6.05	5.89	99.00	0.095	0.54	5.87	98.88	0.079	0.65
		9.65	9.60	99.48	0.110	0.74	9.62	99.69	0.104	1.19
		16.75	16.54	99.21	0.167	1.48	16.45	98.88	0.123	1.53
Primox tablet	CPE (TCP)	6.05	5.88	98.94	0.130	0.79	5.85	98.75	0.110	0.74
		9.65	9.58	99.27	0.190	1.23	9.60	99.48	0.180	0.92
		16.75	16.64	99.59	0.220	1.64	16.70	99.81	0.270	1.66
	PVC (o-NPOE)	6.05	5.80	98.44	0.170	0.63	5.83	98.62	0.150	0.68
		9.65	9.57	99.17	0.220	1.32	9.61	99.59	0.270	1.52
		16.75	16.48	98.99	0.320	1.88	16.65	99.63	0.360	2.45

The results summarized in Table 6 show that the proposed method is an accurate one, as indicated by the percentage recovery values, for the determination of MOEX.HCl in its pharmaceutical preparations without interferences from the coformulated adjuvants.

4.4. Precision

In order to determine the precision of the proposed methods, solutions containing three different concentrations of MOEX.HCl were prepared and analyzed in four replicates and the analytical results are summarized in Table 7. The low values of the relative standard deviation (% RSD) also indicate the high precision and the good accuracy of the proposed potentiometric method. RSD (%) and SD values were obtained within the same day to evaluate repeatability (intra-day precision) and over five days to evaluate intermediate precision (inter-day precision).

4.5. Robustness and Ruggedness

The robustness of this proposed method was done by investigating to what extent the capacity of the method remains unaffected by a small but a deliberate variation in method parameters and hence provides an indication of its reliability during normal usage [21, 22]. The ruggedness of the proposed method was done by investigating the reproducibility of the results obtained by the analysis of the same samples under different conditions such as different instruments, laboratories and analysts. The results obtained using another model of pH-meter (HANNA 211, Romania) were compared with those obtained using Jenway 3505 pH-meter. The results obtained are close and also reveal validity of the method (Table 1).

5. CONCLUSION

The carbon paste electrode is a good tool for direct MOEX.HCl determination and can be used for direct applications in real samples without any pretreatment. It was possible to determine MOEX.HCl contained in pharmaceutical samples following the standard addition and potentiometric titration methods using the PVC and CPE electrodes. A good analytical performance has been demonstrated. The proposed potentiometric method shows a low detection limit, good sensitivity and excellent stability of carbon paste electrode over the PVC membrane. The carbon paste electrode and PVC membrane have shown good Nernstian slope, rapid response time and relatively long term stability. Application of these electrodes for the potentiometric determination of this antihypertensive drug in quality control department in drug sector and controller section is more economic and less time consuming compared with the most frequently used HPLC method.

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