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Novel and selective potentiometric membrane sensor for amiloride determination in pharmaceutical compounds and urine

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ABSTRACT

A new PVC membrane sensor is described as a potentiometric sensor for amiloride. The sensor having amiloride–sodium tetraphenyl phthalate (ion-pair) as an electroactive material and dibutyl phthalate (DBP) as an anion excluder in PVC matrix in the percentage ratio of 4:66:30 (ion-pair: DBP:PVC) (w/w). The membrane sensor exhibits suitable response to amiloride in a concentration range of 1.0×10^{-2} to 1.0×10^{-6} mol L^{-1} with a limit of detection of 9.9×10^{-7} mol L^{-1}. The slope of the system was -54.3 ± 1.0 mV decade^{-1} over pH range of 2.0–7.0. Selectivity coefficients for amiloride relative to a numbers of potential interfering substances were investigated. The sensor was highly selective for amiloride over a large number of similar compounds. The sensor showing a fast response time of 6 s and was used over a period of 2 months with a good reproducibility. The sensor was successfully applied to determination of amiloride in pharmaceutical samples with satisfactory results.

1. Introduction

Amiloride hydrochloride, 3,5-diamino-*N*-(diaminomethylene)-6-chloropyrazine-carboxamide monohydrochloride (Fig. 1), is a potassium-conserving relatively weak natriuretic diuretic with anti-hypertensive activity [1]. It is a therapeutic drug and a pharmacological tool usually used in combination with thiazide diuretics or other kaliuretic–diuretic agents in congestive heart failure or hypertension [2]. Amiloride is used for its potassium-sparing effect in the treatment or prevention of hypokalemia induced by thiazide or other kaliuretics in patients with congestive heart failure or hypertension [1]. This natriuretic agent can be applied as a doping substance. In sports, diuretics are abused mainly for two reasons [3]. The first is to obtain a rapid diminution of corporal weight, which is important in sports that are divided into different weight categories. The second is to reduce the concentration of medical drugs in urine by diluting the latter by means of the rapid production of an elevated volume of urine, leading to a smaller possibility of detecting other doping substances. An advantage in the use of amiloride is that low doses lead to high-volume urine excretion, obstructing its determination and therefore highly sensitive methods are required.

Owing to the uncontrollable use of amiloride, the International Olympics Committee, since 1990 has included it in the list of forbidden substances [4]. Consequently there is a need for the development of selective and fast method for determining this doping substance. The therapeutic and doping dose of amiloride varies from 5 to 20 mg daily (one administration only). It is incompletely absorbed and it does not appear to be metabolized. The half-life in plasma varies from 6 to 10 h and about 50% of an oral dose is excreted in the unchanged form in urine [5]. Consequently, the determination of amiloride in urine demands highly selective methods. There have been only a few reports on the determination of amiloride in tablets [6–9] or in biological fluids [10,11]. Normally the determination of amiloride at therapeutic levels by liquid chromatography requires various tedious preliminary procedures, such as extraction and preconcentration in an organic solvent. This causes many disadvantages (such as low recoveries), since all these procedures are based on equilibrium reactions. Amiloride has been determined in pharmaceutical preparations and biological fluids using several methods including, spectrophotometry [2,12–14], fluorimetry [15–17], high performance liquid chromatography [18,19], differential pulse polarography [20,21], capillary isotachophoresis [22], and chemiluminescence oxidation [23]. Many of the above methods suffer from many interfering substances and/or suffer from time-consuming procedure.

Potentiometric detection based on ion-selective electrodes (ISEs), offers several advantages such as speed and ease of preparation and procedures, simple instrumentation, relatively fast response, wide dynamic range, reasonable selectivity, and low cost [24,25]. Based of our knowledge, there is not any report for the determination of amiloride based ISE. In this paper, we introduced a new potentiometric sensor for selective determination of amiloride in pharmaceutical compounds. The method is based on the ion-pair formation between amiloride and sodium tetraphenyl phthalate as

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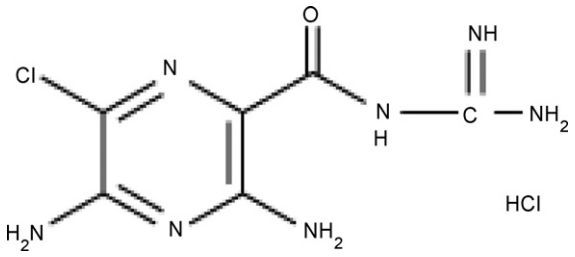

Fig. 1. Structure of amiloride hydrochloride.

an electroactive material and dibutyl phthalate (DBP) as an anion excluder in PVC matrix.

2. Experimental

2.1. Reagents

All chemicals used were of analytical reagents grade and were used without further purification. All solutions were prepared by dissolving the salts of the metal nitrates in distilled deionized water.

PVC of high relative molecular weight, dibutyl phthalate (DBP), dioctyl phthalate (DOP), sodium tetraphenyl borate (NaTPB), sodium tetraphenyl phthalate and tetrahydrofuran (THF) and all other chemicals were of highest purity available from Aldrich, and were used without further purifications, except THF, which was distilled before using.

A stock solution of 1.0×10^{-1} mol L^{-1} amiloride hydrochloride was prepared by dissolving an accurate mass of amiloride hydrochloride in water, kept in a dark glass bottle and then stored at 4 °C. More dilute solutions of amiloride hydrochloride were prepared by accurate dilution of the stock solution with water.

Urine samples were obtained from fasting healthy people during morning hours.

2.2. Apparatus

Potentials were measured by direct potentiometry at 25 ± 0.1 °C with the help of ceramic junction calomel electrodes and the cell set-up was as follow:

$$Hg/Hg_2Cl_2, KCl(sat'd)|Internal\ electrolyte(0.010\ mol\ L^{-1})$$

$$amiloride|Membrane|Sample\ solution|Hg/Hg_2Cl_2, KCl(sat'd)$$

A brief scheme of the cell is shown in Fig. 2. All potentiometric measurements were made with a pH/mV meter (Corning, Model 140). All emf measurements were carried out in a 50-mL double walled glass cell with a constant magnetic stirring. Response times were determined after the potential of the solution had became constant, and similar measurements were carried out in another solution of 100-fold lower concentration.

A pH-meter (Corning, Model 140) with a double junction glass electrode was used to check the pH of the solutions.

2.3. Sample preparation

Commercial pharmaceutical formulation samples of three different brands were evaluated for amiloride analysis. In each case, a group of five tablets was individually weighed, finely powdered and mixed. A portion of each of the powder (40–60 mg) was accurately weighed and transferred into a 50-mL volumetric flask using 25 mL of H_2O. After being continuously shaken for 30 min, the flask was made up to volume with distilled H_2O, and the solid was left to decant for 30 min; then, 1.0 mL aliquot was diluted to 25 mL with H_2O in a 25-mL volumetric flask.

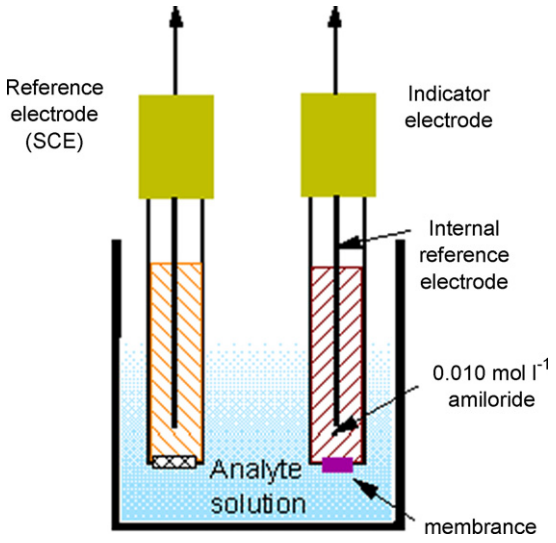

Fig. 2. Schematic diagram of the cell.

2.4. Electrode preparation

For preparation of the membrane, 5.0 mL of 1.0×10^{-1} mol L^{-1} aqueous amiloride solution was added to 10 mL of 0.050 mol L^{-1} solution of sodium tetraphenyl phthalate. The resulting precipitate was filtered and washed with deionized water and dried, protected from light in a desiccator at room temperature. Then, about 0.040 g of this precipitate was mixed with 0.300 g PVC and 0.660 g DBP previously dissolved in 6 mL of THF. The resulting homogeneous mixture was then poured into a 20 mm Petri dish, covered with a filter paper and the solvent was allowed to evaporate at room temperature. Semi-transparent PVC membrane was obtained with an average thickness of about 0.2 mm. A Pyrex tube (3 mm i.d.) was dipped into the mixture for about 10 s so that a membrane was formed. Then, the tube was then pulled out from the mixture and kept at room temperature for 12 h. The tube was then filled with the internal solution (1.0×10^{-2} mol L^{-1} amiloride). The filled electrode was conditioned by soaking into 1.0×10^{-3} mol L^{-1} amiloride. The first conditioning time was approximately 24 h and then was about 30 min for successive uses. A calomel electrode was used as an internal reference electrode. The lifetime of the sensor was at least 2 months when conditioned by soaking in 1.0×10^{-3} mol L^{-1} amiloride solution for 1 day before measurements and stored in air when not in use.

3. Results and discussion

3.1. Influence of membrane composition

Amiloride hydrochlorides behave as cations in acidic medium, due to presence of the amino groups. This fact suggests the use of anionic type of ion exchangers, sodium tetraphenyl phthalate and sodium tetraphenyl borate with their low solubility products and suitable grain size. The PVC was used as a polymer matrix in fabrication of membrane sensors. Amiloride was found to form 1:1 ion association complexes with each sodium tetraphenyl phthalate as proved by IR data. IR spectra of amiloride showed two band of C=N at 1615 and 1547 cm^{-1}, whereas for the ion-pair showed at 1611 and 1594 cm^{-1}. On the other hand, the $-NH_2$ band for the ion-pair was sharper than for amiloride. In addition the amide spectra for

amiloride appear at 1695 cm^{-1}, whereas for the ion-pair appeared at 1683 cm^{-1}. This means that amiloride has a strong interaction with sodium tetraphenyl phthalate.

In a preliminary experiment, membranes with and without carrier were constructed. The membrane with no carrier displayed insignificant selectivity toward amiloride and their response was not reliable. However, in the presence of the ion-pair (amiloride–sodium tetraphenyl phthalate), the optimized membrane demonstrated Nernstian response and remarkable selectivity for amiloride over several compounds, such as amiloride–sodium tetraphenyl phthalate, amiloride–sodium tetraphenyl borate. The selectivity of the membrane to amiloride is due to the fact that insufficient interaction of the other substances with amiloride–sodium tetraphenyl phthalate. The preferential response of the membrane toward amiloride is believed to be associated with the interaction of amiloride with the ion-pair. Besides the critical role of the nature of the ion-carrier in preparing membrane-selective sensors, some other important features of the PVC membrane such as amount of the ionophore, nature of the solvent mediator (plasticizer), amount of plasticizer to PVC ratio, and especially the nature of additives used are known to significantly influence the sensitivity and selectivity of the sensor [8,9]. Thus, several membrane compositions were investigated by varying the ratio of PVC, plasticizer, and the ionophore. The potentiometric response of the membrane was greatly improved in the presence of the ionophore.

A membrane is a phase and is finite in space which separates two other phases and exhibits individual resistance to the permeation of different species. Polymer matrix provides mechanical stability of the membrane, chemical stability, clean surface of the resulting membrane, chemical inertness and can be adjusted to exhibit extra requirements, i.e., physiological fluids sample, biocompatibility, adhesion, etc. As the results showed, among the two different plasticizers used, DBP was a more effective solvent mediator in preparing the amiloride membrane sensor. It should be noted that the nature of the plasticizer influences both the dielectric constant of the membrane and the mobility of the ionophore and its complex. Initially, plasticizers were applied to the polymer matrix in order to decrease its viscosity and provide mobility of the membrane constituents within the membrane phase. In relation to the role of plasticizer in a PVC membrane, it should be noted that plasticizer acts as a membrane solvent, affecting membrane selectivity through both extraction of ions into the organic phase. Both membrane solvents of low dielectric constants ε (adipates, sebacates and phthalates, $\varepsilon \sim 4$) and those of relatively high dielectric constants (nitroaromatics ($\varepsilon \sim 24$) and carbonates ($\varepsilon \sim 65$)) are available [17]. The drastic influence of the dielectric constant on the membrane selectivity stems from the contribution of the dielectric medium to the free energy of transfer. The introduction of polar or polarizable groups prevents these plasticizers from being exuded but they all have somewhat worse selectivity than the analogues because of the lack of such groups. The critical response characteristic of the proposed electrode was investigated according to IUPAC recommendations [14,15]. Different membrane composition was checked

Table 1
Optimized membrane compositions and their potentiometric response properties in Amiloride selective electrodes

No.	Composition (%)			Slope (mV decade^{-1})	Dynamic range (mol L^{-1})
	PVC	L	DBP/DOP		
1	30.00	4.00	66.00, DBP	−54.3	1.0×10^{-2} to 1.0×10^{-6}
2	46.43	9.26	44.31, DOP	−58.0	1.0×10^{-3} to 1.0×10^{-4}
3	48.50	5.09	46.41, DBP	−53.0	1.0×10^{-4} to 1.0×10^{-5}
4	25.88	3.63	60.93, DBP	−51.0	1.0×10^{-2} to 1.0×10^{-4}

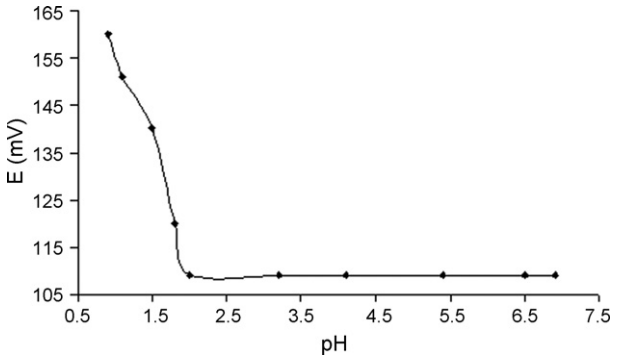

Fig. 3. Influence of pH on the response of the membrane (1.0×10^{-3} mol L^{-1} amiloride).

for the electrode response as presented in Table 1. The results show that the membrane with a composition of 66.0% DBP, 30.0% PVC, and 4.0% of the ion-pair generated produced a stable potential response after conditioning for 24 h in a 0.0010 mol L^{-1} amiloride.

3.2. pH effect

The effect of test solution pH (for 1.0×10^{-3} mol L^{-1} amiloride) on the potential response of the sensor was investigated by following the potential variation of the sensor over the pH range of 0.9–7.0. The pH was adjusted by introducing very small drops of hydrochloric acid solution (0.10 mol L^{-1}) and/or sodium hydroxide solution (0.10 mol L^{-1}). The results (Fig. 3) showed that the potential of the sensor remain constant from pH of 2.0 to 7.0. With more acidic conditions, amiloride may be protonated. On the other hand, in basic solution, hydroxide ion may react with amiloride to produce neutral species, which could not extract into the membrane. The results showed that the sensor has a stable response during pH of 2.0–7.0.

3.3. Response time, reproducibility and life time

The response time of the sensor was defined as t_{95} for the slope of the calibration curve of amiloride solution when the amiloride concentration was rapidly increased from 1.0×10^{-5} to 1.0×10^{-2} mol L^{-1} (Fig. 4), where t_{95} is the time required for the sensor to reach 95% of the steady state (final signal that does not change during 60 s) potentiometric value. From the results, the best response time of 6 s was recorded for membrane having the optimized conditions. After new solutions are exposed to the electrode the response changed rapidly and remains at a constant value

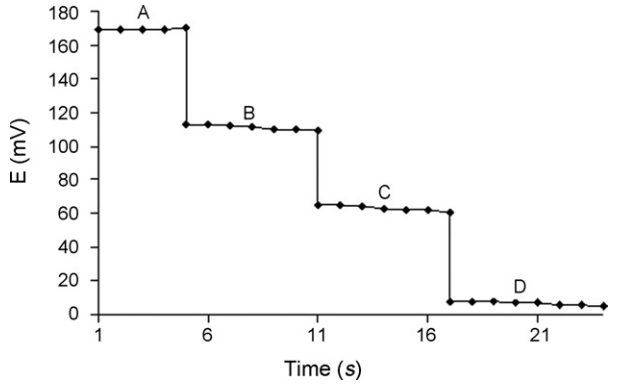

Fig. 4. Response time of the electrode: (A) 1.0×10^{-2} mol L^{-1}, (B) 1.0×10^{-3} mol L^{-1}, (C) 1.0×10^{-4} mol L^{-1}, and (D) 1.0×10^{-5} mol L^{-1} amiloride.

Table 2
ANOVA test method for the measuring of the reproducibility and repeatability of the slope for the sensor

	Day 1	Day 2	Day 3	Day 4
Electrod 1	−54.3	−54.4	−54.2	−54.6
Electrod 2	−54.4	−54.3	−54.1	−54.0
Electrod 3	−54.7	−54.3	−54.2	−54.3
Electrod 3	−54.3	−54.3	−54.3	−54.1
Repeatability of preparation sensors on any day (%)	99.70	99.89	96.80	99.30
Reproducibility of preparation sensors (%)		99.62		
Beetween-sample mean squre		0.086385		
Within-sample mean squre		0.360036		
$F_{cal(3,12)}$		0.640		
$F_{tab(3,12)}$		4.066		

before 6 s of the exposure. The potential generated by the membrane (when it's remained constant in one solution of amiloride) remained constant for 5 min, after which it started slow deviating (−0.5% per min).

The stability and reproducibility of the sensor were also tested. The standard deviation of slope of the calibration for 12 replicate measurements for several amiloride concentrations (1.0×10^{-5} to 1.0×10^{-2} mol L^{-1}) over periods of 20 min and 2 h were ≤0.5%. ANOVA test method used to show the reproducibility and repeatability of the sensor for amiloride concentration of 1.0×10^{-5} mol L^{-1}. The results are given in Table 2. The results of the calculations showed that $F_{cal(3,8)}$ (=0.640) was less than that $F_{tab(3,8)}$ (=4.066), meaning that there was not any significant difference between the sensor responses signals during measurements, and confirmed the stability and reproducibility.

The lifetime of the sensor depends on the distribution coefficient of the ionophore between the aqueous and membrane phases [19]. Hence, the lifetime of sensors depends on the components of the test solution and the measured specimens with the sensor. The lifetime of the sensor was worked out by performing calibrations periodically with standard solutions and calculating the slopes over the concentration ranges of 1.0×10^{-5} to 1.0×10^{-1} mol L^{-1} of amiloride. The experimental results showed that the lifetime of the present sensor was over 60 days (Table 3). During this time, the detection limit and the slope of the electrode remained almost constant. Subsequently the electrochemical behavior of the sensor gradually deteriorated which may be due to aging of the polymer (PVC), and the plasticizers. Therefore, the sensor can be used for at least 2 months, without a considerable change in their response characteristic towards amiloride.

3.4. Potentiometric selectivity

The selectivity behavior is obviously one of the important characteristics of sensors in which reliable measurement of the target sample is determined to be possible or not. Potentiometric selectivity coefficient (K_{Am}) describing the preference of the membrane for an interfering substance/ion M^{n+} relative to amiloride was determined by the separate solution method (SSM). Table 4 lists the potentiometric selectivity coefficients data of the sensor for several substances relative to amiloride. In addition, match potential method (MPM) was used to determine the selectivity of the sensor toward amiloride in the presence of potential interfering substances such as lactose, fructose, sucrose and glucose. The results showed the same selectivity of the potentiometric sensor to amiloride as the SSM. Therefore, the sensor has been found to be chemically inert to other substances. The inorganic cations did not interfere owing to the differences in ionic size, and consequently their mobility and permeability, as compared with those of amiloride. The selectivity of the membrane to amiloride is due to the fact that insufficient interaction of the other substances with amiloride–sodium tetraphenyl phthalate. The response of the sensor for different substances shows the best selectivity to amiloride.

Table 3
Response of the sensor during 90 days

Time (day)	Slope (mV decade^{-1})	Dynamic range (mol L^{-1})	Detection Limit (mol L^{-1})
1	−54.3 ± 0.1	1.0×10^{-6} to 1.0×10^{-2}	9.9×10^{-7}
5	−54.3 ± 0.1	1.0×10^{-6} to 1.0×10^{-2}	9.9×10^{-7}
20	−54.3 ± 0.2	1.0×10^{-6} to 1.0×10^{-2}	9.9×10^{-7}
34	−54.3 ± 0.2	1.0×10^{-6} to 1.0×10^{-2}	9.9×10^{-7}
50	−53.3 ± 0.3	1.0×10^{-6} to 1.0×10^{-2}	9.9×10^{-7}
60	−53.3 ± 0.3	5.0×10^{-6} to 1.0×10^{-2}	2.3×10^{-6}

Table 4
Values of the selectivity coefficients of the amiloride-selective electrode

Interfering ion	log K
Pb^{2+}	−7.01
Fe^{3+}	−6.14
K^{+}	−4.44
Zn^{2+}	−7.47
Cu^{2+}	−4.82
Ni^{2+}	−6.65
Sn^{2+}	−6.71
Ti^{3+}	−7.23
Na^{+}	−3.05
Co^{2+}	−6.71
Mg^{2+}	−6.71
Ba^{2+}	−6.77
Lactose	−5.32
Fructose	−9.15
Sucrose	−6.30
Glucose	−5.92
Citric acid	−5.56
EDTA	−9.83
NH_4OH	−10.0
Uric acid	−4.1

3.5. Calibration range

Using the optimized membrane composition and conditions described above, the potentiometric response of the sensor was studied with amiloride concentration in the range of 1.0×10^{-1} to 1.0×10^{-8} mol L^{-1} at 25 °C. The calibration curve of the electrode is shown in Fig. 5. The results show a Nernstian response of −54.3 ± 0.6 mV decade^{-1} (n = 5) of amiloride concentration with a wide linear range concentration range from 1.0×10^{-6} to

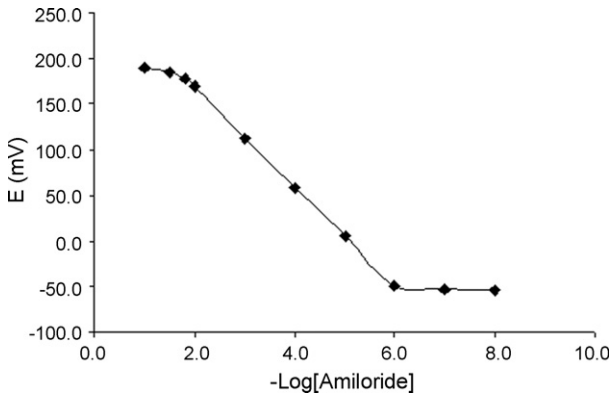

Fig. 5. Potentiometric response of the electrode with the optimum conditions.

Table 5
Recovery of amiloride in urine and pharmaceutical samples

Sample	Amiloride added	Amiloride found	Recovery (%)	Standard method [25]
Uine	–	<LOD	–	<LOD
Urine	1.00×10^{-3} (mol L^{-1})	$1.05(\pm0.05) \times 10^{-3}$ (mol L^{-1})	105.0	$0.93(\pm0.08) \times 10^{-3}$(mol L^{-1})
Urine	3.00×10^{-5} (mol L^{-1})	$3.14(\pm0.05) \times 10^{-5}$ (mol L^{-1})	104.7	–
Tablet 1*	–	10.07 ± 0.05 mg	–	9.89 ± 0.08 mg
Tablet 1	2.00	12.03 ± 0.05 mg	98.0	–
Tablet 1	4.00	14.12 ± 0.07 mg	101.2	–
Tablet 2**	–	9.85 ± 0.05 mg	–	10.10 ± 0.07 mg
Tablet 2	2.00	12.03 ± 0.04 mg	101.5	–
Tablet 2	4.00	13.92 ± 0.07 mg	98.0	–

LOD is limit of detection; *Amirolide citrate, 10.0 mg as amiloride content; **As amiloride, 10.0 mg content; ± Shows the standard deviation for three replicates analysis.

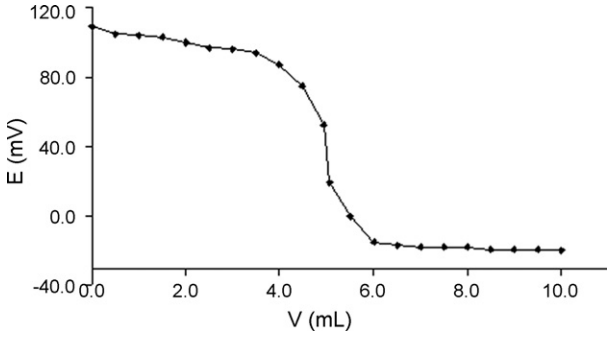

Fig. 6. Application of the amiloride electrode based on amiloride to the potentiometric titration of 50 mL 0.0010 mol L^{-1} amiloride solution with 0.010 mol L^{-1} soduim tetraphenylborate solution.

1.0×10^{-2} mol L^{-1} amiloride. Higher concentration of amiloride cause interaction saturated.

The limit of detection defined as the concentration of amiloride obtained when extrapolating the linear region of the calibration curve to the base-line potential was 9.9×10^{-7} mol L^{-1} amiloride (Fig. 5).

4. Analytical applications

The developed sensor was evaluated in the determination of amiloride in pharmaceutical formulations. The obtained results when compared with those furnished by the reference method showed a relative deviation from −1.2 to 2.4%. Aiming at the evaluation of the accuracy of the results obtained with the developed procedure, amiloride hydrochloride bulk drug was analyzed according to the *United States Pharmacopoeia* by non-aqueous titration in glacial acetic acid with perchloric acid using crystal violet as an indicator [26]. The proposed membrane sensor was found to work well under laboratory conditions. It can be seen that the amount of amiloride can be accurately determined using the proposed sensor. To assess the applicability of the proposed sensor to real samples, an attempt was made to determine amiloride in urine. Each sample was analyzed in triplicate by standard addition, using the sensor. The results are given in Table 5, which shows that the amount of amiloride recovered with the help of the sensor are in good, thereby reflecting the utility of the proposed method.

The sensor was also successfully applied as an indicator electrode in the potentiometric titration of amiloride solution with NaTPB. Typical results for the titration of a 50 mL of 1.0×10^{-3} mol L^{-1} amiloride solution with 1.0×10^{-2} mol L^{-1} NaTPB is shown in Fig. 6 with a very good inflection point, showing perfect stoichiometry that is observed in the titration plot. Before the titration end point, the measured potential shows a usual logarithmic change with amount of the titrant added, while the potential response after the end point was almost constant, due to the low concentration of free amiloride ions in the solution. The concentration of amiloride could be determined accurately by extrapolation of the two linear portions of the titration plot.

5. Conclusion

This sensor has shown to have good operating characteristics including reasonable detection limit, relatively high selectivity, wide dynamic range, and fast response for amiloride determination. These characteristics and the typical applications presented in this paper make the sensor suitable for measuring amiloride content in pharmaceutical samples without a significant interaction from concomitant substances.

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