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Novel Drug Sensing: Properties and Applications of Amiloride Hydrochloride Membrane

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***Abstract*— The influence of possible interfering species, such as common inorganic cations, was studied. The construction and electrochemical response characteristics for Amiloride Hydrochloride are described by two electrodes that were prepared based on (Amiloride Hydrochloride, Bromophenol blue as ion pair complex in a PVC matrix and plasticized by two plasticizers, Tri-butyl phosphate (Tri-BP) and Acetophenone (APh). (D1 and D2) are Amiloride Hydrochloride electrodes gave slopes (52.697 and 50.893mV/decade) and the linear range from (10^{-4}-10^{-2}M) for D1and ($3*10^{-4}$-10^{-2}M) for D2 electrodes. Based on Tri-BP plasticizer, the best electrode (D1) had a slope of 52.697 mV/decade, a detection limit (5×10^{-6}M), a correlation coefficient (0.9997), and a 13-day lifespan. The suggested electrode was used to measure the amount of amiloride hydrochloride in pharmaceutical samples and showed high stability and repeatability. The electrodes were used for the determination of the drug in tablets by potentiometric analysis.**

***Keywords*— Amiloride Hydrochloride (Ah), Bromophenol blue, Potentiometric determination, Ion selective electrode (ISE).**

I. INTRODUCTION

Ah is frequently used in diuretic treatments to reduce and restrict excessive potassium loss. A few number of papers exist about the quantification of Ah in tablet form [1].3,5-diamino-6-chloro-N-(diaminomethylidene) pyrazine-2-carboxamide hydrochloride dihydrate is amiloride hydrochloride (C6H8ClN7O.HCl.2H2O). In Figure 1, the structural formula is displayed [2]. It is an odorless, solid, yellow crystal powder that dissolves in water, alcohol, and dimethylsulfoxide (DMSO) [3]. It is essentially insoluble in chloroform, ether, and acetone [4]. 302.12 g/mol is its molecular weight. A quick and easy way to determine amiloride hydrochloride at the same time is to use digital derivative spectrophotometry. [5] HPLC was used to analyze amiloride hydrochloride [6]. Pharmaceutical analysis continues to be interested in the applications of ion-selective electrodes [7]. The rationale is that these electrodes offer a number of benefits, including easy operation and design, quick reaction, affordability, suitability for turbid and colored solutions, and good selectivity [8-9] This study examined the characteristics of manufactured electrodes, the pH impact, and the selectivity of the sensor used to detect amiloride hydrochloride in pharmaceutical samples.

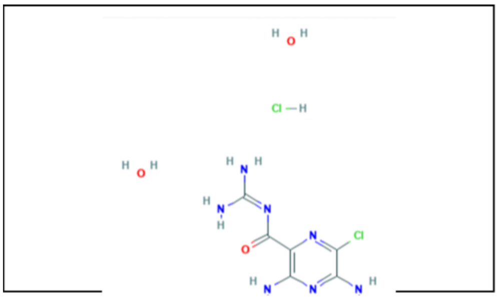

Fig. 1: Amiloride hydrochloride structure formula. [1]

II. MATERIAL AND METHODS

A. *Apparatus*

This investigation used a silver-silver chloride wire, a saturated calomel reference electrode, as well as a pH combination electrode made in Germany (SenTix® 82 WTW). For potentiometric and pH measurements, a digital pH/ion meter, made in Germany (inoLab 740, terminal 740-WTW), was used.

B. *Materials and reagents*

Samara-IRAQ-SDI provided standard Amiloride hydrochloride. Saluretic tablets, which were commercially manufactured in Egypt, contained 50 mg of Hydrochlorothiazide and 5 mg of Ah. Molecular weight 327.33 g·mol^{-1}, a comparatively high molecular weight. Polyvinyl chloride (PVC) and Bromophenol blue were acquired from Fluka, E. Merck Tetrahydrofuran, a Swiss company, in which both the Tri-BP and Aph were made. Furthermore, the source of the remaining solvents and compounds was BDH.

(0.1 M) Stock solutions were prepared for each of the following by dissolving 0.3722, 1.2077, 1.2066, 1.7115, and

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1.5000 g in distilled water (50 mL): Sucrose, KCl, Cu(NO3)2.3H2O, and AlCl3.6H2O.

C. Procedure

1) Preparation of standard drug solution:

Amiloride hydrochloride (Ah) stock A (0.01M) Ah standard solution was prepared by dissolving 0.151g of the standard in distilled water by using ultrasonication to achieve a final volume of 50ml. The remaining standard solutions were acquired through diluting the stock solution, ranging from 10^{-7} M to 10^{-2} M in order to acquire the required solution.

2) Ion pair preparation:

An equimolar solution of amiloride hydrochloride (AMH) in distilled water was mixed with a 0.01 M solution of (Bb) in ethanol to form the ion pair. This procedure involved the utilization of ultrasonicator equipment (inoLab 740 with terminal 740-WTW, Germany). A precipitate developed 24 hours later.

3) Membrane Preparation and ISE Construction:

Two membranes were fabricated. The initial mixture comprised ion-pair (AMH-Bb), Tri-B P plasticizer, and PVC, all dissolved in 5-6 mL of THF [10]. The membrane was cut at the electrode's edge to match the external diameter. The alternative membrane, composed of AMH-Bb with APh, was fabricated as the first electrode, similarly to how these membranes were utilized as sensors for the quantification of Ah. The membrane was submerged in a standard solution of Ah prior to conducting measurements.

4) Electrode Calibration:

The sensors were calibrated using standard solutions of AMH with concentrations varying from 1.0 x 10^{-4} to 1.0 x 10^{-2} mol/L. The cell configuration (Ag/AgCl | internal solution || membrane || testing solution | Saturated Calomel Electrode) was used to perform all potentiometric measurements. After each measurement, the sensor was washed with distilled water and then dried with tissue paper.

5) Preparation of Pharmaceutical Specimens:

Ten pills were accurately crushed and measured. The reported average weight of Saluretic is 0.2364 g. Each tablet contains 0.005 g, which is used to prepare a (0.7139 g) Ah solution of (10^{-3} M) by using distilled water to dissolve it, and by utilizing an ultrasonicator for 5 minutes. The precipitate underwent filtration and washing, with the filtrate subsequently collected in a 50 mL volumetric flask.

6) Estimation of the Selectivity coefficient ($K^{pot}_{A,B}$) :

A separate solution method was utilized for measuring the selectivity coefficient, as outlined in equation (1):[11,12]

$$\log K^{pot}_{A,B}=(E_B-E_A)/S+(1-z_A/z_B)\log a_A \quad (1)$$

where E_A, E_B, are the potentials, z_A, z_B, and a_A represent the activities and charge numbers for the primary A ion. aA is equal to aB.

The fixed interference method was employed to determine the selectivity coefficients utilizing equation (2) presented below: [13,14]

$$K^{pot}_{A,B}=a_A/(a_B)^{zA/zB} \quad (2)$$

III. RESULTS AND DISCUSSION

Bb interacted with AMH to produce a complex. The synthesized compound was characterized and analyzed as an ion exchange site in a PVC membrane sensor sensitive to Amiloride hydrochloride. Two electrodes were made from the complex. The first one, D1, consists of (AMH+Bb+Tri-Bp), which gives a slope of 52.697 mV/decade, and the second electrode, D2, consists of (AMH+Bb+APh), which gives a slope of 50.893 mV/decade. The plasticizer's compatibility with the electro-active substance allows electrode D1 to demonstrate a linear response from 10^{-4} to 10^{-2} M, exhibiting a Nernstian cationic slope of 52.697 mV/decade. The detection limit, established at the junction of the extrapolated segments of the two linear portions of the calibration curve, is 5×10^{-6} M. Fig. (2) displays a typical plot of the electrodes D1 and D2 calibration curves.

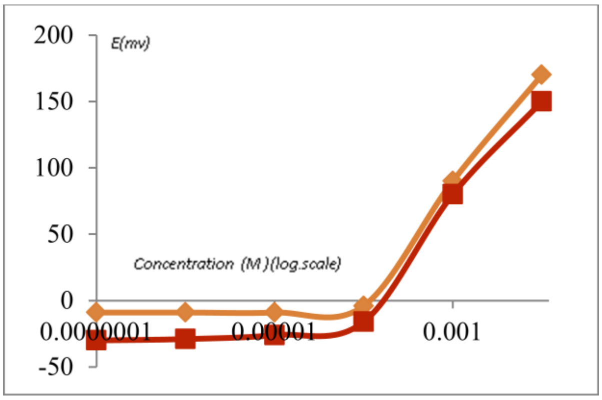

Fig. 2: Amiloride hydrochloride electrodes calibration curves

For electrodes based on Tri-Bp and APh (membranes D1 and D2), the slopes were determined to be 52.697 and 50.893 mV/decade, respectively, with correlation coefficients of 0.9997 and 0.9991. For these electrodes, the linear range is 10^{-4}–10^{-2} M, and the corresponding detection limits are 5×10^{-6} and 7×10^{-6}M. Table 1 provides the results along with other parameters.

TABLE I. THE PARAMETERS FOR TWO AMILORIDE HYDROCHLORIDE ELECTRODES

Electrode	*D1*	*D2*
Slope (mV/Decade)	52.697	50.893
Correlation coefficient (r)	0.9997	0.9991
Linear concentration range (M)	10^{-4}-10^{-2}	$3*10^{-4}$-10^{-2}
Detection limit (M)	5×10^{-6}	7×10^{-6}
Response time (sec) 10^{-2}	20	10
Response time 10^{-3}	25	15
Lifetime (day)	13	7

A. Determination of selectivity coefficients

Equation (1) established the distinct approach for determining the selectivity of the AMH sensor in the presence of other cations, whereas equation (2) established the fixed interfering method (FIM). Table (2) and Table (3) provide the selectivity coefficient values for both techniques, and Fig. (3) displays the calibration curve of the fixed interfering approach using the (D1) AMH selective electrode for (K+). The sensor aided the potentiometric measurement of AMH drug in pure solutions.

TABLE II. VALUES OF KPOTA, B USING A SEPARATE METHOD WITH THE D1 ELECTRODE.

cations	***Separate method***	
	$\log K^{pot}_{A,B}$	$K^{pot}_{A,B}$
Mg^{+2}	-4.561	2.747×10^{-5}
Mn^{+2}	-4.110	7.762×10^{-5}
Na^{+}	-2.856	1.393×10^{-3}
Fe^{+3}	-4.011	9.749×10^{-5}
K^{+}	-2.858	1.386×10^{-3}

TABLE III. VALUES OF KPOTA, B USING FIM WITH D1 ELECTRODE

cations	*FIM ($K^{pot}_{A,B}$)*
Mg^{+2}	1.130×10^{-4}
Mn^{+2}	2.699×10^{-4}
Na^{+}	3.912×10^{-3}
Fe^{+3}	4.889×10^{-5}
K^{+}	5.833×10^{-3}

Where $a_{K^+}=7*10^{-2}$ M

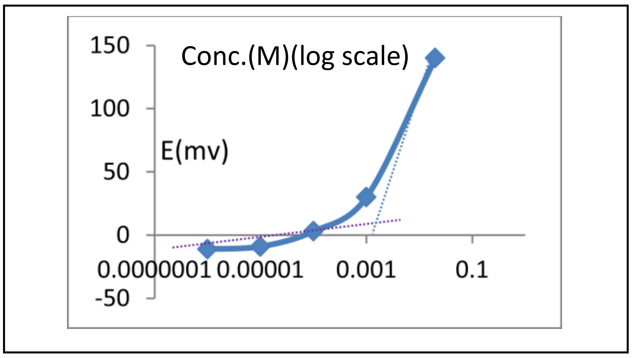

Fig. 3: D1 electrode calibration curve using FIM

B. pH Effect

The pH effect in the AMH test solution on the potential of these sensors was examined. The potential was assessed at a concentration of the AMH solution (1 × 10^-3 mol/L) throughout a pH range from 2 to 12. The solution was acidified using minimal quantities of 0.1N HCl, after which the pH was incrementally elevated using 0.1N NaOH. The potential was measured with two pH/mV meters at each pH level. The potential readings associated with various pH levels were documented and graphed. The findings indicated that the voltage remained stable despite pH variations between 1.6 and 7.9, demonstrating the electrode's usefulness within this pH range (Figure 4).

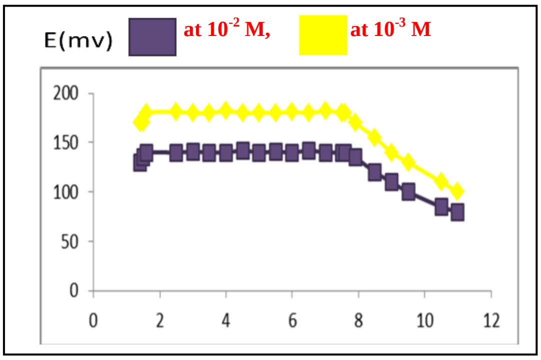

Fig. 4: pH Effect on the potential electrode D1.
Where (y axis is E(mv) and x axis is pH)

C. Analyses of AMH:-

-Titration method:

Plotting antilog (E/S) against the addition of standard AMH amount allowed for the coverage of concentration, as seen in Fig. 5.

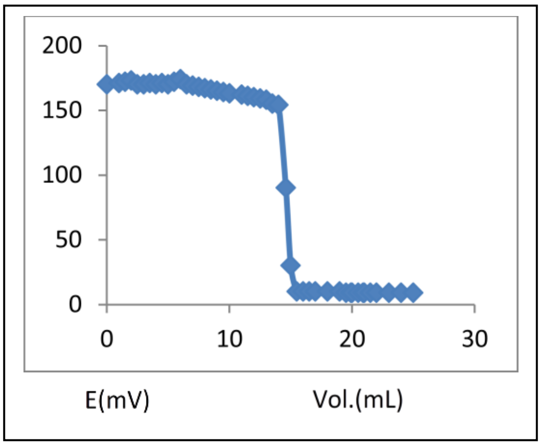

Fig. 5: D1 electrode Titration curve (15 mL sample solution 0.01 M AMH with 0.01 M of Tri-Pb as a titrant solution)

- Direct method (DM) and Standard addition method (SAM):

These methods were used for the determination of AMH:

$C_U = C_S / 10^{\Delta E/S} [1+ (V_U / V_S)] - (V_U / V_S)$

Where:

C_U and $C_{S:}$ the concentrations of the unknown solution and the standard solution.

V_U and $V_{S:}$ the volumes of the unknown solution and the standard solution.

-Multiple standard additions (MSA):

$C_U = V_S \times C_S / V_U$

Where C_U is the concentration of the unknown solution, and C_S is the concentration of the standard solution. V_S is the volume of the standard solution as shown in Fig. 5).

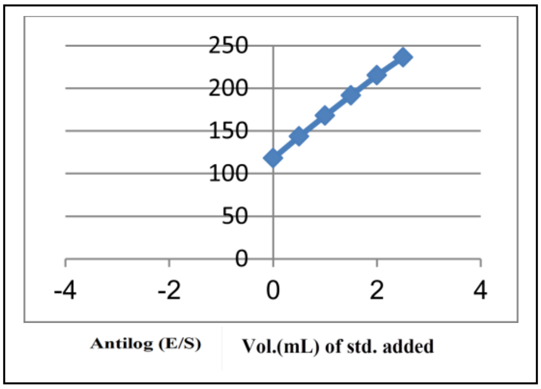

Fig. 6: Antilog (E/S) calibration curve vs. the volume added of standard (10^{-2} M) for the determination of 20mL AMH solution 10^{-3} M using (MSA).

Table 4 presents the results of the calculation of (Er% %); the relative error, (Re% %); the recovery, and (RSD% %); the relative standard deviation for the titration technique.

TABLE IV. ANALYSIS OF AMH BY FOUR POTENTIOMETRIC TECHNIQUES USING THE D1 ELECTRODE

Conc. (M)	*Found (M)*	*RSD *%*	*Re %*	*Er %*	*S*	x□□□□ts□√N□
TITRATION METHOD**						
1.000$\times10^{-2}$	***0.970*** $\times10^{-2}$	***0.4%***	***97.0%***	***3%***	---	--
DIRECT METHOD*						
1.000 $\times10^{-4}$	***0.972*** $\times10^{-4}$	***0.396 %***	***97.2 %***	***2.8 %***	***3.760*** $\times10^{-7}$	***0.972*** $\times10^{-4}$□***0.631*** $\times10^{-6}$
MULTI SAM*						
1.000 $\times10^{-3}$	***1.003*** $\times10^{-3}$	-----	***100.3%***	***- 0.3%***	---	----
SAM*						
1.000 $\times10^{-3}$	1.030 $\times10^{-3}$	0.661 %	103. 1 %	-3.1 %	6.711 $\times10^{-6}$	1.030 $\times10^{-3}$□0.910 $\times10^{-5}$

The potentiometric measurement in pharmaceutical preparations of AMH was taken to benefit from electrode D1. Table 6 shows the data acquired for pharmaceutical samples.

TABLE V. AMH ANALYSES IN PHARMACEUTICAL SAMPLES

Conc. (M)	*Found (M)*	*RSD *%*	*Re %*	*Er %*	*S*	x□□□□ts□√N□
TITRATION METHOD**						
1.000 $\times10^{-2}$	0.966 $\times10^{-2}$	0.4 %	96.6 %	3.4 %	---	---
Direct method*						
1.000 $\times10^{-4}$	0.971 $\times10^{-4}$	0.394 %	97.1 %	2.9 %	3.861 $\times10^{-7}$	0.971 $\times10^{-4}$□0.632 $\times10^{-6}$
Multi SAM*						
1.000 $\times10^{-3}$	1.001 $\times10^{-3}$	---	100.1%	-0.1%	---	--
SAM*						
1.000 $\times10^{-3}$	1.020 $\times10^{-3}$	0.671 %	103.2 %	-3.2 %	6.513 $\times10^{-6}$	1.020 $\times10^{-3}$□0.912 $\times10^{-5}$
RSD*% for n=5, t=2.7						
RSD**% for n=3, t=4.3						
RSD***% for n=2, t=12.7						

IV. CONCLUSIONS

Two newly designed sensors were created for the determination of Amiloride hydrochloride throughout a broad concentration range. The electrodes exhibited excellent selectivity for AMH amidst numerous prevalent inorganic cations. Consequently, these electrodes may serve as alternate analytical instruments to spectrophotometric and chromatographic techniques for the quantification of this medication in bulk powder and pharmaceutical formulations.

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CONFLICTS OF INTEREST:

The authors declare no conflict of interest.

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