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Characteristic of Membrane Sensors for the Selective Determination of Some Anti-histaminic Pharmaceutical Formulations

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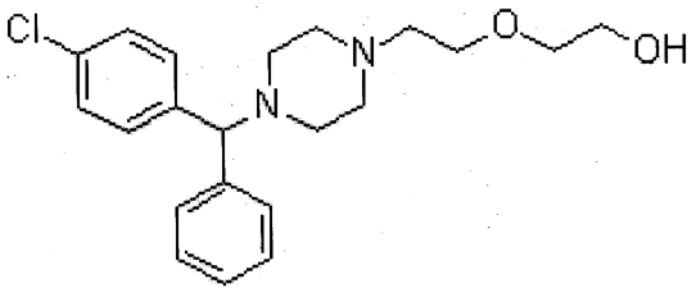
Abstract- The construction and general performance characteristics of potentiometric sensors responsive to some anti-histaminics Hydroxyzine hydrochloride (HYZ), Meclozine hydrochloride (MOZ) were described. The membranes incorporate the ion-association complex of the drugs with Sodium 12-Tungstophosphate (TP) sensor-1, Ammonium Reineckate (AR) senser-2, and Ammonium Molbydate(AM) senser-3as electroactive materials. These sensors exhibit fast, stable, and near-Nernstain response over the concentration range 10^{-2} to 10^{-7} M with slopes of 53.07 and 52.14 mV per concentration decade for sensors 1, 2. No interferences are caused by many inorganic and organic cations. The sensors have a fast response time (20-40 s) and applicaple over a wide range of pH (2-7), low detection limit (1.8×10^{-7} M) and good stability (5-6 weeks).The sensors were used for direct potentiometric of anti-histaminics in some pharmaceutical preparations. Validation of the method according to the quality assurance standards shows suitability of the proposed sensors for use in the quality assurance of these drugs. Results with a recovery of 99.5 % and a mean standard deviations of ±1.3 % of the nominal are obtained which compared fairly well with data obtained using the British pharmacopoeia method.

Keywords-Sensors, Anti-histaminic, Tungstophosphate, Ammonium Reineckate, Ammonium Molbydate

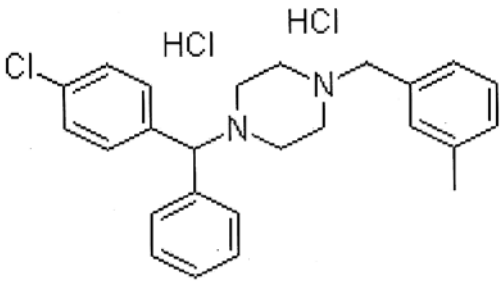
1. INTRODUCTION

Histamine H1-receptor antagonist (antihistamines) are drugs used for the treatment of allergic conditions such as urticaria and allergic rhinitis. Many antihistamine drugs are known to cause sedation, and patients warned against their use when driving, the second-generation antihistamines are assumed to be non-sedative and are frequently prescribed for drivers. However, concern about their connection to traffic accidents has arisen. To study the possible role of antihistamines in car accidents, a sensitive and selective method for the identification and quantitation of those drugs was required.

A literature survey reveals that there are various methods have been reported for simultaneous determination of hydroxyzine4)] -4] -2] -2Chlorophenyl) phenymethyl] -1-piperazinyl] ethoxy] ethanol dihydrochioride .Meclozine l-[(4- Chlorophenyl)- phenyl methyl]-4- [(3-methyl phenyl) methyl] piperazine di hydrochloride (schemes 1,2),using chromatography technique [1-8], spectrophotometric methods [9-12], potentiometric methods [13-15], and electrophoresis methods [16-17].



Scheme 1. The chemical structure of Hydroxyzine hydrochloride



Scheme 2. The chemical structure of Meclozine hydrochloride

The present work describes the construction, electrochemical evaluation and pharmaceutical applications of three novel potentiometric sensors for antihistamines. These sensors incorporate the ion-association complexes of antihistamines with Sodium 12-Tungstophosphate, Ammonium Reineckate, and Ammonium Molbydate counter in a plasticized PVC matrix .

2. EXPERIMENTAL

2. 1. Apparatus

A Jenwoy (model 3510) pH, mV meter was equipped. A jenwoy single junction Ag/AgCl reference electrode (model 924001) filled with 10% (W/V) KCl or a double junction Ag/AgCl Jenwoy reference electrode (model 924005) with 10% KNO_3 in the outer compartment was used in conjunction with the drug sensors. A Cyperscon 500 digital pH meter with glass combination electrode was served to carry out the pH measurements, and Band line sonorex, (RK-5105), magnetic stirrer as used .

2. 2. A puree samples

The drug under investigation is hydroxyzine hydrochloride (HYZ), and Meclazine hydrochloride (MOZ). All puree drugs were kindly supplied by National organization for drug control and research, Cairo, Egypt. The purity of the sample was found to be not less than 99.00 5 for HYZ, 98% for MOZ on the dried basis according to British pharmacopeia (BP) methods (100-102).

2. 3. Reagents and materials

All pure drugs were kindly supplied by the national organization for drug control and research, Cairo, Egypt. The purity of the sample was found to be not less than 99.0 % in case of HYZ, 98.0% in case of MOZ, on the dried basis according to British pharmacopeia (BP) methods [18-20]. A stock solution (1.0×10^{-3}) of investigated drugs were prepared by dissolving 0.0448 gm of HYZ, 0.0464 in of MOZ, of pure sample in 15 ml of (ethanol in case of MOZ, distilled water in case of HYZ) and transferred to 100 ml measuring flask and finally diluted with water to the mark. Further dilution was carried out with distilled with water to obtain a solution containing 100 µg/ml of the studied drug.

2. 4. Preparation of ion-exchangers

The ion pair complexes were prepared by slow addition of 20 ml of 10^{-2} mol L^{-1} (Tungstophosphate, Ammonium Reineckate, or ammonium molbydate) solutions to 10 ml aliquots of 10^{-2} mol L^{-1} aqueous solutions of the drugs. The mixtures were stirred for 10 min, the precipitate filtered off on G4 sintered glass crucible, washed with distilled water, dried and ground to fine powder [21].

2. 5. Preparation of membrane electrodes

A portion of drugs ion pair complexes (10 mg) was thoroughly mixed with 190 mg of PVC, 350 mg of DOP and 5 ml THF in a glass Petri-dish (5 cm diameter) covered with filter paper and left to stand over night to allow slow evaporation of the solvent at room temperature. A master PVC membrane (ca. 0.1 mm thick) was obtained and used for construction the sensors as previously described [22]. The internal reference solution consists of equal volume of 1×10^{-2} mol L^{-1} of the dug solution and 1×10^{-2} mol L^{-1} sodium chloride solution.

2. 6. Sensors assembly and calibration

Sensors were assembled using a disk an appropriate diameter (about 8 mm) were cut from the previously master membrane and connected to the flat end of PVC tubing with THF.

The sensors were conditioned by soaked in the same solution when not in use. The membrane sensors were calibrated by immersion in 1×10^{-7}-1×10^{-2} mol L^{-1} (HYZ), (MOZ) solutions and allowed to equilibrate with constant stirring in conjunction with a Jonway reference electrode. The electrode potential was recorded as a function of (HYZ) and (MOZ) concentration.

3. RESULTS AND DISCUSSION

3. 1. Sensors characteristics and calibration data

Sodium 12-Tungstophosphate, Ammonium Reineckate, and Ammonium Molbydate anions were tested as ion-pair agents for the preparation of electroactive ion association complexes with studied drugs. HYZ.HCl reacted with phosphotungestic acid and ammonium Reinckeate to form stable 1:1 water insoluble ion association complexes having the following suggested compositions HYZ.HCl TA ($24WO_3.2H_3PO_4.48H_2C$) or R($C_4H_{10}CrN_7S_4$) and MOZ TA($24WO_3.2H_3PO_4.48H_2C$). Sensors incorporating membranes with the composition 34.5 wt. %PVC as a plastic matrix, 63.5 wt. % dioctyl phthalate as a solvent mediator and 2 wt. %HYZ&MOZ ion- pair were prepared and electrochemically evaluated at 25±1 ^{o}C using the recommendation of IUPAC [23].

The performance characteristics of the sensors, based on data collected over a period of 7 weeks for three sensor assemblies for studied drugs under static conditions are given in Table (1,2). The sensors displayed constant potential readings within ±1 mV from day to day and the calibration slopes did not change more than 2 mV decade over period of two months for sensors.

The dynamic response times of the HYZ and MOZ sensors were tested for 10^{-2}–10^{-7} mol L^{-1} test solutions. The sequence of measurements was from low to high concentrations. The time required for the sensors to reach values within ±1.5 mV of the final equilibrium

potential after increasing the drug concentration 10-fold was measured. The response time of the sensors for 10^{-3} mol L^{-1} was 20 s. long term potential stability of the sensors was fairly good as it practically unchanged over a period of 6 weeks.

Typical calibration graph of sensors are shown in Figs. 1, and 2.

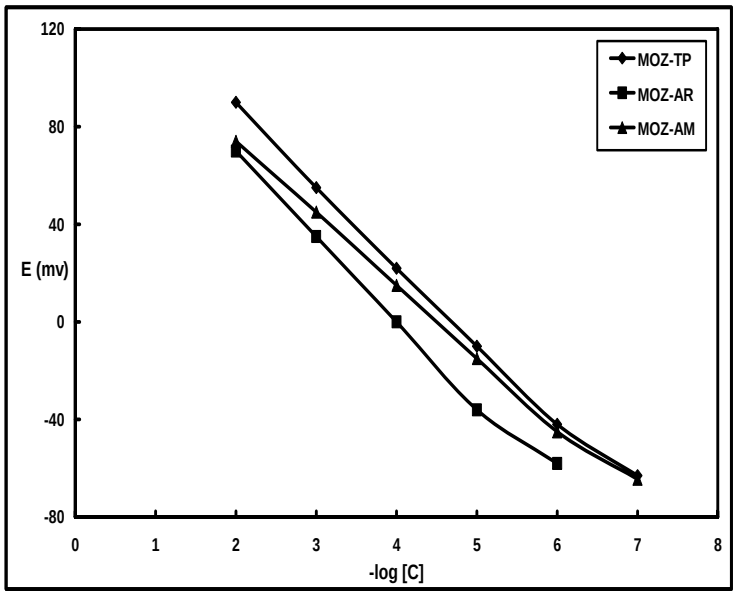


Fig .1. Profile of the potential (mV) to the –log concentration of sensor MOZ-TP

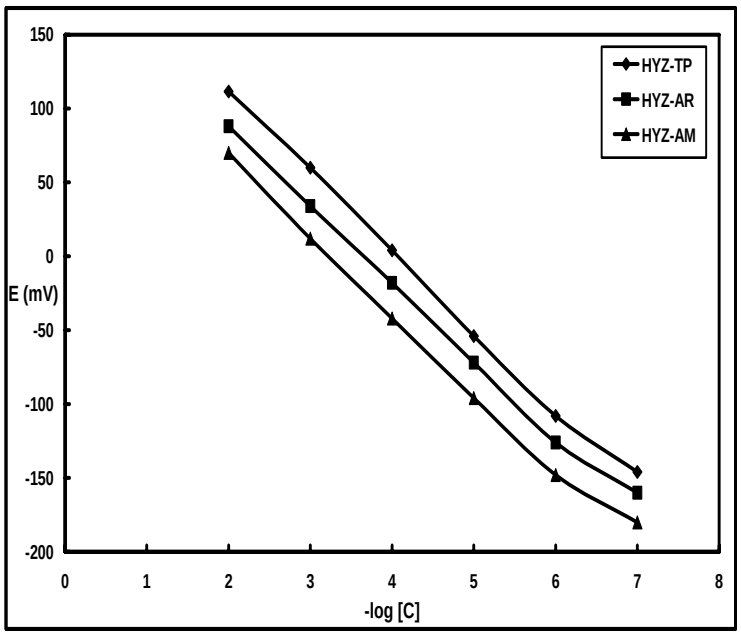


Fig .2. Profile of the potential (mV) to the –log concentration of sensor HYZ-TP

Table 1. Response characteristics of Hydroxyzine HC1, PVC membrane based Sensors

Parameter	**Sensors**		
	TP	**AR**	**AM**
Slope, (mV decade^{-1})	-53.07	-51.3	-52.14
Intercept (mV)	217.6	189.8	173.1
Correlation Coefficient (r)	0.9988	0.9987	0.9977
Lower limit of linear range, (mol L^{-1})	5×10^{-7}	7×10^{-7}	5.5×10^{-7}
Lower limit of detection, (mol L^{-1})	1.8×10^{-7}	5×10^{-7}	2.6×10^{-7}
Response time for 10^{-3} M,(S)	20	20	20
Recovery time (S)	40	40	40
Working pH range	2.5-6.5	3-6.5	3-7
Concentration range (mol L^{-1})	10^{-2}-10^{-7}	10^{-2}-10^{-7}	10^{-2}-10^{-7}
Standard Deviation*	1.29	0.94	1.09
Accuracy (%)	99.6	99.2	99.5
Life span (weeks)	5-6	5-6	5-6

*Average of six measurements

3. 2. Effect of pH and other compounds

The effect of pH on the potential readings was studied by immersing the combination glass electrode, drug membrane sensors, and a single junction Ag/AgCl reference electrode in 50 ml beakers containing 25 ml aliquots of drug aqueous solutions. The pH of each solution was gradually changed by adding small aliquots of concentrated sodium hydroxide and/or hydrochloric acid solutions. The potential reading at each pH value was recorded. Fig (3-8) the pH–mV profile of each drug concentration was plotted for each membrane sensors. From Table (1,2), and Fig (3-8) it was observed that the sensors did not affect to the pH change in the range from (2.5-6.5). Above and below this pH range, the potential displayed by the electrodes were noisy.

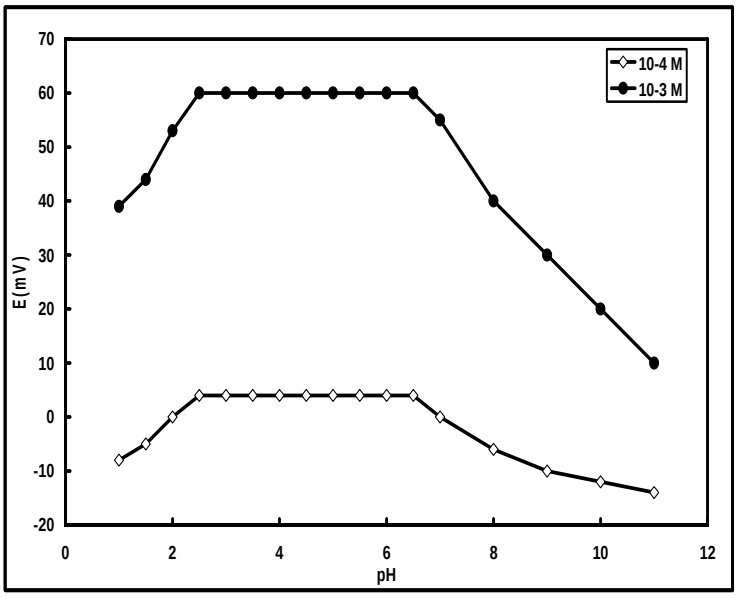


Fig. 3. Effect of pH on the potential response of HYZ-TP membrane electrode

Table 2. Response characteristics of meclozine HC1, PVC membrane based Sensors

Parameter	**Sensors**		
	MOZ-TP	**MOZ-AR**	**MOZ-AM**
Slope, (mV decade^{-1})	-31.37	-32.6	-28.57
Intercept (mV)	150.17	132.8	130.23
Correlation Coefficient (r)	0.998 1	0.9973	0.9983
Lower limit of linear range, (mol L^{-1})	8.2×10^{-7}	9.0×10^{-7}	5.5×10^{-7}
Lower limit of detection, (mol L^{-1})	6.8×10^{-7}	7.2×10^{-7}	3.4×10^{-7}
Response time for 10^{-3} M,(S)	20	20	20
Recovery time (S)	40	40	40
Working pH range	4-7	4-6.5	3-7
Concentration range (mol L^{-1})	10^{-2}-10^{-7}	10^{-2}-10^{-6}	10^{-2}-10^{-7}
Standard Deviation*	0.99	1.15	0.97
Accuracy (%)	99.2	99.4	98.9
Life span (weeks)	6	6	6

3. 3. Selectivity

The potentiometric selectivity coefficients ($K_{D.I}^{pot}$) of the sensors were determined using the separate solutions (SSM) [24] method at a concentration level of 1×10^{-3} M of both drug solution and interfering cations. Influences of 12 different organic and inorganic cations on the response of the sensors were evaluated by measuring the selectivity coefficients. The results are listed in Table (3,4). The results obtained show that the sensors display significantly high selectivity for the response drug over many common organic and inorganic cations. The effect of drug excepients and diluents (e.g., glucose, lactose, maltose, starch, and magnesium stearte) were also studied. No effect of these substances on the response of the (HYZ) and (MOZ) sensors by using the concentration of substances up to 104 - fold excess.

Table 3. Potentiometric selectivity coefficient [(a)] $K_{D.I}^{Pot}$ of hydroxyzine HCl, PVC membrane based sensors

Parameter	$K_{D.I}^{Pot}$		
	HYZ-TP	**HYZ-AR**	**HYZ-AM**
K^+	1.4×10^{-3}	6.1×10^{-3}	8.1×10^{-4}
Na^+	6.5×10^{-4}	4.2×10^{-3}	5.4×10^{-4}
NH_4^+	9.2×10^{-4}	2.54×10^{-3}	2.4×10^{-3}
Mg^{2+}	1.7×10^{-4}	1.3×10^{-3}	7.4×10^{-3}
Glucose	1.3×10^{-4}	7.8×10^{-3}	4.5×10^{-4}
Fructose	4.2×10^{-4}	1.9×10^{-3}	1.3×10^{-3}
Starch	3.4×10^{-4}	2.4×10^{-4}	2.6×10^{-3}
Triethanolamine	6.07×10^{-4}	5.3×10^{-4}	4.6×10^{-3}
Glycine	2.1×10^{-3}	2.5×10^{-3}	3.6×10^{-4}
***p*- aminophenol**	2.3×10^{-3}	4.2×10^{-3}	2.2×10^{-4}
Lactose	2.01×10^{-3}	1.19×10^{-3}	3.7×10^{-4}
***p*-Nitroaniline**	1.0×10^{-3}	1.3×10^{-3}	5.07×10^{-4}

[a] Average of three measurements

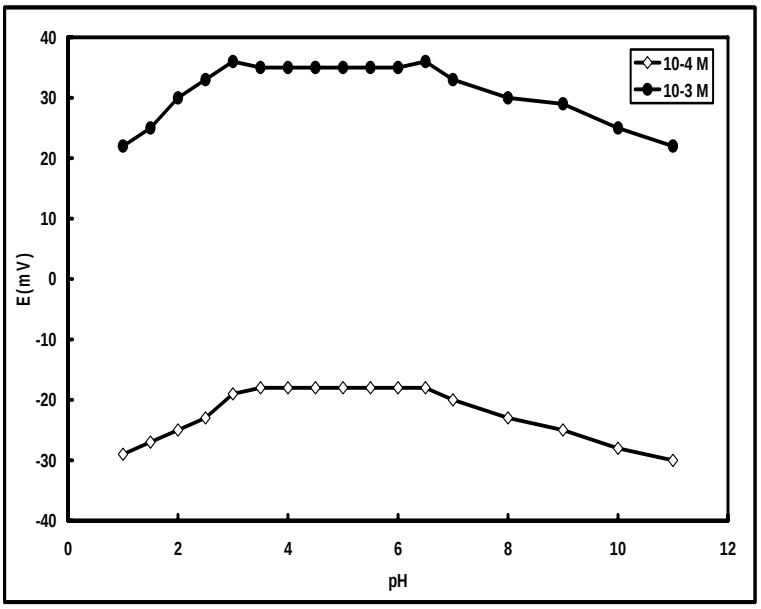


Fig . 4. Effect of pH on the potential response of HYZ-AR membrane electrode

Table 4. Potentiometric selectivity coefficient [(a)] $K_{D.I}^{Pot}$ of meclozine HCl, PVC membrane based sensors

Parameter	$K_{D.I}^{Pot}$		
	MOZ-TP	**MOZ-AR**	**MOZ-AM**
K^+	3.06×10^{-4}	5.07×10^{-4}	1.5×10^{-4}
Na^+	1.5×10^{-3}	2.17×10^{-3}	6.7×10^{-5}
NH_4^+	5.9×10^{-4}	1.8×10^{-3}	6.12×10^{-4}
Mg^{2+}	2.2×10^{-4}	2.8×10^{-3}	2.5×10^{-3}
Glucose	8.96×10^{-4}	8.9×10^{-3}	1.37×10^{-3}
Fructose	1.68×10^{-4}	7.59×10^{-3}	2.44×10^{-4}
Starch	4.6×10^{-4}	3.36×10^{-3}	8.79×10^{-4}
Triethanolamine	1.14×10^{-4}	4.16×10^{-3}	1.66×10^{-3}
Glycine	4.05×10^{-4}	6.5×10^{-3}	8.5×10^{-5}
***p*- aminophenol**	4.8×10^{-3}	1.0×10^{-3}	9.6×10^{-4}
Lactose	2.5×10^{-4}	6.2×10^{-3}	1.48×10^{-3}
***p*-Nitroaniline**	1.2×10^{-3}	4.07×10^{-3}	7.02×10^{-4}

[a]Average of three measurements

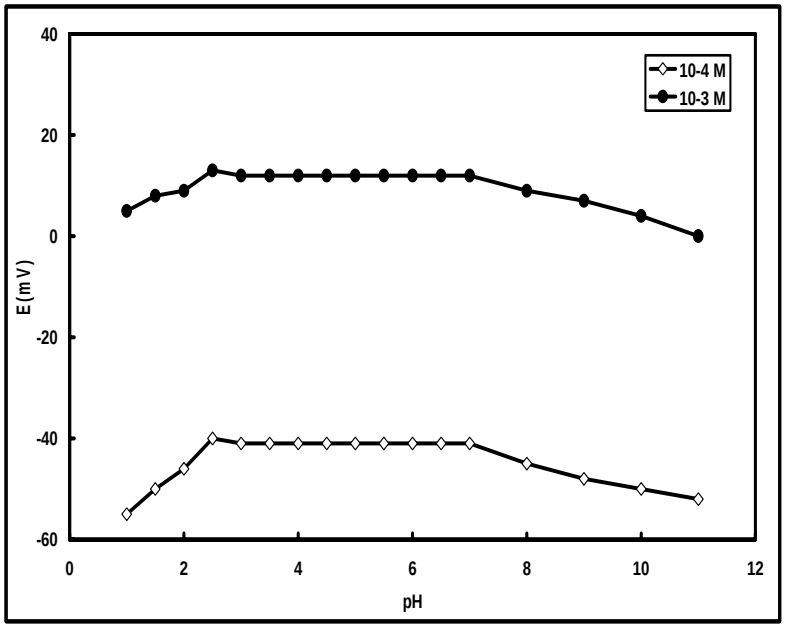


Fig. 5. Effect of pH on the potential response of HYZ-AM membrane electrode

3. 4. Analytical applications

The investigated sensors were proved to be useful in the potentiometric determination of the studied drug in pure solutions and in pharmaceutical preparations by the standard addition method. Collective results are given in Table (5,6) from the results; it is evident that the present sensors will be very useful as a micro determination of drug in its pure solutions and pharmaceutical preparations. The data for pharmaceutical preparations show that the assay results were in good agreement with values obtained using official method .

The direct determination of (HYZ), (MOZ) and were carried out using the developed membrane sensors with (TP, AR and AM) give an average recovery of 98.8, 99.27 and 97.3% Table (5,6).

Table 5. Application of Hydroxyzine membrane sensors in some Pharmaceutical preparations

Trade name and nominal content	Recovery[a]			Reference method
	HYZ-TP	HYZ-AR	HYZ-AM	
Atarax [c] (10 mg of hydroxyzine/tablets)	98.8±0.81	99.27±0.41	97.3±1.2	99.8±1.4
t-value [b]	0.717	0.389	1.031	
F-test [b]	2.048	2.221	1.927	
Bronchaline [c] (10 mg of hydroxyzine/tablets.)	98.6±1.2	99.3±0.85	99.5±0.75	99.9±0.8
t-value [b]	0.509	0.382	0.479	
F-test [b]	2.379	2.412	2.054	

[a] Average of 6 measurements ± S.D

[b]Theoretical value for t- and F- values for five degrees of freedom and 95 % confidence limits are 2.57 and 5.05, respectively

[c] CID-Pharma Company, Cairo, Egypt

A comparison of the performance of the proposed potentiometric sensors with other instrumental methods used for these anti-histaminic drug assessments reveals the advantages of the simple fabrication, low cost and application over at least three decades of concentration without prior separation, extraction steps commonly used with these techniques.

3. 5. Validity of the proposed methods

3. 5. 1. Limit of quantification and limit of detection

The potentials obtained for the five analyses were averaged at each concentration. The average potential was plotted versus concentration. The sensors display a linear response over the concentration range of 10^{-2}–5×10^{-7},1×10^{-2}–7×10^{-7},1×10^{-2}–5.5×10^{-7} M (HYZ) with slope of 53.07,51.3, 52.14 mV/ concentration decade and 10^{-2}–8.2×10^{-7},10^{-2}–9.0×10^{-7},10^{-2}–5.5×10^{-7} M (MOZ) with slope of 31.37 ,32.6 ,28.57 mV/concentration decade.

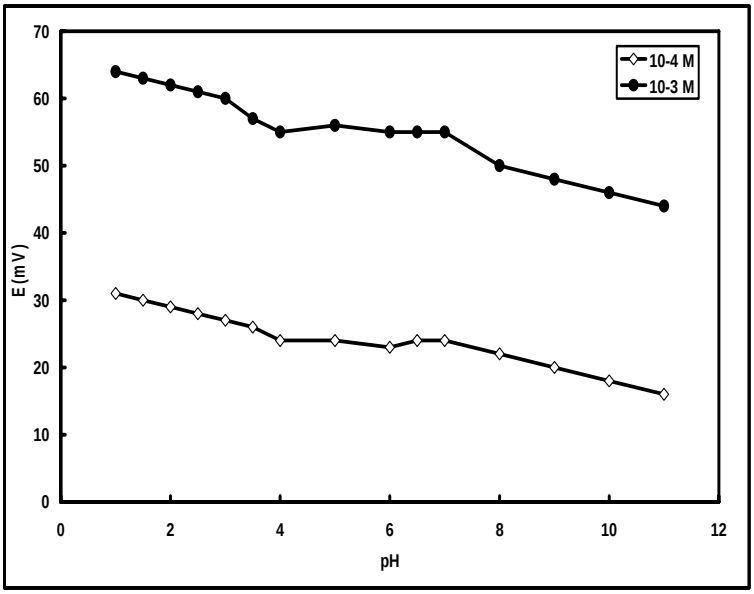


Fig. 6. Effect of pH on the potential response of MOZ-TP membrane electrode

The limits of detection (LOD) and limits of quantification (LOQ) were determined using the formula LOD or LOQ=KS.D.a/b, where K=3 for LOD and 10 for LOQ, S.D.a is the standard deviation of the intercept, and b is the slope. Also lower limit of detection (LOD) is the concentration of (HYZ), (MOZ) corresponding to intersection of the extrapolated linear segment of the calibration graph.

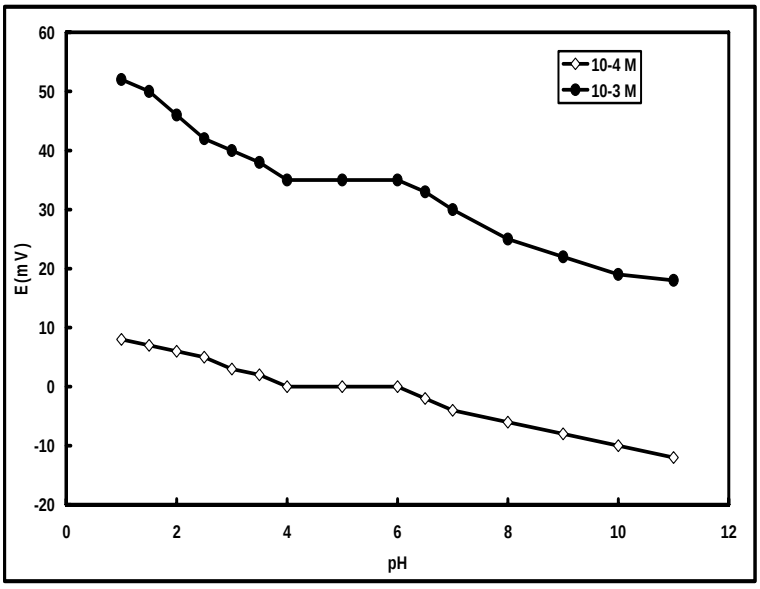


Fig. 7. Effect of pH on the potential response of MOZ-AR membrane electrode

Table 6. Application of meclozine membrane sensors in some Pharmaceutical preparations

Trade name and nominal content	Recovery[(a)]			Reference method
	HYZ-TP	HYZ-AR	HYZ-AM	
Navoproxine [(c)] (25mg of meclozine/tablets)	98.2±0.7	97.6±1.3	97.2±0.85	99.5±0.5
t-value [(b)]	0.88	0.67	0.7	
F-test [(b)]	2.97	1.54	1.23	
Vomidoxine [(d)] (25 mg of meclozine /tablets)	99.4± 0.8	99.4± 0.9	98.4±0.95	100.4±0.9
t-value [(b)]	0.58	0.29	0.39	
F-test [(b)]	2.60	2.48	3.39	
Ezadoxine [(e)] (25 mg of meclozine /tablets)	98.4± 1.3	99.8± 0.6	99.2± 1.1	99.3± 0.7
t-value [(b)]	0.29	0.81	0.66	
F-test [(b)]	3.02	1.84	1.64	

[a]Average of 6 measurements ±S.D

[b]Theoretical value for t- and F- values for five degrees of freedom and 95 % confidence limits are 2.57 and 5.05, respectively

[c]Delta Pharma S.A.E 10th of Ramadan City, Egypt

[d] Pharo-Pharma, Pharaonia Company, Cairo, Egypt

[e] Multipharma for Pharmaceutical and chemical company, S.A.E., Egypt

3. 5. 2. Precision and accuracy of the method

The parameters of the repeatability and reproducibility were investigated in order to assess the precision of the technique. For the repeatability monitoring 6 replicate standards samples at the limit of quantification range. The precision and accuracy of the method are expressed as R.S.D. and % of deviation of the measured concentration. Also reproducibility (day to day or intra-day) was investigated. The results obtained (table-5,6) are within the acceptance range of less than 1.03% (precision).

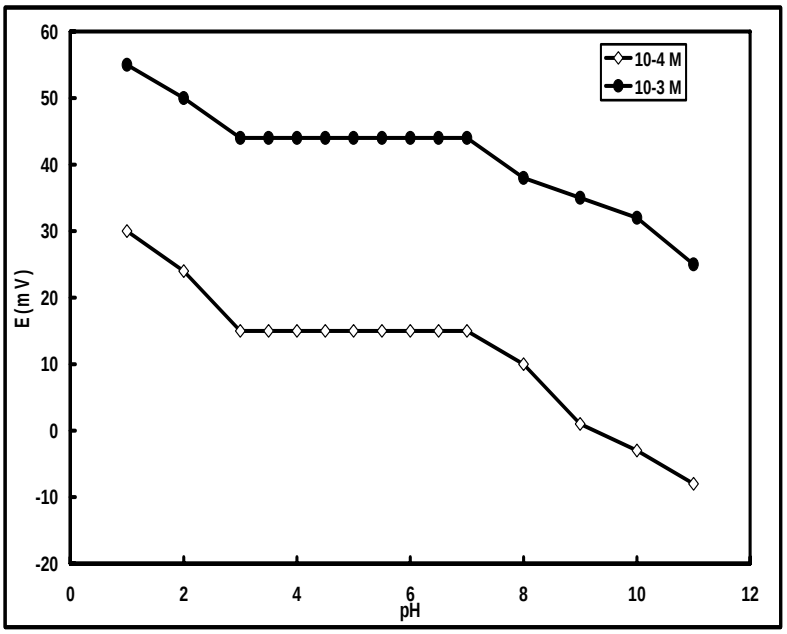


Fig. 8. Effect of pH on the potential response of MOZ-AM membrane electrod

4. CONCLUSION

Potentiometric sensors for anti-histaminics (hydroxyzine hydrochloride, meclozine hydrochloride) are prepared, characterized and used for drug determination. The sensors are simple and sufficiently specific for quantitative determination of some anti-histaminics at a concentration level as low as 10^{-7} mol L^{-1} with an accuracy of 99.1±1.3%. The drugs are determined in pure powders and in dosage forms. The sensors offer the advantages of fast response, reasonable selectivity, elimination of drug pretreatment or separation steps, low cost and possible interfacing with computerized and automated systems. Further advantages offered by using Sodium 12-Tungstophosphate, Ammonium Reineckate, and Ammonium Molbydate based membrane sensors are the low LOD, long life span (5-6 weeks), and wide pH working(2-7). These are probably due to the extremely poor solubility and low leachability of the ion exchange from the membrane of the sensors .

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