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Modified membrane sensors applied for determination of cetrizine in presence of its degradation product

Khalid A.Attia, Nasr M.El-Abasawy, Mohamed M.Shahin*

Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Al-Azhar University, 11751, Nasr City, Cairo, (Egypt)

E-mail: omar_shahin44@yahoo.com

ABSTRACT

The construction and electrochemical response characteristics of modified PVC, coated graphite and modified carbon paste electrodes were described. The cited electrodes used for determination of cetirizine hydrochloride (CTZ) in presence of its oxidative degradation product were based on the use of ion-association complex of the cetirizinium cation (CTZ^+) with phosphotungestic acid (PTA). It reveals a fast, stable and linear response for (CTZ) over the concentration ranges $5x10^{-5}$ - $1x10^{-2}$, $5x10^{-5}$ - $1x10^{-2}$ and $1x10^{-5}$ - $1x10^{-2}$ with slopes of 59.68, 56.03 and 61.6 mV/decade^{-1} respectively. The proposed electrodes were fully characterized in terms of ion pair contents, plasticizer type, response time, life span, pH and temperature. The performance characteristics, sensitivity and selectivity of these electrodes were evaluated according to IUPAC recommendations.

KEYWORDS

Cetirizine;
PVC;
Coated graphite;
Carbon paste electrode;
Phosphotungestic acid.

INTRODUCTION

Cetirizine hydrochloride (Figure 1) is a piperazine derivative and its chemical name is (±) - [2-[4- [(4-chlorophenyl) phenyl methyl] -1- piperazinyl] ethoxy] acetic acid, dihydrochloride. Cetirizine drug is considered as a member of the second generation antihistamines and used for the symptomatic relief of hypersensitivity reactions including rhinitis and chronic urticaria[1,2]. Its H1-antagonist activity is primarily due to its R- enantiomer, levocetirizine which can be considered as the third-generation non-sedative antihistamine, developed from the second-generation antihistamine cetirizine. Chemically, levocetirizine is the active enantiomer of cetirizine, in which it works by blocking histamine receptors[3]. It is also reduces asthma attacks in children by 70%[4] and slightly crosses the blood brain barrier,eliminating the sedative side-effect common with older antihistamines; however it still causes mild drowsiness[5]. Several analytical techniques have been reported for the determination of cetirizine which include liquid chromarography[6-10], gaschromarography[11], spectrophotometry[12-14] capillary electrophoresis[2], and voltammetry[16], fluorimetry[17]. Most of these methods, however, utilize expensive instrumentation, involve careful control of the reaction conditions or derivatization reactions, and require time-consuming pretreatment steps which affect their usefulness for routine analysis. On the other hand, application of potentiometric sensors in the field of pharmaceutical and biomedical analysis have been advocated[18-20] The approach provides simple, fast, and

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selective technique for various drugs[21,22] Some potentiometric sensors for assessment of cetirizine were reported[23-25]. The present work describes preparation, characterization and application of three potentiometric sensors for static and continuous monitoring of cetirizine in pharmaceutical preparations. The sensors exhibit high accuracy, high analytical through put and good response stability with short measurement time, low limit of detection and high selectivity in the presence of many interferents and its oxidative degradation product.

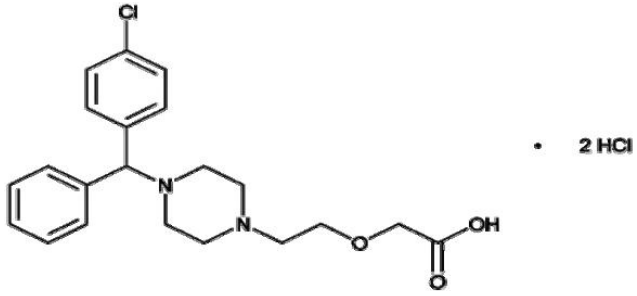

Figure 1 : Structural formula of Cetirizine hydrochloride

CDs are naturally occurring macrocyclic oligosaccharides formed of 1, 4-glucosidic bond linked D (+) glucopyranose oligomers of 6, 7, and 8 glucose units yielding α-, γ- and β -CD, respectively, with toroidal three-dimensional cage configuration[26-28]. Due to the presence of primary and secondary hydroxyl group pointing outside the cavity, the exterior surface is hydrophilic whereas the interior surface, lined with C-H groups and ether-liked oxygen atoms, is hydrophobic. CDs can form inclusion complexes with different types of guests without the formation of chemical bonds or changing their structure[29] where the binding forces associated with the inclusion formation are attributed to number of factors, such as hydrophobic forces, hydrogen bonding, size of the cavity, shape of the guest molecule and electrostatic interaction. Such unique properties introduced CDs as a sensing material in potentiometric sensors for many pharmaceutically important drugs.

The discovery of carbon nanotube (CNT) in 1991 by Iijima, gave rise to a new era in material science and nanotechnology[30]. Carbon nanotubes CNTs are allotropes of carbon obtained as single-walled (SWCNTs) or multi-walled (MWCNTs) material with a cylindrical nanostructure. Due to their special and unique electronic and photonic characteristics, such as large specific surface area, wide electrochemical window, flexible surface chemistry, ability to accelerate electronic transfer, these materials became very attractive in many scientific fields from electronics to medicinal chemistry[31]. Carbon nanotubes have increasingly been used for the construction of electrochemical sensors aiming to improve their analytical response.

EXPERIMENTAL

Apparatus

The potentiometric measurements in batch mode were carried out using pH- meter Jenway 3510 (England) with Ag/AgCl reference electrode in conjugation with the drug sensor, Bandelin sonorox, Rx 510 S, magnetic stirrer (Hungarian) and hot plate (Torrey pines Scientific, USA).

Chemicals andreagents

All chemicals were of analytical grade and bidistilled water was used. Tetrahydrofuran (THF) 99% (Lab scan), high molecular weight (10000) polyvinylchloride (PVC) powder (Aldrich), Phosphotungestic acid (PTA) (Aldrich), β-cyclodextrin (fluka), graphite powder, MWCNTs (Sigma), dioctyl phthalate (DOP), tributyl phosphate (TBP) (Fluka).

Pure samples

Pure grade of (CTZ) was kindly supplied by, Glaxosmithkline.pharm.co., Egypt

Market samples

Zyrtec® tablet (10mg/tab), provided by Glaxosmithkline.pharm.co. Company.

Preparation of stock solutions

Stock solution (10^{-2}M) in water or acetate buffer pH 4.2 was freshly prepared by transferring 461mg of (CTZ) powder into two separate 100mL measuring flasks, either water in case of studying optimum parameters or acetate buffer for calibration and determination with optimum pH were added, shaken and completed to volume with the same solvent.

Working standard solutions

(CTZ) working standard solutions ($1x\ 10^{-6} \times\times 1\ x\ 10^{-2}$ M) were prepared by suitable dilution from its stock solution using either water or acetate buffer PH 4.2.

Preparation of pure degradation product

Stock solution of degradation product ($1.0x10^{-3}$ M) was prepared from complete degradation of 10mL of ($1.0x10^{-2}$ M) standard solution of (CTZ) in 30 volume hydrogen peroxide refluxed for 5 hrs at 70-80^{0}C to achieve complete degradation then the solvent was evaporated using rotator[32] and the obtained residue was transferred quantitavely into 100mL measuring flask and completed to volume with acetate buffer pH 4.2.

Procedures

(a) Preparation of the working electrodes

(1) Preparation of the ion-exchanger

The ion-exchanger cetrizine phosphotungestic acid, (CTZ-PTA) was prepared by the addition of 150 ml of ($1.0x10^{-2}$ M) CTZ solution to 50 ml of ($1.0x10^{-2}$M) of phosphotungestic acid (PTA). The resulting precipitate were left in contact with their mother liquor overnight to assure complete coagulation, filtered and washed with distilled water, and left to dry at room temperature for at least Three days.

(2) Fabrication of PVC sensor electrode

The sensing membrane was fabricated by mixing the required amounts of PVC, plasticizer**,** different percentages of ion-pair (covers the ranges of 1–5%); (TABLE 1) the total weight of constituents in each batch was fixed at 0.35g. This mixture was dissolved in minimum volume of tetrahydrofuran (THF), and the resulting mixture was transferred into a Petri dish of 7 cm diameter. The Petri dish was then covered with a What man No. 3 filter paper and left to stand overnight to allow for solvent evaporation at room temperature. A master membrane with a thickness of 0.1 mm was obtained. An 8-mm diameter disk was cut out from the prepared membrane and glued using PVC-THF paste to the polished end of a plastic cap attached to a glass tube. The resulting electrodes body was filled with equal portions of ($1 x 10^{-2}$) molL $^{-1}$ KCl and ($1 x10^{-2}$) molL^{-1} CTZ. The sensor was preconditioned by soaking in ($1x10^{-2}$) molL^{-1} drug solution for 10hrs. When not in

TABLE 1: Optimization of membrane composition (w/w%) for CTZ electrodes

Electrode	Composition% (w/w)						LR (molL^{-1})	LOD (molL^{-1})	Slope (MV/decade^{-1})	R^2
	CTZ-PTA	PVC	Graphite	DOP	β-CD	MWCNTS				
pvc A	1	49.5	_____	49.5	____	_____	5×10^{-5} - 1×10^{-2}	2.8×10^{-5}	47.53	0.9981
B	2	49	_____	49	____	_____	5×10^{-5} - 1×10^{-2}	2.5×10^{-5}	48	0.9972
C	3	48.5	_____	48.5	____	_____	5×10^{-5} - 1×10^{-2}	2.6×10^{-5}	56.28	0.9982
D	4	48	_____	48	____	_____	5×10^{-5} - 1×10^{-2}	1.9×10^{-5}	58.13	0.9998
E	5	47.5	_____	47.5	____	_____	5×10^{-5} - 1×10^{-2}	3×10^{-5}	49.26	0.9974
F	4	37	_____	48	11	_____	5×10^{-5} - 1×10^{-2}	2.2×10^{-5}	59.68	0.9999
CGP	_____	39	_____	50	11	_____	1×10^{-4} - 1×10^{-2}	7.9×10^{-5}	62.7	0.9974
H	4	37	_____	48	11	_____	5×10^{-5} - 1×10^{-2}	1.99×10^{-5}	56.03	0.9998
CPX	4	_____	50	43	____	3	1×10^{-5} - 1×10^{-2}	5.6×10^{-6}	61.6	0.9996

use, the sensor was stored in air.

(3) Fabrication of CG electrode

The sensing membrane was prepared by using commercial graphite rod that is 5 cm length and 4 mm diameter was inserted in polyethylene tube. The two ends of the rod were washed with acetone before using. One of the two ends of the rod was used for connection while the other, about 1 cm length, was dipped in a solution of the same optimum membrane composition used for the modified PVC type and left to dry in air. The process was repeated several times till a layer of the proper thickness were formed covering the terminal of the rod. The prepared sensor was preconditioned by soaking for 12hrs in ($1x10^{-2}$) $molL^{-1}$ drug solution. When not in use, the sensor was stored in air.

(4) Fabrication of carbon paste electrode

Carbon paste was prepared by hand making of desired amounts of graphite, plasticizer and modifier as shown in table. The paste components were mixed well in mortar until uniformly homogenized paste obtained. The mixture was used by filling electrode body. The electrode surface was polished using filter paper to produce reproducible working surface. The electrode was preconditioned by soaking in 10^{-2}M CTZ solution for 3hrs.

Sensors calibration

The conditioned electrodes were immersed in conjunction with double-junction Ag/AgCl reference Electrode in solutions of (CTZ) in the range of (10^{-6}-10^{-2}) $molL^{-1}$. They were allowed to equilibrate while stirring until achieving a constant reading of the potentiometer. Then, the electromotive forces (e.m.f) were recorded to within ± 1 mV. Calibration graphs were plotted that related the recorded electrode potentials from the each sensors versus the -log molar concentrations of the corresponding drug. The regression equations for the linear part of the curves were computed and used for subsequent determination of unknown concentrations of (CTZ).

Application to laboratory prepared mixtures:

Aliquots of standard drug solution (10^{-3} mol L^{-1}) were mixed with its degraded sample (10^{-3} mol L^{-1}) in different ratios. The e.m.f values of these laboratory-prepared mixtures were recorded and the concentration of CTZ was determined from the corresponding regression equation.

Application to pharmaceutical preparation

Ten tablets were accurately weighed and finely powdered. An amount equivalent 0.461g transferred to 100 ml volumetric flask and the volume was completed to the mark with bi distilled water. The concentration of this solution is claimed to be (1×10^{-2}) mol L^{-1}. The e.m.f. produced by immersing the prepared electrodes in conjunction with Ag/AgCl reference electrode in the prepared solution was determined then the concentration of CTZ was calculated from the regression equation of the corresponding electrode.

RESULTS AND DISCUSSION

Optimization of membrane composition

The sensitivity and selectivity of ISEs are known to be dependent on not only on the nature of ionophores, but also significantly on the composition of the membrane ingredients. Therefore, it was of interest to study the effects of the membrane composition, ion exchange and type of plasticizer on the potential response of the proposed sensors[33].

Effect of ion exchanger

Ion-exchanger complex used in ISEs should have rapid exchange kinetics, adequate formation constants; good solubility in the membrane matrix and sufficient lipophilicity to prevent leaching into the sample solution[34]. The ion exchanger CTZ-PTA was prepared and tested as modifier for the proposed sensors. It was studied by varying the percentages of the ion exchanger, as shown in TABLE 1. The sensors made of 4% (w/w) modifiers, (sensors F, H and X), exhibit the best performance as shown in Figures 2 (a) and (b). However, further addition of the modifier displays somewhat smaller slopes and sensitivity, most probably due to some in homogeneities.

Effect of plasticizer

The nature of the plasticizer influences key performance indicators of the ISEs such as slope, the domain of linear response and the selectivity. A plasticizer for the membrane preparation has to be compatible with the polymer and also with the ion exchanger, and have

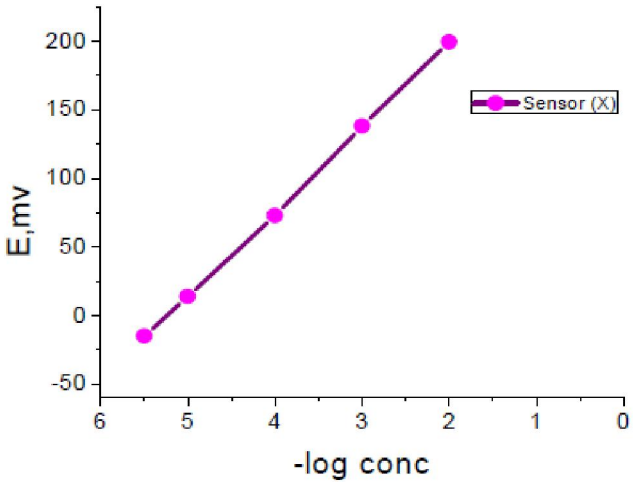

Figure 2a : Calibaration graph of electrode(X)

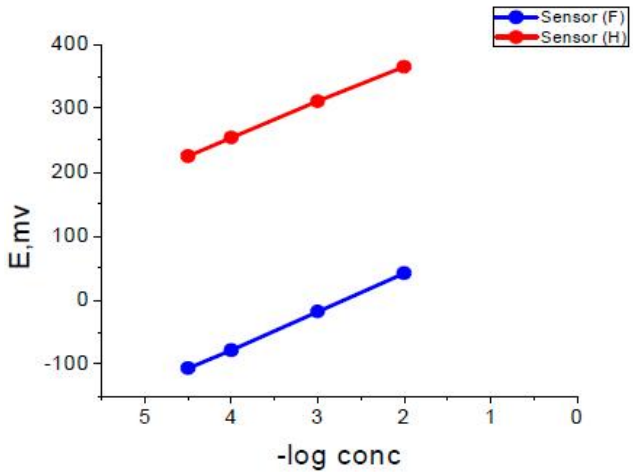

Figure 2b : Calibaration graph of electrode(f),(H)

a high lipophilicity and low solubility in aqueous solution[35]. In exploration for a suitable plasticizer, we used two plasticizers, DOP and TBP and the results were summarized in TABLE 2. The electrode with DOP as a plasticizer produced the best response. It is likely due to relatively high molecular weight, low dielectric constant and high lipophilicity that maybe avoid exudation and to considerably affect dissolution of ion-associations within the membrane[36].

TABLE 2 : Effect of plasticizer type on the slopes of the calibration graph of (F),(H) and (X) electrodes

Plasticizer type	Slope (mVdecade^{-1})		
	(F)	)H)	(X)
DOP	59.68	56.03	61.6
TBP	57.96	55.66	62

Effect of soaking

Freshly prepared electrodes must be soaked to activate the surface of the membrane to form an infinitesimally thin gel layer at which ion exchange occurs. This preconditioning process requires different times depending on diffusion and equilibration at the electrode test solution interface; a fast establishment of equilibrium is certainly a condition for a fast potential response[37]. For this purpose, the PVC, CG and CP type electrodes were soaked in ($1x10^{-2}$) mol L^{-1} CTZ. The slopes obtained from calibration curves were recorded after 0, 2, 4, 8, 12, 16, 24, 36 hr as shown in TABLE 3. The optimum soaking time was found to be 10, 12, and 3 for PVC, CG and CP electrodes, respectively. Continuous soaking of the electrodes in ($1x10^{-2}$) M CTZ affects negatively their response to the cetrizinium cation, this is attributed to leaching of the active ingredients (ion-exchangers and plasticizer) to the bathing solution, thus the slopes of the calibration graphs obtained by the preconditioned electrodes decrease gradually after 6weeks.

TABLE 3 : Effect of soaking on CTZ electrodes

Electrode(F)		Electrode(H)		Electrode(X)	
Soaking time/h	Slope (mVdecade^{-1})	Soaking time/h	Slope (mVdecade^{-1})	Soaking time/h	Slope (mVdecade^{-1})
0	53.5	0	52.5	0	55
2	55.5	2	53.2	2	56.5
4	55.9	4	54	4	57.6
8	57.8	8	54.7	8	61.5
12	59.6	12	56	12	62.4
16	58	16	55.1	16	62
24	57.2	24	55	24	61.9
36	57	36	55	36	62

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Response time

The response time of the investigated sensors was tested by measuring the average time required to achieve a steady potential within ±1 mV of the final steady-state value on successive immersion of the sensor in a series of the CTZ concentration (1.0×10^{-5} - 1.0×10^{-2} ML^{-1}) according to IUPAC definition[38]. The electrodes were found to have a response time of 20, 35,100 s for PVC, CG and CP sensors, respectively.

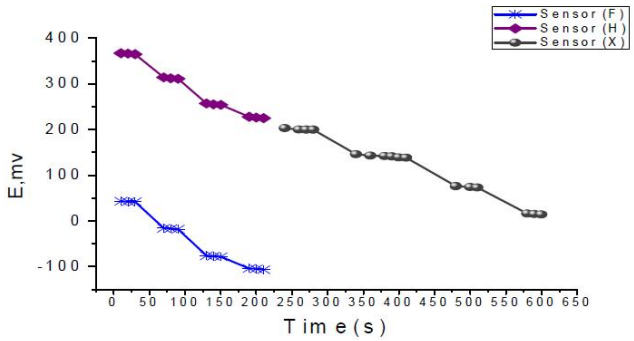

Figure 3 : Dynamic response time of the optimum sensors

Effect of pH

The stability of the sensors potential reading was investigated over a wide pH range to determine the working pH range of each electrode. The investigations were performed in CTZ solution ($1x10^{-2}$). The pH values were adjusted with solutions of NaOH and HCl (0.1–1.0 mol L^{-1} each). Representative curves for effect of pH on PVC, CG and Cp electrodes are shown in Figure 4. The results revealed that, the change in pH does not affect the potential readings within the pH range of 2.5–6.5, 2.5–6.5 and2.5–7in case of PVC, CG and CP sensors. However, there is a slight deviation at pH values lower than 2.5 which may be due to H^+ interference. On the other hand, the potential decreases gradually at pH values higher than 6.5 or 7. The decrease may be attributed to the decrease in the protonated CTZ^+ in the medium.

Effect of temperature

Calibration plots (cell potential versus CTZ conc.) were constructed at different test solution temperatures (25, 30, 35, 40, 45, and 50°C) for PVC, CG and CP electrodes. The variations of calibration plot potentials with temperature for the electrodes were shown in Figure 5. For the determination of the thermal coefficient (dE^o/dt) of the electrodes, the standard electrode potentials (E^o) at different temperatures were obtained from the calibration plots as the intercepts at p CTZ = 0 and plotted versus (t-25), where t is the temperature of the test solution in °C. Astraight-line plot is obtained according to equation[39]:

$$E^o = E^o(25) + (dE^o/dt)(t-25)$$

The slopes of the straight lines obtained represent the isothermal coefficients of the electrodes, amounting to (0.0005114, 0.00076 and0.0006229V/C°) for electrode (F), (H) and (X) respectively. These low values of isothermal temperature coefficients reveal that electrodes have high thermal stability within the studied temperature range (25–50 °C).

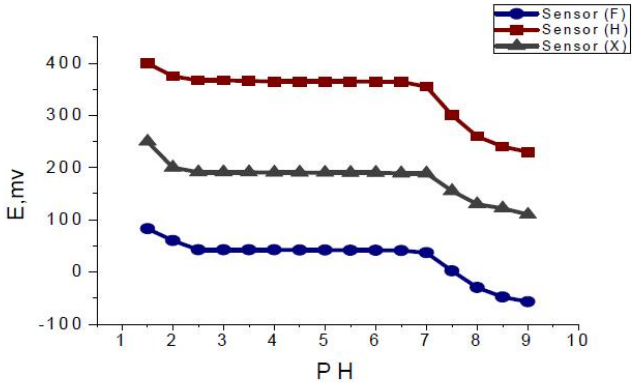

Figure 4 : Effect of PH on optimum electrodes

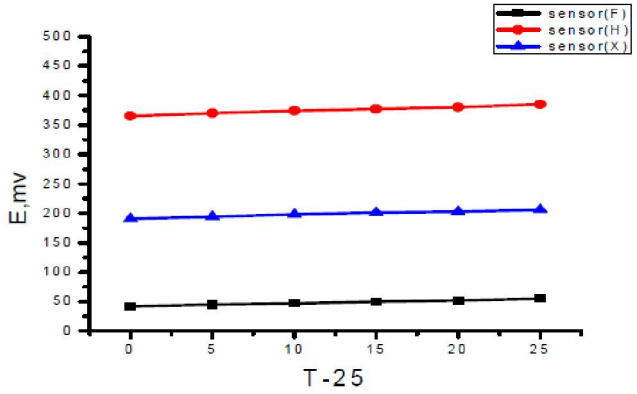

Figure 5 : Effect of temperature on optimum sensors

Sensors selectivity

The influence of some cations and sugars on the response of the electrodes towards their respective drug was investigated. The separate solution method (SSM)[39] which depends on measuring the potential of both drug and the interfering ion separately and the selectivity Coefficient $K^{pot}_{Durg,J^{+z}}$ was calculated by Appling the following equation:

$$K^{pot}_{Durg,J^{+z}} = \frac{E_2 - E_1}{S} + \log [Drug] - \log [J^{+(z)}]^{(1/Z)}$$

Where E_1 and E_2 are the electrode potential of 10^{-3}M solution of each of investigated drug and interferent ion $[J^{+(z)}]$, respectively, and S is the solpe of calibration curve For interferent molecules, such as glucose, urea and glycine, The results of the calculated selectivity coefficients showed that the proposed sensors displayed high selectivity and no significant interference was observed from the interfering species as shown in TABLE 4. The high selectivity towards degradation product and other interfering ions can be attributed to the differences in polarity and to the lipophilic nature of their molecules relative to CTZ ion The mechanism of selectivity is mainly based on the stereo specificity and electrostatic environment and is dependent on how much fitting is present between the locations of the lipophilicity sites in two competing species in the bathing solution side and those present in the receptor of the ion exchanger[41].

TABLE 4 : Selectivity coefficients and tolerance values for optimum electrodes

Interferent	Electrode(F)	Electrode(H)	Electrode(X)
Degradate	1.9×10^{-3}	1.1×10^{-3}	3.7×10^{-3}
KCl	1.1×10^{-4}	1.3×10^{-3}	2.8×10^{-3}
$Cacl_2$	8.7×10^{-5}	9.2×10^{-4}	2.6×10^{-3}
$Mgcl_2$	7.7×10^{-5}	6.6×10^{-4}	2.4×10^{-3}
Nacl	1.2×10^{-4}	1.7×10^{-3}	3.06×10^{-3}
$Nicl_2.6H_2O$	1.4×10^{-4}	2.5×10^{-3}	5.8×10^{-3}
Glucose	7.5×10^{-4}	5.1×10^{-4}	1.9×10^{-3}
Sucrose	2×10^{-4}	2×10^{-3}	1.7×10^{-3}
Citric acid	7.6×10^{-3}	7.1×10^{-3}	8.8×10^{-3}
Glycine	4×10^{-4}	2.6×10^{-4}	1.3×10^{-3}

Analytical applications

(a) Potentiometric determination of CTZ in the presence of its degradation product

The results obtained upon analysis of laboratory-prepared mixtures containing different ratios of intact drug and degradion product are shown in TABLE 5. The results revealed that, the sensors can be successfully used for selective determination of intact drug in the presence of 60% of its degradation product in case of sensors X, and in the presence of 70% in case of sensors F and H.

(b) Potentiometric determination of CTZ in pharmaceutical preparations

The proposed sensors were employed for assaying CTZ in the pharmaceutical Formulation in $molL^{-1}$ (Zyrtec tablets). The results prove the applicability of the sensors, as demonstrated by the accurate and precise percentage recoveries. The susceptible tablet excipients did not show any interference. Thus, the determination of CTZ was carried out without prior treatment or extraction

Statistical comparison of the obtained results with reference method

The validity of the proposed sensors was tested applying both Students't- and F-tests (at 95%

TABLE 5 : Determination of cetirizine in presence of its oxidative degredation

Degradation product%	Electrode(F) Recovery%	Electrode(H) Recovery%	Electrode(x) Recovery%
10	100.1	98.9	99.9
20	100.4	99.8	100
30	100.5	100.7	100.7
40	101.5	101.2	100.9
50	101.6	101.5	101.5
60	102	101.7	102.3
70	102.2	102.9	105
80	106.4	105.8	107
90	109.8	107	110

TABLE 6 : Determination of cetirizine in pharmaceutical preparations

Sample	Electrode(F)	Electrode(H)	Electrode(X)
Zyrtec	Recovery%	Recovery%	Recovery%
$1x10^{-2}$	100.5	99.8	100.7
$1x10^{-3}$	99.4	99.8	99
$5x10^{-4}$	100	100.8	98
$1x10^{-4}$	100.1	98.9	101.5
$5x10^{-5}$	99.4	99.4	100.3
$1x10^{-5}$	----------	----------	99.2
M±SD	99.9±0.698	99.74±0.624	100.06±1.39

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TABLE 7 : Statistical comparison for the results obtained by the proposed electrodes and official method for analysis of cetirizine in pure form[25]

parameter	Electrode(F)	Electrode(H)	Electrode(X)	Official method
Mean	99.9	99.74	100.06	99.8
SD	0.698	0.624	1.394	1.43
N	5	5	5	5
Variance	0.488	0.39	1.945	2.047
Student's t-test	0.252	0.196	0.022	----------
F-value	4.194	4.194	1.052	----------

confidence level)[42]. The results show that the calculated t- and F-values did not exceed the theoretical values as shown in TABLE 7. The assay results were in good agreement with values obtained by applying the reference method[43].

CONCLUSION

This work introduced three types of potentiometric sensors were constructed for determination of CTZ. The sensors demonstrated advanced performances with good operating characteristics including reasonable detection limit, relatively high selectivity, wide dynamic range, and fast response. The sensors offer viable techniques for the determination of Cetirizine hydrochloride in pure solutions and pharmaceutical preparations. The methods are a stability indicating one, as the degradation products are not interfering in the estimation of the intact drug. The suggested methods are found to be simple, accurate, selective and equally sensitive with no significant difference of the precision compared with the reference method.

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