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Novel Ionophore for the Potentiometric Determination of Cetirizine Hydrochloride in Pharmaceutical Formulations and Human Urine

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Cetirizine (CT) membrane sensors of conventional (CE) and carbon paste (CPE) have been prepared, based on β-cyclodextrin (βCD) as ionophore and potassium tetrakis[3,5-bis(trifluoro-methyl) phenyl]borate (KTFPB) as anionic membrane additive. The sensors exhibit a linear response with a mean calibration graph slopes of 60.2 and 57.4 mV per decade at 25 °C for conventional and carbon paste electrodes, respectively, with the concentration ranges $1x10^{-1}$-$5x10^{-6}$ M for conventional and $1x10^{-1}$-$7x10^{-6}$ M for carbon paste. The electrodes fully characterized in terms of composition, usable pH range, life span and response time. The electrodes showed a very good selectivity for CT with respect to some inorganic and organic cations and other related compounds. Use of the sensors for the assay of formulation of CT drug and in spiked human urine, show a mean average recovery of 100.04 % and a mean precision of ± 0.4. Significantly improved response time, stability, selectivity, accuracy, simple, and low cost are offered by potentiometric sensors compared with other standard methods.

Keywords: Cetirizine**;** sensors; potentiometry; β-cyclodextrin; carbon paste electrodes**;** human urine; pharmaceutical formulation

1. INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides formed from the enzymatic degradation of starch by bacteria [1]. The unique property of these compounds is that they have a hydrophilic shell and a relatively polar cavity. CDs have the ability to form inclusion cavities with a specific receptor function [2]. Among CDs, β-cyclodextrins were previously applied as sensor ionophores to ion-selective electrodes for determination of onium ions [3], chiral molecules incorporating aryl rings,

protonated amines [3, 4], amino acids and drugs [5, 6]. The inclusion complexation of drug with cyclodextrins was studied by potentiometry [7].

Cetirizine hydrochloride (Figure 1) is a piperazine derivative and its chemical name is, (±) - [2-[4- [(4-chlorophenyl)phenylmethyl] -1- piperazinyl] ethoxy]acetic acid, dihydrochloride. It is a non-sedating antihistamine or histamine (H-1) receptor blockers. The mechanism of action of CT is block the ability of histamine to promote the allergic reactions in the body. Cetirizine is used in the treatment of perennial and seasonal allergetic rhinitis and also for chronic uticaria. Few methods have been used for quantitative determination of cetirizine. These methods include fluorimetry [8], spectrophotometry [6, 9-14], titrimetry and conductimetry [15], gas chromatography [16], high-performance liquid chromatography [14, 17-19], liquid chromatography [20, 21] and ion-selective electrodes [22], based on the formation of ion-pair complex of cetirizine with tetraphenylborate.

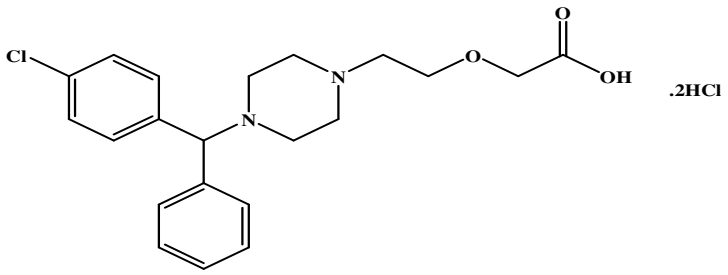

Figure 1. Chemical structure of cetirizine dihydrochloride.

Carbon paste is an ideal electrode substrate due to its; chemical inertness, low cost, fast response time, ease of fabrication in different configuration and size and renewal. These attractive features of carbon electrodes are the reason for the considerable attention at the production of carbon-based electroanalytical sensors. Recently, carbon paste technique was used in the construction of amperometric enzyme electrode [23], urea [24] and potentiometric determination of drug [25].

The present work describes the possibility of using β-cyclodextrin as ionophore in the preparation of cetirizine-selective electrodes in which PVC was used as polymeric matrix for immobilization of the conventional sensor. Carbon paste and conventional forms are prepared, characterized, compared and application of using two forms in the quantitative analysis of drug in pharmaceutical preparations and human urine.

2. EXPERIMENTAL PART

2.1. Apparatus

Potentiometric measurements at 25±1°C were made with an Orion digital ion-analyser (model) 420A and CT conventional and carbon paste membrane sensors based on β-cyclodextrin as ionophore. A CT membranes were used in conjunction with an Orion 90-02 Ag-AgCl double-junction reference electrode containing a 10% (w/v) KNO_3 solution in the outer compartment. Adjustment of the pH was made with an Orion 91-20 combination glass electrode.

2.2. Reagents

All chemicals were of analytical-reagent grade, unless otherwise stated, and bidistilled deionized water was used throughout. Cetirizine hydrochloride, paraffin oil and β-cyclodextrin were obtained from Sigma Chem. Co. (St. Louis, MO., USA). Nitrophenyl octyl ether (*o*-NPOE) plasticizer, tetrahydrofuran (THF) (freshly distilled prior to use) and graphite powder (1-2 μ) were obtained from Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). Potassium tetrakis[3,5-bis(trifluoro-methyl) phenyl]borate (KTFPB), was obtained from Fluka (Ronkonkoma, NY). Pharmaceutical preparations containing cetirizine hydrochloride were obtained from local drug stores. Aqueous 10^{-2}–10^{-6} M drug solutions were freshly prepared by accurate dilutions of a standard 10^{-1} M stock drug solution by using 0.05 M acetate buffer, pH 3.5.

2.3. Sensors preparation and calibration

2.3.1. Conventional membrane-type sensor

The general procedure used for preparation of PVC membrane is similar to the previously described [26, 27]. The membranes were prepared by dissolving 2 mg of ionophore, 0.2 mg of KTFPB, 66.5 mg of PVC and 126 mg of *o*-NPOE in about 3 ml of tetrahydrofuran (THF).The solution mixture was poured into about 3 cm Petri dish and left to dry overnight at room temperature. A transparent master PVC membrane with an average thickness of ~ 0.1 mm was sectioned with a cork borer (10 mm diameter) and glued to polyethylene tube. The electrochemical system used was as follows: **Ag/AgCl sat. KCl/test solution/membrane/internal filling solution of pH 3.5/sat. KCl/Ag/AgCl**. The internal solution was a mixture of an equal volume of CT drug and KCl solutions (1 x 10^{-2} M). The prepared sensor was conditioned by soaking in cetirizine hydrochloride solution (1 x 10^{-2} M) for 9 h and was stored in the same solution when not in use.

2.3.2. Carbon paste membrane sensor

3 mg portion of β-cyclodextrin, ionophore was thoroughly mixed in a glass petri dish (3 cm diameter) with 70 mg of carbon powder, 27 mg of paraffin oil as a pasting liquid. The resulting paste was then packed firmly into the electrode cavity (3.0 mm diameter and 5 mm depth) of a rubber sieve. The oil from the carbon paste prevents the leach of βCD from the membrane into solution. The paste surface was smoothed on a weighing paper. The surface of the resulting paste electrode was polished using a filter paper to reproducible working surface and rinsed carefully with double distilled water.

2.3.3. Calibration of the sensors

Calibration was made by immersing the conventional cetirizine or carbon paste cetirizine sensor in conjunction with a double junction Ag-AgCl reference electrode in 50 ml beakers containing 10 ml aliquots of standard 1 x 10^{-6} to 1 x 10^{-2} M drug solution. The pH of the solution is adjusted to 3.5

using acetate buffer. The potential readings were recorded for the drug starting from the low to high concentration, when became stable. The potential response was plotted as a function of the logarithm of drug concentrations. The calibration plot was used for subsequent measurements of unknown drug concentrations.

2.4. Sensor Selectivity

The potentiometric selectivity coefficients ($K_{CT,B}^{Pot}$) of the cetirizine sensors were measured using the separate solutions method (SSM) [28, 29]. A 1.0 ml aliquot of 1 x 10^{-2} M of the drug solution was transferred into a 50 ml beaker containing 9.0 ml of acetate buffer of pH 3.5. The drug sensor in conjunction with a double junction Ag-AgCl reference electrode was immersed in the solution and the potential was measured. In a separate run, a 1.0 ml aliquot of 1 x 10^{-3} M of the interfering solution was transferred into 50 ml containing 9.0 ml of the same buffer and the potential reading was recorded. Selectivity coefficients were calculated from the equation:

$$\log (K_{CT,B}^{Pot}) = (a_{CT}/(a_B)^{Z_{CT}/Z_B}$$

Where E_1 and E_2 are the potential readings observed after 1 min. of exposing the sensor to the same activity of cetirizine and interferents ions, respectively, and $^{Z}_{CT}$ and $^{Z}_{B}$ are the charges of cetirizine and interferent cation.

2.5. Determination of Cetirizine

2.5.1. Pharmaceutical Preparations

The contents of five tablets weighed and finely powdered in a small dish. An accurately weighed portion of the powder, equivalent to one tablet, was dissolved in about 20 ml acetate buffer solution pH 3.5, and filtered into a 50 ml volumetric flask. The solutions were completed to the mark with acetate buffer pH 3.5. An aliquot (10 ml) of each solution was transferred to a 50 ml beaker, the drug sensor in conjunction with a double junction reference electrode were immersed and compared with the calibration graph. Alternatively, the potentials were measured before and after addition of 1.0 ml of 10^{-2} M standard cetirizine solution to the test solution and the unknown concentration was calculated using the standard addition method [27]. Also, the contents of five ampoules of the drug were mixed by shaking and an accurately volume equivalent to one ampoule was transferred to a 50 ml volumetric flask and diluted to the mark with 0.05 M acetate buffer solution pH 3.5. The EMF of the solution was measured as described above and compared with the calibration plot.

2.5.2. Human urine samples

A determination of the cetirizine concentration in urine samples was carried out by diluting the urine samples with a 0.05 M acetate buffer solution of pH 3.5 in a ratio of 3:27 urine to buffer.

Aliquots of cetirizine solutions of different concentrations (1 x 10^{-5}-1 x 10^{-1} M) were spiked to these urine samples. Also, the standard addition was applied with the urine samples. The results were compared with the calibration curve.

3. RESULTS AND DISCUSSION

3.1. Performance haracteristics of the sensors

In the preliminary experiments, conventional and carbon paste with and without ionophore were prepared. The conventional and carbon paste with no ionophore displayed no measurable response towards CT^+ ion, whereas, in the presence of the proposed ionophore, the optimized sensors demonstrated an appreciable response and remarkable selectivity for CT^+ over several common inorganic, organic and some related compounds.

The conventional sensor incorporating βCD membrane plasticized with (*o*-NPOE) were prepared with the composition of 2 wt.% βCD, 33.1 wt.% PVC, 65.3 wt.% *o*-NPOE and 0.1 wt. % KTFPB. The sensor show linear potentiometric response over the concentration range of 5x10^{-5} to 1 x 10^{-1} M with cationic slope of 60.2 mV per decade. The response time of the sensor was less than 10-25 s for 6 x 10^{-5} to 1 x 10^{-1} M cetirizine drug and the life span of the sensor was about 6 weeks. Carbon paste sensor was prepared with the compostion of 2 wt. % βCD and 0.1 wt. % KTFPB, which exhibits the best performance, slope 57.4 mV per decade at 25°C, usable concentration range 6x10^{-5} to 10^{-1} M, detection limit 7x10^{-6} - 10^{-1} M and response time 15-30 s for 10^{-5} to 10^{-1} M cetirizine drug and the life span of the sensor was about 6 weeks.

The effect of membrane additive was studied by adding 0.1 wt. % to the membrane mixture of CE and CPE. The presence of Potassium tetrakis[3,5-bis(trifluoro-methyl) phenyl]borate (KTFPB) not only improve the response behavior and selectivity but also enhances the sensitivity of the sensors. Apart from the critical role of the nature and the amount of ionophore used in the preparing the membrane mixture, some other important features, such as nature of the solvent mediator, the pasting solvent/graphite ratio and the nature of any additives used, are known to significantly influence the sensitivity and selectivity of the prepared electrode [30, 31]. The sensing mechanism can be explained on the basis of electrostatic interaction and the formation of 1:1 inclusion complex. The critical electrochemical performance characteristics of the sensors were systematically evaluated according to IUPAC recommendations [32]. Data collected over a period of four months from seven different assemblies of each type of sensor are summarized in Table 1. Typical calibration plots of the sensors are shown in Figure 2. The mechanism of response of βCD in the membrane phase to the drug cation can be explained as;

$$\textbf{Cetirizine}^+ \leftrightarrow \textbf{Cetirizine}^+ + \textbf{βCD} \leftrightarrow \textbf{Cetirizine - βCD}$$

(Aqueous) (Organic membrane)

Table 1. Response characteristics of cetirizine membrane sensors

Parameter [a]	CE	CPE
Slope, (mV per decade)	60.2 ± 0.5	57.4 ± 0.5
Correlation coefficient, (r)	0.998	0.996
Lower limit or linear range, (M)	5×10^{-5}	6×10^{-5}
Lower limit of detection, (M)	5×10^{-6}	7×10^{-6}
Response time for 10^{-3} M, (s)	10 ± 2	15 ± 2
Recovery time for 10^{-3} M, (s)	25 ± 2	30 ± 2
Working range, (pH)	2 - 4	2 – 4
Life span, (week)	6	6
Accuracy (%)	99.5	99.3
Repeatability, CV_w (%)	0.8	0.9
Between day-variability, CV_b (%)	1.2	1.3
Relative standard deviation, RSD (%)	1.1	1.2
Robustness [b]	100.3±1.5	100.6±1.3
Ruggdness [c]	101.4±1.7	101.8±1.4

[a.] Average of five measurements

[b] Comparing the obtained results by different sensors prepared using *o*-NPOE, ACROS Organics, New Jersey, USA.

[c] Comparing the results by those obtained by different sensors assemblies using Jenway 720 potentiometer.

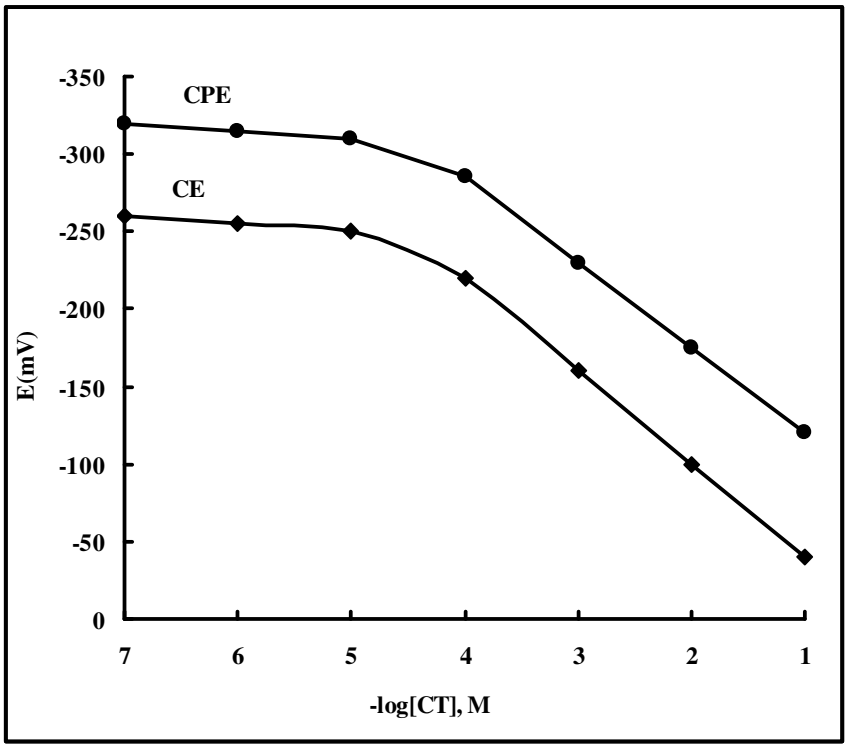

Figure 2. Potentiometric responses of cetirizine membrane sensors: CE (Conventional) and CPE (Carbon paste cetirizine membrane sensors).

3.2. Effect of pH and foreign ions

The effect of pH on the potential readings of the two electrode systems was studied by immersing the combination glass electrode, cetirizine membrane sensor and a single junction Ag/AgCl reference electrode in 50 ml beakers containing 25 ml aliquots of 1 x 10^{-3} and 1 x 10^{-4} M cetirizine 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. The pH–mV profile of each cetirizine concentration was plotted for each electrode system. From Figure 3, it was observed that the sensors did not affect by the pH change in the range 2-4 for conventional and carbon paste cetirizine electrodes. At pH value less than 2, the potential increases which may be due to the formation of diprotonated species, while at pH value higher than 4, the potential decreases, this may be due to the deprotonation of cetirizine drug.

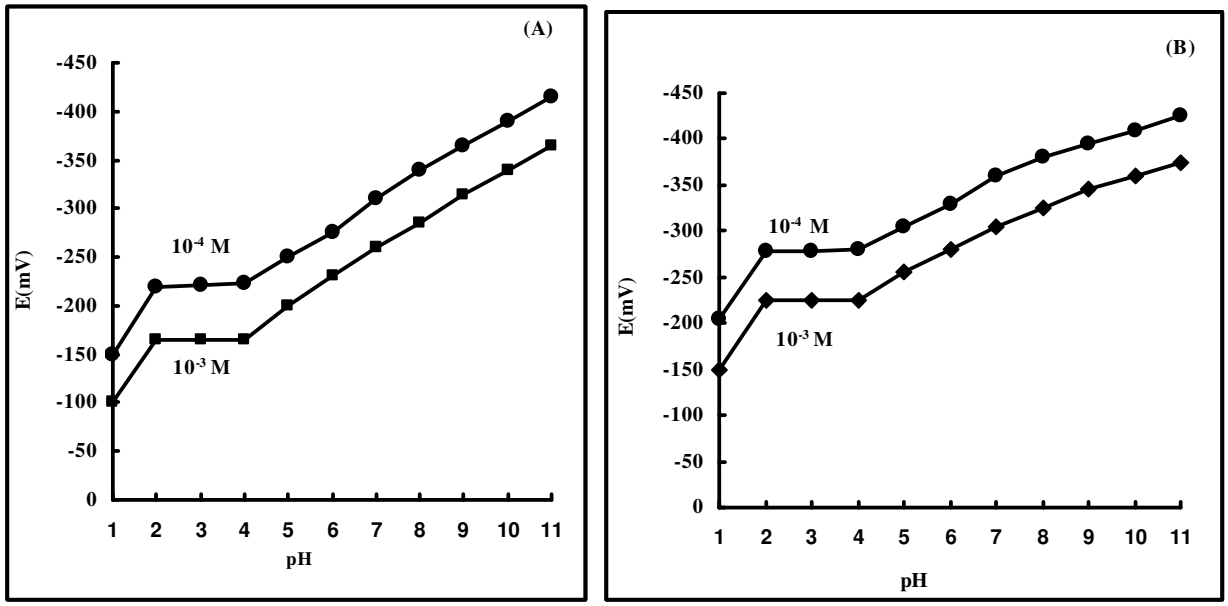

Figure 3. Effect of the pH on the potential responses of (A) Conventional (CE) an (B) Carbon paste cetirizine membrane sensors (CPE).

The potentiometric selectivity coefficients ($K_{CT,B}^{Pot}$) of cetirizine sensors based on β-cyclodextrin were determined using the separate solutions (SSM) method at a concentration level of 1 x 10^{-3} M of both drug solution and interfering cations. Influences of 25 different organic and inorganic cations on the response of the sensors were evaluated by measuring the selectivity coefficients. The results are listed in Table 2. The results obtained show that the cetirizine sensors display significantly high selectivity for cetirizine over many common organic and inorganic cations.

The effect of drug excipients and diluents (e.g., glucose, lactose, maltose, starch, talc powder, mannitol, carboxymethyl cellulose and magnesium stearate) was also studied. No effect of these substances on the response of the cetirizine sensors by using the concentration of substances up to 10^4-fold excess.

Table 2. Potentiometric selectivity coefficient [a] ($K_{CT,B}^{Pot}$) for cetirizine sensors

Interferent, B	$K_{CT,B}^{Pot}$	
	CE	CPE
K^+	1.3×10^{-6}	1.4×10^{-5}
Na^+	2.2×10^{-6}	2.3×10^{-6}
NH_4^+	8.2×10^{-5}	7.2×10^{-4}
Mg^{2+}	2.7×10^{-6}	3.1×10^{-5}
Ni^{2+}	2.6×10^{-3}	2.8×10^{-4}
Fe^{2+}	6.8×10^{-3}	5.6×10^{-3}
Co^{2+}	3.6×10^{-4}	3.5×10^{-5}
Glucose*	7.1×10^{-3}	7.4×10^{-3}
Fructose*	3.8×10^{-4}	4.2×10^{-4}
Lactose*	5.4×10^{-4}	6.3×10^{-4}
Vitamin C	6.8×10^{-2}	2.3×10^{-2}
Vitamin B_2	5.3×10^{-3}	1.4×10^{-3}
Glycine	5.4×10^{-4}	3.4×10^{-5}
Cysteine	4.7×10^{-3}	7.8×10^{-3}
Histidine	7.5×10^{-3}	5.3×10^{-3}
Tyrosine	3.3×10^{-3}	5.7×10^{-3}
5- nitrobarbiturate	7.5×10^{-3}	6.4×10^{-3}
p- aminophenol	1.1×10^{-5}	2.2×10^{-5}
p- aminobenzoate	6.6×10^{-4}	2.5×10^{-4}
Catecholate	7.8×10^{-4}	3.4×10^{-3}
Resorcinolate	5.8×10^{-3}	6.5×10^{-4}
Pyrogallate	2.8×10^{-4}	2.1×10^{-4}
p-Nitroaniline	1.1×10^{-5}	3.1×10^{-5}

[a.] Average of five measurements

*Fixed interference method [32] (FIM) was used.

4. ANALYTICAL APPLICATIONS

The investigated sensors were proved to be useful in the potentiometric determination of cetirizine drug in pure solutions and in pharmaceutical preparations by the standard addition method. Collective results are given in Table 3. From the results, it is evident that the present sensors will be very useful as a microdetermination of CT drug in its pure solutions and pharmaceutical preparations. The mean recoveries obtained were 99.5 ± 0.4, 99.8 ± 0.3 and 98.1 ± 0.5 % for conventional electrode, carbon paste electrode and spectrophotometric method, respectively. The data for pharmaceutical preparations show that the assay results were in good agreement with values obtained using spectrophotometric method [10], which based on the reaction of CT with bromocresol purple dye to form ion-pair complex extractable with chloroform and subsequently measured spectrophotometrically. The determination of CT drug in spiked urine samples was carried using the

standard addition technique, the mean recoveries obtained were 100.9, 99.9 and 98.6 % for conventional electrode, carbon paste electrode and spectrophotometric method, respectively, Table 4. The proposed method can therefore be applied for determination of CT in pure form, pharmaceutical formulations and in urine samples without fear of interference caused by the excipients expected to be present in tablets or in the constituents of body fluids.

A comparison of the performance of the proposed potentiometric sensors with other instrumental methods used for cetirizine assessment 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 [9, 10, 18-21]. On the other hand, the proposed sensors possess three distinct advantages, Table 5, over the previous potentiometric method [22]. These are wide detection limit (4.6 μg ml^{-1}- 46.2 mg ml^{-1}), lower selectivity coefficients for most interferents (1.3×10^{-6}-7.5×10^{-3}) and better pH range (2-4).

Table 3. Application of cetirizine membrane sensors in some pharmaceutical preparations

Phramceutical formulations	Nominal content	Accuracy, [a] %		
		CE	CPE	UV-Vis [10]
Cetrak (Pharco Pharm., Egypt)	10 (mg/ tablet)	99.5±0.3	98.4±0.4	98.5±0.6
Tomazine (Alpha Chem. Advanced pharma. Industries Co., Egypt)	10 (mg/ tablet)	99.3±0.7	98.1±0.5	98.3±0.4
Epirizine (Epico, Egypt)	10 (mg/ tablet)	99.2±0.5	97.8 ± 0.5	97.3±0.7
Zyrtec, (Glaxosmithkline, Egypt)	10 (mg/ tablet)	100.5±0.2	101.4±.2	98.7±0.5
Histazine-1,(Amriya, Egypt)	1 (mg ml^{-1} syrup)	99.1±.3	98.5±0.1	98.1±0.3

[a] Average of five measurements

Table 4. Potentiometric determination of cetirizine hydrochloride in spiked urine samples using cetirizine responsive membrane sensors.

Method	Taken/mg ml^{-1}	Recovery [a]	SD
CE	2.5	101.52	1.102
	5.0	100.35	0.981
CPE	2.5	99.72	0.621
	5.0	100.11	0.832
UV-Vis	2.5	98.63	1.512
	5.0	98.71	1.365

[a] Average of five measurements

Table 5. Comparison of the published and present potentiometric methods

Method	Slope (mV per decade)	Concentration range (M)	pH range	Selectivity
Published [22]	66.8	$3.16 \times 10^{-5} - 3.16 \times 10^{-3}$	1.5–2.8, 2.25–3.25	7.0×10^{-5}– 3.1×10^{-3}
Present (CE)	60.2	5×10^{-6}– 1×10^{-1}	2–4	1.3×10^{-6}– 7.5×10^{-3}
Present (CPE)	57.4	7×10^{-6}– 1×10^{-1}	2–4	2.3×10^{-6}– 7.8×10^{-3}

5. CONCLUSIONS

Simple and direct potentiometric assay methods for determining cetirizine is described based on the use of β-cyclodextrin (βCD) as ionophore in plasticized poly(vinyl chloride) for conventional system and the membrane containing KTFPB as anionic additive for conventional and carbon paste electrodes. This approach is cost-effective and offer the advantages of high accuracy, sensitivity, fast response and utilization for direct quantification of cetirizine in dosage forms at room temperature without prior treatments. The application of this methodology is useful for quality control/quality assurance in drug production.

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