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Ion Selective Electrodes for Determination of Cefditoren Pivoxil in Pharmaceutical Formulations and Biological Fluids

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Newly developed coated wire electrodes have been developed for determination of cefditoren pivoxil (CTP) in pure form, pharmaceutical preparations and in biological fluids. The selective electrodes were fabricated based on the incorporation of cefditoren pivoxil with the ion exchangers, phosphomolybdic acid (CTP-PMA), phosphotungstic acid (CTP-PTA) and a mixture of both (CTP-PMA/PTA). The potential responses of the electrodes were influenced by the pH of tested solution. Under the condition of pH 5-10, the electrodes exhibit linear response over concentration range 1.0×10^{-7} - 1.0×10^{-2} mol/L with Nernstian slopes (56.29 ± 0.09, 54.60 ± 0.09 and 58.17 ± 0.28 mV/ decade at 25 °C) for the three electrodes, respectively. The influence of possible interfering species such as common inorganic cations, amino acids and different pharmacological related compounds was studied. The electrodes were successfully applied to determination of the drug in tablets by direct and standard addition potentiometry. Statistical student's *t*-test and F-test showed insignificant systematic error between proposed and reported methods.

Keywords: Cefditoren pivoxil; Ion-selective electrodes; Potentiometric determination; pharmaceutical formulations; Biological fluids

1. INTRODUCTION

Potentiometry with ion-selective electrodes (ISEs) is still one of the most promising analytical tools capable of determining both inorganic and organic substances in medico-biological practice. There is a constant increase in the number of electrodes capable of selectivity identifying various drugs. Suitable ISEs for drugs have enough selectivity towards the drugs over pharmaceutical excipients and they can be useful in the quantitative analysis of the drugs in pharmaceutical preparations without prior separation. In particular, ISEs are useful in the case of drugs which are unstable during prior separation [1]

Potentiometric sensors posses many advantage over traditional methods of analysis and provide accurate, reproducible, fast and regular selective determination of various ionic species. In addition, ISEs allow non-destructive, on line monitoring of particular ions in a small volume of sample without pretreatment [2, 3].

Cefditoren pivoxil (CTP) is chemically known as (6R)-7-[[(2Z)- 2-(2-amino -1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-[(Z)-2-(4-methyl-1,3-thiazol-5-yl) ethenyl]-8- oxo-5-thia-1-aza bicyclo [4.2.0]oct-2-ene-2-carboxylic acid, Figure 1.

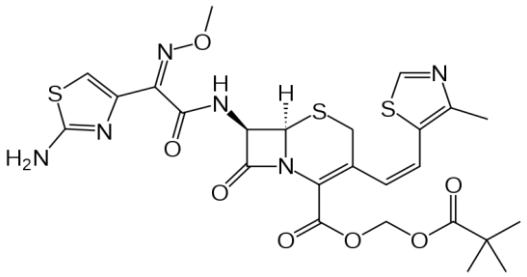

Figure 1. Chemical structure of cefditoren pivoxil

Molecular formula and molecular weight of CTP are $C_{25}H_{28}N_6O_7S_3$ and 620.73 g/mol respectively. It is a third generation cephalosporin with antibacterial activity against gram-positive and gram-negative pathogens. It is a prodrug which can be hydrolyzed by esterase during absorption to the active drug, cefditoren, and the drug is distributed in the circulating blood as an active cefditoren. CTP is used in the treatment of mild to moderate pharyngitis, tonsillitis, uncomplicated skin, skin structure infections, and acute exacerbations of chronic bronchitis [4]. Few spectrophotometric methods have been reported for CTP determination individually as well as in combination with other drugs [5-8]. RP-HPLC methods have been reported for determination of CTP in bulk, in presence of degradation product, in pharmaceutical dosage forms and in tablet formulations [9-11]. The bioequivalence and pharmacokinetic studies of CTP on rats has been done by HPLC method [12]. The pharmacokinetic/pharmacodynamic serum and urine profiles of CTP have been studied by HPLC method [13]. A HPTLC method has been reported for determination of CTP in human plasma [14].

Revealing the literature review no potentiometric method was found for determination of CTP, in bulk, dosage forms and in biological fluids by ion selective electrodes. In this work a simple, accurate, precise and sensitive potentiometric method is described for determination of CTP using coated wire electrodes.

2. EXPERIMENTAL

2.1. Instrumentation

The electrochemical measurements were carried out with HANNA instrument 211 microprocessor pH-meter and Metrohm pH-meter Model 744 for measuring pH. Ag/AgCl electrode was used as external reference electrode.

2.2. Materials and reagents

All chemicals used were of analytical grade. Pure grade CTP and its tablets (MEIACT® 200 mg/tablet) were supplied from Tabuk pharmaceutical, MFG. Co., Saudi Arabia. Methanol 99.9%, dioctyl phthalate (DOP) 99.0% and tetrahydrofuran (THF) 97.0% were provided by Fluka, Switzerland. Poly vinyl chloride (PVC) high molecular weight, phosphotungstic acid (PTA) 99.1% and phosphomolybdic acid (PMA) 99.9% were purchased from Aldrich, Germany. Urine samples were obtained from healthy volunteers and serum samples (Multi -Serum Normal, Randox laboratories UK) were obtained from commercial sources.

2.3. Standard drug solution

Stock CTP solution 0.1mol/ L was prepared daily by dissolving 1.552 g of drug in 25 mL methanol. Working solutions ranging from 1.0 $x10^{-7}$-1.0 $x10^{-2}$ mol/L were prepared by appropriate dilution with methanol.

2.4. Preparation of cefditoren pivoxil ion-pair

The ion-pair was prepared by mixing 50 mL of 1.0 x 10^{-2} mol/L CTP and 50 mL of 1.0 x 10^{-2} mol/L PMA or PTA or (PMA/PTA). The resulting precipitates were filtered, washed thoroughly with distilled water and air dried. The membranes were prepared by dissolving required amount of ion-pair, PVC and plasticizer (DOP), in 5 mL THF. The solution mixture was poured into a petri dish (3 cm diameter), covered with a filter paper and the solvent was allowed to evaporate slowly at room temperature.

2.5. Electrode construction

Pure aluminum wire of 20 mm diameter and 12 cm length was tightly insulated by polyethylene tube leaving 1.0 cm at one end for coating and 0.5 cm at other end for connection. Prior to coating, the polished surface was washed with a detergent, then rinsed with water, and dried. The sensor ending part was dipped into the coating solution. The prepared electrode was conditioned by soaking for 24 h in 1.0 x 10^{-3} mol/L CTP solution.

2.6. Electrode calibration

The calibration of the sensors was preceded using standard solutions of CTP ranging from 1.0 $x10^{-7}$ - 1.0 $x10^{-2}$ mol/L. All potentiometric measurements were performed using the following cell assembly: Al/membrane/test solution//KCl salt bridge// Ag/AgCl. The sequence of measurements was carried out from low concentration to a higher one. The measured potential was plotted against the

logarithm of drug concentration. The sensor (s) was washed with distilled water and dried with tissue paper between measurements.

2.7. Sensor selectivity

Selectivity coefficients $K^{pot}_{CTP\ j}{}^{+z}$ of the electrodes towards different cationic species were determined by the separate solution method [15] in which the following equation was applied:

$$\text{Log } K^{Pot}_{CTP\ J}{}^{z+} = (E_2-E_1)/S + \log [CTP] - \log (J^{z+})^{1/z}$$

Where, E_1 is the electrode potential in 1.0 x 10^{-3} mol/L CTP solution, E_2 is the electrode potential in 1.0 x 10^{-3} mol/L of the interferent ion J^{z+} solution and S is the slope of the calibration plot.

2.8. Effect of pH

The effect of pH of the CTP test solution on these sensors potential was investigated. The potential was measured at a specific concentration of the CTP solution (1x10^{-3} mol/L) from the pH value of 2 up to 12. The solution was acidified by the addition of very small volumes of 0.1N HCl then the pH value was increased gradually using 0.1N NaOH for each pH value, the potential was measured using two pH/mV meters. The potential readings corresponding to different pH values were recorded and plotted.

2.9. Standard addition method

The fabricated electrode(s) was immersed into CTP sample of 50 mL with unknown concentration and the equilibrium potential was recorded. Then 0.1 mL of 0.1 mol/L of standard drug solution was added into the testing solution and the equilibrium potential was recorded. The concentration of the testing sample was calculated from the change of potential ΔE.

2.10. Analytical applications

2.10.1. Determination of cefditoren pivoxil in pharmaceutical dosage forms

2.10.1.1. Determination of cefditoren pivoxil in tablets

Ten tablets of MEIACT® (200 mg/tablet) were finely powdered. An accurate weight containing 1.552 g CTP was dissolved in 50 mL methanol to obtain a standard stock solution. Working solutions in the range of 5.0×10^{-7}-1.0×10^{-3} mol/L for standard addition method and 1.0×10^{-7}-1.0×10^{-2} mol/L for direct determination method were prepared by serial dilutions with methanol. The procedure under *2.6.* section was then followed.

2.10.1.2. Content uniformity assay of cefditoren pivoxil tablets:

Ten individual tablets of MEIACT® (200 mg/tablet) were placed in separate 100 mL measuring flasks and dissolved in 100 mL methanol. The sensor(s) was directly immersed into 50 mL of drug sample for three times and then washed with distilled water to reach steady potential between the individual measurements. The mean potential was used to evaluate the content uniformity from the calibration graph.

2.10.2. Application to biological fluids

2.10.2.1. Serum

1.0 mL aliquots of serum were transferred into a series of centrifugation tubes. Aliquots of standard methanolic solution of CTP were added so that the final concentration is in the range of 1.0×10^{-7}-1.0×10^{-2} mol/L. The tubes were mixed well and 10.0 mL of diethyl ether was added to each tube and centrifuged for 2 min at 1500 rpm. Then, the deproteinated layer was transferred to a 100-mL measuring flask and completed to volume with methanol. These solutions were analyzed as described above under electrode calibration or using standard addition methods.

2.10.2.2. Urine

1.0 mL aliquots of urine were transferred into a series of 100-mL measuring flasks. Aliquots of standard methanolic solution of CTP were added so that the final concentration was in the range of 1.0×10^{-7}-1.0×10^{-2} mol/L. The flasks were mixed well and completed to volume with methanol. These solutions were analyzed as described above under electrode calibration or using standard addition methods.

3. RESULTS AND DISCUSSIONS

Conventional coated wire electrodes with different compositions were prepared. The slope and working concentration range for the different coated wire sensors are given in Table 1. The best performance was exhibited by a mixture of both (CTP-PTA/PMA). This sensor showed a nearly Nernestian response with slope of 58.17 mV/decade and a linear concentration range of 1.0×10^{-7}-1.0×10^{-2} mol/L. CPT with the ion exchangers (CTP-PMA) and (CTP-PTA) coated wire electrodes showed a Nernestian responses with slopes of 56.29 and 54.60 mV/decade, respectively (Figure 2). However, they still have sufficient sensitivity with good linear range and can thus be used for the determination of CTP in solution. For linearity and limit of detection as mentioned before, the investigated drug was measured using CTP-electrodes over the concentration range 1×10^{-7} -1×10^{-2} mol/ L at lower limits of detection 1.48×10^{-9}, 5.01×10^{-8} and 5.01×10^{-8} mol/ L for (CTP-PMA), (CTP-PTA) and (CTP-PMA/PTA) coated wire sensors, respectively.

The electrodes exhibit a fast dynamic response of 20, 25 and 15s for a period of 40, 30 and 45 days for (CTP-PMA), (CTP-PTA) and (CTP-PMA/PTA) coated wire sensors, respectively, without significant change in the electrodes parameters.

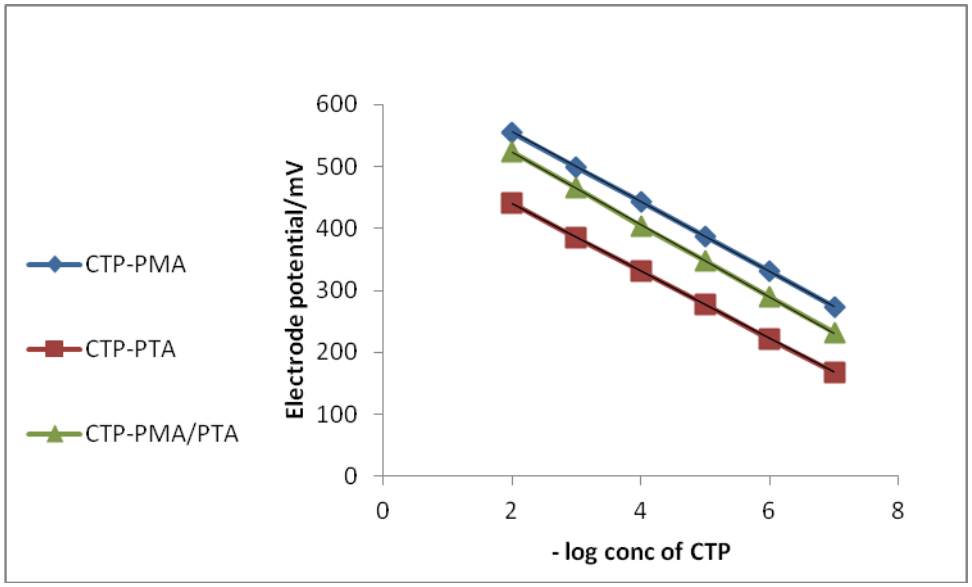

Figure 2. Typical calibration graphs of CTP

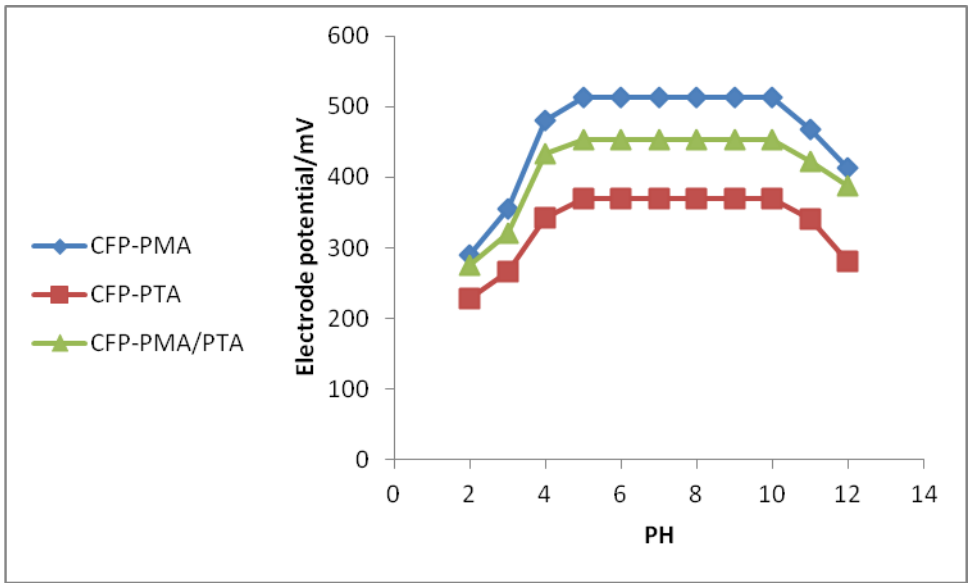

Figure 3. Effect of pH on CTP electrode potential

To examine effect of pH on the three electrode responses, the potential was measured at specific concentration of CTP solution (1.0×10^{-3} mol/L) from the pH value of 2.0 up to 12.0. The results showed that the potential remained constant despite the pH change in the range of 5.0 to 10.0, which indicates the applicability of this electrode in the specified pH range (Figure 3).

Table 1. Critical response characteristics of CTP coated wire sensors

Parameter	CTP-PMA	CTP-PTA	CFP – PMA/ PTA
Slope (mV/decade)	56.29	54.60	58.17
Intercept	668.29	549.53	638.77
Correlation coefficient (r)	0.9999	0.9999	0.9999
Linear range (mol/L)	1.0×10^{-7} -1.0×10^{-2}	1.0×10^{-7} -1.0×10^{-2}	1.0×10^{-7} -1.0×10^{-2}
LOD (mol/L)	1.48×10^{-9}	5.01×10^{-8}	5.01×10^{-8}
Response time for 10^{-3}M CTP/s	20	25	15
Life time/day	40	30	45
Working pH range	5 – 10	5– 10	5 – 10
Robustness[a]	99.62±0.35	99.34±0.55	99.69±0.22
Ruggedness[b]	99.65±0.20	99.47±0.39	99.79±0.25

[a]A small variation in method parameters were carried out as pH of borate buffer (pH 7.0 ±1).
[b] Comparing the results by those obtained by different sensors assemblies using (Jenway 3510 pH meter).

Relatively noteworthy fluctuations in the potential *vs.* pH behavior took place below and above the formerly stated pH limits. In detail, the fluctuations above the pH value of 10.0 might be justified by removing the positive charge on the drug molecule. Fluctuations below the pH value of 5.0 were caused by removal of the ion-pair in the membrane or analyte in the solution. For three electrodes the same trend was observed [16].

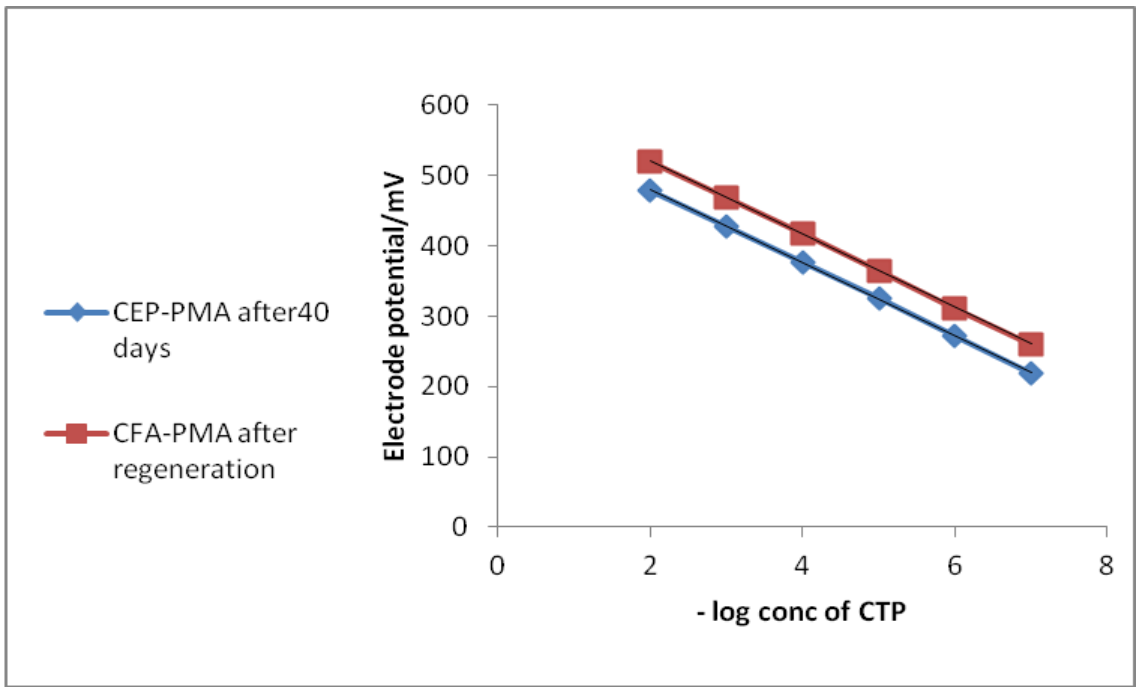

Figure 4. Regeneration of CTP-PMA coated wire electrode

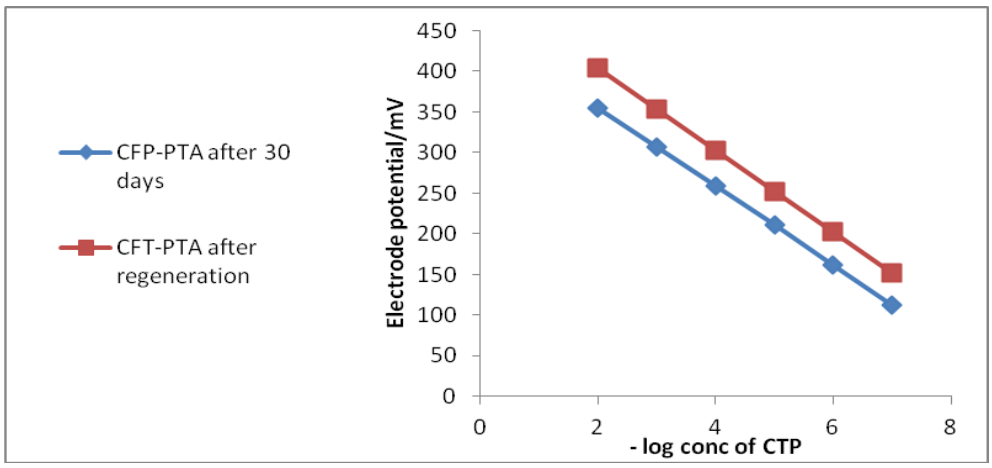

Figure 5. Regeneration of CTP- PTA coated wire electrode

The effect of soaking time and regeneration of the electrodes was studied. The three electrodes were employed in 1.0 x10^{-3} mol/L solution of CTP and the calibration graphs were plotted after optimum soaking time of 24 h. The slopes of calibration curves were 56.29, 54.60 and 58.17 mV/decade at 25 ºC for (CTP-PMA), (CTP-PTA) and (CTP-PMA/PTA) coated wire electrodes, respectively. The calibration plots slopes decreased slightly to be 51.74, 48.37 and 53.46 mV/decade after 40, 30 and 45 days for (CTP-PMA), (CTP-PTA) and (CTP-PMA/PTA) coated wire sensors, respectively.

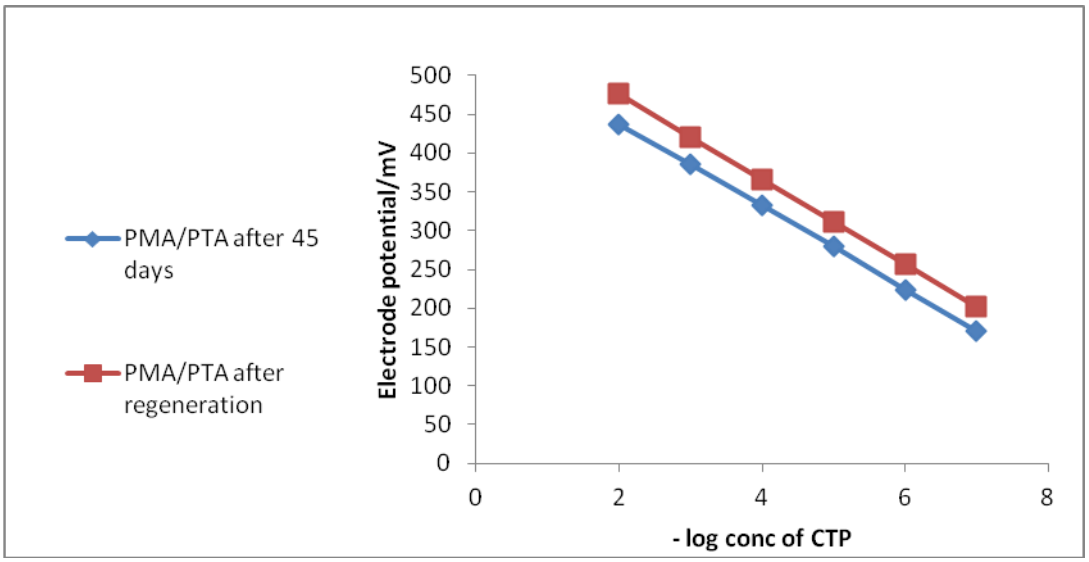

Figure 6. Regeneration of CTP-PMA/PTA coated wire electrode

This reveals that soaking of electrodes in the drug solution for a long time has a negative effect on the response of membrane. The same effect appears after working with the electrodes for a long time. The regeneration of the electrodes was tried simply by reformation of the ion-pair on the external

gel layer of membrane [17]. The regeneration of the (CTP-PMA), (CTP-PTA) and (CTP-PTA/PMA) coated wire sensors was successfully achieved by soaking the exhausted electrodes for 24 h in solution that was 1.0 $x10^{-2}$ mol/L phosphotungstic acid (PTA) or phosphomolybdic acid (PMA), followed by soaking for 6 h in 1.0 $x10^{-2}$ mol/L CTP solution. Figures 4-6, show the calibration graphs for exhausted electrodes (slopes 51.74, 48.37 and 53.46 mV/decade) and after regeneration (slopes 52.26, 50.49 and 54.77 mV/ decade) for (CTP-PMA), (CTP-PTA) and (CTP-PTA/PMA) coated wire electrodes, respectively.

Table 2. Selectivity coefficients (K^{pot}) of the CTP coated wire sensors calculated by the separate solution method ($1x10^{-3}$ M of both CTP and the interferent) at 25ºC

Interferent	-log $K^{pot}_{CTP\ J^{z+}}$		
	CTP-PMA	CTP -PTA	CTP – PMA/ PTA
Thymidine	$3.9x10^{-5}$	$8.7x10^{-4}$	$3.8x10^{-5}$
Glutamine	$2.8x10^{-5}$	$2.2x10^{-3}$	$1.9x10^{-5}$
Serine	$1.7x10^{-4}$	$1.2x10^{-3}$	$8.1x10^{-5}$
Cystine	$4.8x10^{-5}$	$2.1x10^{-3}$	$2.3x10^{-4}$
Uracil	$3.6x10^{-5}$	$2.3x10^{-3}$	$7.2x10^{-5}$
Ornithine	$1.0x10^{-4}$	$2.6x10^{-3}$	$1.5x10^{-4}$
Thymine	$2.7x10^{-4}$	$9.9x10^{-4}$	$1.2x10^{-4}$
Histadine	$1.3x10^{-4}$	$2.9x10^{-4}$	$3.1x10^{-5}$
Glycine	$1.0x10^{-4}$	$1.5x10^{-3}$	$3.6x10^{-6}$
Cu^{2+}	$9.7x10^{-5}$	$7.4x10^{-4}$	$1.5x10^{-5}$
Ca^{2+}	$1.5x10^{-4}$	$1.6x10^{-3}$	$2.8x10^{-5}$
Na^{+}	$5.7x10^{-5}$	$1.3x10^{-3}$	$1.3x10^{-5}$
NH_4^{+}	$2.7x10^{-6}$	$2.3x10^{-4}$	$2.9x10^{-4}$
Zn^{2+}	$6.7x10^{-5}$	$7.1x10^{-4}$	$1.4x10^{-4}$
Ni^{2+}	$1.6x10^{-4}$	$1.7x10^{-3}$	$3.8x10^{-5}$
Cd^{2+}	$1.4x10^{-4}$	$2.6x10^{-4}$	$3.1x10^{-5}$
Mn^{2+}	$4.6x10^{-5}$	$1.1x10^{-3}$	$3.1x10^{-4}$
K^{+}	$1.3x10^{-4}$	$1.5x10^{-3}$	$4.8x10^{-5}$
Mg^{2+}	$1.5x10^{-4}$	$5.3x10^{-4}$	$2.3x10^{-5}$
Sn^{2+}	$1.1x10^{-4}$	$1.9x10^{-3}$	$1.4x10^{-5}$
Cephalexin	$4.2x10^{-4}$	$5.5x10^{-4}$	$1.1x10^{-5}$
Cefadroxil	$4.4x10^{-5}$	$5.7x10^{-4}$	$1.2x10^{-4}$
Cephradine	$1.3x10^{-4}$	$1.6x10^{-3}$	$5.5x10^{-5}$
Cefuroxime	$2.2x10^{-4}$	$2.2x10^{-3}$	$2.3x10^{-4}$
Cefotaxime	$2.4x10^{-3}$	$9.5x10^{-4}$	$2.5x10^{-4}$

The selectivity of the sensors of CTP in the presence of other cations was determined using the matched potential method [18–20]. The influence of a variety of some inorganic cations, amino acids and some pharmacologically related compounds on the CTP electrodes was investigated. The electrodes exhibit good tolerance towards some inorganic cations, amino acids and some pharmacologically related compounds such as cephalexin, cefadroxil, cephradine, cefuroxime and

cefotaxime. Table 2 summarizes the selectivity coefficient factors of the coated wire sensors for some common cations, amino acids and some pharmacologically related compounds. The sensors were proved to be useful in the potentiometric determination of CTP drug in pure solutions by both the standard addition and the calibration methods.

Table 3. Analysis of CTP in pure form by proposed and reported methods

method		CTP-PMA		CTP -PTA		CTP – PMA/ PTA		Reported method[7]
	Taken (mol/L)	Found [-log conc.] (mol/L)	Recovery %	Found [-log conc.] (mol/L)	Recovery %	Found [-log conc.] (mol/L)	Recovery %	Recovery %
Calibration method	$1.0x10^{-7}$	7.00	100.00	6.99	99.86	7.02	100.29	99.85
	$1.0x10^{-6}$	5.98	99.67	5.95	99.17	5.98	99.67	99.93
	$1.0x10^{-5}$	4.97	99.40	4.98	99.60	4.96	99.20	99.50
	$1.0x10^{-4}$	3.98	99.50	3.97	99.25	3.97	99.25	99.63
	$1.0x10^{-3}$	2.96	98.67	2.96	98.67	2.98	99.33	99.06
	$1.0x10^{-2}$	1.98	99.00	1.99	99.50	1.98	99.00	99.28
	Mean±S.D	99.37±0.48		99.34±0.41		99.46±0.46		99.54±0.33
	%SE**	0.19		0.17		0.19		0.14
	%RSD	0.48		0.41		0.47		0.33
	t-test	0. 720(2.23)*		0.908(2.23)*		0.339(2.23)*		
	F-test	2.091(5.05)*		1.545(5.05)*		2.00 (5.05)*		
Standard addition method	$5.0x10^{-7}$	6.31	100.16	6.26	99.37	6.32	100.31	
	$1.0x10^{-6}$	5.97	99.50	5.97	99.50	6	100.00	
	$5.0x10^{-6}$	5.29	99.81	5.23	98.68	5.28	99.62	
	$1.0x10^{-5}$	4.97	99.40	4.98	99.60	4.96	99.20	
	$1.0x10^{-4}$	3.99	99.75	3.95	98.75	3.98	99.50	
	$1.0x10^{-3}$	2.96	98.67	2.99	99.67	2.98	99.33	
	Mean±S.D	99.55±0.51		99.26±0.44		99.66±0.42		
	%SE**	0.21		0.18		0.17		
	%RSD	0.51		0.44		0.42		
	t-test	0.034(2.23)*		1.228(2.23)*		0.545(2.23)*		
	F-test	2.364 (5.05)*		1.727(5.05)*		1.636 (5.05)*		

*The Figures in parentheses are the tabulated t- and F- tests at p = 0.05[21]
**%Error= %RSD/√n

The direct potentiometric determination of CTP in pure form using the proposed electrodes gave mean %recoveries of 99.37±0.48, 99.34±0.41 and 99.46±0.46 for (CTP-PMA), (CTP-PTA) and (CTP-PMA/PTA) coated wire electrodes, respectively. The application of standard addition method to determine CTP in pure form using the proposed electrodes gave mean %recoveries of 99.55±0.51, 99.26±0.44 and 99.66±0.41 for (CTP-PMA), (CTP-PTA) and (CTP-PMA/PTA) coated wire

electrodes, respectively. The proposed sensors were evaluated by measuring the drug concentration in some pharmaceutical formulations.

Table 4. Analysis of CTP in dosage form MEIACT ® Tablets (200mg) by proposed and reported methods

method		CFP-PMA		CFP -PTA		CFP – PMA/ PTA		Reported method[7]
	Taken (mol/L)	Found [-log conc.] (mol/L)	Recovery %	Found [-log conc.] (mol/L)	Recovery %	Found [-log conc.] (mol/L)	Recovery %	Recovery %
Calibration method	$1.0x10^{-7}$	6.95	99.29	6.91	98.71	6.99	99.86	100.14
	$1.0x10^{-6}$	5.96	99.33	5.96	98.33	5.99	99.83	99.67
	$1.0x10^{-5}$	4.99	99.80	4.99	99.80	5.01	100.20	99.35
	$1.0x10^{-4}$	3.99	99.75	3.97	99.25	3.99	99.75	99. 90
	$1.0x10^{-3}$	3.00	100.00	2.97	99.00	2.96	98.67	99.57
	$1.0x10^{-2}$	1.97	98.50	2.00	100.00	1.99	99.50	99.50
	Mean±S.D	99.45±0.54		99.35±0.48		99.64±0.52		99.69±0.29
	%SE**	0.22		0.19		0.21		6
	%RSD	0.54		0.49		0.52		0.08
	t-test	0.958 (2.23)*		1.513 (2.23)*		0.207 (2.23)*		0.12
	F-test	3.494(5.05)*		2.875(5.05)*		3.375(5.05)*		0.29
Standard addition method	$5.0x10^{-7}$	6.31	100.16	6.26	99.37	6.31	100.16	
	$1.0x10^{-6}$	5.96	99.33	5.97	99.50	6.00	100.00	
	$5.0x10^{-6}$	5.24	98.87	5.25	99.06	5.26	99.25	
	$1.0x10^{-5}$	4.98	99.60	4.96	99.20	4.98	99.60	
	$1.0x10^{-4}$	3.99	99.75	3.99	99.75	3.99	99.75	
	$1.0x10^{-3}$	2.99	99.67	2.98	99.33	2.96	98.67	
	Mean±S.D	99.56±0.43		99.37±0.24		99.57±0.54		
	%SE**	0.18		0.09		0.22		
	%RSD	0.44		0.24		0.55		
	t-test	0.601 (2.228)*		2.065 (2.228)*		0.479 (2.228)*		
	F-test	2.375(5.05)*		1.333(5.05)*		3.494(5.05)*		

*The Figures in parentheses are the tabulated t- and F- tests at p = 0.05[21]
**%Error= %RSD/√n

The recovery results are shown in Tables 3 and 4. Three replicate determinations at different concentration levels were carried out using the three electrodes to test the precision of the method. The standard deviations were found to be ≤ 1.5, indicating reasonable repeatability and reproducibility of the selected method. The precision of the method was calculated in terms of (intra-day and inter-day). The %RSD values of intra-day and inter-day studies for the repeated determinations were less than 2% indicating good precision (Table 5). The robustness of the proposed method was carried out by using

borate buffer pH 7±1 (Table 1). The reproducibility upon using another model of pH-meter (Jenway 3510) was indicated by the results obtained (Table 1).

Table 5. Validation of the proposed method for the determination of CTP in pure form

Conc.(mol/L)	CTP-PMA			CTP-PTA			CFP-PMA/ PTA		
	Recovery %	%RSD *	Error** %	Recovery %	%RSD	Error%	Recovery %	%RSD	Error %
Intraday precision									
$1.0x10^{-6}$	99.56 ± 0.34	0.35	0.19	99.83 ± 0.34	0.34	0.19	99.89 ±0.35	0.35	0.20
$1.0x10^{-5}$		0.42	0.24		0.40	0.23	99.67 ±0.23	0.23	0.13
$1.0x10^{-4}$	99.13 ± 0.42	0.38	0.22	99.20 ± 0.40	0.44	0.25	99.25 ±0.43	0.44	0.25
Interday precision	99.42 ± 0.38			99.50 ±0.43					
$1.0x10^{-6}$		0.26	0.10		0.26	0.15	99.56±0.34	0.35	0.19
$1.0x10^{-5}$		0.31	0.18		0.62	0.35	99.73±0.31	0.31	0.18
$1.0x10^{-4}$		0.38	0.22		0.25	0.14	99.33±0.29	0.29	0.17
	99.28±0.25			99.45 ±0.25					
	99.53 ±0.31			99.27 ±0.61					
	99.58 ±0.38			99.50 ±0.25					

*%RSD=(S.D/Mean)100
**%Error= %RSD/√n

Table 6. Determination of CTP in spiked human serum and urine by the CTP electrodes.

Sample	CTP-PMA		CTP-PTA		CFP-PMA/ PTA	
	Calibration Method*	Standard addition method*	Calibration Method*	Standard addition method*	Calibration Method*	Standard addition method*
Urine	99.52±0.61	99.41±0.28	99.25±0.52	99.33±0.54	99.75±0.79	99.41±0.63
Serum	99.39±0.86	99.55±0.53	99.27±0.33	99.47±0.54	99.36±0.52	99.53±0.47

* Mean±S.D of six determinations

To compare the proposed method statisticaly to one of the reported methods [7], CTP in pure form and MEIACT ® tablets was assayed by spectrophotometry using 1,10- phenanthroline. Statistical comparison [21] of the results of the proposed and reported methods (Tables 3 and 4) was performed with regard to accuracy and precision using the t- and F-ratio tests. At 95% confidence level, the calculated t- and F-values did not exceed the critical values, indicating that there is no significant difference between the proposed and the spectrophotometric comparison method [7] with regard to accuracy and precision. Comparing the proposed method with other reported methods [8, 10, 11 & 14] for estimating CTP, it was found that the proposed method has a wider linear range with high sensitivity and lower detection limit. On the other hand, the proposed method has the best values for correlation coefficients than [8, 10 & 14] and lower values of %RSD than [8], in addition to the ease of the proposed method without the need of separation or create a complex or use of a buffer solution [8, 10 & 11]. The proposed method described good accuracy and precision for the quality control tests, the content uniformity assay showed that the RSD < 2%, with mean % recoveries ± standard deviation of 99.41±0.46, 99.32±0.49 and 99.68±0.34 for (CTP-PMA), (CTP-PTA) and (CTP-PMA/PTA) coated wire electrodes, respectively.

Cefditoren pivoxil is an orally absorbed prodrug that is rapidly hydrolysed by intestinal esterases to the microbiologically active cephalosporin cefditoren .In healthy volunteers, single doses of cefditoren pivoxil 200 and 400mg achieved maximal plasma concentrations of 2.6 to 3.1 mg/L and 3.8 to 4.6 mg/L, respectively [22]. Within 24 hours after administration of 100, 200 and 300 mg, 19.93 ± 5.20, 20.24 ± 3.72 and 21.29 ± 5.47%, respectively, of the dose were excreted into urine in an unchanged form [23].

In order to investigate the applicability of the new sensors to determination of the drug in biological fluids, the proposed sensors were applied to recover CTP from urine and serum samples. The drug was determined by the proposed electrodes, using the calibration and standard addition methods, the results are given in Table 6.

4. CONCLUSION

New three constructed sensors were developed for cefditoren pivoxil determination over a wide range of concentration. The electrodes showed a very good selectivity to CTP in the presence of various common inorganic cations, amino acids and different pharmacological related compounds. Thus, these electrodes can be used as alternative analytical tools to spectrophotometric and chromatographic methods, for the determination of this drug in bulk powder, pharmaceutical preparations and biological fluids.

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