RESEARCH ARTICLE

Novel Carbon Paste Electrode for Determination of Cefixime in the Pharmaceutical Formulations and Human Fluids

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ABSTRACT

The novel and very sensitive potentiometric sensor were made with excellent electrochemical properties using carbon paste electrodes to determine Cefixime (CFX). The electrodes were produced using the ion-pair compound of Cefixime-crystal violet (CFX-CV) as the electroactive component and plasticizers Tris (2-Ethylhexyl) phosphate (TEHP), Di-butyl phthalate (DBPH) and Di-butyl phosphate (DBP). The slope of Cefixime (CFX) electrodes gave a Nernstain response equal to 55.33, 41.61 and 42.88, mV/decade for electrodes A, B and C, respectively with a linear range of (1×10^{-5}–1×10^{-2}), (5×10^{-5}–1×10^{-2}) and (1×10^{-5}–1×10^{-2}) M, respectively, a detection limit of 9.8×10^{-6}, 4.6×10^{-5} and 8.9×10^{-6} M, a lifetime of 62, 12 and 9 days, respectively. Electrode A offers the best results; therefore, it was specifically chosen for the application of pharmaceutical and human fluids. The recovery percentage was 103, 98, 93, and 95 for Cefixime capsules (400 mg), Cefixime oral suspension (100 mg/5 mL), urine and plasma by standard addition method, respectively.

Keywords: Carbon paste, Cefixime, Crystal violet, Human fluids, Potentiometric.

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INTRODUCTION

Cefixime (CFX) is chemically known as (6R,7R)-7-[[(Z)-2-(2-Aminothiazol-4-yl)-2-[(carboxymethoxy) imino] acetyl] amino]-3- ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid trihydrate (). CFX is a crystalline powder with a white to pale yellow colour. It has a molecular formula of $C_{16}H_{15}N_5O_7S_2$, 3H2O and a molecular weight of 507.5 (British Pharmacopeia).[1] Cefixime is effective against susceptible bacteria causing infection of the middle ear, tonsillitis, throat infections, bronchitis, gonorrhoea, laryngitis, urinary tract infections (UTIs).[2-4] The methods were reported to determine Cefixime including UV–spectrophotometry,[5] liquid chromatographic,[6] spectrophotometric method,[7] and high-performance liquid chromatography (HPLC).[8,9] The ion-selective cell, like any other potentiometric sensor, can be treated as a galvanic half-cell and represented by the schemes as: metal | internal contact | membrane | solution (S_1). Correspondingly, the galvanic cell (with ISE) can be represented by the following scheme: metal | ISE | solution | liquid-junction (salt bridge) | reference electrode | metal (S_2).[10]

A new sensor of carbon paste electrodes (CPEs) (Figure 2) has been widely applied as potentiometric sensors due to their unparalleled characteristics such as very low cost, ease of fabrication, renewability, minimum background current, stable response, low-level determination of the analyte and, lack of internal solution, capability to access a fresh surface electrode after each time usage.[11-13]

The work aims to provide a new carbon paste electrode based on the dissolution of an ionophore in plasticizer, which is low permeable, with the addition of graphite powder and works in electrochemical measurements as the main carbon paste component ensuring the efficient function of an electrode or a sensor.[14] The prepared electrodes were used for the determination of CFX in the pharmaceutical dosage form and human fluids.

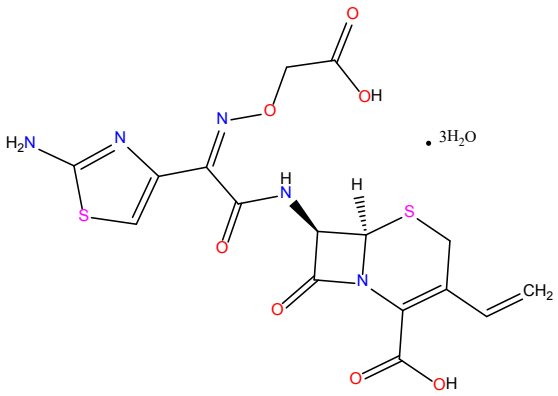

Figure 1: Chemical structure of CFX

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MATERIALS AND REAGENTS

The used chemicals were analytical or pharmacopoeia grade. Millipore water was used to prepare solvents. Cefixime trihydrate CFX was obtained from Sigma-Aldrich, the pharmaceutical formulations cefixime (CFX capsules and CFX oral suspension) were supplied by Tabuk, Saudi Arabia. TEHP ($C_{24}H_{51}O_4P$), purity (97%), DBPH ($C_{16}H_{22}O_4$), purity (99%), $C_8H_{19}PO_4$, purity (99%), were obtained from Fluka. Stock solution of 0.01 M (LiCl, KCl, NaCl, $MgCl_2$, $CaCl_2$, $ZnCl_2$, $AlCl_3$, $FeCl_3$, and $CrCl_3$) was prepared. Remaining diluted solutions were prepared with subsequent dilution of the stock solutions.

Preparation of Ion-pair Complex

The preparation of the cefixime carbon paste electrode depends on the use of cefixime-crystal violet (CFX-CV) as an electroactive substance. The preparation of CFX-CV ion-pair was done by mixing 100 mL of 0.01 M solution of CFX with 100 mL of 0.01 M CV under stirring. The formed precipitate was filtered, washed with Millipore water, and then dried for one day. The ion-pair composition was obtained by using fourier transform infrared spectroscopy (FTIR) (Figures 4 and 5).

Carbon Paste Electrode Preparation

Carbon paste electrode was prepared by thoroughly mixing 0.04 g of ion pair matrix (CFX-CV), (0.51) g of high purity graphite powder and 0.45 g of plasticizer till it forms a uniformly wetted paste. The mixture was packed at the end of a polypropylene syringe (3 mm i.d., 1-mL) (Figure 3). A copper wire is used to make an electrical contact to the carbon paste. The carbon paste was smoothed on the paper till it appears shiny. Further it was used directly for potentiometric measurements with no preconditions.[14]

Calibration Curve

The prepared electrode was calibrated by transferring an appropriate amount of the aqueous CFX solution 1×10^{-6} - 1×10^{-2} M, and by inundating the CFX membrane electrode composed of the reference electrode in a similar solution. The readings were recorded after the stabilizing the potentials. The calibration curve was built between potentials and the CFX concentrations logarithm.

Selectivity

Two methods were employed for the determination of the selectivity coefficient of the potentiometric electrodes against various species. These 2 methods can eb termed as separate solution method (SSM) and match potential method (MPM).[17]

In the SSM method, the following equation was used:

$$K^{pot}A,B = aA = \frac{1-zA}{zB}e\frac{(EB-EA)zAF}{(RT)}$$

Where EA is the drug potential and EB for the interfering ions.

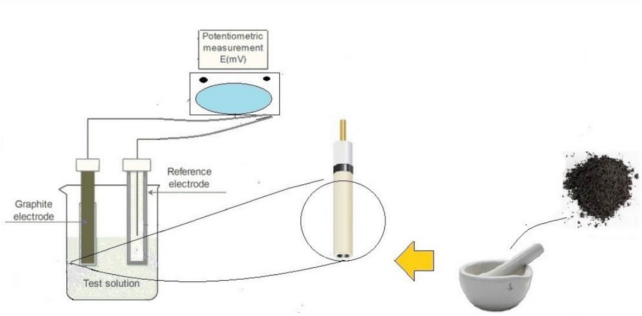

Figure 2: A diagram of the ISE cell for carbon paste electrode[15]

Figure 3: A carbon paste electrode

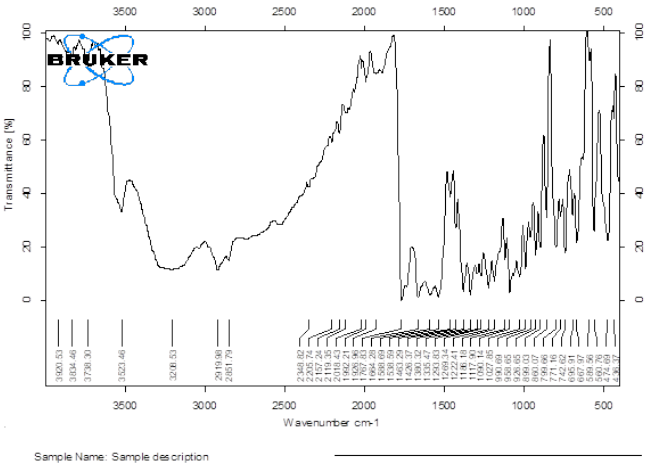

Figure 4: FTIR spectrum of CFX

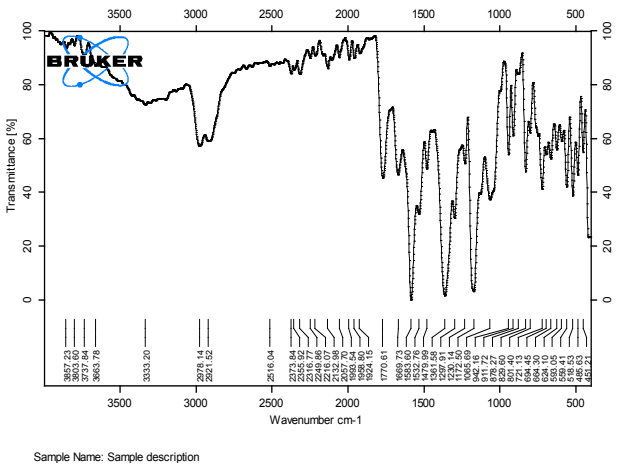

Figure 5: FTIR spectrum of CFX-CV ion pair

The equation used for MPM method is:

$$K^{pot}A,B = \frac{(aA'-aA)}{aB}$$

Preparation of Standard Solution

Stock solutions of 0.01 M of LiCl, KCl, NaCl, $ZnCl_2$, $CaCl_2$, $Mg(NO_3)_2.6H_2O$, $FeCl_3.6H_2O$, $AlCl_3$ and $CrCl_3.6H_2O$ were prepared in distilled water. More diluted solutions were developed by subsequently dilution of the stock solutions. A standard solution of 0.01 M CFX was prepared by dissolving 0.1269 g standard and completing the solution up to 25 mL. The other CFX standard solutions were prepared by subsequent dilution of the stock solution**.**

Sample Analysis

The sample of various concentrations 1.0×10^{-6} to 1.0×10^{-2} M was applied, and the potential was recorded to create the calibration curve in the direct method. The standard addition method in which 0.1-mL of 1×10^{-2} M CFX were added to 10 mL of a sample of various concentrations 1×10^{-4} M, after each increment was recorded. The potential was applied and used to determine the concentration of CFX in a drug sample.

Determination of CFX in Human Fluids

A total of 2.5 mL of serum and urine from a healthy person were taken, and 0.5 mL of (1×10^{-2}) M CFX standard solution was added to a 25 mL volumetric flask, which was then filled to the mark with distilled water and subjected to potentiometric analysis.

RESULTS AND DISCUSSION

Effect of Plasticizers

The role of plasticizers on the response of the CFX electrode was studied using three plasticizers: DBPH, TEHP, and DBP (Figures 6–8).

In order to provide optimal selectivity and sensitivity to the prepared electrode, plasticizers were added to dissolve the ion-pair complex and set the membrane permittivity and ion-exchanger mobility.

Effect of pH

Effect of pH on the electrode's potential was evaluated by measuring the potential of the cell at the concentrated of (1×10^{-4} and 1×10^{-3}) M of CFX solution. The pH adjustment was done by adding some drops of 0.1 M hydrochloric acid or sodium hydroxide drops (Figures 9 to 11 and Table 1).

From Figures 9 to 11, it can notice that CFX electrodes do not respond to pH changes in the range 4 to 9.

Response Time and Lifetime

The electrode response time is the required time for the electrode to reach a stable potential after immersing the CPE electrode and the reference electrode in 1×10^{-6} and 1×10^{-2} M of CFX solution (Figures 12–14). The electrode's lifetime was measured by employing it for 5 weeks' period. And then, the slope decreases, and the detection limit rises, and the calibration curve is plotted with a series of standard solutions ranging from (1×10^{-6} to 1×10^{-2}) M of CFX solution.

It was noticed from the obtained results, the (CFX-CV/TEHP) electrode response is gradually decreasing in slope from 55.33 mV/decade to (49.65) mV/decade. These results are clearing for (CFX-CV/TEHP) electrode that it is fitting for using after eight weeks from manufacturing with accepted efficiency. After this time the (CFX-CV/TEHP) electrode becomes less sensitive toward CFX, which may be due to gradual leach the ion-pair from the paste to the external solution.

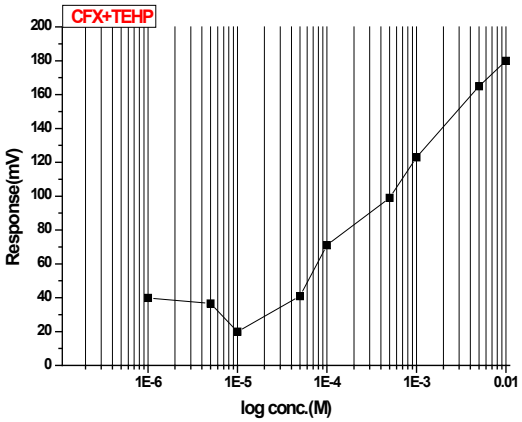

Figure 6: Calibration curve of (CFX-CV) first electrode with TEHP as plasticizer

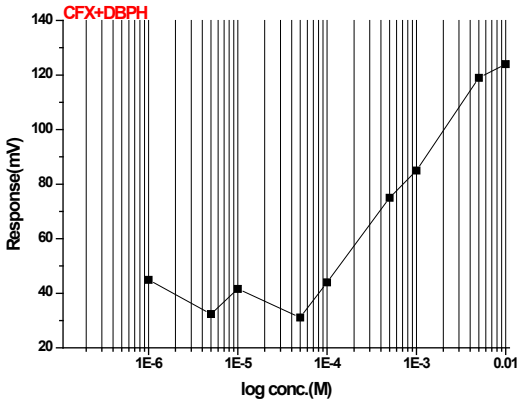

Figure 7: Calibration curve of (CFX-CV) second electrode with DBPH as plasticizer

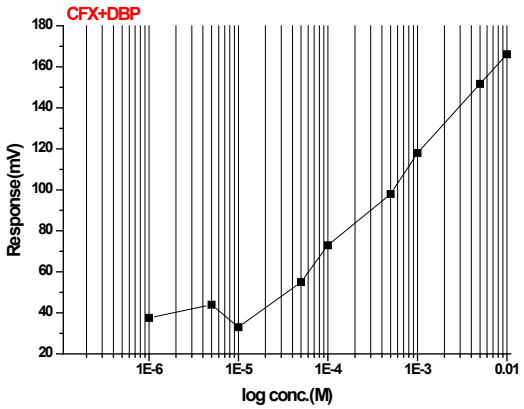

Figure 8: Calibration curve of (CFX-CV) third electrode with DBP as plasticizer

Selectivity

The interferences were studied of some inorganic cations (like Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, Al^{3+}, Cr^{3+} and Fe^{3+}) with employing separate solution method and match potential method. Figures 18–20 and Table 2 show the values of the selectivity coefficients.

Figures 18, and 20 shows no interferences of the cations on CFX electrode by match method, the selectivity coefficients cannot be determine because there is no different in potential between the drug solution and interfering cation even at 5 or 10 mV.

From the above tables, the selectivity coefficient values for monovalent cations are greater than those for divalent and trivalent cations by separation solution method, which could be related to differences in ionic size, permeability and mobility; the order of selectivity is:

mono valent > di valent > tri valent

Analytical Application

By direct technique and standard addition method, the suggested electrode was effectively used to determine CFX in the standard drug, pharmaceutical preparations (capsules and oral suspension), and human fluids (plasma and urine); the obtained results are presented in Tables 3 and 4.

In the standard addition method, the CFX concentration was determined by adding 0.1 mL of 1 × 10^{-2} M CFX were

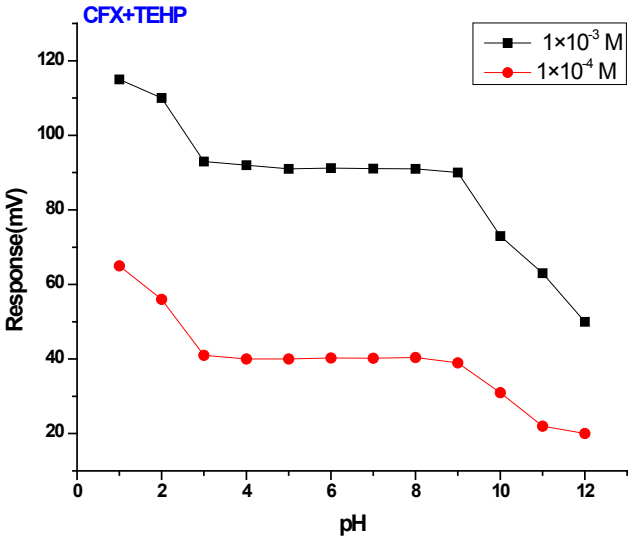

Figure 9: Effect of pH for (CFX -CV) electrode using TEHP as plasticizer

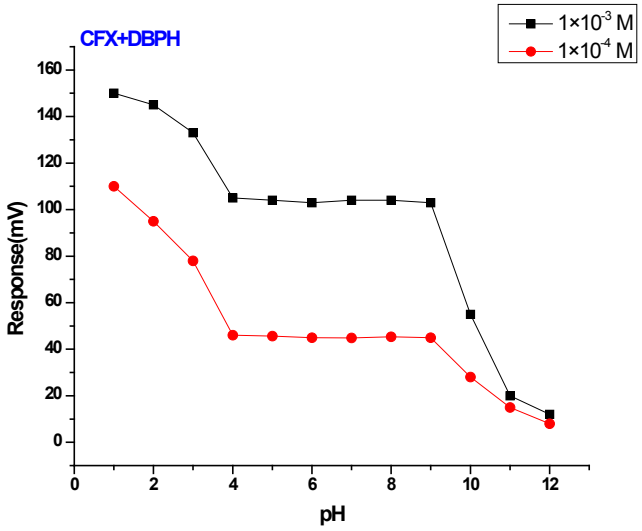

Figure 10: Effect of pH for (CFX-CV) electrode using DBPH as plasticizer

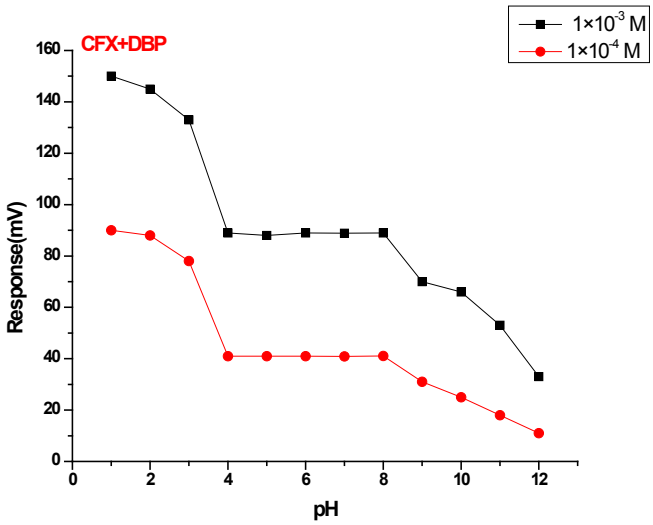

Figure 11: Effect of pH for (CFX-CV) electrode using DBP as plasticizer

Table 1: Effect of plasticizers on the parameters of CFX electrode

	CTX		
Parameters	*DBPH*	*TEHP*	*DBP*
Slope (mV/decade)	41.61	55.33	42.88
Linear Range (M)	5×10^{-5}–1×10^{-2}	1×10^{-5}–1×10^{-2}	1×10^{-5}–1×10^{-2}
pH	4–9	3–9	4–8
Life time (days)	12	62	9
Response time(min.)	2.3 at 10^{-2} M 5.8 at 10^{-6} M	2.2 at 10^{-2} M 4.1 at 10^{-6} M	1.7 at 10^{-2} M 3.8 at10^{-6} M
Detection limit (M)	4.6×10^{-5}	9.8×10^{-6}	8.9×10^{-6}
Correlation coefficient (R)	0.9977	0.9973	0.9967

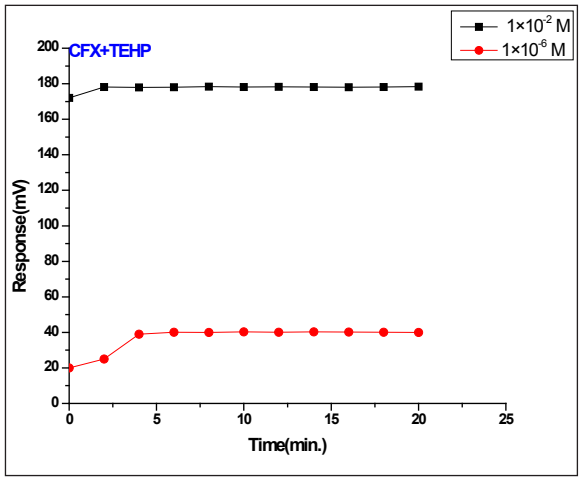

Figure 12: Response time of (CFX -CV) electrode using TEHP as plasticizer

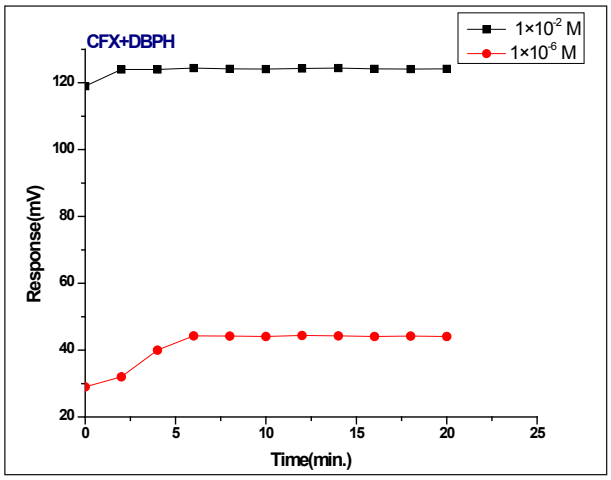

Figure 13: Response time of (CFX -CV) electrode using DBPH as plasticizer

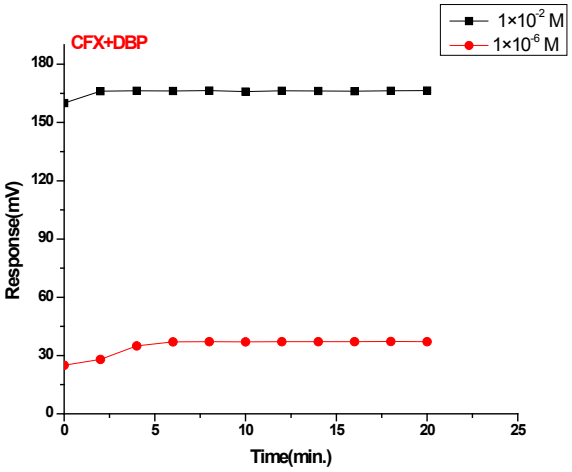

Figure 14: Response time of (CFX -CV) electrode using DBP as plasticizer

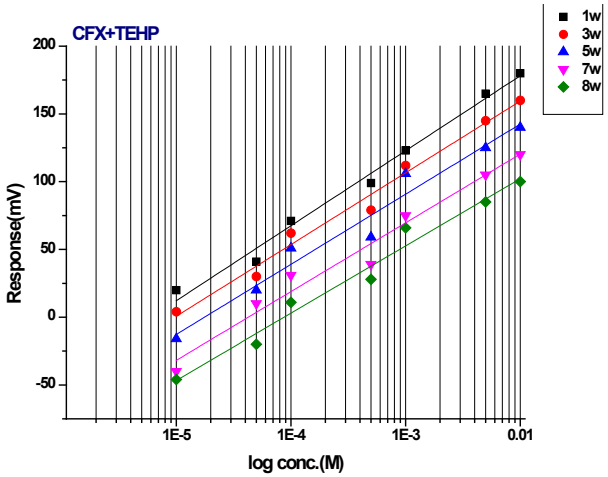

Figure 15: Life time of (CFX -CV) electrode using TEHP as plasticizer

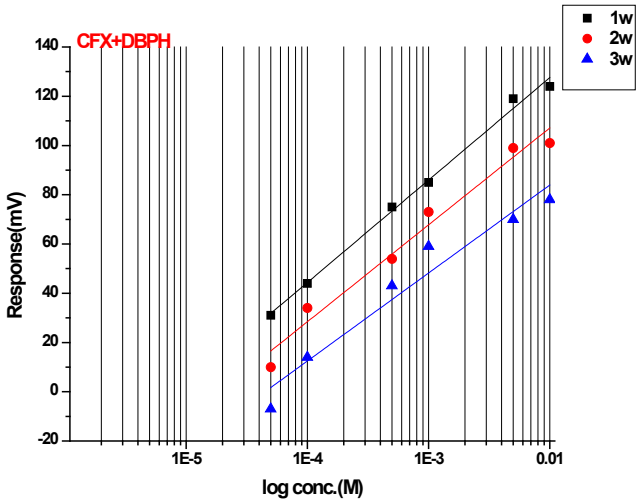

Figure 16: Life time of (CFX -CV) electrode using DBPH as plasticizer

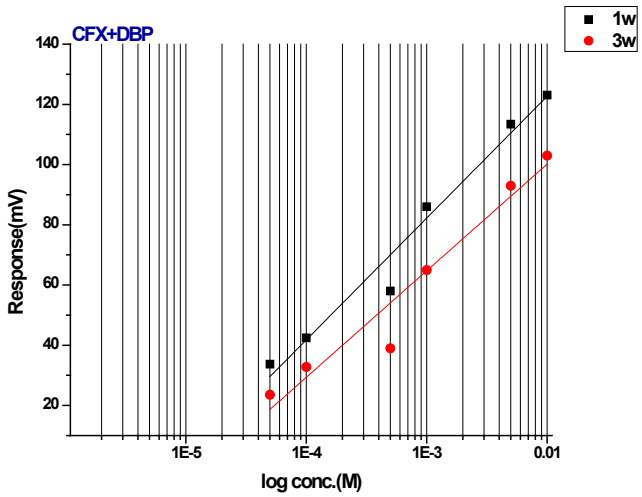

Figure 17: Life time of (CFX -CV) electrode using DBP as plasticizer

added to 10 mL of 1 × 10^{-4} M. The change in potentials readings was recorded after each addition by the following equation:[18]

$$Cx = \frac{C_s V_s}{(V_x + V_s)} \times 10^{\Delta Es} - Vx$$

C_x is the concentration and Vx is volume of the unknown sample. Cs and Vs were the respective concentration and volume of standard solution. S was the slope value of the calibration curve, and ΔE was the change in the potential of the electrode. In comparison to the standard addition method, the obtained results from the multi standard addition method have precision and accuracy, as shown in the table above. This could be because of eliminating the dilution factor during solution preparation in the normal work technique compared to the multi standard addition method. As a result, there are fewer errors.

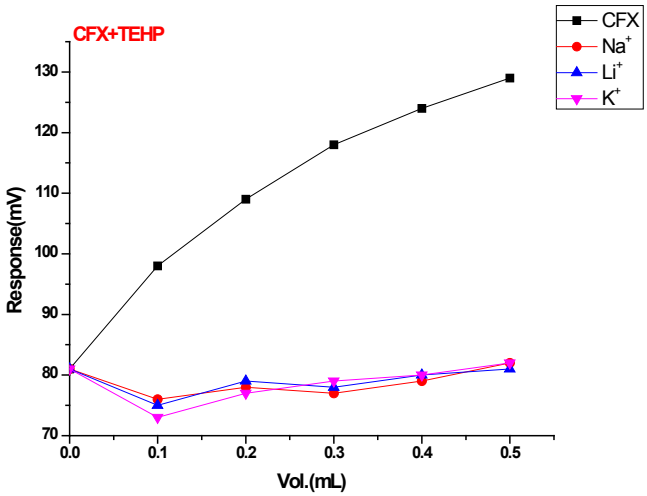

Figure 18: Selectivity for CFX-CV+TEHP for mono-cations by match potential method

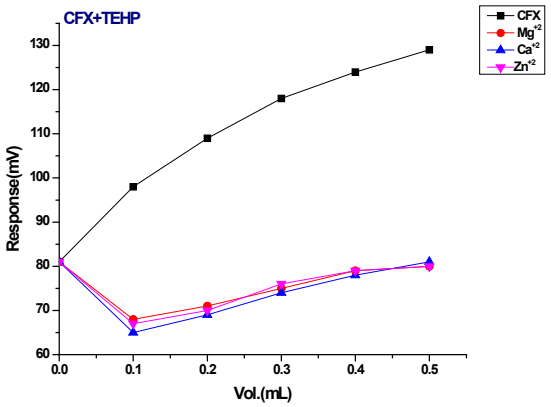

Figure 19: Selectivity for CFX-CV+TEHP for di-cations by match potential method

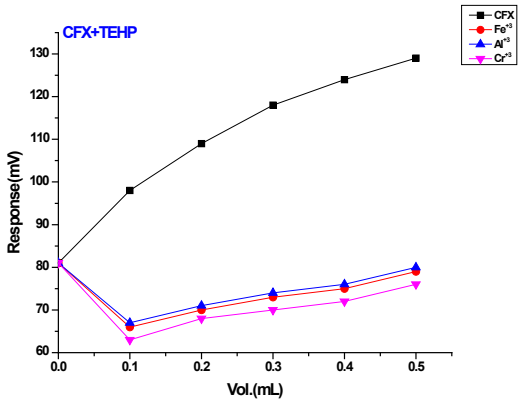

Figure 20: Selectivity for CFX-CV+TEHP for tri-cations by match potential method

Table 2: Values of selectivity coefficient for different interfering ions using CFX-CV+TEHP electrode

	$K_{A,B}$								
Conc.(M)	Na^+	K^+	Li^+	Ca^{+2}	Mg^{+2}	Zn^{+2}	Al^{+3}	Cr^{+3}	Fe^{+3}
1×10^{-2}	0.05	0.05	0.06	2.0×10^{-3}	1.6×10^{-3}	3.4×10^{-3}	1.2×10^{-3}	6.2×10^{-4}	1.3×10^{-4}
5×10^{-3}	0.07	0.07	0.08	1.8×10^{-3}	2.1×10^{-3}	1.3×10^{-3}	1.1×10^{-3}	3.6×10^{-4}	3.1×10^{-4}
1×10^{-3}	0.07	0.04	0.05	1.7×10^{-3}	2.0×10^{-3}	2.0×10^{-3}	1.4×10^{-3}	1.7×10^{-4}	3.4×10^{-4}
5×10^{-4}	0.08	0.06	0.09	1.9×10^{-3}	3.3×10^{-3}	1.0×10^{-3}	0.2×10^{-3}	6.3×10^{-4}	2.9×10^{-4}
1×10^{-4}	0.12	0.10	0.25	2.7×10^{-3}	3.4×10^{-3}	1.1×10^{-3}	0.9×10^{-3}	2.9×10^{-3}	1.4×10^{-4}
5×10^{-5}	0.05	0.06	0.05	2.8×10^{-3}	2.6×10^{-3}	0.9×10^{-3}	5.5×10^{-4}	1.9×10^{-4}	9.0×10^{-4}
1×10^{-5}	0.31	0.23	0.18	3.3×10^{-3}	3.7×10^{-3}	6.4×10^{-4}	6.9×10^{-4}	2.8×10^{-4}	3.7×10^{-4}
5×10^{-6}	0.45	0.32	0.30	2.3×10^{-3}	1.2×10^{-3}	8.0×10^{-4}	9.4×10^{-4}	9.0×10^{-4}	8.4×10^{-4}
1×10^{-6}	0.38	0.42	0.57	4.9×10^{-3}	6.5×10^{-3}	4.4×10^{-3}	5.4×10^{-4}	8.9×10^{-4}	7.7×10^{-4}

Table 3: Estimation of the standard, pharmaceutical application and human fluids by standard potentiometric method

Drug	*Original conc. (M)*	*Found conc. (M)*	*RSD% n= 3*	*RC%*	*RE%*
Standard of Cefixime	1×10^{-4}	0.99×10^{-4}	0.561	99.0	-1.0
Cefixime oral suspension (100 mg/5 mL)	1×10^{-4}	0.98×10^{-4}	0.412	98.0	-2.0
Capsules (400 mg)	1×10^{-4}	1.03×10^{-4}	0.221	103.0	3.0
Urine	1×10^{-4}	0.93×10^{-4}	0.783	93.0	-7.0
Serum	1×10^{-4}	0.95×10^{-4}	0.896	95.0	-5.0

Table 4: Volume at intercept with X axis and calculation the concentration C_U(M) for the CFX-CV+TEHP and CTX-CV+DBPH electrodes by (MSA) method.

Drug	*Original conc. (M)*	*V(mL) at intercept*	*C_U (M)*	*RC%*	*RE%*
Standard of Cefixime	1.0×10^{-4}	0.0980	0.98×10^{-4}	98.0	-2.0
Cefixime oral suspension (100 mg/5 mL)	1.0×10^{-4}	0.0990	0.99×10^{-4}	99.0	-1.0
Capsules (400 mg)	1.0×10^{-4}	0.0990	0.99×10^{-4}	99.0	-1.0
Urine	1.0×10^{-4}	0.0960	0.96×10^{-4}	96.0	-4.0
Serum	1.0×10^{-4}	0.0980	0.98×10^{-4}	98.0	-2.0

CONCLUSION

The developed electrode (CPE) provides new analytical methods for the determination of the CFX drug in pharmaceutical preparations and human fluids (serum and urine). It was used to determine CFX in its pure form, pharmaceutical formulations, and human fluids. It was a sensitive, precise, fast, and affordable approach. The electrode has demonstrated superior performance with weeks of time stability.

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