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A New Cyproheptadine PVC Ion Selective Electrode and their Applications in Pharmaceutical Preparations and Human Fluids

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Abstract

A simple, sensitive and rapid method for the determination of Cyproheptadine in the pharmaceutical preparations and human fluids. The construction and electrochemical response characteristics of a poly vinyl chloride (PVC) membrane selective electrode for the determination of CPH are described. The proposed sensor was composed of cyproheptadine-Bromophenol blue as ion-exchanger and Di-butylphthalate (DBPH) (electrode A), Tris (2-ethylhexyl) phosphate (TEHP) (electrode B) and Ortho-nitrophenyloctylether (ONPOE) (electrode C) as plasticizers. The slopes were 53.10, 58.72 and57.44 mV/decade for electrode A, B and C. The linear ranges were 1×10^{-5} - 1×10^{-2}, 5×10^{-5} -1×10^{-2} and 5×10^{-5} -1×10^{-2} M and the detection limits were 9×10^{-6},4.5×10^{-5} and 4×10^{-5} M for Electrode A,B and C respectively. The electrode B based on TEHP showed the best results. Electrodes were successfully applied to the determination of the cyproheptadine in tablets and human fluids by direct and standard addition potentiometry.

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1. Introduction

Cyproheptadine (CPH) C21H21N is a piperidine antihistamine drug as shown in figure 1, that used to relieve allergy symptoms such as the runny nose, watery eyes, itching, sneezing and hives. This drug working by blocking certain natural substance which is histamine that the body produces while the body is under an allergic reaction. CPH was used to treat some of the hormonal disorders and can be used also for treating the side effect of taking antidepressants [1]. Some methods were used for the assay of CPH in pharmaceutical formulations. Gas liquid chromatography [2,3], liquid chromatography-mass spectrometry (LC-MS)[4], and high performance liquid chromatography (HPLC)[5,6] have been used to assay CPH. An ion selective based potentiometry was another technique that can be applied to the analysis of CPH containing tablets. The potentiometric membrane ion selective electrodes were used in the analysis of pharmaceutical and biological fluids during the last decades [7, 8]. This is because these electrodes give the advantage of simple design, easy operation, fast response, low cost, good accuracy, low detection limit and wide concentration range. The type of ion-selective electrode that is commonly utilized for drug analysis is the traditional liquid membrane electrode, which is based on the dissolution of ion exchanger in the plasticizer (hydrophobic solvent) which is low primitive, with PVC which is high molecular weight as supporting material. The electrode's membrane is positioned between two phases of aqueous solutions, the outer one is the sample solution and the other one is the inner reference solution that has a fixed analyte ion's concentration. Across the electrode's membrane, the potential difference is measured with two reference electrodes placed in the aqueous phase. The investigation deals with the production and characterization of liquid membrane ion-selective electrode for determination of cyproheptadine.

This research aimed to build up a new ion-selective electrode for the determination of Cyproheptadine, The sensitivity of this electrode is based on the combination of cyproheptadine-bromophenol blue as the sensing material. The electrode was successfully used for the determination of cyproheptadine in the pharmaceutical formulations and human fluids.

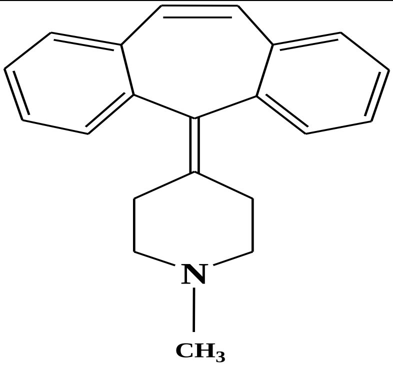

Figure 1. Chemical structure of cyproheptadine.

2. Materials and Methods

2.1 Apparatus

Expandable ion analyzer (Orion Research model EA940) was used in the potentiometry measurements in combination with a reference electrode (metrohm AG 9100 herisau). pH meter (pH professional benchtop model BP3001) was used to measure the pH of the solution and a magnetic stirrer was used to carry out the measurements as shown in figure 2.

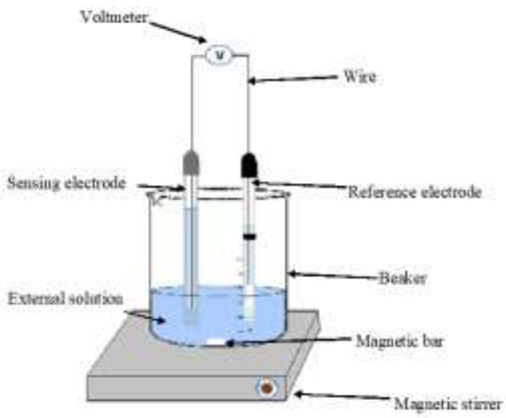

Figure 2. Diagram of ISE cell.

2.2 Materials and reagents

Cyproheptadine standard (C21H21N) was obtained from Middle East Drug Industries. The pharmaceutical formulations cyproheptadine (tablets) and prevet (syrup) were supplied Micro labs limited-India and Pharaonia-Egypt, respectively. Bromophenol blue was obtained from Fluka. Di-butylphthalate (C16H22O4) (99%) , Tris(2-ethylhexyl) phosphate (TEHP) (C24H51O4P) and Ortho –nitro phenyl octyl ether (ONPOE) (C14H21NO3) were supplied by Ferak. poly vinyl chloride (PVC) (CH2-CHCl)n with high molecular weight, tetrahydrofuran (C4H8O), hydrochloric acid and Fe2(SO4)3.5H2O were supplied by Fluka. potassium chloride, acetic acid, LiCl, CaCl2, MgCl2.6H2O, Al2(SO4)3.16H2O and CrCl3.6H2O were purchased from BDH. NaCl was obtained from Fisher scientific. ZnCl2 was obtained from Flucka AG. All chemical solutions used in this work were prepared from distilled water.

2.3 Preparation of the ion -pair

The ion-pair of CPH -BPB was synthesized by mixing 0.01 M of Cyproheptadine with 0.01 M of bromophenol blue. The obtained precipitated was filtered and washed with distilled water, then dried in room temperate. This ion-pair was used for synthesis of electrode membrane

2.4 Preparation of membrane

Three membranes were prepared by mixing an amount of ion-pair (CPH-BPB) with DBPH,THEP or ONPOE and PVC which dissolved in 8-10 mL of THF [9]. The membrane was cut equal to the external diameter at the edge end of the electrode. These membranes were used as sensors for the determination of cyproheptadine. It is worth to be mentioned the membrane was immersed in standard of cyproheptadine in 2 hours before using for measurements.

2.5 Selectivity

Two methods were used in order to determine the selectivity coefficient of the potentiometric electrodes toward various species which are the separate solution method (SSM) and match potential method (MPM) [10]. In the SSM method, the following equation was used:

$$K_{A,B}^{POT.} = a_A \left(1 - \frac{z_A}{z_B}\right) \exp\left(\frac{(E_B - E_A)\, z_A}{RT}\right) \quad \dots (1)$$

where E_A is the potential of the drug and E_B for the interfering ions.

While in the MPM method, the equation (2) was used:

$$K_{A,B}^{POT.} = \frac{(a_{A'} - a_A)}{a_B} \quad \dots (2)$$

2.6 Potentiometric analysis for determination of cyproheptadine

Direct method was consisted of the measured response for sample solution and read the concentration from the calibration graph that prepared from cyproheptadine standard solutions. In the standard addition method, 0.1 mL of cyproheptadine standard solution (0.01) was added to 50 mL of the same sample pure or pharmaceutical formulations. The change in electrode response was recorded and used to calculate the concentration of sample by equation (3):

$$C_U = \frac{C_S}{10^{\frac{\Delta E}{S}}\left[1+\frac{V_U}{V_S}\right]} - \frac{V_U}{V_S} \quad ...(3)$$

where CU, CS the concentration of unknown and standard solution, respectively, VU , VS are the volume of unknown and standard solution, respectively, S: the slope of electrode, ΔE: the potential difference [11].

2.7 Determination of CPH in human fluids:

A urine or blood sample was obtained from a healthy volunteer and spiked with 1×10-2 M CPH standard solution. The synthetic urine or blood sample was centrifuged at 2500 rpm for 10 min. Then, the top layer was separated then directly analyzed using the proposed sensors [12].

3. Result and Discussion

3.1 Effect of plasticizers:

Three plasticizers DBPH, TEHP and ONPOE were investigated (Table 1). Table 1 exhibits that TEHP is the best of the plasticizers examined due to high mixing between plasticizer and PVC that leads to the production of homogeneous membrane. Therefore TEHP plasticizer gave near-Nernstian response as shown in figure 3 while DBPH and ONPOE show the poor sensitivity on the electrode response. The reason for this must be to the high viscosity of the plasticizer which decreases the ion-exchange process as shown in figures 4 and 5.

Table 1. Effect of the plasticizers on the electrode response

Parameters	DBPH	TEHP	ONPOE
Slope (mV/decade)	53.10	58.72	57.44
Detection limit (M)	9×10^{-5}	7.5×10^{-5}	6×10^{-5}
Linear range (M)	1×10^{-5} to 1×10^{-2}	5×10^{-5} to 1×10^{-2}	5×10^{-5} - 1×10^{-2}
Response time (min.)	1.8 at 10^{-2} 3.9 at 10^{-6}	1.2 at 10^{-2} 5.6 at10^{-6}	0.8 at 10^{-2} 4.2 at10^{-6}
Life time (day)	35	42	2
pH	3-7	4-7	4-8
R^2	0.9956	0.9965	0.9975

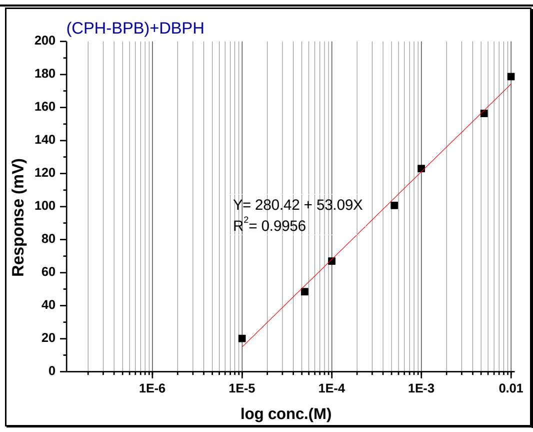

Figure 3. Calibration curve of CPH-DBPH

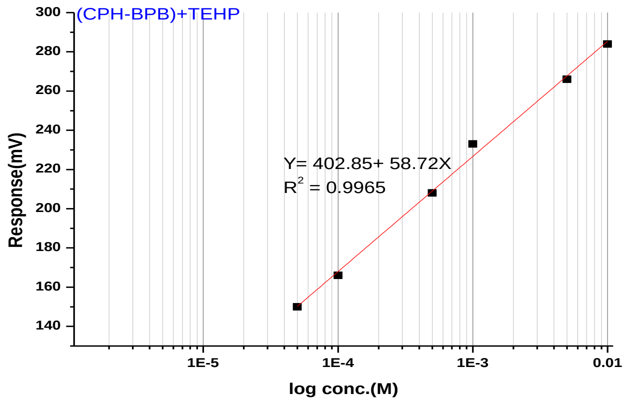

Figure 4. Calibration curve of CPH-TEHP.

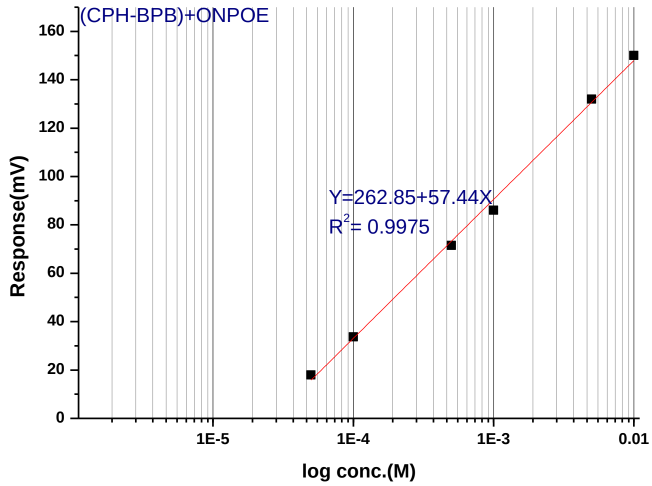

Figure 5. Calibration curve of (CPH+ONPOE).

3.2 Effect of pH:

The pH effect on the response of the sensor was studied by measuring the potentials of the electrode at 1×10-4 and 1×10-3 M of CPH solution, where the pH value was adjusted from (1) to (11) by adding HCl or NaOH as shown in figures 6, 7 and 8.

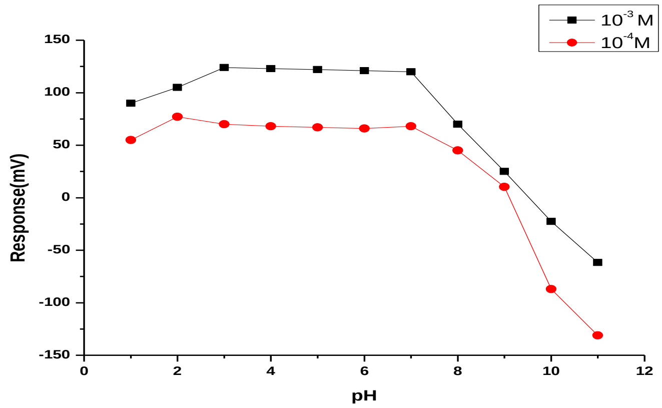

Figure 6. Effect of pH on the CPH-DBPH electrode response

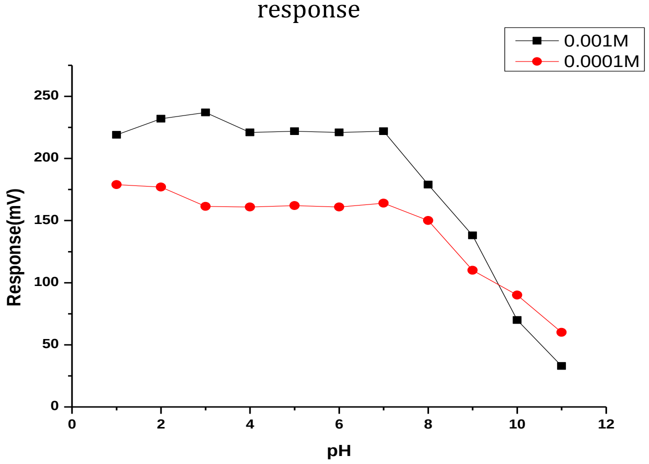

Figure 7. Effect of pH on the CPH-TEHP electrode response

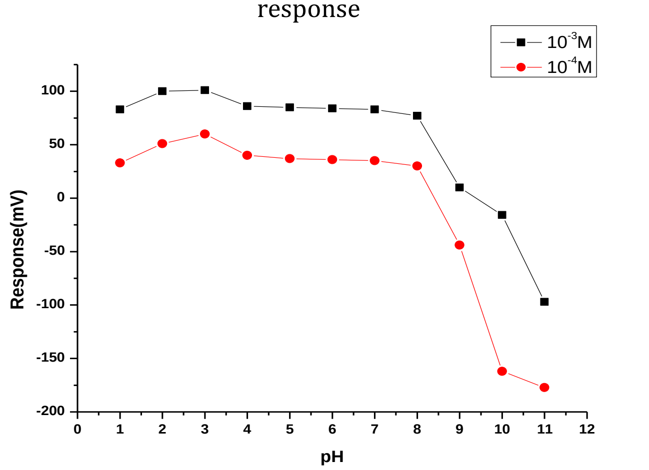

Figure 8. Effect of pH on the CPH-ONPOE electrode response

Figure 7 illustrates the CPH -BPB electrode can be used in the pH range of 4-7 with good sensitivity[10] . From figures 6 and 8, It should be noted increasing pH (pH >8) leads to decrease electrode response due to that cyproheptadine was insoluble in basic solution. The electrode response increases in strong acid (pH < 3) solution. This indicates that ion-pair (CPH -BPB) might probably respond to hydrogen ions.

3.3 Effect of soaking:

The three constructed electrodes required 2 hours for conditioning in 1.0 × 10-2 M CPH solution at room temperature to reach the stable potential. A calibration curve was created for electrode and the slope for the (CPH-DBPH), (CPH-TEHP) and (CPH-ONPOE) electrodes after 2 hours of soaking were 53.10, 58.72 and 57.44 respectively, but after 6 weeks of soaking the slope become 47.92, 51.75 for electrode A and B respectively as shown in figures 9 and 10, while electrode C the slope become 42.44 after 3 days as shown in figure 11.

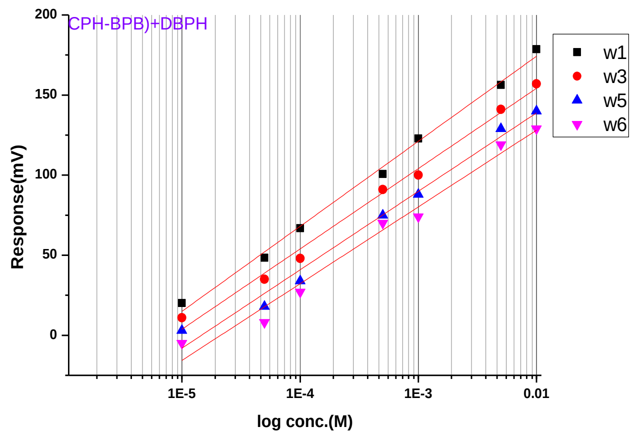

Figure 9. Life time of (CPH-DBPH).

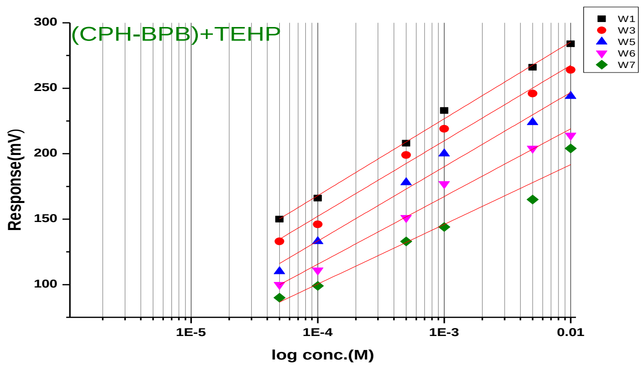

Figure 10. Life time of CPH-TEHP

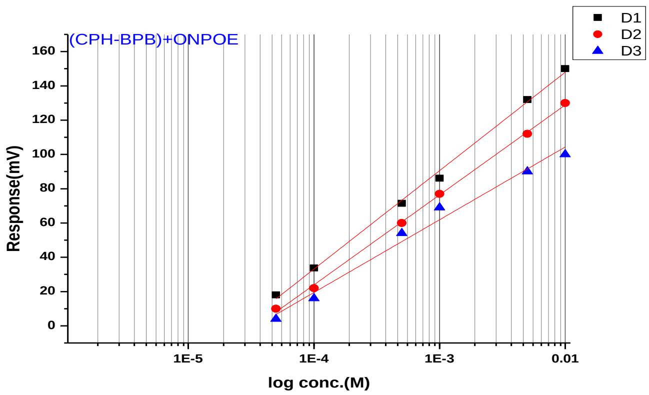

Figure 11. Life time of CPH-ONPOE.

3.4 Response time

The response time was measured for the cyproheptadine electrode based on DBPH, TEHP and ONPOE for two concentrations (1×10-2, 1×10-6) M as shown in figures 12, 13 and 14. The values of response time increase as the concentration decrease. This is attributed to the need for more time to reach the equilibrium between the ion- pair in the membrane and the external solution when the concentration of the external solution is too low.

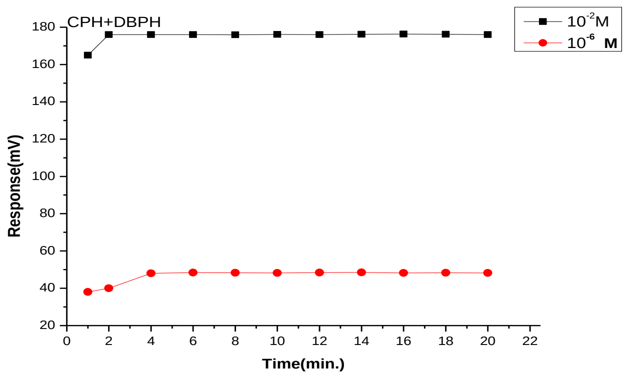

Figure 12. Response time of CPH-DBPH electrode.

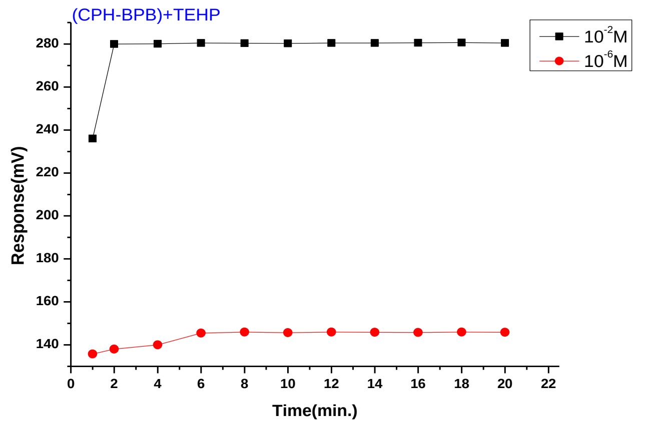

Figure 13. Response time of CPH-TEHP electrode.

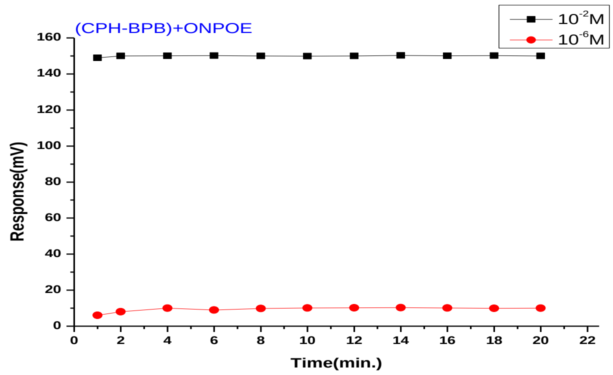

Figure 14. Response time of CPH-ONPOE electrode.

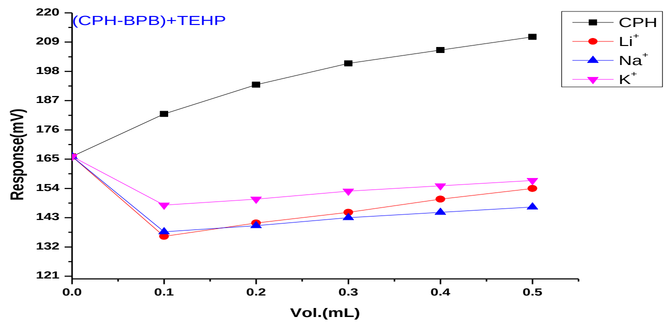

Figure 15. Selectivity for CPH-TEHP for mono-cations by match potential method.

Table 2. Selectivity coefficient value for different interfering ions using (CPH-TEHP) electrode.

Conc. (M)	$K_{A,B}$								
	Li^+	Na^+	K^+	Ca^{+2}	Mg^{+2}	Zn^{+2}	Cr^{+3}	Fe^{+3}	Al^{+3}
1.0×10^{-2}	5.73×10^{-6}	3.65×10^{-6}	3.41×10^{-6}	6.08×10^{-4}	2.50×10^{-4}	4.94×10^{-4}	1.40×10^{-4}	1.30×10^{-4}	8.75×10^{-5}
5.0×10^{-3}	9.58×10^{-6}	9.77×10^{-6}	7.42×10^{-6}	1.07×10^{-3}	6.08×10^{-4}	8.28×10^{-4}	2.00×10^{-4}	2.48×10^{-4}	1.22×10^{-4}
1.0×10^{-3}	4.07×10^{-5}	3.60×10^{-5}	3.76×10^{-5}	1.90×10^{-3}	1.48×10^{-3}	1.59×10^{-3}	2.93×10^{-4}	3.21×10^{-4}	1.94×10^{-4}
5.0×10^{-4}	7.99×10^{-5}	4.40×10^{-5}	6.34×10^{-5}	2.53×10^{-3}	1.51×10^{-3}	3.22×10^{-3}	5.20×10^{-4}	5.10×10^{-4}	3.19×10^{-4}
1.0×10^{-4}	1.52×10^{-3}	1.42×10^{-4}	2.89×10^{-4}	1.97×10^{-3}	1.56×10^{-3}	3.06×10^{-3}	3.37×10^{-4}	2.41×10^{-4}	2.10×10^{-4}
5.0×10^{-5}	3.86×10^{-3}	2.74×10^{-4}	4.95×10^{-4}	3.49×10^{-3}	2.55×10^{-3}	2.50×10^{-3}	2.42×10^{-4}	1.94×10^{-4}	1.45×10^{-4}
1.0×10^{-5}	7.73×10^{-3}	2.67×10^{-4}	3.52×10^{-4}	1.65×10^{-3}	1.51×10^{-3}	1.35×10^{-3}	1.59×10^{-4}	1.10×10^{-4}	8.20×10^{-5}
5.0×10^{-6}	1.11×10^{-2}	4.91×10^{-4}	4.70×10^{-3}	2.29×10^{-3}	1.93×10^{-3}	1.04×10^{-3}	1.17×10^{-4}	6.85×10^{-5}	5.85×10^{-5}
1.0×10^{-6}	1.43×10^{-2}	4.70×10^{-4}	3.34×10^{-3}	1.42×10^{-3}	7.99×10^{-4}	7.02×10^{-4}	3.22×10^{-5}	2.37×10^{-5}	1.24×10^{-5}

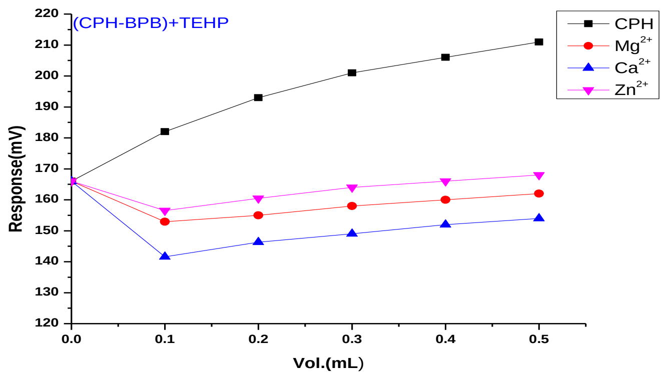

Figure 16. Selectivity for CPH-TEHP for di-cations by match potential method.

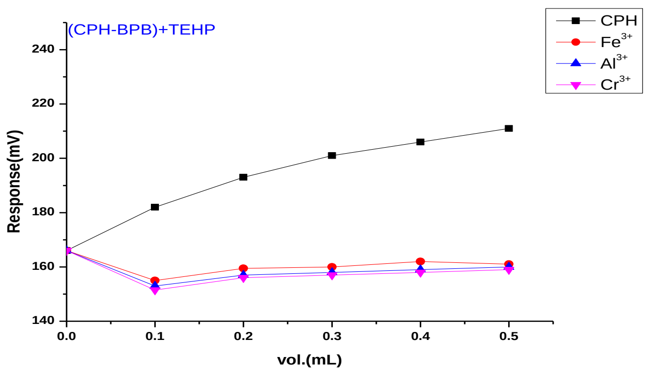

Figure 17. Selectivity for CPH-TEHP for tri-cations by match potential method.

3.5 Selectivity:

Selectivity behavior is distinctly one of the most important characteristics of the ion-selective electrode. It is determining whether a dependable measurement can be gained by the proposed electrode [13]. Consequently, the potential response was evaluated in the presence of different interfering ions using the separate solution and match potential method as shown in figure 15, 16 and 17. The selectivity coefficient values of the SSM are listed in the table (2).
From figures 15 – 17 show no interferences of the cations on cyproheptadine hydrochloride at concentrations 10^{-4} M. Therefore, the selectivity coefficients cannot be determined because there is no difference in potential between the drug solution and interfering cation even at 5 mV or 10 mV.

3.6 Analytical application

In investigating electrode to the determination of cyproheptadine in pharmaceutical preparations Cyproheptadine tablets and Prevet syrup using direct and standard addition methods [14]. The results were summed up in tables 3 and 4. The suggested electrode was demonstrated to be useful in the potentiometric determination of CPH in the pharmaceutical products by standard addition and multi standard addition method

Table 3. Estimation of the pharmaceutical application and human fluids by standard addition method.

Drug	Original Conc. (M)	RSD% $_{n=3}$	Found Conc. (M)	RC%	RE%
Standard of cyproheptadine	1×10^{-4}	1.44	1.01×10^{-4}	101	1
Cyproheptadine (tablets)	1×10^{-4}	1.95	1.03×10^{-4}	103	3
Prevet (syrup)	1×10^{-4}	0.85	0.99×10^{-4}	99	-1
Urine	1×10^{-4}	1.38	1.02×10^{-4}	102	2
Plasma	1×10^{-4}	1.99	1.04×10^{-4}	104	4

Table 4. Estimation of the pharmaceutical application and human fluids by multi standard addition method.

Drug	Original Conc. (M)	Found Conc. (M)	RE%	RC%
Standard of cyproheptadine	1×10^{-4}	0.98×10^{-4}	-2	98
Cyproheptadine (tablets)	1×10^{-4}	0.99×10^{-4}	1	99
Prevet (syrup)	1×10^{-4}	0.91×10^{-4}	-9	91
Urine	1×10^{-4}	1.05×10^{-4}	5	105
Plasma	1×10^{-4}	1.08×10^{-4}	8	108

4. Conclusions

In the present study, the observation of new three constructed electrodes of CPH was based on a plasticized poly (vinyl chloride) (PVC) membrane containing the ion-exchanger that formed between CPH and BPB. It provides a sensitive, precise, rapid and inexpensive method in the pure form, pharmaceutical preparations and human fluids. The ion-selective electrode has shown good performance with the time stability up to (42) days.

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