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Synthesis New Liquid Selective Electrodes of Ciprofloxacin Hydrochloride for Determination Ciprofloxacin in Pure form and Pharmaceuticals Preparation.

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Abstract:

New membrane electrodes for determination of ciprofloxacin hydrochloride were prepared depending on ciprofloxacin hydrochloride - phosphotungstic acid (CFH-PT) as an active material and these electrodes were made with three plasticizers: Di-octylphenylphosphonate(DOPH), Di-butyl phosphate (DBP)Tri-n-butyl phosphate(TBP), in PVC matrix. One of the ciprofloxacin electrodes was gave Nernstian slope equal to 57.21 mV/ decade for DOPH membrane with concentration range from 1.5×10^{-5} to1.0×10^{-1} M, and detection limit equal to 1.5×10^{-6} M .Lifetime was 93 days. Non- Nernstian responses equal to 39.40 and 30.70 mV/ decade for membranes DBP, TBP, respectively. These electrodes were gave concentration range from 1.0×10^{-5} to 1.0×10^{-2} and from 4.0×10^{-5} to 1.0×10^{-2} M,respectively. Detection limits were 7.0×10^{-6}, and 1.7×10^{-6}M, respectively. Lifetimes were 5,2 days, respectively. Also selectivity, influence of PH and samples analysis of ciprofloxacin in a pharmaceutical preparations were studied.

Keywords: Ciprofloxacin, Liquid membrane, Reaction of ciprofloxacin, PVC membranes.

Introduction:

Ciprofloxacin hydrochloride is: 1cyclopropyl -6-fluoro-1, 4-dihydro-4-oxo-7- (1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride, as shown in Figure 1.Molecular weight was equal to 367.8 g/mol. A hygroscopic powder, crystalline slightly, weak yellow. Practically insoluble in acetone, in ethyl acetate and methylene chloride very slightly soluble in anhydrous ethanol, slightly soluble in methanol. Soluble in water, was used as antibacterial[1].

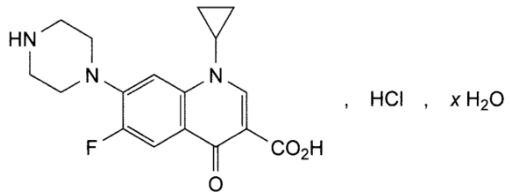

Figure 1. Chemical Structure of ciprofloxacin hydrochloride.

More chemical methods were used for determination of ciprofloxacin; one of these depended on derivative spectrophotometric for ciprofloxacin with complexation of Cu(II) in aqueous medium[2]. Reaction between 1,2-naphthaquinone-4-sodium sulphonate in medium of allkaline, product was measurable at 487 nm[3].Recovery rates were 97.4 -104.3;detection limits were 0.11,0.35,1.56µg/ml by HPLC with UV methods, RSD% were less than 5% for repeatability, and lower than5.15% for intermediate [4]. Flow injection analysis was used to determin ciprofloxacin, RSD% was lower than 2%(n=6) with r =0.9927,detection limit was equal to 0.55mmol^{-1}[5]. Analysis of drugs have been made extensively by using the technique of ion-selective electrodes. Several electrodes were prepared by using phosphotungustate as an ionophore such as clozapine ion selective electrodes which used phosphotungustate as an active material one with di-octylsebacate, slope was 57.46 mV/ decade with range of concentration (10^{-5} to10^{-2} M), PH range was from4.5 to 8.0[6]. Selective electrodes of benoxinate were prepared based on XB-phosphotungustate with plasticizers, di-octylphthalate and nitro phenyl octyl ether. Slopes were near to 61.1, 55.8, 59.4, 58.6 mV/ decade with PH range that was about 4 to 6;linear range was from 5×10^{-5} to 10^{-1}M [7]. Sensors for determination Benzydamin HCl(BZ) were based on BZ/Naphosphotungestate, BZ/Na-tetraphenylborate, BZ/ammonium-reineckate, BZ/K- trtrakis, BZ/phsphomolybdate [8]. Flavoxate-phosphotungestic acid (FLX-PTA) ion pair for determination flavoxate HCl with plasticizer

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(NPOE), recovery range was 98.1-101.6[9]. In this research three ciprofloxacin hydrochloride electrodes were prepared depending on phosphotungestic acid as ionophore with several plasticizers and were evaluated the pH effect, selectivity coefficient measurements.

Material and Methods:

Apparatus

1-Microprocessor, pH/mV/C Meter, pH211, HANA, Made in Roman.

2-Gallen Kamp (USA) as Calomel Reference Electrode.

3-Electrode of PH, H11131, HANA Instruments.

Chemicals

1-Ciprofloxacin hydrochloride was supplied from (SamaraIRAQ-SDI) Drug Industries and State Company and Medical Appliance.

2-Zindolin(500mg), Remedics. Ltd. Limas sol-Cyprus- Europ.

3-Ciprofloxacin hydrochloride (CFH) (film coated) (500 mg) from Manufactured By Kontam Pharmaceuticals (ZHONGSHAM) Co.,LTD.

4-Cipropharm(500mg),Mfg.by pharma International Co.Amman- Jordan.

5-Chemical PVC was from U.K.Ltd, Breon S110/10 B.P.

6-THF, was eqquiped from(BDH).

7-Plasticizers: Di- octylphenylphosphonate(DOPH), Di-butyl phosphate (DBP), Tri-n-butyl phosphate (TBP), were obtained from Fluka AG.

8-Dissolving 0.3678 gm of standard to prepare 0.01 M of ciprofloxacin hydrochloride making the solution up to 100 mL with deionized water.

9-Solutins of $AlCl_3$, $FeCl_3$,$CaCl_2$, $MgCl_2$, KCl ,and LiCl were prepared from 0.1M of Stock solutions, complementary thinned solutions prepared by succeeding dilution of the stockpile solution.

10-Additional all chemicals materials of analytical were supplied from Fluka, Aldrich and BDH.

Procedure

By filling 3/4 tube of glass with 0.1 M of ciprofloxacin hydrochloride solution as an inner filling solution, the immobilization and structure of the electrode were made. The membrane got ready by dipping in 0.1 M standard solution of ciprofloxacin hydrochloride at minimum 2 hours before use for measurements[10].

Selectivity Measurements

Selectivity coefficient was calculated by separate solution method by applying the equation: [11,12]

$$\mathbf{Log}\ K^{pot}_{A,B} = [(EB - EA) / (2.303RT/zF)] + (1 - zA/zB)\log aA$$

the potentias E*A*, E*B*; charge numbers z*A*, z*B*; and activities, a*B*,for interfering B ions and a*A* for the main A.

Result and Discussion:

Phosphotungstate anion reacted with ciprofloxacin cation to form water insoluble ion association complex. The prepared complex was identified and examined as ion exchange site in PVC membrane sensor responsive for ciprofloxacin hydrochloride. The electrochemical performance characteristics of the membrane was evaluated according to IUPAC reference and results were abridged in Table.1 and Fig. 1.By use plasticizers DBP, TBP, the membrane 2 and 3 had little values of slopes equal to 39.40,30.70 mV/decade, respectively, that may be attributed to the effect of steric, which lessened the bond strength with the compound of electroactive or may be because the type of plasticizers used, which included a long alkyl chain committed to the phosphate group, which may diminution the ion exchange method between the external solution of ciprofloxacin and electroactive (CFH-PT). Potential response electrode 1 was gave a slope of 57.21 mV/decade at different concentrations of ciprofloxacin, lifetime was around 93 days, and detection limit was equal to 1.5×10^{-6} M; therefore, the reproducibility of the response potential for membrane 1 was the best.

Table 1. Response of ciprofloxacin hydrochloride electrodes (CFH-PT).

Type of membrane	CFH+ DOPH+PT (1)	CFH+ DBP+PT (2)	CFH+TBP+PT (3)
Concentration range(M)	1.5×10^{-5}-1.0×10^{-1}	1.0×10^{-5}-1.0×10^{-2}	4.0×10^{-5}-1.0×10^{-2}
Correlation coefficient (R)	0.9990	0.9998	0.999
Detection limit(M)	1.5×10^{-6}	7.0×10^{-6}	1.7×10^{-6}
Slope (mV/decade)	57.21	39.40	30.70
Regre. Eq. $Y = mX + b$	Y=24.842ln(x)+289.2	Y=17.111ln(x)+206.4	Y=13.333ln(x)+145.7
Lifetime (day)	93	5	3

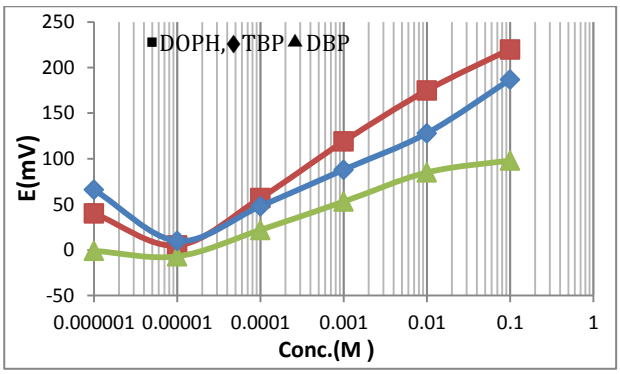

Figure 1. Calibration curve for ciprofloxacin hydrochloride electrodes.

Response Time

One of the important factors is response time for ion-selective electrode. In this study, by changing solution with different ciprofloxacin concentrations from1.0×10^{-5} to 1.0×10^{-1}M,the practical response time was recorded in Table 2, which shows the longer response time reached around 32 and 30 s at 10^{-5} M. Ciprofloxacin electrodes were given nearly the same range of response times.

Table 2. Response Time of ciprofloxacin electrodes.

Conc.(M)	CFH+DOPH+PT Electrode 1	CFH+DOP+PT Electrode 2	CFH+TBP+PT Electrode 3
10^{-1}	11	13	15
10^{-2}	13	15	17
10^{-3}	17	20	19
10^{-4}	22	24	22
10^{-5}	23	30	32

Influence of PH

The influence of pH on the electrode potentials for ciprofloxacin selective membrane electrodes was studied by measuring the potential of ciprofloxacin solutions at different concentrations(10^{-2},10^{-3},10^{-4}) M.

PH was adjusted by using sodium hydroxide and hydrochloric acid solutions. Results are listed in Table 3.Fig. 2 shows the scheme for the pH effect on electrode 1 which depended on (CFH+DOPH+PT).

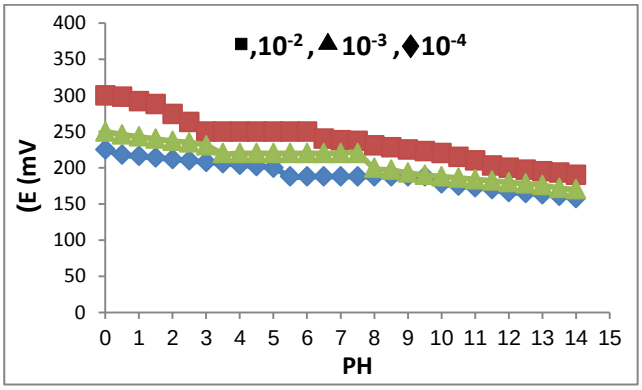

Figure 2. Working of PH for (CFH+DOPH+PT) electrode.

Table 3. Range of PH for ciprofloxacin electrodes.

Number	Membrane composition	pH range		
		10^{-2}	10^{-3}	10^{-4}
1	*CFH+DOPH+PT*	3.0-6.0	3.5-7.5	5.5-9.5
2	*CFH+DBP +PT*	4.5-8.0	3.5-7.0	4.0-9.0
3	*CFH+TBP +PT*	2.5-5.0	3.0-6.5	3.0-7.5

Measurements of Selectivity

One of the most important characteristics was potentiometric selectivity coefficient of an electrode. Determine the selectivity coefficient of to the ISE, the separate solution method (SSM) is mentioned by IUPAC.SSM and is founded by Nickolsky-Eisenman equation[13].We studied the influence of some interfering inorganic cations, Fe^{3+}, Al^{3+}, Ca^{2+}, Mg^{2+}, Na^{1+}, and Li^{1+} on the electrode response. Separate solution method was used to calculate selectivity of the electrode 1 depending on DOPH with concentration range from 10^{-5} to 10^{-1} M. Results were recorded in Table 4 and shown in Fig. 3.

Very small value of the selectivity coefficients was found. This means that there is no interference of these interfering ions with the response of ciprofloxacin electrodes.

Table 4. Selectivity coefficient for ciprofloxacin electrode (CFH+DOPB+PT) at different concentrations.

Electrode 1 Concentration of Ciprofloxacin hydrochloride				
Ion	10^{-5}	10^{-4}	10^{-3}	10^{-2}
Li^{1+}	0.0133	1.003×10^{-3}	1.299×10^{-4}	1.818×10^{-5}
K^{1+}	8.941×10^{-4}	7.288×10^{-5}	8.406×10^{-6}	1.425×10^{-6}
Ca^{2+}	$1.922`\times10^{-6}$	2.256×10^{-5}	9.133×10^{-7}	1.66×10^{-7}
Mg^{2+}	1.600×10^{-7}	2.432×10^{-7}	2.076×10^{-6}	9.547×10^{-7}
Fe^{3+}	2.822×10^{-7}	1.407×10^{-7}	1.565×10^{-7}	9.038×10^{-8}
Al^{3+}	1.933×10^{-7}	1.642×10^{-7}	5.525×10^{-8}	5.267×10^{-8}

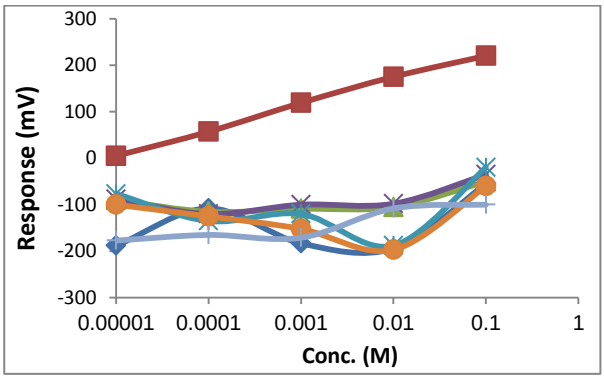

Figure 3. Selectivity of electrode 1 (CFH+DOBH+PT) for interferings [■, CFH,♦Li^{1+},▪ Al^{3+},• Fe^{+3},✕Ca^{2+},▲K^{1+},✱ Mg^{2+}].

Analytical Application

Direct, titration method and multiple standard addition. Were applied for the determination ciprofloxacin hydrochloride using membrane 1 based on DOPH as a plasticizer, and by standard addition method, the concentration of ciprofloxacin was calculated as the following equation:

$$CU=CS/10^{\Delta E/S}\,[1+(VU/VS)]-(VU/VS)$$

Where the concentration and volume of unknown and standard solution, respectively CS, CU, VS and VU. In the Figure of antilogarithm (E/S) vs. the volume of the multiple addition of the standard solution was used to determine the concentration of CFH in the multi standard addition method (MSA) is shown in Fig. 4 and the results listed in Table 5.A 10^{-3} M of phosphotungestate was used as a titrant For potentiometric titration, distinctive titration scheme is shown in Fig. 5. Recovery (Re %), relative error (Er %) and relative standard deviation (RSD %) for each method were calculated.

Table 5. Potentiometric methods of electrode (CFH+ DOPH+PT) to evaluated ciprofloxacin.

Electrode Type	Sample	Concentration(M) Response by potentiometric method			
		Direct	SAM	MSA	Titration
CFH+ DOPH+PT	1×10^{-3}	0.9847×10^{-3}	0.9675×10^{-3}	0.9979×10^{-3}	0.9988×10^{-3}
	RSD%	0.56	0.37	-	-
	Re%	98.47	96.75	99.79	99.88
	Er%	-1.53	-3.25	-0.21	-0.12
	1×10^{-4}	0.9875×10^{-4}	0.9965×10^{-4}	0.9899×10^{-4}	0.9680×10^{-4}
	RSD%	0.46	0.26	-	-
	Re%	98.75	99.65	98.99	96.80
	Er%	-1.25	-0.35	-1.01	-3.20

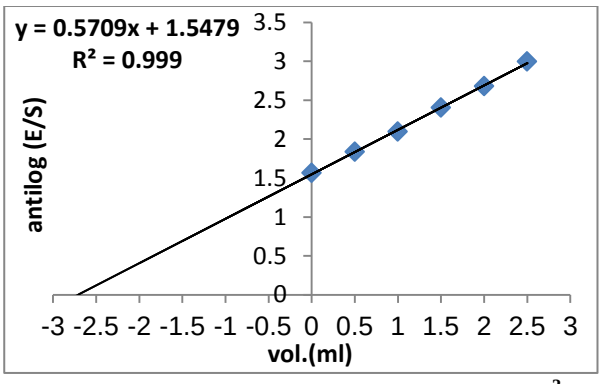

Figure 4. Antilog (E /S)versus volume of 10^{-3} M added of ciprofloxacin using electrode1 (CFH+DOPH+PT).

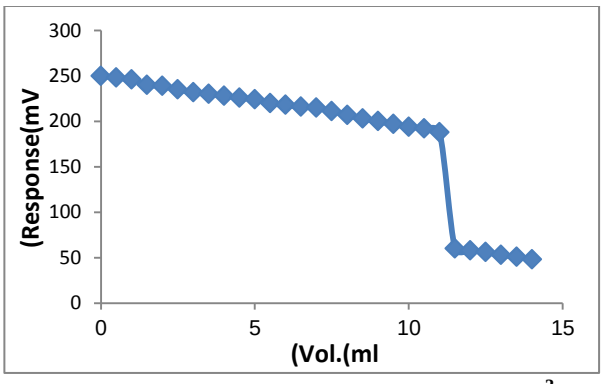

Figure 5. Titration curve for sample(1×10^{-3}M) CFH with(1×10^{-3}M) PT standard by electrode 1 (CFH+ DOPH+PT).

From Table 5,it is shown that the%Er for titration method which is equal to(- 0.12) is less than %Er for MSA method which equal to (- 0.21), thus,it may be due to errors of instruments or by founded errors through preparation standard solutions of drugs or may be attributed to the precipitation of CFH-PT on the surface of the membrane and destroying the electrode [14]compared with concentration10^{-4} M ,Er% for titration was highest than Er% for MSA method. For determination of ciprofloxacin in pharmaceutical tablets (Zindoline, Cipropharm Ciprofloxacin HCl), the direct potentiometric method was applied because there is no interference of all species on membrane response; therefor, the value of recovery obtained by standard addition method agrees with the results of direct method [15]. End results are listed in Table.6 using the electrode1.Standard deviation was about 0.1, by calculating average of 3 measurements for each sample. Average recovery was around 99.62 for ciprofloxacin determination in tablets.

Table 6. Potentiometric methods of electrode (CFH+ DOPH+PT) to evaluated ciprofloxacin in tablets.

Pharmaceutical tablets	Zindoline	Cipropharm	Ciprofloxacin HCl
Conc.of CFH(prepared)	1.00×10^{-3}	1.00×10^{-3}	1.00×10^{-3}
Conc. of CFH (found)	1.0138×10^{-3}	0.9880×10^{-3}	0.9870×10^{-3}
Re%	101.38	98.80	98.70
Er%	1.3	-1.2	-1.3

Conclusion:

In this work, potentiometric methods were applied for determination of ciprofloxacin hydrochloride in pharmaceutical formulations by using an ion-selective electrode. Membrane with complex (CFH-PT) depending on di-octylphenylphosphonate as a plasticizer that was the best electrode.

The advantage of the method is its simplicity and selectivity in measuring ciprofloxacin above wide concentration ranges and pH without whichever major interference from trivalent or divalent and monovalent metal ions.

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تحضير أقطاب جديدة انتقائية سائلة لسيبروفلوكساسين هيدروكلورايد في المادة النقية والمستحضرات الصيدلانية

امينة محسن عباس

قسم الكيمياء، كلية العلوم، جامعة النهرين، بغداد العراق

الخلاصة:

تم تحضير أغشية جديدة لتقدير السايبروفلوكساسين هيدروكلورايد بالاعتماد على: سايبروفلوكساسين- فوسفوتنكستنك اسيد (CFH-PT) كمادة فعالة نشطة.صنعت هذه الاقطاب بأستخدام المواد الملدنة : Di-octyl phosphonate(DOPH), Tri-butyl phthalate(TBP),Di-butyl phosphate (DBP) في قالب من البولي فاينيل كلورايد.أعطت أقطاب السايبروفلوكساسين ميلا نيرنستيا مسا و الى 57.21 ملي فولت/حقبة لغشاء (DOPH) مع مدى تركيزي من 1.5×10^{-5} الى 1.0×10^{-1} مولاري،وحد تحسس مساوي الى 1.5×10^{-6} مولاري.عمر القطب كان بمقدار 93 يوما.كما اعطت اقطاب DOP،TBPاستجابة غير نيرنيستية مساوية الى 30.70,39.40 ملي فولت/حقبة،على التوالي.كما اعطت هذه الاقطاب مدى تركيزي تقريبا من 1.0×10^{-5} الى 1.0×10^{-2} ومن 4.0×10^{-5} الى 1.0×10^{-2} مولاري ،على التوالي.حد التحسس كان بمقدار 7.0×10^{-6} و1.7×10^{-6} مولاري ،على التوالي.عمر الاقطاب كان بمقدار 5 و2 يوم.كما تم دراسة الانتقائية وتأثير الدالة الحامضية وتحليل العينات للمادة الدوائية سايبروفلوكساسين في المستحضرات الصيدلانية.

الكلمات المفتاحية: سايبروفلوكساسين،الاغشية السائلة ،تفاعلات السايبروفلوكساسين ،أغشية البولي فاينيل كلورايد.