Construction of Promethazine Hydrochloride Selective Electrodes in A Pvc Matrix Membrane

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Abstract

Promethazine hydrochloride selective electrodes were constructed based on promethazine-Molybdophosphoric acid ion pair. Promethazine hydrochloride electrodes (1, 2, 3, 4 and 5) using these plasticizers Di-butyl phthalate (DBPH); Di-octyl phthalate (DOP); Di-butyl phosphate (DBP); Tri-butyl phosphate (TBP); ortho-nitro phenyl octyl ether (ONPOE) in PVC matrix respectively. These electrodes give slopes (57.27, 54.08, 49.79, 46.76 and 44.52 mV/decade) and give linear ranges from (1×10^{-5}-1×10^{-1}, 1×10^{-4}-1×10^{-1}, 1×10^{-5}- 1×10^{-1}, 5×10^{-4}-1×10^{-1} and 1×10^{-4}-1×10^{-1} M) respectively. The best detection limit was 6×10^{-6} M for the electrode based on DBPH. The measurement interferences in the presence of (Na^{+}, K^{+}, Mn^{+2}, Cu^{+2}, Ca^{+2}, Fe^{+3}, Al^{+3}, Paracetamol, sucrose and Galaten) were studied using separate and mixed methods for selectivity coefficient determination. The pH and life time of the electrodes were also studied. The results were compared with UV-spectrophotometer technique by using F-test.

Keywords:Promathazine-hydrochloride selective electrodes, Molybdophosphoric acid, promethazine determination.

Introduction

Promethazine Hydrochloride, N,N-dimethyl-1-(10H-phenothazin-10-yl) propane-2-aminehydrochloride, $C_{17}H_{20}N_2S.HCl$, as show in Fig.(1), is a white or faintly yellowish crystalline powder with molecular weight of 320.9, it melts at about (222^0C),with decomposition. It is very soluble in water; freely soluble in alcohol and in methylene chloride.[1]

Promethazine is aphenothiazine derivative that competitively blocks histamine receptors without blocking the secretion of histamine.

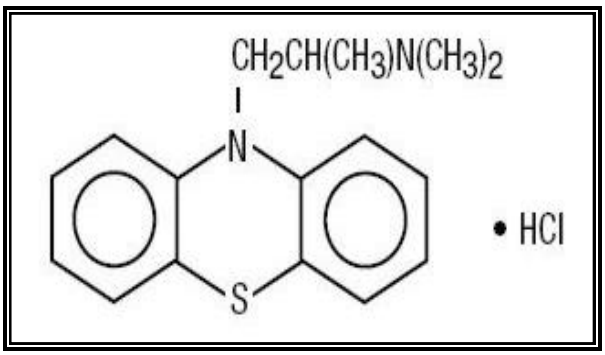

Fig.(1) Structure formula of Promethazine hydrochloride.

Slow oxidation may occur upon prolonged exposure to air usually causing blue discoloration.[2] Promethazine is commonly used to relieve itchy, irritated, and watery eyes, runny nose, sneezing and itchy skin. Promethazine hydrochloride is an important compound in the large group of phenothiazine derivatives. It is widely used as therapeutic agent for treating various mental disorders or for enhancing the analgesic, anesthetic and sedative effect with other medicines.[3]

Different methods have been reported for the determination of promethazine in products and biological samples such as high performance liquid chromatography [4], the UV-spectrophotometry [5,6], Chemiluminescence [7],Potentiometric study [8].

Potentiometric membrane sensors are playing an important role in pharmaceutical analysis because of their simplicity, rapidity and accuracy over some other analytical methods like spectrophotometry and HPLC. Also, other mentioned methods are elaborate and time consuming methods and involve sophisticated equipment that might not be available in most analytical laboratories.

In this work, several promethazine hydrochloride electrodes were constructed

based on Molybdophosphoric acid as ionophore with different plasticizers. The properties of the prepared electrodes, pH effect, and selectivity coefficient measurements were evaluated.

Experimental Part

Equipment

An expandable ion analyzer (Orion model EA-940, USA), a pH meter (WTW model pH 522, Germany), Double beam UV-Vis spectrophotometer model (UV-1650 PC) SHIMADZ (Japan) and a Silver-silver chloride electrode were used in this work.

Chemicals and Reagents

High molecular weight poly (vinyl chloride) (PVC), tetrahydrofuran (THF) was purchased from Lancaster, Promethazine hydrochloride standard was a gift from the State Company of Drug Industries and Medical Appliances (Samara IRAQ-SDI). COLDEIN tablets (5mg promethazine hydrochloride + 450mg Paracetamol and 5mg Phenylephrine hydrochloride) made in Samara-IRAQ-SDI.

Di-butyl phthalate (DBPH); Di-octyl phthalate (DOP); Di-butyl phosphate (DBP); Tri-butyl phosphate (TBP); ortho-nitro phenyl octyl ether (ONPOE) were obtained from Fluka AG, Switzerland.

Stock solutions of 0.1 M for each of NaOH, KCl, NaCl, $CaSO_4$, $CuSO_4$, $MnSO_4$, $Fe_2(SO_4)_3.9H_2O$, $AlCl_3.6H_2O$, sucrose, Paracetamol and galaten were prepared by dissolving 0.2922, 0.3729, 0.680, 0.7980, 0.7550, 2.5301, 1.2075, 1.7115 , 1.50 and 0.7560 g in 50 mL of distilled water.

A solution of 0.1 M promethazine hydrochloride was prepared by dissolving 1.6045 g of standard solution and making the solution up to 50 mL with distilled water. The working solutions 10^{-7}-10^{-1} M were prepared by serial appropriate dilution of the stock solution.

Procedure

Preparation of ion-pair compound

The ion-pair of Promethazine hydrochloride-Molybdophosphoric acid (PMH-PM) was prepared by mixing 50 mL of 0.01 M promethazine hydrochloride (PMH) with 50 mL of 0.01 M Molybdophosphoric acid (PM) with stirring. The resultant precipitate was filtered, washed with water, and dried at room temperature.

Assembly of ion-selective electrodes

The construction of the electrode body and the immobilization were done as described by Craggs et al [9]. The glass tube was 3/4 filled with 0.01 M promethazine hydrochloride solution as an internal filling solution. The membrane was conditioned by immersing in a standard solution of 0.1 M promethazine hydrochloride for at least 2hour before measurements. The pH of 10^{-2}, 10^{-3} and 10^{-4} M promethazine hydrochloride was adjusted with dilute solutions of sodium hydroxide and hydrochloric acid.

Selectivity measurements

A separate solution method [10] was used for the selectivity coefficient measurement, and was calculated according to the equation:

$$\log K^{pot}_{A,B}=(E_B-E_A)/S+(1-z_A/z_B)\log a_A \quad .....(1)$$

E_A, E_B; z_A, z_B; and a_A, are the potentials, charge numbers, and activities for the primary A ion, respectively, at $a_A = a_B$.

The selectivity coefficients were also measured by the mixed method (Fixed interference method) [11,12] according to the equation:

$$K^{pot}_{A,B}=a_A/(_{aB})^{zA/zB} \quad .....(2)$$

Results and Discussion

Five electrodes of Promethazine hydrochloride based on Promethazine hydrochloride-Molybdophosphoric acid (PMH-PM) ion-pair complex as the electro-active material and soluble in organic solvents such as tetrahydrofuran. The complex was incorporated into a PVC membrane with the following plasticizers: Di-butyl phthalate (DBPH) membrane 1; Di-octyl phthalate (DOP) membrane 2; Di-butyl phosphate (DBP) membrane 3; Tri-butyl phosphate (TBP) membrane 4; and ortho-nitro phenyl octyl ether (ONPOE) membrane 5. Non-Nernstian slopes were obtained for electrodes based on DBP, TBP and ONPOE (membranes 3, 4 and 5). The slopes are 49.79, 46.76 and 44.52 mV/decade with correlation coefficients of 0.9991, 0.9999 and 0.9998 respectively.

The linear range for these electrodes $1x10^{-5}$-1×10^{-1}, 5×10^{-4}-1×10^{-1} and 1×10^{-4}-1×10^{-1} M with detection limits of 6×10^{-6} M, 6×10^{-4} M and $8x10^{-5}$ M respectively. The parameters of promethazine hydrochloride electrodes are listed in Table (1). The non-Nernstian slope behaviors could be attributed to the high viscosity of DBP (112.89 CST), which decrease the ion-exchange between ion-pair complex (PMH-PM) in membrane and the external solution of Promethazine. Moreover, the steric effect of the alkyl group on the DBP may decrease the bond strength of the ion pair complex. The TBP, which has a low viscosity (3.11 CST), which causes rapid leaching of the complex out of the membrane when it is in contact with aqueous solution. Also the low viscosity of ONPOE (11.44 CST) give non-Nernstian slope also the life time of this electrode was short time around 7 days, this may be due to the low viscosity of ONPOE or incompatibility of the plasticizer with the complex in PVC. However, the DBPH electrode gave a slope of 57.27 mV/decade with a correlation coefficient of 0.9999, a linear concentration range of 1×10^{-5}-1×10^{-1} M, and a detection limit of 8×10^{-6} M. The life time of the DBPH electrode was around 72 days. A typical plot for calibration curves of electrodes based on five plasticizers DBP, DBPH, DOP, TBP and ONPOE are shown in Fig.(2).

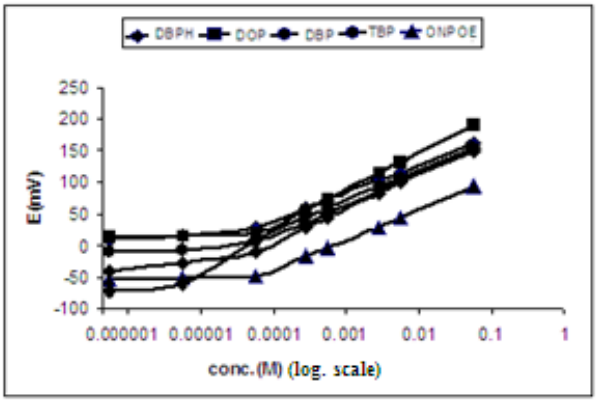

Fig.(2) Calibration curves of promethazine hydrochloride selective electrodes using DPB, DBPH, DOP, TBP and ONPOE plasticizers.

Table (1)
The parameters of five Promethazine hydrochloride electrodes.

Electrode	*Parameters*						
number	*Slope mV/decade*	*slope±(ts/√N)*	*Linearity range (M)*	*Detection Limit (M)*	*Correlation Coefficient*	*RSD *%*	*Life time (days)*
1-PMH-PM+DBPH	57.27	57.27±0.225	1×10^{-5}– 1×10^{-1}	8×10^{-6}	0.9999	0.159	~62
2-PMH-PM +DOP	54.08	54.08±0.249	1×10^{-4}–1 $\times10^{-1}$	6×10^{-5}	0.9997	0.358	~22
3-PMH-PM +DBP	49.79	49.79±0.603	1×10^{-5}–1×10^{-1}	6×10^{-6}	0.9991	0.674	~35
4-PMH-PM +TBP	46.76	46.76±0.871	5×10^{-4}– 1×10^{-1}	6×10^{-4}	0.9999	0.708	~19
5-PMH-PM+ONPOE	44.52	44.52±0.626	1×10^{-4}– 1×10^{-1}	8×10^{-5}	0.9998	0.743	~7

**** The result of three times repeated; t=4.3; N=3.***

Effect of pH

The effect of pH on the electrode was examined by measuring the e.m.f. for the three different Promethazine hydrochloride concentrations 10^{-4}, 10^{-3} and 10^{-2}M. A representative plot for the DBPH electrode is shown in Fig.(3). The response of electrode is remained constant at pH range from 2 to 8 and decrease when the pH increase, this may be attributed to low solubility in the alkali solution. Working pH ranges for electrode 1 (PMH-PM+DBPH) show in Table (2).

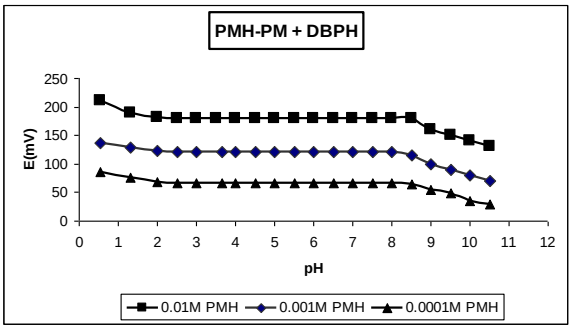

Fig.(3) Effect of pH on the potential of promethazine hydrochloride selective electrode using DBPH plasticizer.

Table (2)
Working pH ranges for electrode 1 (PMH-PM+DBPH).

Membrane	*pH range*		
PMH-PM+DBPH	10^{-2} M	10^{-2}M	10^{-2}M
	2.1 – 8.1	2.3 – 7.8	1.9 – 8.3

Selectivity measurements

The values of the selectivity coefficients for separate method are listed in Table (3). The selectivity coefficients were very small, this mean that there is no interference of these interfering ions with the response of promethazine electrodes.

In mixed method, The potential values obtained are plotted vs. the logarithm of the concentration of the Promethazine hydrochloride. The intersection of the extrapolated linear portions of this plot indicates the value of (a_A) as show in Fig.(4). The results of selectivity coefficients listed in Table (4).

Table (3)
Selectivity coefficient values according to separet metode using promethazine hydrochloride selective electrode using DBPH plasticizer.

Interfering Ion	E_B *(mV)*	$K_{A,B}$
K^+	-20.3	0.315×10^{-3}
Na^+	-14.1	0.403×10^{-3}
Cu^{+2}	-6.9	0.171×10^{-4}
Mn^{+2}	-19.1	0.104×10^{-4}
Ca^{+2}	-5.2	0.183×10^{-4}
Al^{+3}	31.1	0.243×10^{-4}
Fe^{+3}	-12.3	0.424×10^{-5}
Paracetol	5.8	0.898×10^{-3}
Sucrose	4.9	0.866×10^{-3}
Galaten	-1.2	0.678×10^{-3}

Table (4)
Selectivity coefficient values according to (FIM) using promethazine hydrochloride selective electrode using DBPH plasticizer.

Interfering Ion	$a_B = 5\times10^{-2}$ *M*	
	a_A	$K^{pot}_{A,B}$
K^+	3×10^{-5}	0.60×10^{-3}
Na^+	5×10^{-4}	0.10×10^{-1}
Cu^{+2}	1.4×10^{-4}	0.632×10^{-3}
Mn^{+2}	9×10^{-6}	0.402×10^{-4}
Ca^{+2}	2.5×10^{-5}	0.112×10^{-3}
Al^{+3}	2×10^{-5}	0.537×10^{-4}
Fe^{+3}	2.5×10^{-5}	0.672×10^{-4}
Paracetol	2×10^{-5}	0.40×10^{-3}
Sucrose	1.8×10^{-5}	0.36×10^{-3}
Galaten	3×10^{-5}	0.6×10^{-3}

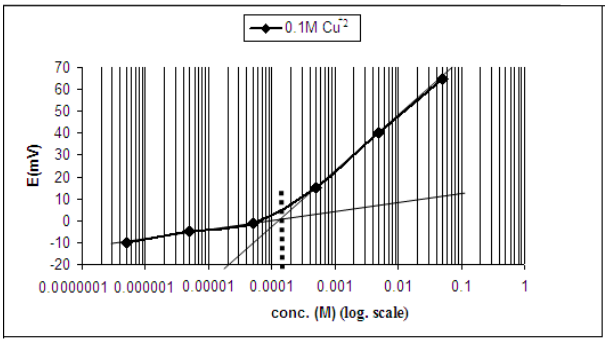

Fig.(4) Calibration curve of fixed interfering method using promethazine hydrochloride selective electrode using DBPH plasticizer.

Sample analysis

Potentiometric techniques were used for the determination of promethazine hydrochloride, these included direct method, standard addition method (SAM), multi standard addition method (MSA) and titration method. In the multi standard addition method (MSA), the plot of anti logarithm (E/S) versus the volume of the multiple addition of the standard solution was used to determine the concentration of promethazine hydrochloride solution. A typical plot is shown in Fig.(5).

For potentiometric titration a 10^{-2} M of Molybdophosphoric acid were used as a titrant. A typical titration plot was shown in Fig.(6). The results are listed in Table (5).

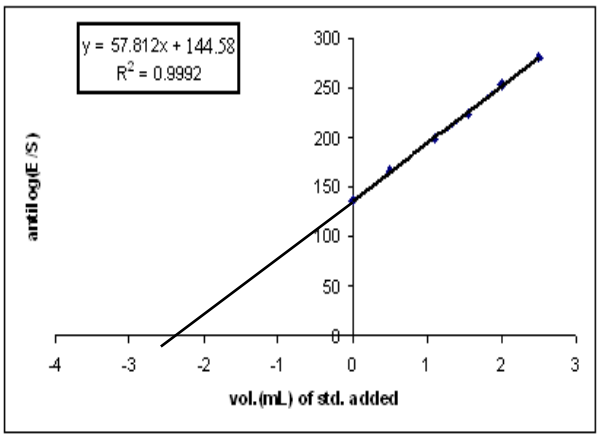

Fig.(5) Plot of antilog (E/S) versus the volume of promethazine using metode using promethazine hydrochloride selective electrode using DBPH plasticizer.

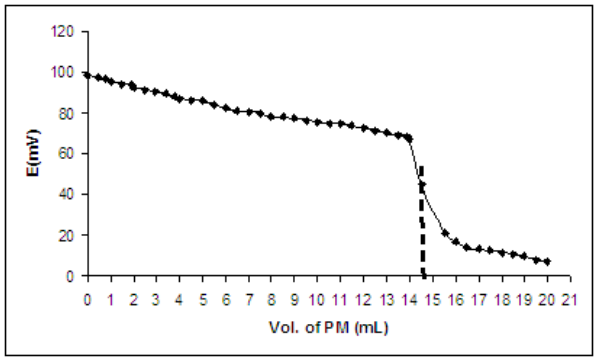

Fig.(6) Titration curve of promethazine hydrochloride selective electrode using DBPH plasticizer.

Due to the vital importance of the rapid assay of pharmaceutical products, in recent years potentiometric measurement using ion selective electrodes has found widespread use in pharmaceutical and clinical analysis, and in the study of drug interactions with other chemicals. The electrode 1 (PMH-PM+DBPH) was used for determination the Promethazine hydrochloride in COLDEIN tablets using potentiometric techniques. The results of quantitative measurements for the electrode are listed in Table (6).

Sample analyses by using UV-Spectrophotometry

Normal UV spectrum of Promethazine show two absorption wavelengths 249 nm and 299 nm. Fig.(7) show the spectra of Promethazine hydrochloride.

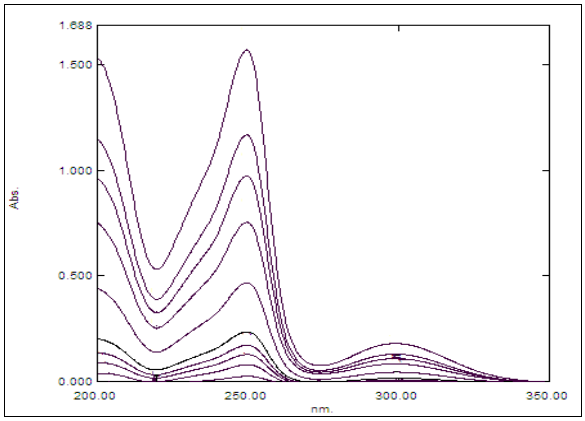

Fig.(7) Spectra for Promethazine hydrochloride solutions at different concentration ranged from 2 to 62 mg/L.

Derivative Spectrophotometry (DS):

The UV derivatives spectra have been taken for normal spectrum of Promethazine hydrochloride solutions 2-62 mg/L.

First Derivative (^{1}D):

First-derivative (^{1}D) spectra for Promethazine hydrochloride solutions 2-62 mg/L have been taken from normal using scale factor=20. Figure 8, show first-derivative spectra of Promethazine hydrochloride. (^{1}D) spectrum of Promethazine hydrochloride shows a fixed peak (P) at 243 nm and two fixed valley (V) at 256 nm and 211 nm. But all peaks and valleys below 220 nm gave a noisy signal, which contained the absorption of impurities.

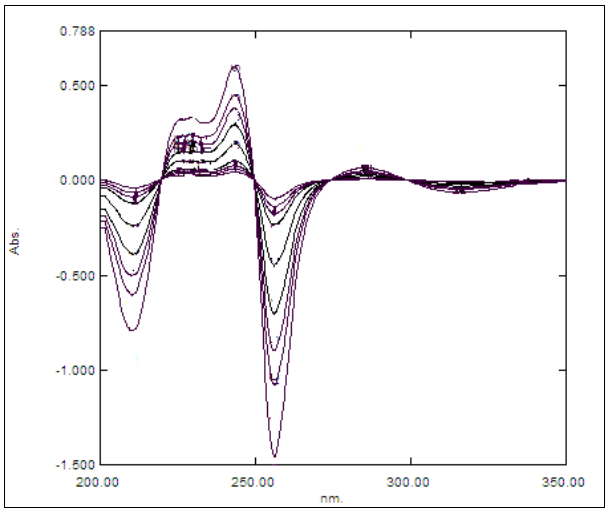

Fig.(8) The first derivative spectra for Promethazine hydrochloride solutions at different concentration ranged from 2 to 62 mg/L.

Comparison between ISE and Normal Spectroscopy Method

The results of comparison between Normal Spectroscopy with direct method of Ion selective electrode by using F-test are shown in the Table (7). The result show, that the Promethazine can be determined by using Ion selective electrode method because the value of the (F) experimental less than the value of the (F) theoretical at 95% confidence limit that equal 6.39.

Table (5)

Analysis of Promethazine hydrochloride samples by potentiometric techniques.

Parameter	*Direct method*	*SAM*	*MSA*	*Titration Method*
Conc.(M)	1.000×10^{-4}	1.000×10^{-3}	1.000×10^{-3}	1.000×10^{-2}
Found(M)	0.995×10^{-4}	0.996×10^{-3}	1.004×10^{-3}	0.9895×10^{-2}
RSD*%	0.372%	0.585%	----------	0.500%
Re%	99.5%	99.6%	100.4%	98.9 %
relative error%	-0.5%	-0.4%	0.4%	-1.1 %

Table (6)

Sample analyses of Colden tablets pharmaceutical Promethazine hydrochloride.

Parameter	*Direct method*	*SAM*	*MSA*	*Titration Method*
Conc.(M)	1.000×10^{-3}	1.000×10^{-3}	1.000×10^{-3}	1.000×10^{-3}
Found(M)	1.003×10^{-3}	0.994×10^{-3}	0.980×10^{-3}	0.9995×10^{-3}
RSD*%	0.634%	0.918%	----------	0.919 %
Re%	100.3%	99.4%	98.0%	99.9 %
relative error%	0.3%	-0.6%	-2.0%	-0.1 %

Table (7)

Calculation of F-test between the two methods ISE and UV-spectrophotometry.

C_U(M) from direct method of ISE	*S**	*C_U(M) from UV-spectrophotometry*	*S**	*The (F) magnitude*
0.999×10^{-4}	3.701×10^{-7}	0.999×10^{-4}	2.881×10^{-7}	1.6504
0.998×10^{-4}		1.001×10^{-4}		
0.996×10^{-4}		0.998×10^{-4}		
0.993×10^{-4}		1.003×10^{-4}		
0.990×10^{-4}		1.005×10^{-4}		

C_U: unknown concentration, S*: standard deviation; n= 5, $F= S_1^2 / S_2^2$, where $S_1>S_2$.

Conclusion

Promethazine hydrochloride selective electrodes based on ion pair complex of PMH-PM and with different plasticizers were constructed. The best promethazine electrode was based on DBPH. This electrode was used for drug determination in pharmaceutical preparations. The electrode based on DBPH gave excellent electrode parameters and no interference with several interferings ions. The proposed analytical method is proved to be simple and rapid, with good accuracy. By

comparison between Ion selective electrode and Normal Spectroscopy method The result show, that the Promethazine can be determined by using Ion selective electrode method by using F-test.

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الخلاصة

الاقطاب الانتقائية للبروميثازين هيدروكلورايد والتي تعتمد على المعقد المحضر (Promethazine-Molybdophosphoric acid) كمادة فعالة.وبأستخدام الملدنات التالية :

Di-octyl (DBPH), phthalate Di-butyl Di-butyl phosphate (DBP), phthalate (DOP), phenyl ortho-nitro (TBP), phosphate Tri-butyl .octyl ether (ONPOE)

الاقطاب البروميثازين هيدروكلورايد (5,4,3,2,1) وباستعمال الملدنات:,DBPH DBP, TBP, DOP, ONPOE كان لها إنحدار (44.52, 46.76, 49.79, 54.08, 57.27) ملفولت/حقبة ومدى التراكيز الخطي للاقطاب هو (1×10^{-4}-1×10^{-1}, 5×10^{-4}-1×10^{-1}, 1×10^{-5}-1×10^{-1}, 1×10^{-5}-1×10^{-1},1×10^{-4}-1×10^{-1}) مولاري. وكان حد التحسس للقطب المستعمل المعتمد على (DBPH) هو 6×10^{-6} مولاري .كذلك تم تعيين معامل الانتقائية ($K^{pot}_{A,B}$) للاقطاب الانتقائية للمتداخلات التالية:

(Na^{+}, K^{+}, Mn^{+2}, Cu^{+2}, Ca^{+2}, Fe^{+3}, Al^{+3}, Paracetamol, Sucrose, Galaten)

بوساطة طريقة المحاليل المنفصلة وطريقة المحاليل الممزوجة.ودراست حدود الدالة الحامضية وعمر القطب.حيث تمت مقارنة النتائج مع الطريقة الطيفية من خلال اجراء ال-F .test