Preparation and potentiometric study of phenytoin selective electrodes based on a PVC matrix membrane

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Abstract:

Phenytion selective electrodes were prepared based on a complex phenytion-phosphomolybdate as an active material using the plasticizers di-octyl phthalate (DOPH), tri-butyl phosphate (TBP), o-nitro phenyl octyl ether (ONPOE) and di-butyl phthalate (DBPH) in a PVC matrix membrane. The properties of the prepared electrodes were studied, such as: slope, concentration range, detection limit, lifetime, pH effect and selectivity. The experimental results showed that the best electrode was based on DOPH and DBPH as plasticizers, displaying a linear range from 1.00×10^{-4} M to 1.00×10^{-1} M and 1.00×10^{-1} M to 5×10^{-4} with a Nernstian slope of 58.5 mV/decade and 55.8 mV/decade, correlation coefficient of 0.9997 and 0.9998, The detection limit was 5.5×10^{-5} M and 8.0×10^{-5}, the lifetime was around 60 and 45 days respectively. The proposed electrodes were successfully applied to the determination of phenytion in a pharmaceutical preparation.

Introduction:

Phenytoin has the molecular formula $C_{15}H_{12}N_2O_2$ and the chemical name 5, 5-diphenylimidazolidine- 2,4-dione with molecular weight of 252.268 g mol^{-1}. Phenytoin is an anticonvulsant drug, which is useful in the treatment of epilepsy (Guliz et al. 2006), (Emillio Perucca 2006), (Putman and Merritt 1937). In several papers phosphomolbdic, tetraphenylborate, and phosphotungstic acid were proposed as ionophores for preparation of drug-sensitive electrodes. (Ayala and Johnston 1977), (Issa et al. 2005), Literature reveals that analytical methods have been reported for quantitation of phenytoin from human serum using HPLC with fluorescence, UV, Diode Array Detection. Supercritical fluid chromatography and nephelometric titration have been reported to estimate the drug content of the

tablet (Kishore et al. 2003), (Santagati et al. 2005), (Natale et al. 2005), (Khoschsorur et al. 2001). Ion-selective electrodes play an important role in pharmaceutical analysis (Meyler et al. 1993) due to their simplicity, rapidity and accuracy. A novel ion selective PVC membrane electrode for the determination of propranolol was developed by Aboul-Enein (Stefan et al.) they used silicotungstic acid as a counter ion with di iso nonyl phthalate as plasticizer. Methacycline ion-selective PVC membrane electrodes were also developed by Aboul-Enein (Aboul-Enein and Sun 2000) based on the use of methacycline-tetraphenylborate as the electroactive substance, and di-octyl phthalate as plasticizer. In this work, several phenytion electrodes were constructed based on phosphomoylbdic acid as ionophore with different plasticizers. The properties of the prepared electrodes, pH effect, and selectivity coefficient measurements were evaluated.

Experimental Part

Equipments

An expandable ion analyzer (WTW model, Germany), a pH meter (WTW model pH 720, Germany), and a saturated calomel electrode (Gallenkamp, USA) were used in this work.

Reagents and solutions

1-Phenytion standard supplied from (Samara IRAQ-SDI).

2-Phenergan tablets (100 mg Phenytion Sodium) (Park-Davis Company, Germany,

and Pfizer Company ,USA) were purchased locally.

3-Di-octyl phthalate 98.9% (DOPH). was obtained from Fluka AG, Switzerland.

4-Tri-n-butyl phosphate 97% (TBP). was obtained from Fluka AG, Switzerland.

5-O-nitrio phenyl octyl ether 98% (ONPOE). was obtained from Fluka AG, Switzerland.

6-Di-n-butyl phthalate 99% (DBPH) was obtained from Fluka AG, Switzerland.

7- Stock solutions of 0.1 M for each of LiCl, NaCl, KCl, $CaCl_2$, $MgCl_2$, $ZnCl_2$, $FeCl_3$, $AlCl_3$, and $CrCl_3$ were prepared. More diluted solutions were prepared by subsequent dilution of the stock solutions.

8- A solution of 0.1 M phenytion was prepared by dissolving 0.6306 g of standard and making the solution up to 25 mL with deionized water.

9-A 0.05 M potassium hydrogenphthalate buffer solution (pH 4.00) was prepared by dissolving 10.21 g of solid potassium hydrogen phthalate in 1 L of deionized water after adjusting the pH.

Procedure

Preparation of ion-pair compound

PHT-PMA ion-pair was prepared by mixing 50 mL of 0.01 M phenytion with 50 mL of 0.01 M phosphomolybdic acid while stirring. The resultant precipitate was filtered, washed with deionized water, and dried at 60 ∘C.

Assembly of ion-selective electrodes

The construction of the electrode body and the immobilization were done as described by (Craggs et al. 1974).

The glass tube was 3⁄4 filled with 0.1 M phenytion solution as an internal filling solution. The membrane was conditioned by immersing in a standard solution of 0.1M for at least 2 hrs. before measurements.

Calibration curves were prepared by plotting the potential versus the concentration of phenytion. The pH of 10^{-4} , 10^{-3} and 10^{-2} M phenytion was adjusted with dilute solutions of sodium hydroxide and hydrochloric acid.

Selectivity measurements

A separate solution method was used for the selectivity coefficient measurement, and was calculated according to the equation (1) (Umezaw et al. 2000):

$$\log K^{pot} = [(E_B - E_A)/(2.303RT/zF)] + (1 - z_A/z_B) \log a_A \qquad (1)$$

E_A, E_B; z_A, z_B; and a_A, a_B are the potentials, charge numbers, and activities for the primary A and interfering B ions, respectively, at $a_A = a_B$. The selectivity coefficients were also measured by the mixed solution method according to the equation (2) (Tohda et al. 2001):

$$K^{pot} = \Delta a_A/a_B \qquad \Delta a_A = a_A - a_A \qquad (2)$$

$$K^{pot} AB = a_A / a_B^{z_A/z_B} \qquad (3)$$

Results and Discussion

Response characteristics of prepared phenytion are summarized in table (1). performances of electrodes prepared using an ion-pair complex as an electractive material and different plasticizers were compared experimentally.

Table (1) Response characteristics of PHT – PMA selective electrodes using different plasticizers.

Membrane Composition	PHT-PMA +DOPH	PHT-PMA +TBP	PHT-PMA +ONPOE	PHT-PMA +DBPH
Slope mV/decade	58.5	53.2	48.08	55.8
Linearity Range/M	$1\times10^{-4} - 1\times10^{-1}$	$5\times10^{-4} - 1\times10^{-1}$	$1\times10^{-4} - 1\times10^{-2}$	$5\times10^{-4} - 1\times10^{-1}$
Correlation coefficient	0.9997	0.9977	0.9968	0.9998
Detection Limit/M	5.5×10^{-5}	2.4×10^{-4}	1.2×10^{-4}	8×10^{-5}
Life time/day	60	5	2	45

The complex was incorporated into a PVC membrane with the following plasticizers: di-octyl phthalate (membrane I), tri-n-butyl phosphate (membrane II), o-nitro phenyl octyl ether (membrane III), and di-n-butyl phthalate (membrane IV). The working characteristics for the electrodes were assessed on the basis of their calibration curves. The physical properties of these membranes were as follows: white, flexible, clear, and transparent (non-crystalline).The slops are 58.5, 53.2, 48.08 and 55.8 mV/decade, respectively.

The correlation coefficients were 0.9997, 0.9977, 0.9968 and 0.9998 respectively. Non-Nernstian slopes were obtained for electrodes based on TBP and ONPOE(membranes IIand

III). The linear range and detection limits for the two electrodes were $(1.00 \times10^{-1}$ to $5 \times10^{-4})$M, 2.4×10^{-4} M and $(1.00 \times10^{-4}$ to$1.00 \times10^{-2})$M, 1.2×10^{-4} M respectively.

The non-Nernstian slope behaviors could be attributed to the low viscosity of ONPOE (11.44 cST), or incompatibility of the plasticizer with the complex in PVC. The TBP, which has a low viscosity (3.11 cST), leads to leaching of the complex from the membrane or may have a high steric effect on methyl groups. Near Nernstian slopes were obtained for the electrodes based on DOPH and DBPH (membranes I and IV). A typical calibration plot for electrodes I and IV are shown in Figure (1).
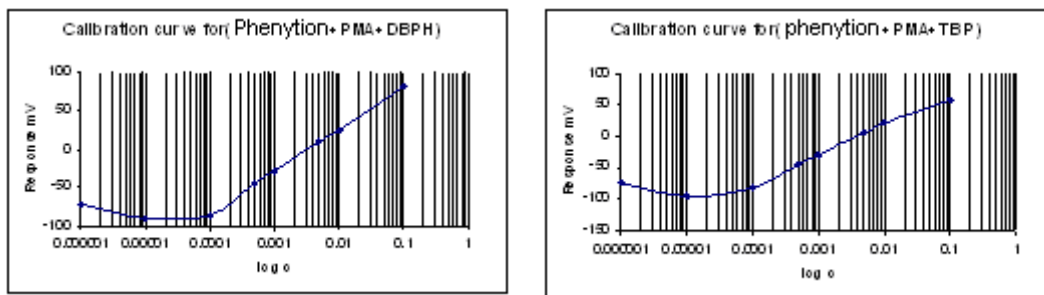
Figure (1) Calibration curves of phenytion selective electrodes. DOPH, TBP

Electrode parameters for DOPH as a plasticizer gave a good response. The electrode had good stabilityand was used for the quantitative determination of pharmaceutical drugs.

Effect of pH:

The effect of pH on the response of the electrodes was examined by measuring the potential variation in the *e.m.f.* over pH range of 1.0 – 12 for three different phenytion concentrations (10^{-2}, 10^{-3} and 10^{-4}) M and the results are listed in table (2)

Table (2) Working pH ranges for phenytion selective electrodes.

Number	Membrane Composition	pH range		
		1×10^{-2}	1×10^{-3}	1×10^{-4}
III	PHT- PMA + DOPH	2.4 – 8.2	2.1 – 7.6	3.3 – 9.8
II	PHT - PMA + TBP	2.6– 8.8	2.2 – 9.8	2.0 – 9.5
III	PHT - PMA + ONPOE	2.8 – 8.6	2.1 – 8.4	2.3 – 9.6
IV	PHT - PMA+ DBPH	2.0 – 9.6	2.2 – 9.8	2.2 – 10.2

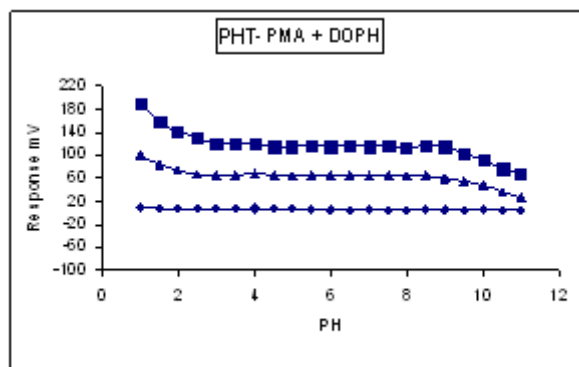The pH was adjusted by adding few drops of ammonia and hydrochloric acid solutions.

Figure (2) Effect of pH on the potential of the Phenytion electrodes at concentrations (■ 10^{-2}, ▲ 10^{-3} and ♦ 10^{-4}) M.

Response time

The response time at t_{95} for all the electrodes at concentrations ranging from $(10^{-6}$ to $10^{-1})$M was calculated from the response versus time plot and is listed in Table (3).

Table (3) Response time of Phenytion electrodes

Conc. (M)	Electrode I(sec)	Electrode II(sec)	Electrode III(sec)	Electrode IV(sec)
10^{-1}	12	17	20	13
10^{-2}	16	23	19	22
10^{-3}	20	28	24	23
10^{-4}	23	30	29	26
10^{-5}	25	32	30	28
10^{-6}	29	36	35	31

As shown, the longer response time reached around 36 s at 10^{-6} M. All the electrodes gave the same range of response times.

Selectivity

The influence of some inorganic cations on the response of phenytion electrods was investigated. Potentiometric selectivity can be measured with different methods that fall into two main groups, namely (Moody and Thomas 1971): mixed solution method, and separate solution method The selectivity of the electrodes based on DOPH and TBP was measured by the separate solution method for a concentration range from 10^{-6} to 10^{-1} M.The potentiometric selectivity coefficients were calculated using equation (1) at cation concentrations ranging between (10^{-6} and 10^{-1}) M. A typical plot is shown in Figure (3) for the interference of Fe^{3+} on the DOPH electrode. The values of the selectivity coefficients for DOPH and TBP electrodes are listed in Table 4.The selectivity coefficients were very small. This means that there is no interference of these cations with the response of phenytion electrodes. The order of selectivity was: Mono-valent > Di-valent > Tri-valent ions. Selectivity coefficients for ONOEP and DBPH as the plasticizers were also calculated by a separate solution method.
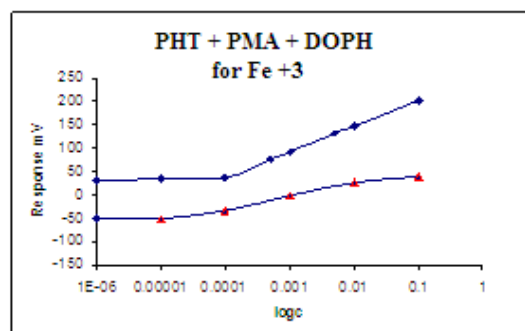

Figure (3) Selectivity of (PHT – PMA + DOPH) I and the interfering cation(Fe^{3+}) by separation method, ♦ Phenytion, ▲ Solution of interfering cation(Fe^{3+}).

Table (4) Selectivity Coefficients for (PHT-PMA+DOPH)I electrodes at different concentrations by separation method.

Interfering ions	Concentrations of Phenytion (M)					
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
	$K_{A,B}$	$K_{A,B}$	$K_{A,B}$	$K_{A,B}$	$K_{A,B}$	$K_{A,B}$
Li^{+}	1.63×10^{-3}	2.21×10^{-3}	1.69×10^{-3}	1.31×10^{-2}	3.25×10^{-2}	3.11×10^{-2}
K^{+}	2.38×10^{-3}	1.33×10^{-3}	1.54×10^{-2}	10.19×10^{-1}	1.66×10^{-1}	6.98×10^{-2}
Ca^{2+}	1.33×10^{-4}	5.62×10^{-5}	9.95×10^{-5}	1.77×10^{-4}	5.37×10^{-5}	2.08×10^{-5}
Mg^{2+}	1.54×10^{-4}	1.10×10^{-4}	1.51×10^{-4}	2.22×10^{-4}	7.26×10^{-5}	8.29×10^{-6}
Al^{3+}	2.28×10^{-5}	3.09×10^{-5}	3.13×10^{-5}	1.87×10^{-4}	2.22×10^{-5}	2.03×10^{-6}
Fe^{3+}	3.99×10^{-4}	4.11×10^{-3}	3.99×10^{-2}	8.12×10^{-2}	8.9×10^{-2}	4.06×10^{-2}

Table (5) Selectivity Coefficients for (PHT-PMA+TBP) II electrodes at different concentrations by separation method.

Interfering ions	Concentrations of Phenytion (M)					
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
	$K_{A,B}$	$K_{A,B}$	$K_{A,B}$	$K_{A,B}$	$K_{A,B}$	$K_{A,B}$
Li^{+}	6.89×10^{-9}	5.99×10^{-7}	4.29×10^{-5}	3.51×10^{-3}	6.54×10^{-2}	5.06×10^{-1}
K^{+}	2.93×10^{-8}	8.93×10^{-7}	6.94×10^{-5}	3.73×10^{-3}	4.08×10^{-2}	2.04×10^{-1}
Ca^{2+}	9.03×10^{-2}	2.01×10^{-1}	3.25×10^{-2}	3.08×10^{-1}	2.91×10^{-1}	2.52×10^{-1}
Mg^{2+}	3.93×10^{-5}	2.99×10^{-4}	4.39×10^{-4}	2.13×10^{-3}	6.93×10^{-4}	9.68×10^{-4}
Al^{3+}	1.99×10^{-2}	1.32×10^{-2}	2.81×10^{-2}	3.94×10^{-2}	2.26×10^{-2}	2.99×10^{-3}
Fe^{3+}	5.02×10^{-7}	3.08×10^{-5}	5.44×10^{-4}	2.01×10^{-2}	3.31×10^{-1}	4.19×10^{-1}

The selectivity coefficients indicate good selectivity for phenytion against some common transition metal ions.Moreover, the selectivity coefficient for monovalent ions is lower than that for divalent ions.This may be due to the differences in ionic size, mobility and permeability.

Mixed solution method (FIM) Also used the potentiometry of a cell comprising an ion-selective electrode and a reference electrode (ISE cell) is measured for solutions of constant activity of the interfering ion (a_B) (5×10^{-3} , 5×10^{-4} and 5×10^{-5}) M that calculated in 20 mL total volume after mixed it with varying of the primary ion that is for the phenytion (a_A). The potentiometry E values obtained are plotted vs. the logarithm of the activity of the primary ion.The results shown in table (6).

Table (6) Values of $K^{pot}_{A,B}$ calculated from the equation

$$[K^{pot}_{A,B} = a_A / (a_B)^{Z_A/Z_B}]$$ **according to FIM .**

Membrane Composition	Interfering ions	a_A when $a_B = 5\times10^{-5}$	$K^{pot}_{A,B}$ when $a_B = 5\times10^{-5}$	a_A when $a_B = 5\times10^{-4}$	$K^{pot}_{A,B}$ when $a_B = 5\times10^{-4}$	a_A when $a_B = 5\times10^{-3}$	$K^{pot}_{A,B}$ when $a_B = 5\times10^{-3}$
PTH-PTA+ DOPH (I)	K^+	5×10^{-4}	10.00	9×10^{-4}	1.8	2×10^{-2}	0.4
	Ca^{+2}	1×10^{-4}	1.414×10^{-2}	8×10^{-4}	3.57×10^{-2}	3×10^{-3}	4.24×10^{-2}
	Fe^{+3}	7×10^{-4}	1.90×10^{-2}	1×10^{-3}	1.25×10^{-2}	3×10^{-3}	1.75×10^{-2}
PTH-PTA+ DBPH (IV)	K^+	7×10^{-4}	14	2×10^{-3}	4	2×10^{-3}	0.4
	Ca^{+2}	3×10^{-4}	4.24×10^{-2}	8×10^{-4}	3.57×10^{-2}	4×10^{-3}	5.65×10^{-2}
	Fe^{+3}	7×10^{-4}	1.90×10^{-2}	2×10^{-4}	2.51×10^{-2}	5×10^{-3}	2.92×10^{-2}

Sample Analyses:

Three different potentiometric techniques were used for the determination of phenytion ion including direct, incremental methods, standard addition (SAM), multiple standard additions (MSA)(Rundl 2004). Synthetic solutions of phenytion at concentrations between (10^{-5} and 10^{-3}) M were used for the standard addition method using DOPH and ONPOE electrodes. The%RSD, % RC, and % RE were calculated and are listed in table (7).

Table (7) Determination of phenytion-ion samples by potentiometric techniques.

Electrode No.	Sample	Concentrations (M)			
		Measurements using potentiometric methods			
		Direct	SAM	MSA	Titration
PHT– PMA+ DOPH (I)	1×10^{-3}	1.012×10^{-3}	0.997×10^{-3}	1.002×10^{-3}	1.03×10^{-3}
	RSD%	1.3*	1.32*	-	-
	RC%	101.2	99.7	100.2	103
	RE%	1.2	-0.3	0.2	3
	1×10^{-4}	0.995×10^{-4}	1.004×10^{-4}	0.998×10^{-4}	1.02×10^{-4}
	RSD%	2.01*	0.25*	-	-
	RC%	99.5	100.4	99.8	102
	RE%	-0.5	0.6	-0.2	2
PHT– PMA + ONOEP (III)	1×10^{-3}	1.021×10	$0.977\times10^{-3-3}$	1.008×10^{-3}	0.97×10^{-3}
	RSD%	1.23*	1.01*	-	-
	RC%	102.1	97.7	100.8	97
	RE%	2.1	-3.3	0.8	-3
	1×10^{-4}	0.973×10^{-4}	0.975×10^{-4}	1.018×10^{-4}	0.95×10^{-4}
	RSD%	2.03*	1.28*	-	-
	RC%	97.3	97.5	101.8	59
	RE%	-2.7	2.5	1.8	-5

 * Each measurement was repeated three times.

The plot of antilog E/S versus the volume of the five addition for 0.1 mLof 1×10^{-1}M standard phenytion solution to the 1×10^{-3} M

phenytion is shown in figure (4) . Gran plot paper with 10% volume correction was used.
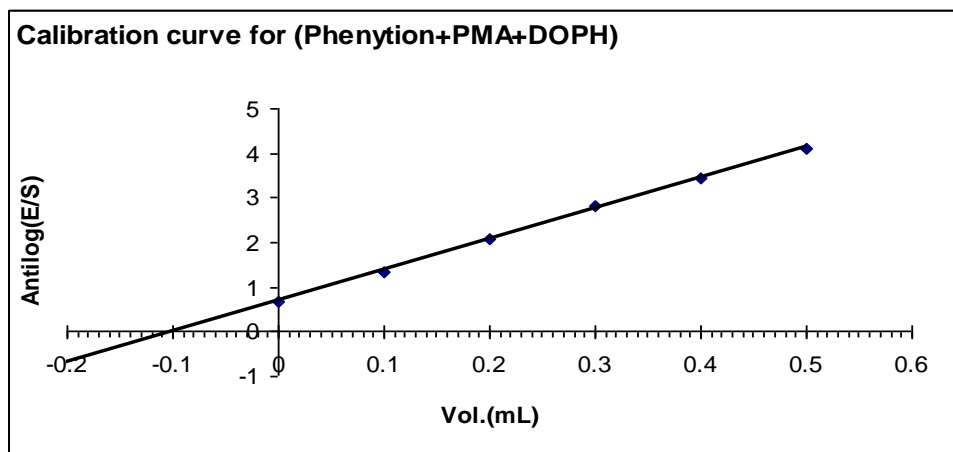

Figure (4) Plot antilog (E/S) versus the value of the added standard for the determination of Phenytion solution (10^{-3} M) by MSA using PT-PMA +DOPH electrode.

The results in table (1) showed that the electrode based on DOBH as a plasticizer was the best electrode.

Figure (5) shows a typical plot for the titration curve of 0.01 M phenytion standard solution

with 0.01 M phsophomolybdic acid as a titrant using the phenytion electrode based on membrane containing DOPH plasticizer.
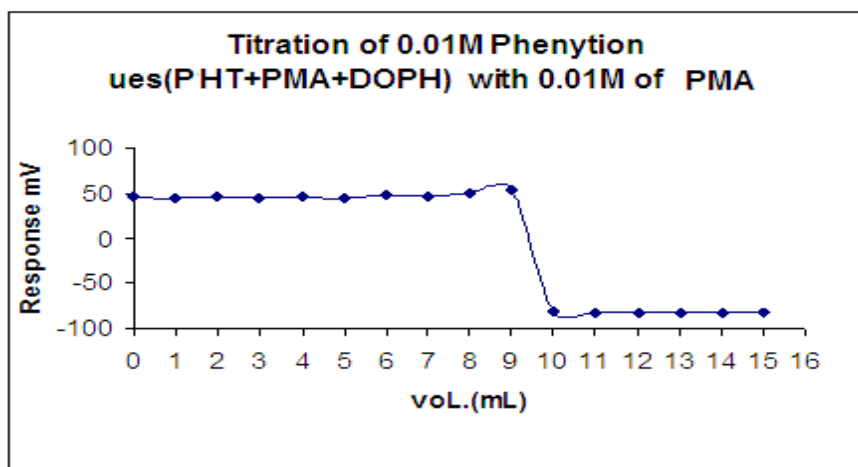

Figure (5): Titration curve of electrode (PHT-PMA +DOPH) for drug solution containing 0.01 M Phenytion with 0.01 M of PMA as titrant solution.

The direct potentiometric method was applied for the determination of Phenytion in pharmaceutical tablets (Epanutin from samara, Germany and USA) as listed in table (8) using the electrode based on membrane (I). The average recovery for phenytion determination in tablets was around 99.03% with astandard deviation of about 0.1, based on an average of 3 measurements for each sample.

Table (8) sample analysis for tablets using the phenytion selective electrode   based on DOPH plasticizer using the direct potentiometric method.

Pharmaceuticl	Epanutin (samara)	Epanutin (Germany)	Epanutin (USA)
Concentration of phenytion(prepared)/M	1×10^{-3}	1×10^{-3}	1×10^{-3}
Concentration of phenytion(found)/M	0.978×10^{-3}	1.011×10^{-3}	0.982×10^{-3}
%recovery	97.8	101.1	98.2
%RE	-2.2	1.1	-1.8
%RSD	2.12	2.46	1.84

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تحضير والدراسة المجهادية للاقطاب الانتقائية الايونية للفينيتون المبنية على غشاء لقالب PVC

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الخلاصة

تم تحضير عدة أقطاب ايونيه في مادة PVC حساسه للفينتون بالاعتماد على المعقد (-Phenytoin phosphomolybdic acid) كماده فعاله. هذه الماده الفعاله تكون مذابه في عدة مواد ملدنه منها , Di-butyl phthalate (DBPH), Tri-butyl phosphate (TBP), O-nitrophenyloctylether (ONPOE), Di-octylphthalate (DOPH),

تم مزج احد هذه الملدنات والمعقد مع PVC لتكوين الغشاء ومن خلال منحنى التدرج تم دراسة خواص هذه الاقطاب والتي تشمل (منحنى الانحدار و مدى التركيز وحد التحسس و عمر القطب و تأثير ال pH) ومن خلال الدراسه وجد ان الأقطاب المتكونه من(DBPH,DOPH) كمواد ملدنه تمتلك مواصفات جيده يمكن الأعتماد عليها في تعيين الفينتون بصوره دقيقه، منحنى الأنحدار لهذه الأقطاب كان يساوي تقريباً (mV/decade) 55.8,58.5 مدى التركيز التي تتحسسهُ هذه الأقطاب تراوحت من (1x10^{-4} الى 1x10^{-}M^{1})،(5 x10^{-4}الى1 x 10^{-1})M حد التحسس لهذه الأقطاب كان بحدود (5.5x10^{-5}M, 8.0 x 10^{-5}M) فيما كان معامل الارتباط (0.9998,0.9997) بالتعاقب.

أيضاً تم دراسة تداخلات بعض الأيونات الموجبه مع الأقطاب بواسطة طريقة المحاليل المنفصله وتم تعيين معامل الأنتقائية لهذه الأيونات، وتبين ان تداخلات الأيونات الأحاديه تكون أكبر من تداخلات الأيونات الثنائيه والثلاثية. استخدمت الاقطاب لتقدير الدواء في نماذج قياسية محضرة وكذلك في نماذج دوائية . وان الطرق التحليلية أثبتت أنها طريقة سريعة وبسيطة وتعطي نتائج جيدة.