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New potentiometric membrane sensor determination of warfarin sodium in pharmaceutical samples

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ABSTRACT

Sensitive and fast-responding potentiometric sensors are described for the determination of warfarin sodium. They consist of PVC matrix membranes containing the drug- phosphomolybdate ionophore complexes as electroactive materials and Tetrahydrofuran as a solvent mediator used various plasticizers: oleic acid (OA), tri-n-butylphosphate(TBP), Nitrobenzen (NB), Acetophenone (AP) and di-octyl phthalate (DOPH).. Linear dynamic response range between 1×10^{-1} and 1×10^{-5} *M* with Nernstian slopes of 21.3–31.6 mV/decade concentration and a detection limit of (7×10^{-6} - 2×10^{-5}) M are obtained, correlation coefficient of 0.9969 and 0.9998, the lifetime was (7-35) days respectively. A wide range of inorganic anions, amino acid and drag excipients do not interfere. Titration of the drugs with a standard phosphomolybdate solution using various sensors in conjunction with an Ag-AgCl working electrode displays *S*-shaped titration curves with sharp potential breaks at stoichiometric 16:2 (drug : phosphomolybdate) reaction. The proposed electrodes were successfully applied to the determination of warfarin in various pharmaceutical preparations are presented and compared. Several advantages over the pharmacopoeial methods and other techniques in current use are offered by the proposed technique.

KEYWORDS

Potentiometry;
Ion-selective sensor;
Warfarin sodium;
Ion-pair;
Pharmaceuticals.

INTRODUCTION

COUMADIN (crystalline warfarin sodium) is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(α-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the *R*- and *S*-enantiomers. Crystalline warfarin sodium is an isopropanol clathrate. Its empirical formula is $C_{19}H_{15}NaO_4$, and its structural formula may be represented by the following:

Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether[1]. The compound was first synthesized by Schroeder and Link [2] with two solid forms available-amor-

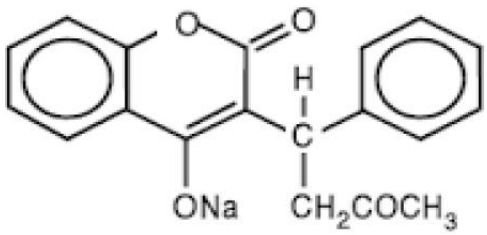

Figure 1 : Structur of warfarin sodium

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phous and crystalline clathrate. The amorphous form isstable in ambient conditions. The crystalline clathrate form is warfarin sodium-isopropyl alcohol complex, which is prepared either from warfarin or amorphous warfarin sodium to eliminate impurities in warfarin sodium[3]. The pharmacologic function of the compound is an anticoagulant that inhibits the synthesis of vitamin K-dependent coagulation factors[4]. Warfarin inhibits the action of vitamin K epoxide reductase, whose gene (VKORC1) was discovered in 2004 by two independent teams[5,6]. In an attempt to decrease the toxicity of warfarin induction,several clinical dosing algorithms have been proposed[7,12], but none has been well accepted. A major barrier to their use is that they were developed for middle-aged inpatients who could tolerate doses of 5–10 mg warfarin dailyand who had daily monitoring of the INR. Today,the typical person taking warfarin is elderly. Because warfarin dose requirements decrease with age,use of existing algorithms tends to overdose the elderly[13,15].

EXPERIMENTAL PART

Equipment

An expandable ion analyzer (Orion model EA-940, USA), a pH meter (WTW model pH 522, Germany), and a saturated calomel electrode (GallenKamp) were used in this work.

Reagents and solutions

Warfarin sodium standard was a gift from the State Company of Drug Industries and Medical Appliances (Samara IRAQ-SDI). tablets (1 mg warfarin sodium) (Bristol-Myers Squibb Company, USA) and tablets (3 mg warfarin sodium)(Actavis-)were purchased locally. Oleic acid 98.9% (OA), tri-n-butyl phosphate 97% (TBP), Nitrobenzene 98% (NB), Acetophenone 98% (AP), di-octyl phthalate 99% (DOPH) and phospho molybdic acid (PMA) were obtained from Fluka AG, Switzerland. Stock solutions of 0.1 M for each of NaCl, KCl, $CaCl_2$,$MgCl_2$,,$FeCl_3$,$AlCl_3$, Alanine,Glycine,Serine, Proline,phenylalanine and Asparginine were prepared. More diluted solutions were prepared by subsequent dilution of the stock solutions.

A solution of 0.1 M warfarin sodium was prepared by dissolving 1.65 g of standard and making the solution up to 50 mL with deionized water.

Preparation of the WFN-PMA ion-pair

WFN-PMA ion-pair was prepared by mixing 50 mL of 0.01 M warfarin sodium with 50 mL of 0.01 M phospho molybdic acid while stirring. The resultant precipitate was filtered, washed with water, and allowed dried at room temperature for two days.

Electrode membrane preparation and measurements

The membranes have the composition ion-pair : PVC: plasticizer in the ratio 1:33:66. The electroactive material and the solvent mediator were mixed together, and then the PVC and the appropriate amount of THF were added and mixed to obtain a transparent solution. This solution was transferred onto a glass plate of 20 cm2, and the THF was allowed to evaporate at room temperature leaving a tough, flexible membrane embedded in a PVC matrix. An 8 mm diameter piece of membrane was cut out and assembled on the Fluka electrode body. The measurements were carried out at room temperature using a WTW Instruments Terminal 740 pH/mV-meter.

Selectivity measurements

A separate solution method was used for the selectivity coefficient measurement, and was calculated according to the equation[16]

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

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 match method according to the equation[17]

$$K_{pot}=\Delta a_A/a_B,\ \Delta a_A=a_A-a_A \quad (2)$$

RESULTS AND DISCUSSION

In this study, improved versions of warfarin sodium selective electrode by using membranes prepared using commercial drugs based on (PMA) the basis of the task was the preparation of the specific ionic liquids. It was investigated phosphate molyb-

dic acid in ion-selective electrodes to fully understand its functions as both an ionophore and plasticizer in potentiometric sensors.

The behaviour of potentiometric sensors with carbon paste electrode depends on the composition of the electrode material used and the condition of the contact solution. It is known that the response of an ion selective electrode depends not only on the nature and amount of an ionophore but also on the nature and the amount of the plasticizer. The influence of the plasticizer type and concentration on the characteristics of the studied warfarin sodium electrode was investigated using five plasticizers with different polarities, including OA, TBP, NB, AP and DOPH. Different plasticizer/WFN /PMA (w/w) ratios were studied to determine the influence of the amount of plasticizer in the electrode. The obtained results are presented in TABLE (1). These results show that the potentiometric responses of the electrodes modified with conventional plasticizers were satisfactory, where as those of the proposed electrode towards warfarin sodium electrodes were greatly improved in the presence of PMA as both an ionophore and a plasticizer.

Warfarin- phosphomolybdate is a stable ion-pair complex which is water insoluble but readily soluble in an organic solvent such as tetrahydrofuran (THF). The obtained complex was incorporated into a PVC membrane with the following plasticizers: oleic acid (OA) (membrane I), tri-n-butylphosphate(TBP) (membrane II), Nitrobenzen (NB) (membrane III), Acetophenone (AP) (membrane IV) and di-octylphthalate (DOPH) (membrane V). The low slope value obtained for membrane(IV)may be attributed to the plasticizers used acetophenone (AP) which formation highly conjugated complex, this may decreased the ion-exchange process between the electro-active compound (WFN-PMA) and the external solution of warfarin sodium, or may be attributed to the steric factor of the plasticizers (AP) which decreased the bond strength with the electro-active compound. Also the non-Nernstian slope behaviors for membrane(IV) could be attributed to the low viscosity of AP (1.68 cST) and lead to leaching of the complex from the membrane to the external pair complex (WFN-PMA) in membrane and the external solution of warfarin sodium. Near Nernstian slopes were obtained for the electrodes based on OA and TBP (membranes I and II). A typical calibration plot for electrodes I and II are shown in Figure (2).

Electrode parameters for oleic acid (OA) as a plasticizer gave a good response that may be due to attributed to the compatibility of the plasticizer used to the electro-active compound from both structure and composition. Also Electrode parameters for TBP as a plasticizer gave a good response that may be attributed to the compatibility of the plasticizer which was used to the electroactive compound from both structure and composition, The electrode had good stability and was used for the quantitative determination of pharmaceutical drugs.

Effect of pH on electrodes response

The pH of each solution was verified, and its effect on the electrode potential at various warfarin sodium concentrations was studied. For this purpose, several concentrations (1.0×10^{-2}M, 1.0×10^{-3} M and 1.0×10^{-4} M) were prepared, and the potential variations of the electrode over a pH range of 1-11 were followed. The pH was adjusted by adding small volumes of hydrochloric acid (1 M) and/or sodium hydroxide (2 M) to the sample solution. The obtained

TABLE 1 : Composition and optimization of warfarin sodium selective electrode

No.	WFN-PMA (%)	PVC (%)	Plasticizer (%)	Linearity Range/M	Slope (mV dec-1)	Detection Limit/M	Life time/day	R^2
I	7.0175	29.8245	63.1578 (OA)	1×10^{-5}_ 1×10^{-1}	31.6	7×10^{-6}	35	0.9995
II	7.0175	29.8245	63.1578 (TBP)	1×10^{-4}_1×10^{-1}	28.07	5×10^{-5}	25	0.9969
III	7.0175	29.8245	63.1578 (NB)	1×10^{-5}_1×10^{-1}	25.06	5×10^{-6}	14	0.9994
IV	7.0175	29.8245	63.1578 (AP)	1×10^{-4}_1×10^{-1}	21.3	2×10^{-5}	7	0.9994
V	7.0175	29.8245	63.1578 (DOP)	1×10^{-4}_1×10^{-1}	26.4	6×10^{-6}	20	0.9998

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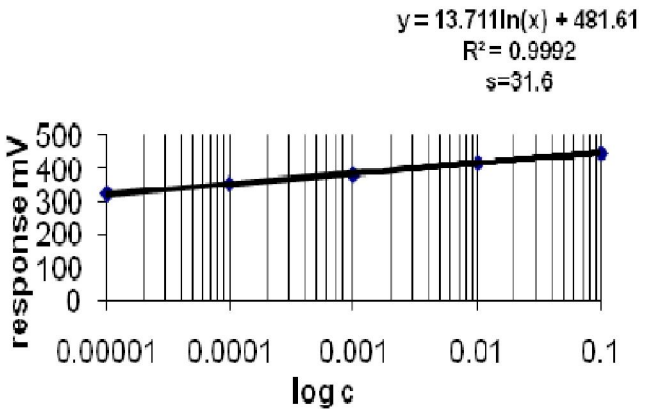

Figure 2 : (a) calibration curve for warfarin-PMA+OA

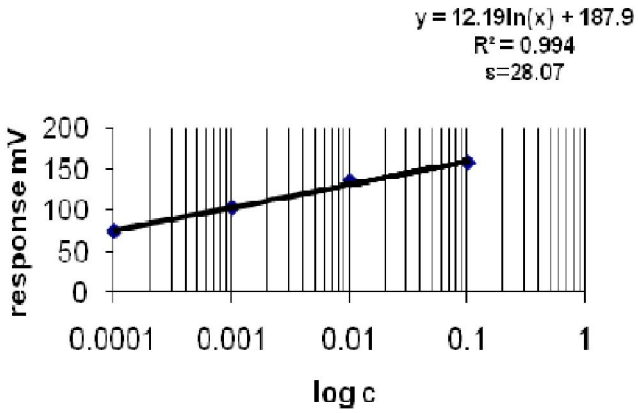

Figure 2 : (b) calibration curve for warfarine-PMA+TBP

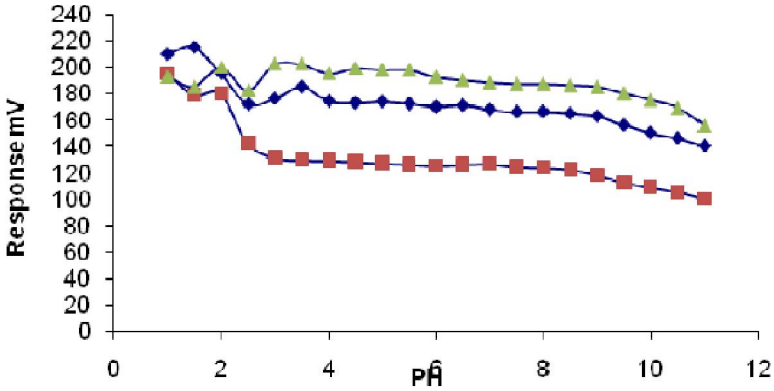

Figure 3 : Effect of pH on the potential response of warfarin sodium electrode at concentrations (■ 10^{-2}, ▲ 10^{-3} and ♦ 10^{-4}) M

results are shown in Figure (3). It can be seen that the electrode potential remain almost constant in the pH range of 4-9. The change in potential at higher pH values may be due to the formation of hydroxy complexes of warfarin sodium[18]. At lower pH values, a sharp decrease in the electrode response is observed; this result is due to the protonation of carboxylic groups on the PMA molecule.

Potentiometric selectivity coefficients

It is well known that the selectivity behaviour of an electrode is one of the most important factors in its evaluation, which is measured in terms of the selectivity coefficient. The selectivity coefficient not only depends on ion charge and concentration, but it can also be affected by the type of interaction between the ion and the ionophore. The selectivity factor, log k^{pot} is a measure of the preference of ion selective electrode for interfering ion relative to the primary ion to be measured. A selectivity factor log k^{pot} below 1 indicates that the preference is for the primary ion. TABLE (2) show that the electrode exhibited better selectivity for the warfarin sodium over a wide variety of other metal ions. The values of the selectivity coefficients, listed in TABLE(2), reflect a very high selectivity of this electrode for warfarin sodium over most of the tested species. Asparginine and phenylalanine caused only slight interference. However, they do not cause any interference at low concentration. This phenomenon suggests a high stability of the complex between warfarin sodium and PMA.

The selectivity sequence of the warfarin sodium electrodes employed for different inorganic cations approximately obeys the order:

Tri > Di > Mono

It is worth mentioning that electrodes have excellent selectivity for the warfarin sodium over other metal ions; this selectivity may be due to the design of PMA to contain negatively charged O-donor groups that enhance its complexing ability for the warfarin sodium over other metals. Here, it is critical to note the existence of a rule of ligand design

TABLE 2 : Selectivity coefficients for electrodes at different concentration of warfarin sodium for (WFN-PMA+OA) electrode

	Concentration 10^{-1}M		Concentration 10^{-2}M		Concentration 10^{-3}M		Concentration 10^{-4}M		Concentration 10^{-5}M	
Interfering Ion	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$
Na+	285.1	4.642×10^{-3}	262.4	9.623×10^{-3}	243.7	1.935×10^{-2}	228.1	1.765×10^{-1}	211.3	1.096×10^{-1}
K+	295.4	1.023×10^{-2}	275.1	2.551×10^{-2}	249.4	2.997×10^{-2}	222.1	1.113×10^{-1}	211.7	1.131×10^{-1}
Ca^{2+}	233.1	2.712×10^{-5}	222.1	4.365×10^{-5}	211.7	5.248×10^{-5}	195.3	1.423×10^{-4}	170.4	1.502×10^{-5}
Mg^{2+}	225.4	1.502×10^{-5}	219.4	3.548×10^{-5}	202.1	2.512×10^{-5}	190.1	9.549×10^{-5}	181.4	3.494×10^{-5}
Fe^{3+}	110.7	1.536×10^{-9}	104.7	2.469×10^{-9}	95.4	2.199×10^{-9}	89.3	8.954×10^{-9}	81.7	2.427×10^{-9}
AL^{3+}	115.7	2.254×10^{-9}	111.2	4.068×10^{-9}	100.7	3.304×10^{-9}	96.4	1.544×10^{-8}	90.1	4.624×10^{-9}
Alanine	150.7	1.537×10^{-7}	147.6	1.434×10^{-6}	142.3	8.066×10^{-6}	136.5	1.561×10^{-4}	130.1	2.154×10^{-4}
Glycine	195.7	4.860×10^{-6}	190.4	3.831×10^{-5}	183.4	1.891×10^{-4}	175.4	3.090×10^{-3}	168.3	4.043×10^{-3}
Serine	90.1	1.468×10^{-9}	85.7	1.239×10^{-8}	79.4	6.456×10^{-8}	70.4	9.77×10^{-7}	64.9	1.445×10^{-6}
Proline	200.1	6.813×10^{-6}	190.1	3.744×10^{-5}	187.3	2.551×10^{-4}	170.3	2.089×10^{-3}	165.3	3.211×10^{-3}

TABLE 3 : Selectivity coefficients for electrodes at different concentration of warfarin sodium for (WFN-PMA+DOPH) electrode

	Concentration 10^{-1}M		Concentration 10^{-2}M		Concentration 10^{-3}M		Concentration 10^{-4}M		Concentration 10^{-5}M	
Interfering Ion	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$
Na+	215.2	7.870×10^{-3}	200.1	1.368×10^{-2}	175.4	1.614×10^{-2}	162.3	1.202×10^{-1}	150.4	1.306×10^{-1}
K+	225.3	1.995×10^{-2}	205.3	2.208×10^{-2}	180.1	2.489×10^{-2}	157.3	7.586×10^{-2}	141.2	5.598×10^{-2}
Ca^{2+}	100.4	6.368×10^{-8}	92.2	6.607×10^{-8}	81.7	9.120×10^{-8}	72.3	3.019×10^{-7}	65.7	1.690×10^{-7}
Mg^{2+}	115.3	2.512×10^{-7}	110.8	3.664×10^{-7}	105.7	8.318×10^{-7}	100.7	4.130×10^{-6}	94.2	2.333×10^{-6}
Fe^{3+}	65.3	1.710×10^{-9}	61.8	1.862×10^{-9}	55.4	2.553×10^{-9}	49.3	7.798×10^{-9}	41.3	2.612×10^{-9}
AL^{3+}	55.3	6.808×10^{-10}	51.7	1.399×10^{-10}	46.2	1.094×10^{-9}	39.7	3.221×10^{-9}	32.4	1.151×10^{-9}
Alanine	60.2	2.349×10^{-7}	52.7	7.217×10^{-7}	43.9	5.412×10^{-6}	38.7	2.154×10^{-5}	26.7	9.905×10^{-5}
Glycine	104.6	1.663×10^{-5}	98.5	5.843×10^{-5}	90.3	4.641×10^{-4}	83.7	1.616×10^{-3}	77.3	1.271×10^{-2}
Serine	130.1	1.920×10^{-4}	125.7	7.943×10^{-4}	118.6	7.012×10^{-3}	111.4	2.304×10^{-2}	104.7	1.761×10^{-1}
Proline	172.3	1.101×10^{-2}	160.3	2.196×10^{-2}	152.3	1.778×10^{-1}	135.1	2.239×10^{-1}	115.4	4.917×10^{-1}

that permits fairly predictable control of selectivity on the basis of metal ion size. Ionic radius is an important parameter in the formation and stability of metal complexes[19].

Dynamic response time

The response time of the electrode is one of the most important characteristics of the ion selective electrode. The IUPAC definition of the response time has changed over time[20,21]. According to IUPAC recommendations, the response time of an ion selective electrode is defined as the time between the addition of the analyte to the sample solution and the time when limiting potential has reached its steady state value within 1± mV. In this study, the response time of the electrode was tested by measuring the time required to achieve a steady state potential (within 1± mV of the final equilibrium value) after successive immersion in a series of warfarin sodium. The results, shown in TABLE (4) indicate that the response time of the electrodes was approximately (12-49)s for the solution of warfarin sodium in the concentration range of 1×10^{-1} -1×10^{-5} M. This result is probably due to the fast complexation of warfarin sodium by the PMA molecule dispersed in the membrane matrix.

Electrodes life time

The life time of the electrode depends on the distribution coefficient of the electrode compositions

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TABLE 4 : Response time of warfarin sodium electrodes

Membrane composition	Concentration (M)	Potential (mV) at t/100	Time (s) at 95%	Time (s) at 100%
WFN-PMA+OA (I)	10^{-1}	2.1	12	13
	10^{-2}	3.4	15	19
	10^{-3}	4.2	22	24
	10^{-4}	6.4	27	30
	10^{-5}	9.4	32	33
WFN-PMA+TBP (II)	10^{-1}	3.8	16	17
	10^{-2}	4.1	21	23
	10^{-3}	5.0	27	29
	10^{-4}	6.5	30	33
	10^{-5}	10.9	38	40
WFN-PMA+NB (III)	10^{-1}	4.4	17	18
	10^{-2}	4.9	23	25
	10^{-3}	6.7	31	32
	10^{-4}	7.8	36	39
	10^{-5}	9.4	43	45
WFN-PMA+AP (IV)	10^{-1}	2.7	19	20
	10^{-2}	4.5	29	31
	10^{-3}	5.5	35	38
	10^{-4}	6.7	42	45
	10^{-5}	8.5	49	52
WFN-PMA+DOPH (V)	10^{-1}	2.7	13	15
	10^{-2}	4.5	17	20
	10^{-3}	6.7	24	25
	10^{-4}	8.9	32	33
	10^{-5}	10.5	38	40

between the aqueous phase and the electrode phase. Accordingly, the life time of the electrode must depend on the electrode components.

In this work, the life time of the electrode was determined by performing periodic calibrations with standard solutions and calculating the slopes over warfarin sodium concentration ranges of 1×10^{-1} to 1×10^{-6} M. The obtained results showed that the present electrodes have varying lifetime up to 35 days (TABLE 5). During this time, the detection limit of the electrodes are affected by the life time, and the slope of the electrodes response decreases during this time. Therefore, the electrode(I) can be used for at least two months without a considerable change in its response characteristic towards warfarin sodium, which may be due to the distribution of membrane components are homogeneous helping to reach a short preprocessing of times.

Sample analysis

Potentiometric techniques were used for the determination of warfarin sodium, these included direct, standard addition (SA), multiple standard addition (MSA), Gran plot, and titration method. Synthetic solutions of warfarin sodium at concentrations between 10^{-3} and 10^{-4}M were used for the standard addition method[22] using oleic acid (OA) and nitrobenzene (NB) electrodes. The %RC, %RSD, and %RE were calculated and are listed in TABLE(6).

The plot of antilog E/S versus the volume of the five addition for 0.1 mL of 1×10^{-1} M standard warfarin sodium solution to the 1×10^{-4} M warfarin sodium is shown in Figure (4). Gran plot paper with 10% volume correction was used. The results in TABLE (1)showed that the electrodes based on(OA) and (NB) as plasticizers were the best electrodes.

TABLE 5 : Life time of warfarin sodium electrode

WFN-PMA-OA (I)	**Time period Day**	**7**	**14**	**21**	**30**
	Slop (mV/decade)	31.6	29.5	26.8	24.8
	Limit of Detection (M)	7×10^{-6}	6×10^{-6}	5×10^{-6}	3×10^{-6}
WFN-PMA-TBP (II)	**Time period Day**	**7**	**14**	**21**	**28**
	Slop (mV/decade)	28.07	26.8	22.6	_
	Limit of Detection (M)	5×10^{-5}	4×10^{-5}	2×10^{-5}	_
WFN-PMA-NB (III)	**Time period Day**	**7**	**10**	**21**	**28**
	Slop (mV/decade)	25.06	22	_	_
	Limit of Detection (M)	5×10^{-6}	3×10^{-6}	_	_
WFN-PMA-AP (IV)	**Time period Day**	**5**	**14**	**21**	**28**
	Slop (mV/decade)	21.3	_	_	_
	Limit of Detection (M)	2×10^{-5}	_	__	_
WFN-PMA-DOPH (V)	**Time period Day**	**7**	**14**	**18**	**28**
	Slop (mV/decade)	26.4	23.4	21.3	_
	Limit of Detection (M)	6×10^{-6}	4×10^{-6}	2×10^{-6}	_

TABLE 6 : Determination of warfarin -ion samples by potentiometric techniques

Electrode No.	**Sample**	**Concentrations (M)**			
		Measurements using potentiometric methods			
		Direct	**SAM**	**MSA**	**Titration**
WFN– PMA +OA (I)	1×10^{-3}	0.951×10^{-3}	1.008×10^{-3}	0.983×10^{-3}	0.95×10^{-3}
	RSD%	0.12*	2.15*	-	-
	RC%	95.1	100.8	98.3	95
	RE%	-4.9	0.8	-1.7	-5
	1×10^{-4}	0.983×10^{-4}	1.002×10^{-4}	0.976×10^{-4}	0.97×10^{-4}
	RSD%	0.12*	2.6	-	-
	RC%	98.3	98.5	97.6	97
	RE%	-1.7	0.2	-2.4	-3
WFN– PMA + NB (III)	1×10^{-3}	0.997×10^{-3}	0.996×10^{-3}	0.968×10^{-3}	0.94×10^{-3}
	RSD%	0.29*	1.08*	-	-
	RC%	97	99.6	96.8	94
	RE%	-3	-0.4	-3.2	-6
	1×10^{-4}	0.977×10^{-4}	1.01×10^{-4}	0.996×10^{-4}	0.96×10^{-4}
	RSD%	0.32*	2.8*	-	-
	RC%	97.7	101	99.6	96
	RE%	-2.3	1	-0.4	-4

*** Each measurement was repeated five times**

Figure (5) shows a typical plot for the titration curve of 0.001 M warfarin sodium standard solu-

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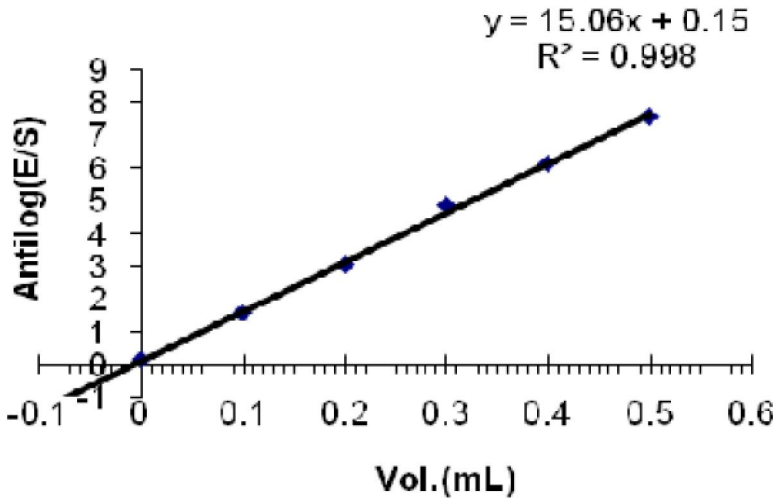

Figure 4 : Plot antilog (E/S) versus the value of the added standard for the determination of warfarin sodium solution (10^{-4} M) by MSA using (WFN-PMA +NB) electrode

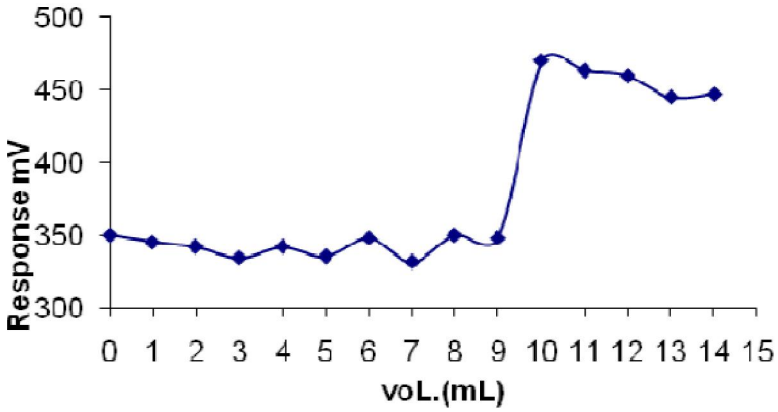

Figure 5 : Titration curve of electrode (WFN-PMA +OA) for drug solution containing 0.001 M warfarine sodium with 0.001 M of PMA as titrant solution at PH 8.0

TABLE 7 : warfarin sodium tablets analyses for electrode (WFN-PMA+OA) and (WFN– PMA + NB)

Electrod NO.	Parameter	Actavis (tablet)		Bristol (tablet)	
WFN– PMA +OA (I)	Concentration(M)	1×10^{-3}	1×10^{-4}	1×10^{-3}	1×10^{-4}
	Found(M)	0.95×10^{-3}	0.976×10^{-4}	0.949×10^{-3}	0.975×10^{-4}
	RSD%	0.15	0.14	0.16	0.15
	RC%	95	97.6	94.9	97.5
	RE%	-5	-2.4	-5.1	-2.5
WFN– PMA + NB (III)	Concentration(M)	1×10^{-3}	1×10^{-4}	1×10^{-3}	1×10^{-4}
	Found(M)	0.969×10^{-3}	1.02×10^{-4}	0.973×10^{-3}	0.97×10^{-4}
	RSD%	0.31	0.28	0.3	0.24
	RC%	96.9	102	97.3	97
	RE%	-3.1	2	-2.7	-3

tion with 0.001 M phsophomolybdic acid as a titrant using the warfarin sodium electrode based on membrane containing (OA) plasticizer.

The electrodes based on (OA) and (NB) as plasticizers appearance good parameters therefore applied for pharmaceutical samples. The direct potentiometric method was applied for the determination of warfarin sodium in pharmaceutical tablet (actavis) and (Bristol) as listed in TABLE (7) using the electrode based on membrane (I) and (III). The average

recovery for warfarin sodium determination in tablets was around (96.2-98.3)% with a relative standard deviation of about(0.15-0.28) %, based on an average of 5 measurements for each sample.

CONCLUSIONS

The membranes incorporating CD carrier have many advantages including: easy preparation, low cost, wide dynamic range, low detection limit, suitable pH range, Nernstian behavior and good reproducibility. The sensor is used successfully to determine the warfarin sodium in pharmaceutical samples with satisfactory results.

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