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Mefenamic Acid Selective Membranes Sensor and Its Application to pharmaceutical Analysis

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Abstract:

PVC membrane sensor for the selective determination of Mefenamic acid (MFA) was constructed. The sensor is based on ion association of MFA with Dodecaphospho molybdic acid (PMA) and Dodeca–Tungstophosphoric acid(PTA) as ion pairs. Nitro benzene (NB) and di-butyl phthalate (DBPH) were used as plasticizing agents in PVC matrix membranes. The specification of sensor based on PMA showed a linear response of a concentration range 1.0×10^{-2} –1.0×10^{-5} M, Nernstian slopes of 17.1-18.86 mV/ decade, detection limit of 7×10^{-5} -9.5×10^{-7}M, pH range 3 – 8 , with correlation coefficients lying between 0.9992 and 0.9976, respectively. By using the ionphore based on PTA gives a concentration range of 1.0×10^{-4} –1.0×10^{-5} M, Nernstian slope of 17.18-18.4 mV/ decade, limit of detection 8.0×10^{-6}-9.3×10^{-5}M,pH range 3 – 8 and correlation coefficients range between 0.9984 and 0.9891, respectively. The measurement interferences in the presence of Li^{+}, Na^{+}, Mg^{2+} Ca^{2+}, $Fe^{3+}$and Al^{3+} were studied using separate and match potential methods for selectivity coefficient determination. The method was applied for the determination of Mefenamic Acid in pharmaceutical preparations.

Key words: Mefenamic acid sensor, Different plasticizers, Ion pairs, Pharmaceutical preparation.

Introduction:

Mefenamic acid belongs to the category of non steroidalanti-inflammatory, analgesic, antipyretic agent with molecular formula $C_{15}H_{15}NO_2$ (M.W. 241.29 $g.mol^{-1}$) and chemical name as 2-(2,3- di-methylphenylaminobenzoic acid[1] occurs as white to light yellow microcrystalline powder, practically insoluble in water, slightly soluble in alcohol and in methylene chloride [2] .The chemical structure of Mefenamic acid is depicted below as shown in Figure 1.

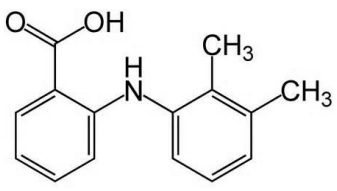

Fig.1. Structure of mefenamic acid

Mechansim is an analgesic action, it acts by binding the prostaglandin synthetize receptors COX-1 and COX-2, inhibiting the action of prostaglandin synthetize [3, 4]. It is used for the treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhea, and mild to moderate pain, inflammation and fever[5,6]. Since hepatic metabolism plays a significant role in mefenamic acid elimination, patients with known liver deficiency may be prescribed lower doses. Kidney deficiency may also cause accumulation of the drug and its metabolites in the excretory system. Therefore, patients suffering from renal conditions should not be prescribed mefenamic acid and Mefenamic acid presence in pharmaceuticals tablets 100 mg, 250 mg, 500 mg. Capsules: 250 mg. Suspension: 50 mg/5 mL Analogous to mefenamic acid, this compound may be synthesized from 2-chlorobenzoic acid and 2,3-dimethylaniline[7]. Known mild side effects of mefenamic acid include headaches, nervousness and vomiting. Serious side effects may include diarrhea, hematemesis (vomiting blood), hematuria (blood in urine), blurred vision, skin rash, itching and swelling, sore throat and fever[8]. Various methods have been reported for the determination of mefenamic acid as pure and in dosages forms. These methods include titrimetric [9,10], chromatographic [11-12], luminescence [13], flow injection [14-15], electrometric[16], spectroflourometric [17-18] and spectrophotometric methods [19-22].

Martials and Methods:

Equipment's

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

2. The electrode used for mefenamic acid was home constructed as follows: The Ag-AgCl electrode was used as the reference electrode and the internal filling solution of 0.1 M mefenamic acid was used. One side of a piece of PVC tube (1-2 cm long) was flattened and smoothed by placing it on a glass plate moistened with THF. A disk of the membrane was cut equal to the external diameter of the PVC tubing and mounted on the polished end.

The other side of the PVC tubing was then connected to the electrode body. The assembled electrodes were conditioned by soaking in 0.1 M mefenamic acid solution for at least 3 h before the use of the electrodes.

Reagents and solutions

1.Mefenamic acid standard was obtained as a gift from the state company of drug industries and medical appliances (IRAQ-SDI -Samara). Ponstane capsules B.P. (500 mg), Belgium-(Pfizer), ponstane capsules B.P. (500mg) China-(Kontam) were obtained from local pharmacies.

2. Plasticizers, di-butyl phthalate (DBPH) and nitrobenzene (NB) were obtained from Fluka AG. Other chemicals and reagents of analytical grade quality were obtained from Fluka, BDH and Aldrich.

Standard solutions

1.The stock Standard solution of 0.1 M mefenamic acid was prepared by dissolving 2.062g of mefenamic in ethanol and diluted to 100 mL, (ultrasonicator)equipment was used to assist the dissolving of the drug, several 100 mL standard solutions ranged from 10^{-6}-10^{-1}M were freshly prepared.

2. The stock standard solution of 0.01MDodeca-molybdophosphoric acid was prepared by dissolving 1.88g in distilled water and diluted up to 100 mL.

3. The stock standard solution of 0.01M Dodeca-tungstophosphoric acid was prepared by dissolving 1.44g in distilled water and diluted up to 100 mL.

4. 0.1M stock solution of each of interfering ions; LiCl, KCl, $CaCl_2$, $MgCl_2$, $Al(NO_3)_3.9H2O$ and $Fe(NO_3)_3.9H_2O$ and NH_4OH, were prepared. The other diluted solutions were prepared in the range needed similar to that present in blood or serum by serial dilution of the appropriate stock solutions.

Preparation of ion-pair compound

The ion-pair of mefenamic acid - molybdophosphoric acid (MFA-PMA) ,dodeca-tungstophosphoric acid(MFA-PTA) were prepared by mixing 25mL of 0.01 M solution of mefenamic acid with 75 mL of 0.01 M Dodeca-molybdophosphoric acid, Dodeca-tungstophosphoric acid with stirring. The resulting precipitate was filtered off, washed with water, and dried at 60◦ C.

Casting the membrane

Mefenamic acid matrix was immobilized into the PVC matrix membrane as described by Davis et al [23], MFA-PT or MFA-PMA (0.04g) was mixed with 0.36 g of plasticizers, DBPH (electrode I) or NB (electrode II). Then 0.17 g of PVC powder was sprinkled on 6 mL of THF with stirring until a clear viscous solution was obtained. The two solutions were then mixed with stirring to homogeneity. The mixture was poured into a glass ring (30-35 mm diameter) resting on a glass plate and a pad of filter was placed ontop of the glass. The solvent was then allowed to evaporate at room temperature for about 2 days. The thickness of the membrane obtained was about 0.5 mm. The size of this membrane was sufficient to prepare about 4 electrodes.

Procedure

Construction of ion-selective electrodes

The construction of the electrode body and the immobilization were done as described by Craggs et al [24]. The glass tube was 3/4 filled with 0.1 M mefenamic acid solution as an internal filling solution. The membrane was conditioned by immersing in a standard solution of 0.1M mefenamic acid for at least 2 hour before measurements.

Preparation of Pharmaceutical Samples

Pestle and mortar were used to grind the tablets to a fine powder. Amounts equivalent to one tablet were weighed and taken into 100 mL volumetric flasks. Samples were mixed by magnetic stirrers for 30 min. and filtered through 0.45 nm cellulose filter paper. Then aliquots of filtrates were diluted to get concentrations of $1.0x10^{-3}$ M mefenamic acid.

Calculation of Selectivity coefficient

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

$\log K^{pot} = [(E_B - E_A)/(2.303RT/zF)] + (1 - z_A/z_B) \log a_A$…….(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 andinterfering B ions, respectivelyata$_A$= a_B.

The selectivity coefficients were also measured by the match method according to the equation[2].

$K^{pot} = \Delta a_A/a_B, \Delta a_A = \bar{a}_A - a_A$ ……..(2)

Results and Discussion:

Four electrodes of mefenamic acid (MFA) (A1, A2, A3, A4) were constructed and based on of an ion – association of mefenamic acid (MFA) with Dodeca-molybdophosphoricacid (PMA) and Dodeca-tungstophosphoricacid (PTA) using two plasticizers such as Nitrobenzen(NB) and Di-butyl phthalate (DBPH) with PVC matrix were examined respectively. Near-Nernstian slopes were obtained for electrodes based on NB and DBPH(membranes A1, A2, A3 and A4).The slopes were 17.1,

18.86,17.18 and 18.4 mV/decade with correlation coefficients of 0.9992, 0.9976,0.9984 and 0.9891, respectively. The linear range for these electrodes $1.0x10^{-4}$-$5.0x10^{-1}$, $1.0x10^{-5}$-$1.0x10^{-2}$, $1.0x10^{-4}$-$1.0x10^{-2}$ and $1.0x10^{-5}$-$1.0x10^{-1}$ M with detection limits of $7.0x10^{-5}$ M, $9.5x10^{-7}$ M, $8.0 x10^{-6}$ and $9.3x10^{-5}$ M, respectively. The results and other parameters are given in Table 1.

Table 1.Specific parameters of different mefenamic acid electrodes.

Membrane composition	MFA-PMA+NB (A1)	MFA-PMA+DBPH (A2)	MFA-PTA+NB (A3)	MFA-PTA+DBPH (A4)
Slope mV/ decade	17.10	18.86	17.18	18.40
Linear range /M	1.0×10^{-4}-5.0×10^{-1}	1.0×10^{-5}–1.0×10^{-2}	1.0×10^{-4}-1.0×10^{-2}	1.0×10^{-5}–1.0×10^{-1}
Correlation coefficient	0.9992	0.9976	0.9984	0.9891
Detection limit /M	7.0×10^{-5}	$9.5x10^{-7}$	8.0×10^{-6}	9.3×10^{-5}
Life time / day	3	15	16	40

The electrode (A1) gives short lifetime, this could be due to the low viscosity of NB (2.030 cst) which causes rapid leaching of the membrane components to the external solution. The electrode (A1) gave slope of 17.1 mV/decade due to the viscosity of the plasticizers; for example, the low viscosity of the NB (2.030 cst) plasticizer which decrease the ion-exchange process between (MFA) in membrane and the external solution of (MFA). Electrodes (A2 and A4) gave high slope values because the high mixing between the (DBPH) and the poly phenyl chloride (PVC) due to the compatibility of the plasticizer used to the electro-active compound in both structure and composition. A typical plot for calibration curves of electrodes based on four plasticizers NB, and DBPH are shown in Fig.2.

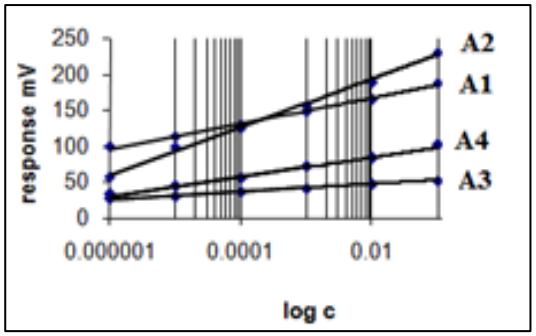

Fig. 2. Calibration curves of mefenamic acid selective electrodes.

Effect of pH

The effect of pH on the electrode potentials for (MFA) selective membrane electrode (A4) was examined by measuring the e.m.f. of the cell in (MFA) solutions at three different concentrations (10^{-4}, 10^{-3}, 10^{-2}) M in which the pH ranged from (1.0-11.0). The pH adjusted by adding appropriate amounts of hydrochloric acid and/or sodium hydroxide solution. The results are shown in Fig. 3.

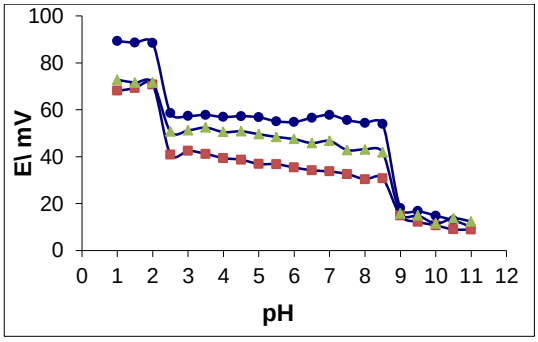

Fig. 3.Effect of pH on the potential of the mefenamic acid electrode A4 at concentrations.

At pH values less than 1.5 or in very high acidity, the electrode response has been increased rather irregularly. This may be due to electrode response to H^+ ions activities and in alkaline solution (pH greater than 8) the electrode response has been decreased, which might be attributed to the decreasing in the solubility of MFA.The working pH was tabulated in Table 2.

Table 2.Working pH ranges for mefenamic acid selective electrodes.

Membrane No.	Membrane composition	pH range		
		1 x 10^{-2}	1 x 10^{-3}	1 x 10^{-4}
A1	MFA-PMA+ NB	2.0-8.0	3.0-8.0	4.5-9.5
A2	MFA-PMA+ DBPH	2.5-8.0	3.0-8.5	2.5-8.0
A3	MFA- PTA+ NB	3.0-8.5	3.5-9.0	3.0-9.0
A4	MFA-PTA+ DBPH	3.0-9.0	3.0-9.0	3.0-9.5

Interference studies

In order to investigate the selectivity of the proposed membrane (A2,A3) ion selective electrode toward mefenamic acid with respect to various interfering ions by using separate solution method. The values of the selectivity coefficients for separate method are listed in Tables 3 and 4.

Table 3.Selectivity coefficients for electrodes A2 at different concentration of mefenamic acid.

	Concentration 10^{-1}M		Concentration 10^{-2}M		Concentration10^{-3}M		Concentration10^{-4}M		Concentration10^{-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)	$K_{A,B}$
Li+	118.2	9.63×10^{-5}	95.3	2.1×10^{-5}	77.9	3.3×10^{-5}	42.1	1.99×10^{-5}	4.2	1.1×10^{-6}
K+	81.3	2.2×10^{-3}	71.2	2.04×10^{-4}	53.5	2.57×10^{-5}	39.9	1.19×10^{-6}	23.1	6×10^{-8}
Ca^{2+}	98.1	2.9×10^{-4}	88.9	3.59×10^{-4}	69.2	1.19×10^{-4}	43.1	2.21×10^{-5}	18.1	1.61×10^{-6}
Mg^{2+}	110.7	2.24×10^{-3}	99.5	2.18×10^{-3}	77.1	8.82×10^{-4}	59.7	5.72×10^{-5}	33.2	5.79×10^{-6}
Fe^{3+}	133.1	1.55×10^{-4}	91.7	1.02×10^{-6}	61.5	3.3×10^{-5}	29.2	1.28×10^{-5}	-33.7	3.32×10^{-6}
AL^{3+}	92.5	1.56×10^{-3}	91.7	9.07×10^{-4}	61.5	1.08×10^{-4}	29.2	3.72×10^{-6}	-33.7	6.09×10^{-7}

Table 4. Selectivity coefficients for electrodeA3 at different concentration of mefenamic acid.

	Concentration 10^{-1}M		Concentration 10^{-2}M		Concentration10^{-3}M		Concentration10^{-4}M		Concentration10^{-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)	$K_{A,B}$
Li+	107.8	4.2×10^{-3}	59.3	1.58×10^{-5}	23.3	4.8×10^{-8}	5.4	1.4×10^{-8}	7.8	4.4×10^{-8}
K+	116.3	2.08×10^{-3}	72.6	1.368×10^{-5}	27.6	7×10^{-8}	7.9	2.6×10^{-8}	6.8	3.25×10^{-7}
Ca^{2+}	108	2.526×10^{-2}	88.8	6.481×10^{-4}	67	4.26×10^{-5}	43	3.06×10^{-5}	24.9	1.161×10^{-5}
Mg^{2+}	100.7	7.41×10^{-2}	80.4	6.57×10^{-3}	73.9	6.48×10^{-4}	61.2	8.61×10^{-5}	40.4	3.307×10^{-6}
Fe^{3+}	94.7	2.59×10^{-2}	89.6	1.53×10^{-2}	75.7	9.24×10^{-4}	61	1.65×10^{-4}	43.5	1.92×10^{-5}
AL^{3+}	77	4.12×10^{-2}	74	9.37×10^{-4}	44.5	2.37×10^{-5}	36.5	7.83×10^{-6}	24.8	1.86×10^{-6}

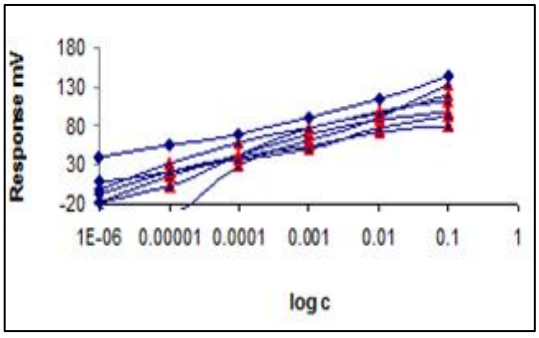

Fig.4. Selectivity of A2 (MFA – PMA + DBPH) and the interfering cations by separation method, ●mefenamic acid, ▲ Solution of interfering cations.

The second method called Match potential method(MPM), in this method the selectivity coefficients measured by using equation (2) is defined by the ratio of the activity of the primary ion relative to an interfering ion when they generate identical potentials in the same reference solution. In this method both mono valent ions are treated in the same manner and the valence of the ions does not influence the selectivity coefficient. The results of selectivity coefficients are listed in Tables 5 and 6 were calculated from the concentration of the interfering ions which endued the same amount of the potential change as that induced by the increase of the concentration of primary ion.

Table 5.Selectivity coefficients for the mefenamic acid electrodes (10^{-3}) drug and (10^{-1}) M of Interfering-ion determined by Match potential method (MPM).

Membrane composition	Interfering ion 10^{-1} M	Log K^{pot}	
		ΔE=10	ΔE=20
MFA-PMA+NB (A1)	Na^{+}	-0.267	-0.586
	Ca^{2+}	-0.287	-0.605
	Fe^{3+}	-0.282	-0.697
MFA-PMA+DBPH (A2)	Na^{+}	-0.226	-0.469
	Ca^{2+}	-0.226	-0.632
	Fe^{3+}	-0.195	-0.510

Table 6.Selectivity coefficients for the mefenamic acid electrodes (10^{-4}) drug and (10^{-1}) M of interfering-ion determined by Match potential method.

Membrane composition	Interfering ion 10^{-1} M	Log K^{pot}	
		ΔE=10	ΔE=20
MFA-PTA+NB (A3)	Na^{+}	-0.729	-1.200
	Ca^{2+}	-0.500	-1.180
	Fe^{3+}	-0.423	-1.080
MFA-PTA+DBPH (A4)	Na^{+}	-0.441	-0.900
	Ca^{2+}	-0.461	-0.711
	Fe^{3+}	-0.542	-0.798

Sample analyses

Four potentiometric techniques were used for the determination of (MFA) including. Direct method, Standard addition method (SAM) follows the equation:

$$C_U = C_S / 10\Delta E/S\ [1+(V_U / V_S)]-(V_U/ V_S)$$

Where C_U, C_S, V_U and V_S are the concentration, volume of unknown and standard solution, respectively. Multiple standard additions (MSA) and titration methods carried as in Table (7).

Table 7.Determination of mefenamic acid –ion samples by potentiometric Techniques.

Electrode No.	Concentration (M)				
	Sample	Measurements using potentiometric method			
		Direct	SAM	MSA	Titration
MFA– PMA +DBPH (A2)	$1x10^{-3}$	0.00099	0.001003	0.00102	0.00098
	RSD%	0.537	1.05	-	1.572
	RC%	99	100.3	102	98
	RE%	1	0.3	2	2
	$1x10^{-4}$	0.000099	0.000102	0.0001003	0.000097
	RSD%	1.02	0.976	-	1.638
	RC%	99	97.6	100.3	97
	RE%	1	2.4	0.3	3
MFA– PTA +NB (A3)	$1x10^{-3}$	0.000975	0.000986	0.000987	0.00095
	RSD%	1.37	0.804	-	1.63
	RC%	97.5	98.6	98.7	95
	RE%	2.5	1.4	1.3	5
	$1x10^{-4}$	0.000102	0.0000993	0.000101	0.000096
	RSD%	2.619	0.174	-	1.416
	RC%	102	99.3	101	96
	RE%	2	0.7	1	4

***** Each measurement was repeated three times

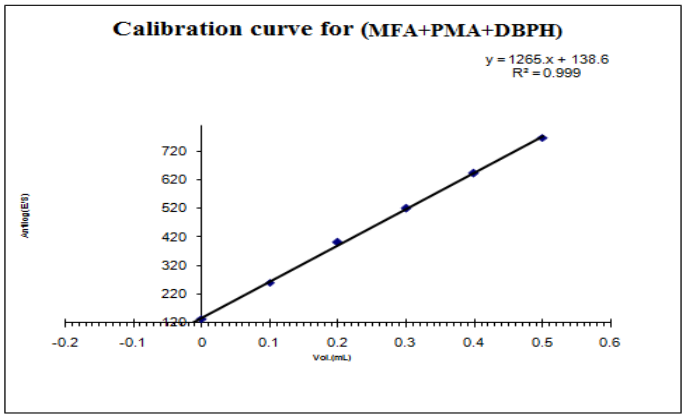

Fig.5. Plot antilog (E/S) versus the value of the added standard for the determination of mefenamic acid solution (10^{-4} M) by MSA using A2 electrode.

The Fig.5 is obtained by plotting antilog (E/S) versus the volume of the five addition of standard MA solution. The calibration curve of MSA was used to determine the concentration of mefenamic acid solutions.

For potentiometric titration a 10^{-2} M of Dodeca-molybdophosphoric acid was used as a titrant and a typical titration plot was shown in Fig.6.

The electrode (A2) was proved to be a useful in the potentiometric determination of mefenamic acid in pharmaceutical preparations and the data obtained for pharmaceutical samples are listed in Table 8.

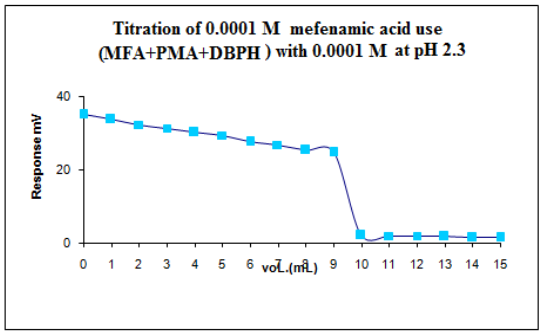

Fig. 6.Titration curve of electrode A2 (MFA-PMA +DBPH) using drug solution containing 0.0001 M menfenamic acid with 0.0001 M of PMA as titrant.

Table 8. Sample analyses of pharmaceutical mefenamic acidusingA2 electrode.

Drug	Method	Direct	SAM	MSA	Titration
China-Kontam	Concentration	1×10^{-3}	1×10^{-3}	1×10^{-3}	1×10^{-3}
	Recovery%	99.0	97.6	98.2	97.5
	RE%	1.0	2.4	1.8	2.5
	RSD%	1.567	1.081	-	0.515
Belgium-Pfizer	Concentration	1×10^{-3}	1×10^{-3}	1×10^{-3}	1×10^{-3}
	Recovery%	97.5	96.8	100.2	97.0
	RE%	2.5	3.2	0.2	3.0
	RSD%	11.624	10.632	-	0.842
China-Kontam	Concentration	1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
	Recovery%	101.0	99.6	100.3	97.0
	RE%	1.0	0.4	0.3	3.0
	RSD%	2.110	0.529	-	0.301
Belgium-Pfizer	Concentration	1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
	Recovery%	99.0	102.0	99.7	97.0
	RE%	1.0	2.0	0.8	3.0
	RSD%	2.061	2.090	-	0.886

***** Each measurement was repeated three times

Conclusion:

Mefenamic liquid electrodes based on ionophoresdodecaphosphomolybdic and dodecaphosphotunstic acids were constructed based on PVC matrix membrane. Excellent electrode parameters were obtained including Nernstain slopes, detection limit and pH. The prepared electrodes were used for mefenamic determination in commercial drugs which gives recovery ranged from 99.0 to 102.0.

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الغشاء المتحسس والانتقائي لحامض المفينامیك وتطبيقاتة في التحليلات الصيدلانية

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الخلاصة:

تم تقدير دواء (حامض الميفينامك) باستخدام اغشية متحسسة وانتقائية مستخدما البولي فاينيل كلورايد كمادة بنائية هذه الدراسة اعتمدت على تفاعل حامض الميفيناميك مع دوديكا-فوسفومولیبدك اسد ودوديكافوفسوتنكستين اسد كزوج ايوني وباستخدام الملدنات داي بيوتل فثاليت ونايتروبنزين ككواشف مرنة في قالب البولي فاينيل كلورايد ومن خلال الدراسة تم الحصول على خطية (1.0×10^{-2} – 1.0×10^{-5}) مولاري وعلى ميل يتراوح بين(17.1-18.86) ملي فولت/حقبة وحد كشف (9.5×10^{-7} – 7.0×10^{-5}) مولاري ضمن دالة حامضية تتراوح بين (3-8) مع عمل تصحيح (0.9992-0.9976) عند احتواء المادة الفعالة على ليكند (فوسفومولیبدك اسد) وعلى خطية تتراوح بين (1.0×10^{-2} – 1.0×10^{-5}) مولاري وعلى ميل يتراوح بين (17.18-18.4) ملي فولت /حقبة وحد كشف (8.0×10^{-6} – 9.3×10^{-5}) مولاري ضمن حامضية (3-8) ومعامل تصحيح يتراوح بين (0.9891-0.9984) عند احتواء المادة الفعالة على ا(الفوسفو تنكيستن اسد) كذلك تتم دراسة التداخلات الايونية مع الايونات اللاعضوية وهذه الطريقة كانت ناجحة في تعيين دواء (حامض الميفينامك) في المستحضرات الصيدلانية .

الكلمات المفتاحية: متحسس حامض الميفينامك، ملدنات مختلفة، مزدوج ايوني، المستحضرات الصيدلانية.