

CONSTRUCTION OF NEW ION SELECTIVE ELECTRODES FOR DETERMINATION IBUPROFEN AND THEIR APPLICATION IN PHARMACEUTICAL SAMPLES

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ABSTRACT

Ion selective potentiometric is a simple analytical technique to measure ionic constituents in complex samples. Ibuprofen ion selective electrodes were constructed from drug complex formation with dodecaphosphomolybdic acid as ionophor and plasticizer, Di-octyl phthalate (DOPH), Tri- butyl phosphate (TBP), Nitro benzene (NB), and Di-butyl phthalate (DBPH) in PVC matrix membrane. The matrix membrane was prepared by blending an appropriate plasticizer and drug complex with PVC the following electrodes were studied, concentration range, slope, detection limit, response time, lifetime, pH effect and selectivity. The result showed that membranes (IP-PMA+DBPH) and (IP-PMA+TBP) gave linear range from 1×10^{-5} to 1×10^{-1} M and 1×10^{-4} to 1×10^{-1} M, respectively, with slopes of (19.13 and 15.4) mV/decade, correlation coefficients are 0.9699 and 0.9897, the detection limit was (8.5×10^{-6} and 7.5×10^{-5} M) and the response time for 10^{-3} M were (23 and 19) second, respectively. The proposed electrodes were successfully applied to the determination of Ibuprofen in pharmaceutical preparation and gave good accuracy.

Keywords: Ibuprofen selective electrode, dodecaphosphomolybdic acid, Different plasticizers.

INTRODUCTION

Ibuprofen, 2-[4-(2-methyl propyl) phenyl] propionic acid, is an NSAID. Its anti-inflammatory properties may be weaker than those of some other NSAIDs. It is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains; it is also used to reduce fever^{1,2} (Fig. 1).

The literature shows a variety of methods (approved and non-approved by health government agencies) to analyze raw ibuprofen (IP for brevity), and pharmaceutical preparations, such as: direct titration with sodium hydroxide in methanol, potentiometric

titration, high performance liquid chromatography, UV spectroscopy and flow injection infrared analysis. More recently, capillary electrophoresis and isotachopheresis have also been used to analyze ibuprofen and other NSAID pharmaceuticals. The direct titration with sodium hydroxide is economical, easily applicable and is described in the European Pharmacopoeia for the quantification of raw IP. However, colored or non-soluble excipients contained in tablets might interfere in the observation of the completion of the reaction through a chemical acid-base indicator. Potentiometric titrations avoid the interference of the excipients since the completion of the reaction is detected through the slope change of the electromotive force EMF (or pH) versus volume of titrant. This method is suitable to analyze raw IP and tablets using tetrabutylammonium in acetonitrile. The analysis of IBU through high performance liquid chromatography is used

worldwide for quality control of pharmaceuticals. This method allows to analyzing both IP and products of degradation such as, 4-isobutylacetophenone³. However, the pretreatment of the sample might be difficult if the excipients or the active ingredient are non-soluble in the mobile phase. Capillary electrophoresis and isotachopheresis are economic, easily applicable and accurate methods to analyze IP. Moreover, non-ionic species such as those involves in the excipients, do not interfere in the analysis. However, the technique requires qualified technicians and is not accepted by the government agencies. Although, infrared spectroscopy is the method described by the pharmacopoeias to identify IP, the literature shows only one investigation concerning the quantification of IP through IR⁴. Various methods have been used for the determination of ibuprofen in pharmaceutical and biological samples. Until now, chromatographic methods (HPLC, GC, HPTLC, TLC)⁵⁻¹², electrophoretic methods¹³⁻¹⁶, spectrophotometric methods^{17,18} and titrimetric methods with visual and potentiometric indications¹⁹⁻²¹ are the major technique for the determination of ibuprofen. The aim of this work was the development and validation of a simple, rapid and selective method for the analysis of ibuprofen in commercial pharmaceutical formulations and human control serum.

Experimental Part

Equipment

1-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.
2. The electrode used for Ibuprofen was home constructed according to reference 12, as follows: The Ag-AgCl electrode and 0.1 M Ibuprofen solution were used as the reference electrode and the internal filling solution of the electrode, respectively. 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 Ibuprofen solution for at least three hours before the use of the electrodes.

Reagents and solutions

1. Ibuprofen standard and profedin tablets (200 mg ibuprofen) were a gift

from the state company of drug industries and medical appliances (IRAQ-SDI -Samara). Apifen tablet, 400 mg profen (Ajanta Pharma, India) were obtained from local pharmacies.

2. Plasticizers, di-butyl phthalate (DBPH), tri-butyl phosphate (TBP), o-nitro phenyl octyl ether (NPOE) and di-octyl phthalate (DOPH) 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 Ibuprofen was prepared by dissolving 2.062g of standard Ibuprofen 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 0.01M Dodeca-molybdophosphoric acid was prepared by dissolving 1.88g in distilled water and diluted up to 100 mL.
3. 0.1M stock solution of each of interfering ions such; LiCl, KCl, CaCl₂, MgCl₂, Al(NO₃)₃.9H₂O, Fe(NO₃)₃.9H₂O and NH₄OH, 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 Ibuprofen- molybdophosphoric acid (IP-MPA) was prepared by mixing 25mL of 0.01 M solution of Ibuprofen with 75 mL of 0.01 M Dodeca-molybdophosphoric acid with stirring. The resulting precipitate was filtered off, washed with water, and dried at 60° C.

Casting the membrane

Ibuprofen matrix was immobilized into the PVC matrix membrane as described by Thomas and Moody.²² A-PT of 0.04g was mixed with 0.36 g of plasticizers: DBPH (electrode I), TBP (electrode II), NPOE (electrode III), or DOPH (electrode IV). 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 on top of the glass. The solvent was then

allowed to evaporate at room temperature over 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 Mahajan et al.²³. The glass tube was 3/4 filled with 0.1 M ibuprofen solution as an internal filling solution. The membrane was conditioned by immersing in a standard solution of 0.1 M ibuprofen for at least 2 hours before measurements.

Preparation of Pharmaceutical Samples

We used pestle and mortar 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 µm cellulose filter paper. Then aliquots of filtrates were diluted to get concentrations of 1.0×10^{-3} M ibuprofen.

Calculation of Selectivity coefficient

A separate solution method was used for the selectivity coefficient measurement, and was calculated according to the equation²⁴.

$$\text{LogKpot} = \frac{(E_B - E_A)}{(2.303RT/zF)} + (1 - \frac{z_A}{z_B}) \log a_A \dots \dots \dots (1)$$

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. $a_A = a_B$. The selectivity coefficients were also measured by the match method according to the equation²⁵.

$$K_{pot} = \frac{\Delta a_A/a_B}{\Delta a_A/a_A} \dots \dots \dots (2)$$

RESULTS AND DISCUSSION

Four electrodes of ibuprofen (IP) (A1, A2, A3, A4) based on using ibuprofen (IP) and Dodeca-molybdophosphoric acid (MPA) as additive, used four plasticizers such as: Dioctyl phthalate (DOPH), Tri-butyl phosphate (TBP), Nitrobenzene (NE) and Di-butyl phthalate (DBPH) with PVC matrix were examined respectively. Near-Nernstian slopes were obtained for electrodes based on DOPH, NB and DBPH (membranes A1, A3 and A4). The slopes are 17.64, 17.7 and 19.13 mV/decade with correlation coefficients of 0.9972, 0.9897 and 0.9699 respectively. The linear range for these electrodes, 1×10^{-1} – 1×10^{-4} and 1×10^{-1} -

1×10^{-4} M with detection limits of 2×10^{-5} M, 3×10^{-5} M and 1×10^{-5} M, respectively. The results and other parameters are given in Table 1. The electrode (A2) gave non-Nernst slope, this could be due to the low viscosity of TPB (3.114 cst) which causes rapid leaching of the membrane components to the external solution. The electrode (A3), gave slope of 17.7 mV/decade due to the viscosity of the plasticizers; for example, the low viscosity of the NB (1.8 cst) plasticizer which decreases the ion-exchange process between (IP) in membrane and the external solution of (IP). Then the A1 electrode gave slope 17.64 mV/decade, due to inhomogeneous gradients between (DOPH), (PVC) and other components in the membrane. Electrode (A4) gave high slope value because of 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 DOPH, TBP, NB and DBPH are shown in Figure 2.

Effect of pH

The effect of pH on the electrode potentials for (IP) selective membrane electrode (A1) was examined by measuring the e.m.f. of the cell in (IP) solutions at three different concentrations (10^{-4} , 10^{-3} , 10^{-2}) M in which the pH ranged from (0.5-11.0). The pH adjusted by adding appropriate amounts of hydrochloric acid and/or sodium hydroxide solution the results shown in Figure 3. 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 that the electrode response to H^+ activities as well as IP ions and in an alkaline solution (pH greater than 8) the electrode response has been decreased, may attribute to the decreasing in the solubility of IP, the working pH were tabulated in Table 2.

Interference studies

In order to investigate the selectivity of the proposed membrane (A1) ion selective electrode toward ibuprofen 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.

The second method called Match potential method (MPM) in this method the selectivity coefficients given 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

monovalent ions are treated in the same manner and the valence of the ions does not influence the selectivity coefficient. The results of selectivity coefficient are shown in Figure 3 and in the Table 5 and 6 were recalculated from the concentration of the interfering ions which ended the same amount of the potential change as that induced by the increase of the concentration of primary ion.

Sample analyses

Four potentiometric techniques were used for the determination of (IP) 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 and volume of unknown and standard solution respectively multiple standard additions (MSA) carried as in Table 7.

The Figure 5 carried as by plotting antilog (E/S) versus the volume of the five addition of

standard (IP), used to of concentration can be covered as compared with working range calibration curve for MSA used to determine the concentration of Ibuprofen solutions. For potentiometric titration a 10^{-2} M of Dodecamolybdophosphoric acid was used as a titrant. A typical titration plot was shown in Figure 7.

The electrode (A1) was proved to be useful in the potentiometric determination of Ibuprofen in pharmaceutical preparations and the data obtained for pharmaceutical samples were listed in Table 8.

CONCLUSION

Ibuprofen selective electrodes can be prepared by complex formation with dedeca phosphomolybdic acid and different plasticizers. Excellent results were obtained by using electrode based on DBPH and TBP plasticizers. The proposed electrodes was used for determination Ibuprofen in pharmaceutical preparation.

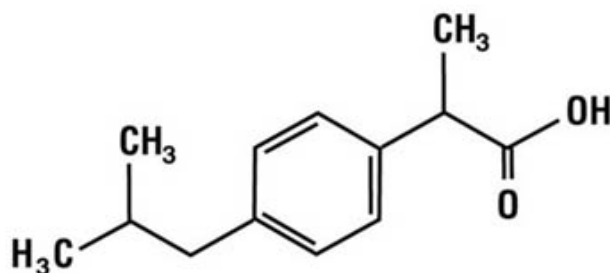


Fig. 1: Structure of ibuprofen

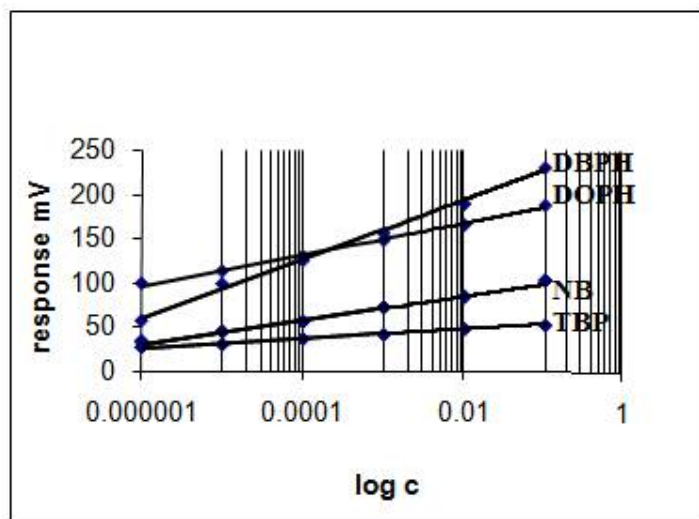


Fig. 2: Calibration curves of Ibuprofen selective electrodes

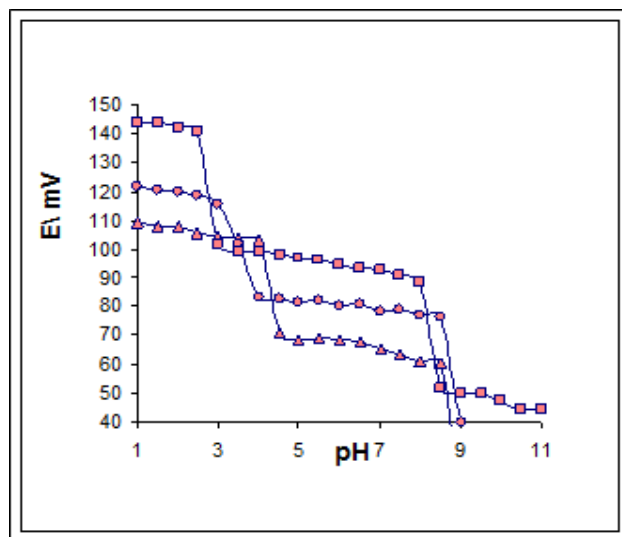


Fig. 3: Effect of pH on the potential of the Ibuprofen electrode A1(IP- PMA+DOPH)at concentrations (\blacksquare 10^{-2} , \bullet 10^{-3} and \blacktriangle 10^{-4}) M

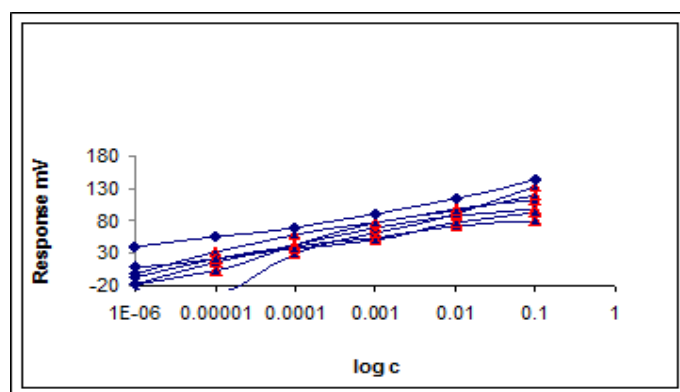


Fig. 4: Selectivity of A4 (IP – PMA + DBPH)and the interfering cations by separation method, \bullet Ibuprofen, \blacktriangle Solution of interfering cations.

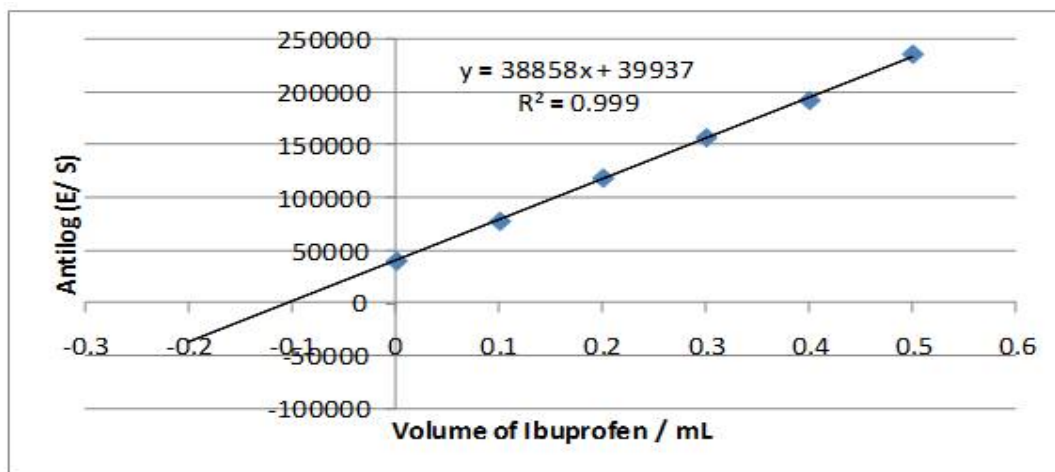


Fig. 6: Plot antilog (E/S) versus

The value of the added standard for the determination of Ibuprofen solution (10^{-3} M) by MSA using (IP-PMA +DBPH) electrode

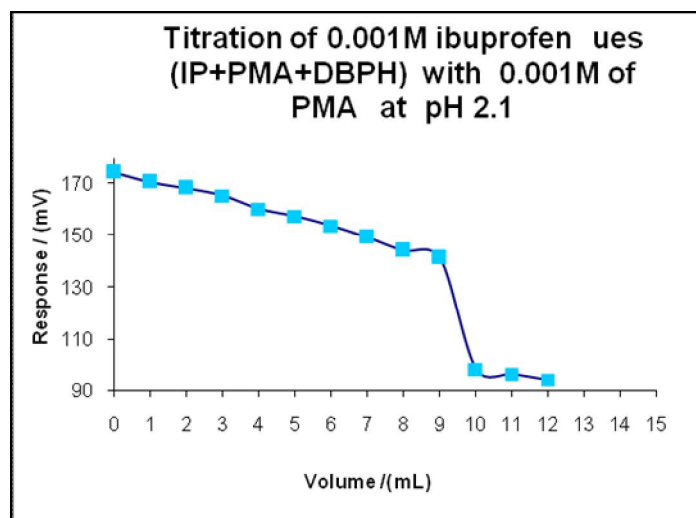


Fig. 7: Titration curve of electrode (IP-PMA +DBPH) for drug solution Containing 0.01 M Ibuprofen with 0.001 M of PMA as titrant solution

Table 1: The parameters for four (IP) electrodes

Membrane composition	IP-PMA + DOPH (A1)	IP-PMA + TBP (A2)	IP-PMA + NB (A3)	IP-PMA + DBPH (A4)
Slope mV/ decade	17.64	15.40	17.70	19.13
Linearity range/ M	$1 \times 10^{-1} - 5 \times 10^{-4}$	$1 \times 10^{-1} - 5 \times 10^{-4}$	$1 \times 10^{-1} - 5 \times 10^{-4}$	$1 \times 10^{-1} - 5 \times 10^{-4}$
Correlation coefficient	0.9972	0.9897	0.9955	0.9699
Detection limit/ M	4×10^{-4}	7.5×10^{-5}	3.5×10^{-5}	8.5×10^{-6}
Life time/ day	35	9	6	40

Table 2: Working pH ranges for Ibuprofen selective electrodes

Membranes	Membrane composition	pH range		
		1×10^{-2}	1×10^{-3}	1×10^{-4}
A1	IP-PMA + DOPH	3.0 – 8.0	4.0 – 9.0	4.5 – 9.0
A2	IP-PMA + TBP	2.5 – 9.0	3.0 – 8.5	2.5 – 7.5
A3	IP-PMA + NB	4.0 – 8.5	3.3 – 8.5	3.0 – 8.5
A4	IP-PMA + DBPH	3.0 – 8.0	3.5 – 8.0	2.5 – 8.5

Table 3: Selectivity coefficients for (IP-PMA +DBPH) electrode at different concentrations of Ibuprofen

Interferin g Ion	Concentration 10^{-1} M		Concentration 10^{-2} M		Concentration 10^{-3} M		Concentration 10^{-4} M		Concentration 10^{-5} M	
	E_B (mV)	K_{AB}	E_B (mV)	K_{AB}	E_B (mV)	K_{AB}	E_B (mV)	K_{AB}	E_B (mV)	K_{AB}
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^{-5}
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^{-5}	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 (IP-PMA +TBP) electrode at different concentrations of Ibuprofen

Interfering Ion	Concentration 10^{-1} M		Concentration 10^{-2} M		Concentration 10^{-3} M		Concentration 10^{-4} M		Concentration 10^{-5} M	
	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}

Table 5: Selectivity coefficients for the Ibuprofen 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}	
		$\Delta E = 10$	$\Delta E = 20$
IP-PMA + DOPH (1)	Na ⁺	-0.267	-0.586
	Ca ²⁺	-0.287	-0.605
	Fe ³⁺	-0.282	-0.697
IP-PMA + TPB (2)	Na ⁺	-0.226	-0.469
	Ca ²⁺	-0.226	-0.632
	Fe ³⁺	-0.195	-0.510

Table 6: Selectivity coefficients for the Ibuprofen electrodes (10^{-4}) drug and (10^{-1}) M of interfering ion determined by match potential method (MPM)

Membrane composition	Interfering ion (10^{-1} M)	Log K^{pot}	
		$\Delta E = 10$	$\Delta E = 20$
IP-PMA + DOPH (1)	Na ⁺	-0.729	-1.200
	Ca ²⁺	-0.500	-1.180
	Fe ³⁺	-0.423	-1.080
IP-PMA + TPB2)	Na ⁺	-0.441	-0.900
	Ca ²⁺	-0.461	-0.771
	Fe ³⁺	-0.542	-0.798

Table 7: Determination of Ibuprofen samples by potentiometric techniques

Electrode No.	Concentration/ M				
	Sample	Measurement by using potentiometric method			
		Direct	SMA	MSA	Titration
IP-PMA + DOPH (A1)	1×10^{-3}	0.00099	0.001003	0.00102	0.00098
	RSD %	0.537	1.050	-	1.572
	RC %	99	100.3	102	98
	RE %	-1	0.3	2	-2
	1×10^{-4}	0.000099	0.000102	0.000100	0.000097
	RSD %	1.02	0.97	-	1.64
	RC %	99	97.6	100.3	79
	RE %	-1	-2.4	0.3	-3
IP-PMA + TBP (A4)	1×10^{-3}	0.00097	0.00098	0.00098	0.00095
	RSD %	1.37	0.804	-	1.63
	RC %	97.3	98.6	98.7	95
	RE %	-2.5	-1.4	-1.3	-5
	1×10^{-4}	0.000102	0.000099	0.000100	0.000096
	RSD %	2.62	-0.17	-	1.42
	RC %	104	99.2	101	96
	RE %	2	-0.7	1	-4

Table 8: Analyses of Ibuprofen samples by using electrode type (IP-PMA+DBPH)

Pharmaceutical	Profedin (IRAQ) (SDI)			
	Direct method	SAM	MSA	Titration
Concentration prepared	1×10^{-3}	1×10^{-3}	1×10^{-3}	1×10^{-3}
Found	0.00099	0.000976	0.000982	0.000975
Recovery %	99	97.6	98.2	97.5
RE %	-1	-2.4	1.8	2.5
RSD %	1.567	1.081	-	0.515
F experimental	8.455	10.512	-	12.87
F theoretical	190	190	190	190
Pharmaceutical	Apifen (INDIA) (AJANTA)			
Concentration prepared	1×10^{-3}	1×10^{-3}	1×10^{-3}	1×10^{-3}
Found	0.000975	0.000968	0.001002	0.00097
Recovery %	97.5	96.8	100.2	97
RE %	2.5	-3.2	0.2	-3
RSD %	1.312	1.21	-	0.842
F experimental	11.624	10.632	-	12.893
F theoretical	190	190	190	190
Pharmaceutical	Profedin (IRAQ) (SDI)			
Concentration prepared	1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Found	0.000101	0.0000996	0.0001003	0.000097
Recovery %	101	99.6	100.3	97
RE %	1	-0.4	0.3	-3
RSD %	2.11	0.529	-	0.301
F experimental	7.926	10.528	-	14.739
F theoretical	190	190	190	190
Pharmaceutical	Apifen (INDIA) (AJANTA)			
Concentration prepared	1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Found	0.000099	0.000102	0.0000992	0.000097
Recovery %	99	102	99.2	97
RE %	-1	2	-0.8	-3
RSD %	2.061	2.09	-	0.886
F experimental	11.295	9.357	-	11.931
F theoretical	190	190	190	190

Table 9: Analyses of Ibuprofen samples using IBP-PMA+TBP electrode

Pharmaceutical	Profedin (IRAQ) (SDI)			
	Direct method	SAM	MSA	Titration
Concentration prepared	1×10^{-3}	1×10^{-3}	1×10^{-3}	1×10^{-3}
Found	0.000972	0.000981	0.000976	0.00097
Recovery %	97.2	98.2	97.6	97
RE %	-2.8	-1.9	-2.4	-3
RSD %	0.666	1.213	-	0.534
F experimental	13.943	7.397	-	10.629
F theoretical	190	190	190	190
Pharmaceutical	Apifen (INDIA) (AJANTA)			
Concentration prepared	1×10^{-3}	1×10^{-3}	1×10^{-3}	1×10^{-3}
Found	0.00097	0.000956	0.00102	0.00096
Recovery %	97	95.6	102	96
RE %	-3	-4.4	2	-4
RSD %	1.21	0.441	-	0.68
F experimental	6.827	12.329	-	13.398
F theoretical	190	190	190	190
Pharmaceutical	Profedin (IRAQ) (SDI)			
Concentration prepared	1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Found	0.000102	0.0000996	0.0001002	0.000096
Recovery %	102	99.6	100.2	96
RE %	2	-0.4	0.2	-4
RSD %	2.672	1.53	-	0.476
F experimental	5.768	11.862	-	7.829
F theoretical	190	190	190	190
Pharmaceutical	Apifen (INDIA) (AJANTA)			
Concentration prepared	1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Found	0.000103	0.0000985	0.0000992	0.000095
Recovery %	103	98.5	99.2	95
RE %	3	1.5	-0.8	-5
RSD %	0.961	1.26	-	0.886
F experimental	6.921	11.318	-	14.728
F theoretical	190	190	190	190

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