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Naproxen Selective Membrane Sensor based on Molecularly Imprinted Polymer and Its Application to Pharmaceutical Analysis

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Abstract: Liquid electrodes of polymers imprinted with naproxen(NPX)was constructed using precipitation polymerization. The molecularly imprinted (MIP) and non imprinted (NIP) polymers were synthesized using NPX as a template. In the polymerization process, acrylamide (AM) was used as monomer ethylene glycol dimethacrylate (EGDMA) as a cross-linker and benzoyl peroxide (BPO) as an initiator. The molecularly imprinted membranes and the non-imprinted membranes were prepared using acetophenone(AOPH) and di octylphathalate(DOP)as plasticizers in PVC matrix. The slopes and detection limits of the liquid electrodes ranged from -19.4 – -21.37 mV/decade and 4.0 x 10-5 – 3.0 x 10-5 M, respectively and their response time was about 1 minute. The Liquid electrodes were filled with 0. 1 M standard solution of drug and their response was stable in a pH range from 1.0 to 11.0 and with good selectivity for over several species. The developed electrodes were successfully applied for the analyte determination in preparation pharmaceutical sample without any time consuming pretreatment steps.

Keywords: Molecularly impressed electrodes, naproxen, potentiometric method, acrylamide (AM) monomer.

INTRODUCTION

Naproxen (6-Methoxynaphthalen-2-yl)propanoic acid**(**Fig. 1) is a 2-arylpropionic acid used as non-steroidal anti-inflammatory drug (2-APANSAID). Naproxen is a white colored and soluble in alcohol. It is useful to treat pain and inflammation, which widely used in the clinic. Naproxen was determined Molecular Imprinting Technology is defined as a technique of copolymerization of functional and cross-linking monomers in the presence of the imprint molecule which is the target analyte acting as a molecular template. Initially, a complex of the functional monomers forms with the imprint molecule. Their functional groups are held in position by the highly cross-linked polymeric structure after the process of polymerization. In addition, the steric arrangement of these interactions around a given substrate, molecular template, is a vital characteristic essential for the formation of binding pockets providing complementary size, shape, and functionality for facilitating selective recognition accompanied by a high affinity toward the target[(1)]. As a consequence, the process of recognition in MIPs may be defined in resemblance with mechanisms proven for enzyme– substrate-complexes.It was determination some drug such as ibuprofen[(2)]and warfarin[(3)] based on molecularly imprinted polymer method. In this study imprinted polymer electrodes were prepared based on naproxen as a template in PVC matrix membrane and electrodes specification were studied. In the present study, S-naproxen was used as a template and chose acrylamide (AM) as functional monomer and Ethylene glycol dimethacrylate (EGDMA) as cross linker to prepare MIPs. The interactions between template and monomer were studied by spectral and computer simulation analysis. The chemical formula of naproxen is $C_{14}H_{14}O_3$,(M.Wt :230.3 $g.mol^{-1}$) and its structural formula show in figure (1)

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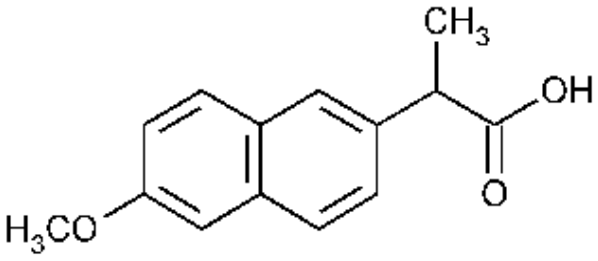


Fig. 1: Chemical structure of the naproxen

According to review Several methods available in the literature for the determination of naproxen in pharmaceuticals and biological fluids are reported. They include chromatographic method: HPLC [4], TLC with densitometry [5], gas chromatography–mass spectrometry [6], capillaryelectrophoresis[7], spectrophotometry[8], spectrofluorymetry[9], chemiluminescence[10], potentiometric titration [11] and other electrochemical methods [12]. These methods are characterized by long and complicated preparation of a sample for analysis as well as expensive instrumental apparatus. On the basis of the literature, there are limited scientific works on the use of ion-selective electrodes for naproxen determination [13,16]. These electrodes have different constructions: the electrode [13]with liquid membrane type, based on the use of naproxen. The purpose of this research was to sensor design as soon as possible better analytical parameters than the so far developed electrodes. In this work new naproxen ion-selective membrane electrode was prepared based on (NPX-MIP+DOP or AOPH) in PVC membrane phase.

EXPERIMENTAL

Chemicals and Materials

Naproxen was obtained from the State Company of Drug Industries and Medical Appliances (IRAQ-SID- Samara). The Commercial naproxen tablets that obtained from local stores are; NAPRON 20 tablets 250 mg from (PiONEER-lraq) Naproxen 20 tablets 500 mg from (Gebze-Kocaeli – TURKEY) NAPROX 20 tablets 500m mg from (Damascus – Syria). Acetophenone(AOPH) and di octylphathalate(DOP) as well as metal salts were purchased from Sigma-Aldrich and were used as they were received. acrylamide (AM) (99%), was used as monomer ethylene glycol dimethacrylate (EGDMA) (99%), and benzoyl peroxide (BPO)(78%) were purchased from Sigma-Aldrich. The chemical used were reagent grade with highest purity and used as received without further purification.

Apparatus

Potentiometric measurements were carried out with a digital voltmeter (HANA pH 211 instrument Microprocessor pH meter). pH measurements were made with a digital pH meter (wissenschaftlich-TechnischeWerkstätten GmbH WTW/pH meter in lab pH720-Germany). The performance of the electrode was investigated by measuring the potential of naproxen solutions at room temperature with a concentrations range from10^{-4} to 10^{-1}M. Each solution was stirred and the potential reading was recorded at equilibrium .The calibration curves obtained by plotting the response against the naproxen concentration logarithmic functions.

Preparing of Standard Solutions for ISEs studies

For preparing standard solution of 0.1 M naproxen by dissolving 3.302 g of standard naproxen in the methanol and completed to 100 mL in the volumetric flask. The other solutions were prepared in 100 mL at the ranged from (1×10^{-4} – 10^{-1})M in the same procedure.

The stock standard solution of 5×10^{-3} M 5×10^{-4} M phosphomolybdic acid was prepared by dissolving 1.1288 g, 0.11288 g of phosphomolybdic acid respectively in distilled water and completed to 100 mL.All interfering ions (K^{+1},Ca^{+2} and Al^{+3}) are preparing of 0.1 M . The other solutions were prepared in 100 ml at the range from (1×10^{-4}-10^{-1}) M

Synthesis of the Imprinted Polymer (MIP)

In a 50mL screw cap glass test tube(50mL), MIPs for (naproxen) was prepared using a bulk polymerization procedure. The template (NPX) 1mmol (0.233g) was dissolved in 5 mL of methanol in a thick walled glass tube.A functional monomer acrylamide (AM) 10mmol (0.710) g, cross-linker ethylene glycol dimethacrylate (EGDMA) 60mmol (11.89) gas a cross-linker and initiator (BPO) 0.7 mmol (0.115g)

were added later to the above solution respectively. The mixture was degassed by purging nitrogen for 30 minutes in an ultrasonic water bath.

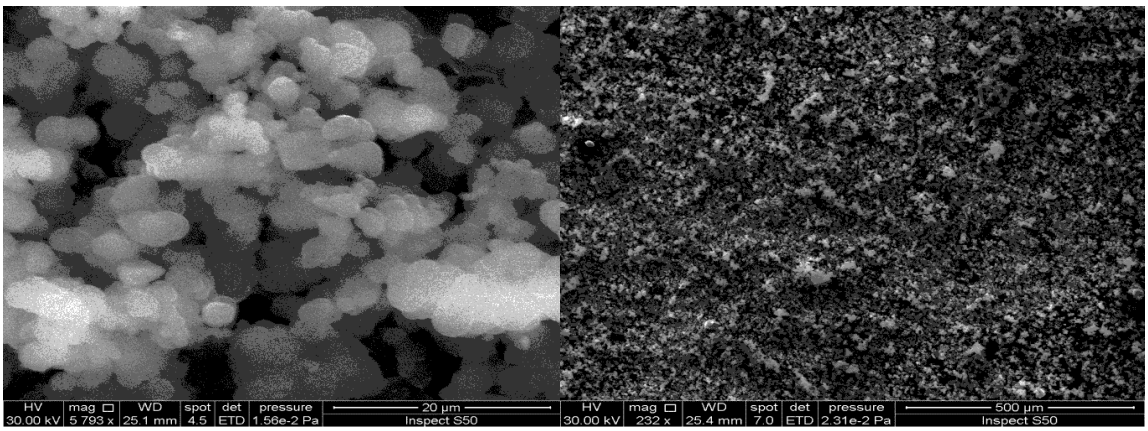
While maintaining flow of nitrogen, the glass tube was removed from the ultrasonic water bath, sealed and placed inside a water bath at 60°C to allow initiation of the reaction. white colored polymers with a rigid structure were for medNon-reacted species (excessive reagents or template) were removed from the polymers by consecutive washout of the particles with methanol then acetic acid and dried at room temperature overnight.

The template was successively removed by repeated washing with the MIPs with 100 mL portions of 30 percent (v / v) acetic acid / methanol solution using soxhlet removal. The polymer was dried at (35-45) 0C for (24-72) hours.

The polymers were then crushed and ground with mortar and pestle and tested to a particle size of 125µm (using 100 mesh sieves):It was used in the selective sensor membrane as an active material. The unprinted polymer (NIP) was produced in the same way, but without the drug template. The sensing PVC membrane was prepared by mixing 0.2 g of high molecular weight PVC, 0.45 g of the plasticizer and 0.036 g of the MIP. After homogenization, 2-4 mL of THF was added and stirred. The mixture was poured in a 5 cm diameter glass ring and evaporated for 24 hours. The electrode was made by attaching the PVC membrane circular disk (10 mm in diameter) to the end of the Tygon tube using a concentrated PVC / THF solution as adhesive. The other end of the Tygon tube was fixed to a glass tube into which a silver wire coated with silver chloride was inserted and filled with 0. 1 M standard solution of naproxen.

Scanning Electron Microscope (SEM)

A scanning electron microscopy(SEM) was used for the primary evaluation of MIP particles. Electron microscope shows the morphology of the MIP and NIP membranes for naproxenprior to and after washing.A porous surface area of about 20 µm figure (2) can indicate the binding sides of the polymer. Figure. (3)shows clear holes of approximately 20-50µm in sizes that were removed by soxhlet extraction.



(a) (b)

Fig. 3: SEM photograph of the surface of (NPX -MIP) a) after washing b) before washing

Construction of Ion-Selective Electrodes

As depicted by Mahajan et al [17], the building of the electrode body and the immobilization were achie ved. The solution of naproxen (0.1) M was filled as an internal solution in the glass tube.The membrane w as preferred to be immersed in a standard solution of (0.1) M naproxen
for at least three hours before measurements representing membrane electrode stipulations.

Preparation of Pharmaceutical Samples

To obtain the powder of pharmaceutical samples from tablets using pestle and mortar to grind the tab lets, a suitable weight was taken for the preparation of 100 ml solutions.Appropriate
quantity of methanol (CH3OH) used for dissolved pharmaceutical samples and completed for more than 3 0 minutes in the volumetric flask of methanol and usingthe magnetic agitator.The solution was then filter ed using 0.07µm cellulose filter paper to prepare and obtained naproxen concentrations of 5 x10 $^{-3}$ M and 5 x 10 $^{-4}$ M.

RESULTS AND DISCUSSION

Ion selective electrodes (ISE) are one of the most common sensors for measuring voltage.

These measurements were used in laboratory testing, industry, process control, physiological andenvi ronmental monitoring [18].Electrodes membranes that responded to the concentrationanalysis using a che mical reaction to produce ions that can be monitored with an ion selective electrode [19].

These membrane electrodes comprised two main categories: Ions Selectiveelectrodes sensitive to ioni c species and selective moleculr electrodes used to determine molecular analytes [20,21].

The main function of ion selective electrodes consists of two different types of electrical conductivity in metals, the electrical current is transmitted by electrons, while the electrical current is transmitted by ions in liquids. In one of these types of galvanic cells, electrolysis and electrical analysis, conductivity measurement can be achieved for each electrochemical process. This type of cell must be in contact with the solution on both sides of the cell membrane, and some ISE arrangements with wire connection on one side of the membrane are also available. Traditional cell composition is:

Outer ref. Test solution membrane internal ref.

Or

Outer ref. Test solution ion-selective electrode

The current passing through the electrolytic cell must be zero depending on this condition that the cell is designed in accordance with the basic design rule for electrolytic cells.

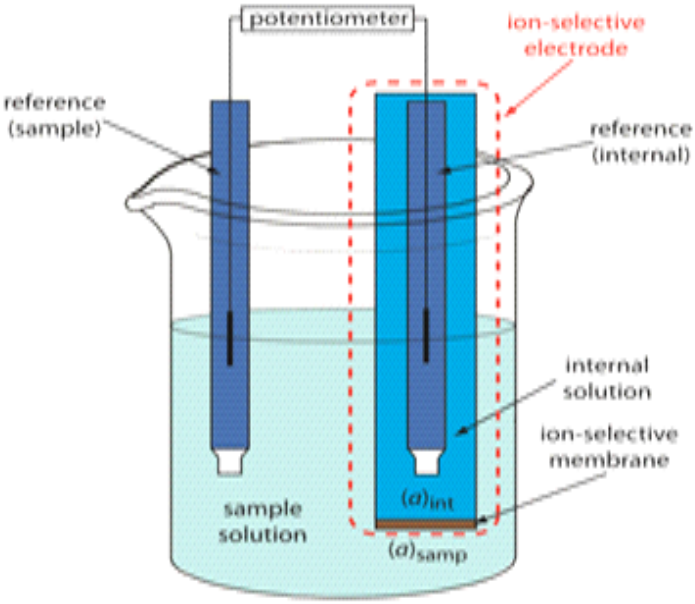


Fig.4: Schematic diagram showing a typical potentiometric cell with an ion-selective electrode.

Using naproxen as a template, acrylamide as monomer, ethyleneglycodimethacry late and benzoyl peroxide as cross-linkers and initiators, MIP have been prepared. An important component of an ISE membrane is a plasticizer. Compatibility with polymer and other membrane components provides a homogeneous membrane environment when plasticizers are used As a membrane solvent, the practical use of the ISE membrane should be avoided, otherwise the electrode performance would be affected over time. On the basis of the PVC matrix, two electrodes were constructed. These plasticizers, for example: di octyl phthalate(DOP) and acetophenone (AOPH). The characteristics of two electrodes based on NPX - MIP(membranes A1,A2) have been studied.This included the range of linearity, correlation coefficients, d etection limit (M) and lifetime (day). The results shown in Table1and Figure (5).

Table 1: Characteristics of the naproxen-MIP electrode based on different functional monomers and plasticizers

Membrane composition	NPX-MIP+ DOP (A1)	NPX-MIP+AOPH (A2)
Slop (mV/decade)	**-21.37**	**-19.4**
Linearity range (M)	**5×10^{-5} -0.1**	**1×10^{-1} - 5×10^{-5}**
Correlation coefficient	**0.9589**	**0.9974**
Detection limit (M)	**3×10^{-5}**	**4×10^{-5}**
Life time (day)	**15**	**17**

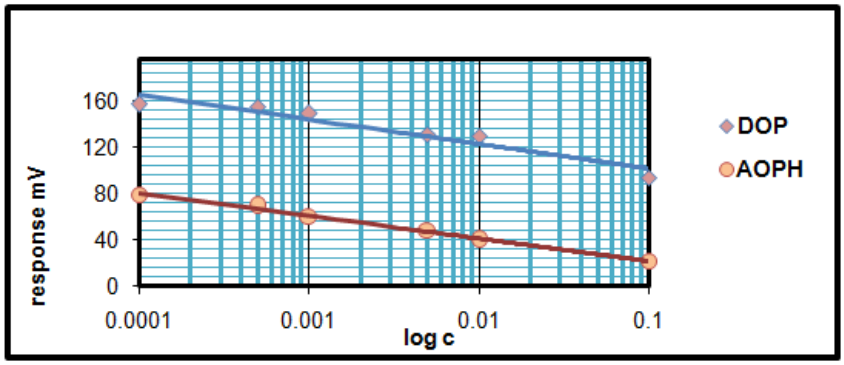


Fig. 5: Calibration curve for NPX-MIP membrane electrodes

Effect of pH on electrodes response

The pH study was carried out on electrodes of NPX membrane using different concentrations of NPX(10-2 5×10 -3and 5×10-4).To measure selective pH(1-11)using hydrochloric acid (0.1M,1M)and/or ammonium hydroxide (0.1 M, 1 M) in pH studies. The results obtained by adding the appropriate volume of HCl / NH4OH as shown in Table (2) and Fig. (6). The change in the potential of differential pH values is due to the composition of electrodes.

Table 2: Working pH range for naproxen selective electrode

Number and composition of MIPs	Membranes	Membrane composition	pH range		
			$^{2-}10$	$^{3-}10\times5$	$^{4-}10\times5$
MIP NPX+AM+EGDMA	A1	NPX-MIP+DOP	7.5-3	8.5-3.5	6.5-2.6
	A2	NPX-MIP+AOPH	8-2.5	8.5-2	9-4

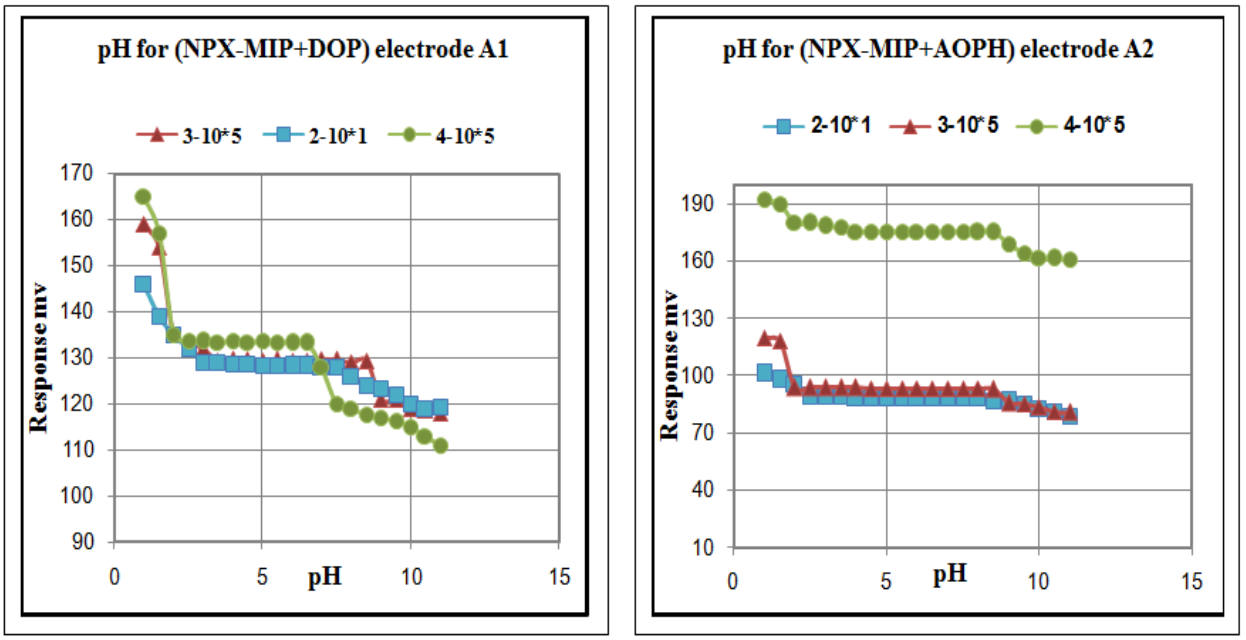


Fig. 6: Effect of pH on the Naproxen {NPX-MIP+ DOP (A1) and NPX-MIP +AOPH (A2) } electrodes at concentration 10^{-2}, 5×10^{-3} and 5×10^{-4}.

Interference Studies

The separate solution method was used to calculate the selectivity coefficient measurement. For these measurements, the separate equation was used according to the equation below.

$$\text{Log K pot} = [(EB - EA)/(2.303RT/z\,F)] + (1 - zA/zB)\log aA$$

EA, EB; zA, zB; and aA, represents the potentials, charge numbers, and activities for the primary A and interfering B ions, respectively at aA = aB.

The results for primary ion selectivity coefficients and interfering ions such as (K^{+1},$Ca^{+2}$and Al^{+3})used in this work have been obtained. The selectivity coefficients also depend on the concentration and composition of electrodes depend on the charges of both the primary ion and the interfering ions. All values for selectivity coefficients were listed in the table 3, 4 and figures(7,8)

Table 3: Selectivity coefficients for (NPX –MIP +DOP) electrode at different concentrations of naproxen.

Con. (M)	Concentrations of Naproxen: concentrations of interference ions (M) Interfering ions					
	K^{+1}		Ca^{+2}		Al^{+3}	
	E_B (mv)	$K_{A,B}$	E_B (mv)	$K_{A,B}$	E_B (mv)	$K_{A,B}$
10^{-1}	130	1.3516×10^{-2}	130.8	3.9216×10^{-3}	130.2	2.8497×10^{-3}
10^{-2}	165	3.4838×10^{-4}	159.4	6.3641×10^{-5}	155.5	4.4935×10^{-5}
5×10^{-3}	174	2.0343×10^{-4}	168.7	1.1378×10^{-5}	165.3	5.1862×10^{-6}
1×10^{-3}	199	1.7126×10^{-5}	188.3	5.4156×10^{-7}	180.3	2.7585×10^{-7}
5×10^{-4}	202	3.2660×10^{-5}	192.8	2.7792×10^{-7}	188.5	6.4768×10^{-8}
1×10^{-4}	206	3.2660×10^{-5}	197.8	7.8922×10^{-8}	196.3	9.2702×10^{-9}

Table 4: Selectivity coefficients for (NPX –MIP +AOPH) electrode at different concentrations of naproxen

Con. (M)	Concentrations of Naproxen (M):concentrations of interference ions (M) Interfering ions					
	K^{+1}		Ca^{+2}		Al^{+3}	
	E_B (mv)	$K_{A,B}$	E_B (mv)	$K_{A,B}$	E_B (mv)	$K_{A,B}$
10^{-1}	115.3	1.4109×10^{-3}	112	6.6007×10^{-4}	118	2.206×10^{-4}
10^{-2}	119.8	1.4448×10^{-3}	120.9	1.2679×10^{-4}	125.4	3.4493×10^{-5}
5×10^{-3}	122.3	1.8537×10^{-3}	123.1	5.3309×10^{-5}	126.5	1.1258×10^{-5}
1×10^{-3}	126.8	1.4448×10^{-3}	124.5	1.8982×10^{-5}	132	1.6786×10^{-6}
5×10^{-4}	128.2	4.6785×10^{-3}	127.5	1.6076×10^{-5}	135.7	8.9126×10^{-7}
1×10^{-4}	134.8	4.3569×10^{-3}	130	7.7019×10^{-7}	160.9	1.9661×10^{-8}

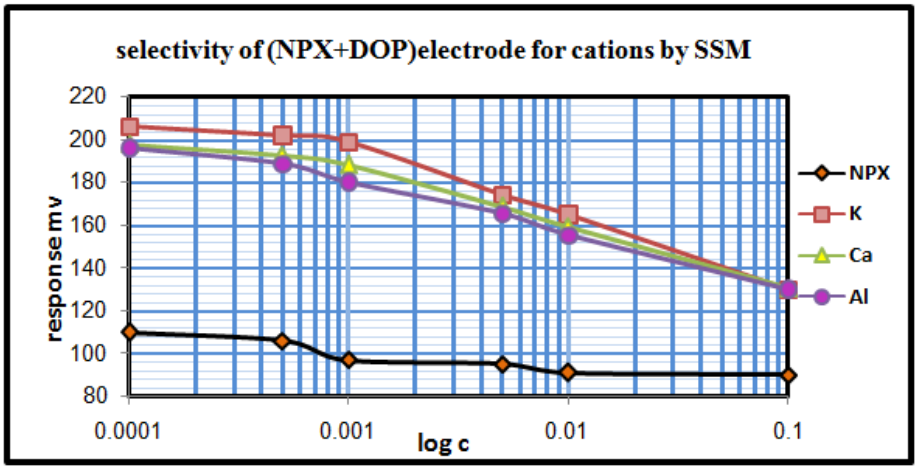


Fig. 7: Selectivity of (NPX-MIP + DOP) electrodes with ions via Separation Solution Method

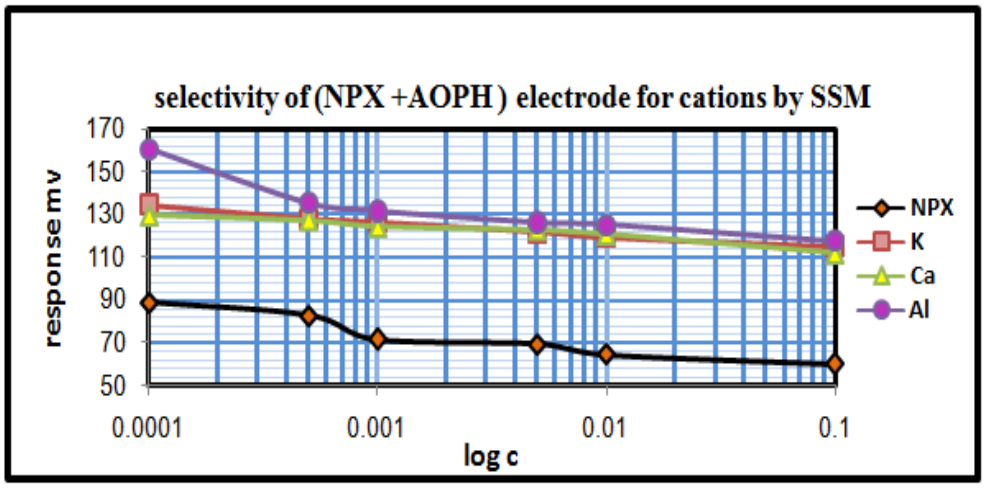


Fig. 8: Selectivity of (NPX-MIP + AOPH) electrodes with ions via Separation Solution Method.

Calculation by Multiple Standard Addition Method (MSA)

The concentrations used for applied in this method (5×10^{-3} & 5×10^{-4}) for two solutions of naproxen for plotting the antilog E/S (Y-axis) against volume of standard naproxen(X-axis). Fig. (9,10) represents the results of naproxen concentrations calculated via the electrodes based on NPX-MIP+ DOP, NPX-MIP+AOPH.

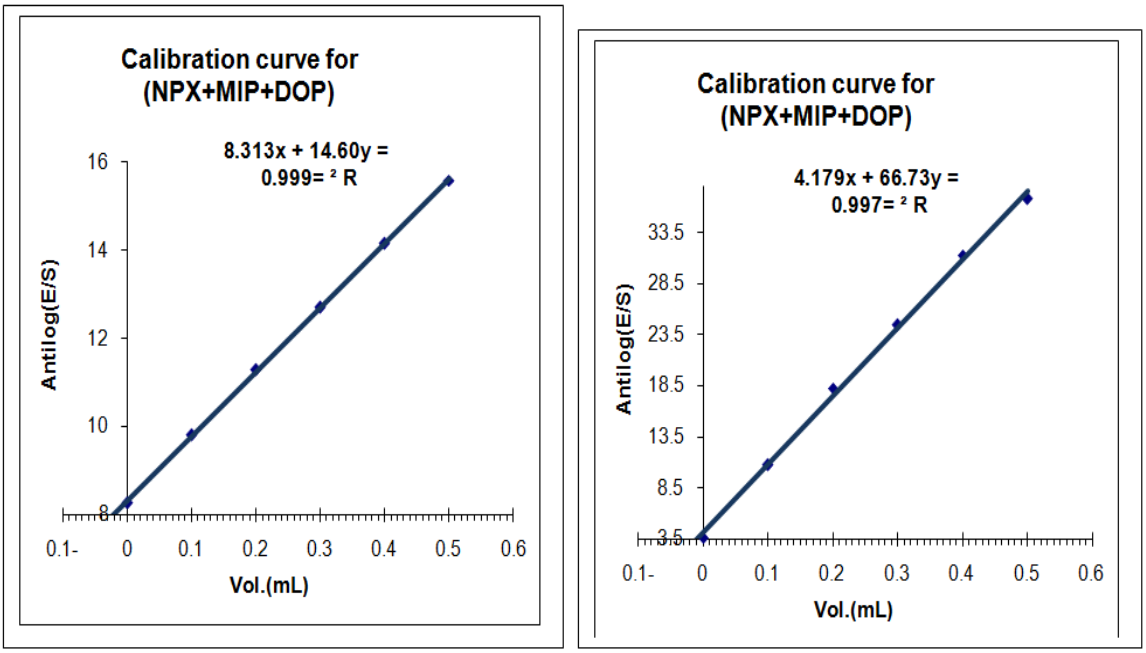


Fig. 9: Antilog (E / S) against the volume of the added standard for the determination of naproxen solution (5×10^{-3} and 5×10^{-4}) by MSA using (NPX–MIP + DOP) electrode

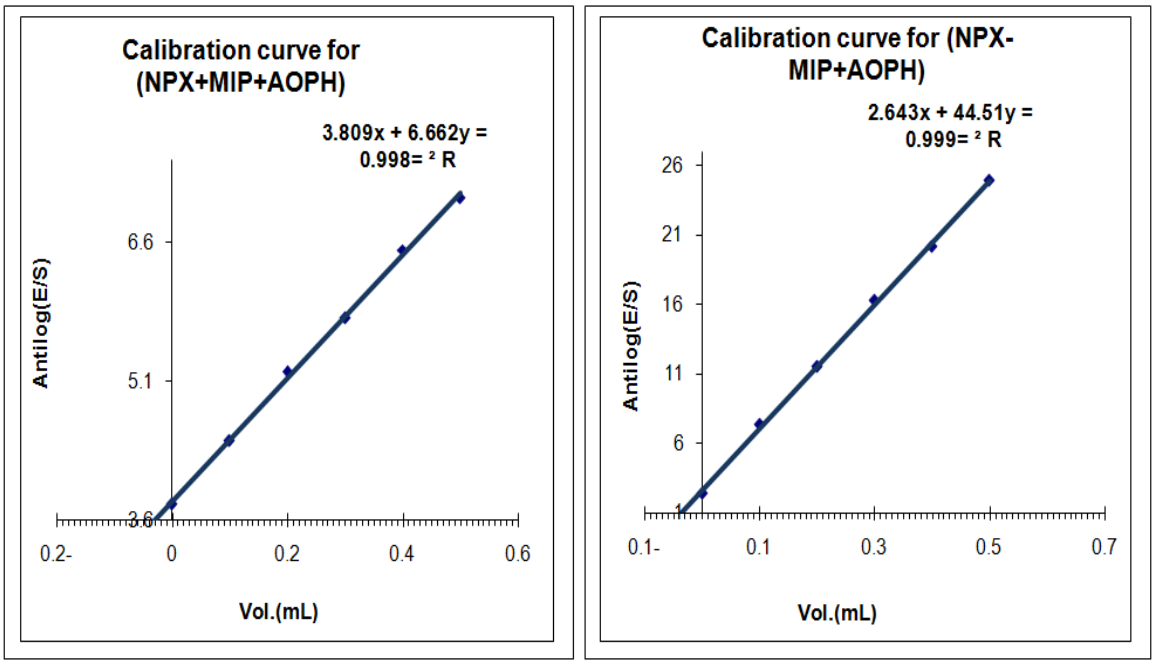


Fig. 10: Antilog (E / S) against the volume of the added standard for the determination of naproxen solution (5×10^{-3} and 5×10^{-4}) by MSA using (NPX–MIP+ AOPH) electrode.

Titration Methods (Titrimetry)

In this method the measurement is depended changes that to be a large shift in the electrode response for the detection of the end point of titration. The process have been achieved by used volumetric analysis of concentrations (5×10^{-3} and 5×10^{-4}) M of naproxen versus solutions (5×10^{-3} and 5×10^{-4}) M of concentrations (PMA).The results for parameters RSD%, RC% and RE%for all electrodes are listed in the table (5).

Table 5: Naproxen sample analyses by using titration method for NPX electrodes

Electrode NO.	Concentration (M) Measured using PMA as titrant		
Pure (NPX)	Parameter	DOP	AOPH
	$5\times10^{--3}$	5.10×10^{-3}	5.10×10^{-3}
	RSD%	2	1.58
	RC%	102	102
	RE%	3	2
	5×10^{-4}	5.15×10^{-4}	5.05×10^{-4}
	RSD%	2.31	1.46
	RC%	103	101
	RE%	3.09	1
NAPRON (PiONEER-Iraq)	5×10^{-3}	5.10×10^{-3}	5.10×10^{-3}
	RSD%	1.55	0.97
	RC%	102	102
	RE%	2	2
	5×10^{-4}	5.154×10^{-4}	5.08×10^{-4}
	RSD%	1.05	1.27
	RC%	103.08	101.72
	RE%	3.08	1.72

Applications of pharmaceuticals

Ion selective electrodes that based on molecularly imprinted polymers were used for determination of naproxen in pharmaceuticals. This ISEs measurements including: standard addition, direct, Gran plot and multiple standard addition method. Preparation solutions of naproxen at concentrations 5×10^{-3} and 5×10^{-4} M. The RE%, RC% and RSD% were calculated of naproxen in pharmaceuticals. The results obtained represented in the table (6).

Table 6: Determination of Naproxen Samples by Ion Selective electrodes (ISEs) techniques based on PVC membranes

Electrode NO. and composition	Measurement by using ISEs methods				
NPX-MIP+ DOP (I)	Standard sample 5×10^{-3}				
	Parameter	RSD%	RC%	RE%	Con. found
	Direct	1.08	101.62	1.62	5.0808×10^{-3}
	SAM	1.24	101.75	1.75	5.0875×10^{-3}
	MSA	-	101.16	1.61	5.0805×10^{-3}
	Standard sample 5×10^{-4}				
	Parameter	RSD%	%RC	RE%	Con. found
	Direct	2.24	102.01	2.01	5.1005×10^{-4}
	SAM	2.98	100.02	0.02	5.0010×10^{-4}
	MSA	-	100.37	0.37	5.0187×10^{-4}
NPX-MIP + AOPH (II)	Standard sample 5×10^{-3}				
	Parameter	RSD%	RC%	RE%	Con. found
	Direct	1.18	101.03	1.03	5.051×10^{-3}
	SAM	2.34	98.6	-1.3	4.934×10^{-3}
	MSA	-	101.9	1.97	5.098×10^{-3}
	Standard sample 5×10^{-4}				
	Parameter	%RSD	%RC	%RE	Con. found
	Direct	1.97	102.09	2.09	5.104×10^{-4}
	SAM	0.75	101.2	1.2	5.060×10^{-4}
	MSA	-	100.92	0.92	5.046×10^{-4}

Table 7: Sample Analysis of Pharmaceuticals Naproxen by using ISE

Membrane composition	NPX-MIP+DOP		
Pharmaceutical	NAPRON(PiONEER -Iraq)		
	DM	SAM	MSAM
Concentration (prepared) M	10×5^{-3}		
Value founded	5.1009×10^{-3}	4.9787×10^{-3}	4.9811×10^{-3}
Recovery %	102.02	99.57	99.62
RE%	2.02	-0.43	-0.38
RSD%	3.39	1.23	_
Concentration (prepared) M	10×5^{-4}		
Value founded	5.045×10^{-4}	5.079×10^{-4}	4.909×10^{-4}
Recovery %	100.92	101.58	98.18
RE%	0.92	1.58	-1.82
RSD%	2.25	1.82	_
Membrane composition	NPX-MIP+AOPH		
Pharmaceutical	NAPRON(PiONEER -Iraq)		
Concentration (prepared) M	10×5^{-3}		
Value founded	5.031×10^{-3}	5.144×10^{-3}	4.981×10^{-3}
Recovery %	100.64	102.8	99.6
RE%	0.64	2.89	-0.37
RSD%	1.8	2.43	_
Concentration (prepared) M	10×5^{-4}		
Value founded	5.124×10^{-4}	4.930×10^{-4}	5.030×10^{-4}
Recovery %	102.49	98.6	100.6
RE%	2.49	-1.4	0.6
RSD%	1.37	0.75	_

***each measurement have been repeated three time.**

CONCLUSION

Naproxen membranes selective electrodes can be constructed by mixing with different plasticizers. These plasticizers DOP AOPH were used to prepared naproxen membranes electrodes based on PVC. The results obtained for all electrodes were excellent as well as applied on standard and pharmaceutical solutions .The aim of construction electrodes for used in determination naproxen in pharmaceuticals analysis .

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