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Abdullah &Al-Bayati

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SYNTHESIS OF NEW LEVOFLOXACIN SELECTIVE MEMBRANE SENSOR BASED ON MOLECULARLY IMPRINTED POLYMERS.

SajaF. Abdullah[1], Yehya K. Al-Bayati[2]
[1]Chemical Assistant, Department of Chemistry, College of Sciences, University of Baghdad, Baghdad, Iraq. sajafarhan95@gmail.com
[2]Professor PhD., Chemistry Department, College of Science, University of Baghdad, Iraq. yahyaalbayti@yahoo.com

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ABSTRACT

Two molecular imprinted polymer (MIP) membranes for Levofloxacin (LEV) were prepared based on PVC matrix. The imprinted polymers were prepared by polymerization of styrene(STY) as monomer, N,N methylene di acrylamide as a cross linker ,benzoyl peroxide (BPO) as an initiator and levofloxacin as a template. Di methyl adepate (DMA) and acetophenone (AOPH) were used as plasticizers , the molecular imprinted membranes and the non molecular imprinted membranes were prepared. The slopesanddetectionlimits of the liquid electrodes ranged from-21.96–-19.38mV/decade and 2×10^{-4}M- 4×10^{-4}M,and Its response time was around 1 minute, respectively. The liquid electrodes were packed with 0.1 M standard drug solution and its response were stable at pH ranges from 1.0 to 11.0 and with good selectivity for more than several type. The electrodes produced have been successfully applied in preparation of the pharmaceutical sample for the determination of the analyte without any time consuming pretreatment steps.

Keywords: Molecularly impressed electrodes, levofloxacin, potentiometric method, styrene (STY) monomer.

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تخليق مستشعر الغشاء الانتقائي الليفوفلوكساسين الجديد على اساس بوليمرات مطبوعة جزيئياً

سجى فرحان عبدالله [1]، *يحيى كمال البياتي* [2]
قسم الكيمياء، كلية العلوم، جامعة بغداد، بغداد، العراق. sajafarhan95@gmail.com
استاذ دكتور، قسم الكيمياء، كلية العلوم، جامعة بغداد، بغداد، العراق. yahyaalbayti@yahoo.com

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الخلاصة

تم تحضير غشاءين من البوليمرالمطبوع جزيئيًا (MIP) لـ Levofloxacin بناءً على مصفوفة PVC .تم تحضير البوليمرات المطبوعة بواسطة بلمرة الستايرين (STY) كمونومرو N، Nميثيلين داي أكريلاميد كموصل متشابك، البنزويل بيروكسيد (BPO) كبادئ وليفوفلوكساسين كقالب. تم تحضير ثنائي ميثيل أديبات (DMA) وأسيتوفينون (AOPH)كمواد ملدنة، وتم تحضير الأغشية المطبوعة جزيئيًا والأغشية غير المطبوعة. تراوحت حدود المنحدرات وحد الكشف للأقطاب السائلة من 19.38- – 21.96- مللي فولت/ عقد و4×10^{-4}M- 2×10^{-4}M، وكان وقت الاستجابة حوالي دقيقة واحدة على التوالي. تمت تعبئة الأقطاب الكهربائية السائلة بمحلول دوائي قياسي 0.1 M وكانت استجابتها مستقرة عند درجة الحموضة من 1.0 الى11.0 وبانتقائية جيدة لأكثر من عدة أنواع. تم تطبيق الأقطاب الكهربائية المنتجة بنجاح في تحضير العينة الصيدلانية لتقدير المادة التحليلية بدون أي خطوات معالجة مسبقة تستغرق وقتًا طويلاً.

الكلمات المفتاحية: الاقطاب المطبوعة جزيئياً، الليفوفلوكساسين، طريقة قياس الجهد، المونمرستايرين (STY).

INTRODUCTION

The first documented in the molecular imprinting technique in 1970**Nishide&Tsuchida (1976)**, molecular imprinting is a commonly emerging technique for producing polymers with different molecular properties for a given compound, its analogs, or an enantiomer**(Whitcombe*et al.*, 1998; Yan & Row, 2006)**.MIPs are the sensing elements of a molecular imprinting electrochemical sensor (MIECS) which are molecularly imprinted. MIECS has many characteristics include: high selectivity, simplest techniques, lower costs, low D.L, highly stable. The combination of both the template molecules and the cavities can also be easily achieved and is carefully applicable even with harmful chemical materials. Thus, MIECS was used for optical and electrochemical application **(Tadi&Motghare, 2016; Al-Bayati&Abd, 2017; Al-Bayati& Al-Safi, 2018; Momeneh & Gholivand, 2018; D'Aurelio*et al.*,2020)**.Molecularly imprint polymers (MIPs) are prepared By combining template molecule(LEV) with functional monomers styrene (STY), a cross-linker N,Nmethylene di acrylamide (N,N MDAM) and initiator benzoyl peroxide (BPO) in appropriate solvent. Most of the time, Aprotic and unipolar solvents.So after polymerization, template molecule extraction reveals recognition cavities that complement the template molecule's shape, height, and chemical functionality, allowing the resulting polymers to selectively rebind the template molecule from a mixture of closely related compounds**(Lavignac*et al.*, 2004)**.In additional, the MIP have easily synthesis and have good mechanical properties, reliability for pressures and temperatures, and thus are cost-effectively and suitable to applicable for harmful chemicals **(Li *et al.*, 2012, Al-Bayati& Aljabari, 2016; Zhang *et al.*, 2019).** Interactions between template and monomer have been studied through spectral and computer simulation research. The utilization of molecular imprinting techniques have increased significantly in recent years, thus illustrating magnificently the ability of MIP model for detection toward the target molecules.**(Bates*et al.*, 2017; Al-Bayati, 2018; Marćet *al.*,2018)**. There Several analytical methods such as High performance liquid chromatography (HPLC)**(Santoro*et al.*, 2006; Mahajan*et al.*, 2007**),chromatography**(Mishal& Sober, 2005)**, fluorescence **(Prat*et al.*, 2006)**, mass spectrometry **(Boxall*et al.*, 2006)** and potentiometric methodwere used for LEV determination in contrast. Such techniques are distinguished by a lengthy and complicated preparation of the sample for analysis, as well as costly instrumental equipment. In this study, a new levofloxacin ion-selective membrane electrode (lev-MIP+DMA or AOPH) in the PVC membrane process was prepared.

LEV is a broad-spectrum racemic fluoroquinolone antimicrobial (Figure 1).It is the ofloxacin 's active L-isomer, and its antibacterial efficacy is around two times that ofloxacin. and are widely used today in both human and veterinary applications Medicine as antibacterial agents of different diseases(**Turiel*et al.*, 2007**). Over the past few years,the research on antibiotic residues in the multiple environmental compartments has been of great importance due to the biodiversity and public health consequences**(Turiel*et al.*, 2007**).

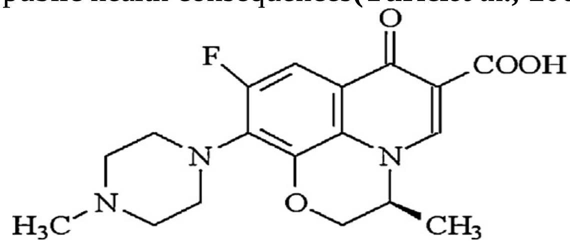

Figure (1): Chemical structure of the levofloxacin.

MATERIALS AND METHODS

Levofloxacin was purchased from company of drug manufacturing and medical supplies (IRAQ-SID-Samara). generic levofloxacin tablets purchased from local pharmacies are; Levoneer 10 tablets 500 mg from (Pioneer-Iraq) levofloxacin 7 tablets 750 mg from (Ilflox-Turkey).Di methyl adepate (DMA) and acetophenone (AOPH) also metal salts, they were obtained by Sigma-Aldrich and used as provided. Styrene (99%), monomer N,N-methylenediacrylamide (N,N-MDAM) (99%),and benzoyl peroxide (BPO)(78%) from Sigma-Aldrich is obtained. the chemical used was the largest purity reagent and was used when obtained without further purification.

Apparatus

A digital voltmeter (HANA pH211instrument Microprocessor pH meter) was used to perform potentiometric measurements. Digital pH meters (wissenschaftlich- Technische Werkstätten GmbH WTW pHmeter in lab pH720-Germany) were used for pH measurements. Electrode efficiency was investigated by calculating the potential of levofloxacin solutions at ambient temperature with a variety of concentrations from 5×10^{-4} M to 10^{-1}M. Every solution was stirred, and the reading potential was recorded at equilibrium. The calibration curves obtained by plotting the response against the levofloxacin concentration logarithmic functions.

Preparing of Standard Solutions for ISEs studies

For the preparation of a standardsolutionof0. 1Mlevofloxacinbydissolves 3.614 gofstandardlevofloxacininthe methanolandcompletedto100mLinthevolumetricflask.In the same procedure, the other solutions were prepared in 100 mL ranging from (5×10^{-5} – 10^{-1})M. Thestockstandardsolutionof1×10^{-3}M1×10^{-4} Mphosphomolybdic acid was preparedby dissolving 1.1288g, 0.11288 gfromphosphomolybdic acidrespectively indistilled waterandcompletedfor100mL. All interferingions (K^{+1},Ca^{+2}andAl^{+3})arepreparingof0.1M.The other solutions at the range from (5×10^{-5}_10^{-1}) M were prepared in 100 ml.

Synthesis of the Imprinted Polymer (MIP)

For the preparation of levofloxacin molecularly imprinted polymer (LEV-MIP), 1 mmol (0.34 g) of levofloxacin was mixed with 2mmol (0.208 g) styrene as the monomer. After this, 10.6mmol (1.634 g) N, Nmehtylene di acrylamide was added to the solution as the cross linker, followed by (0.3g) benzoyl peroxide as the initiator. All these materials were subsequently dissolved in 5 mL mixture of methanol and chloroform, and the mixture was stirred for 5 minutes to obtain a homogenous solution. Afterwards, the gas N2 was passed through the

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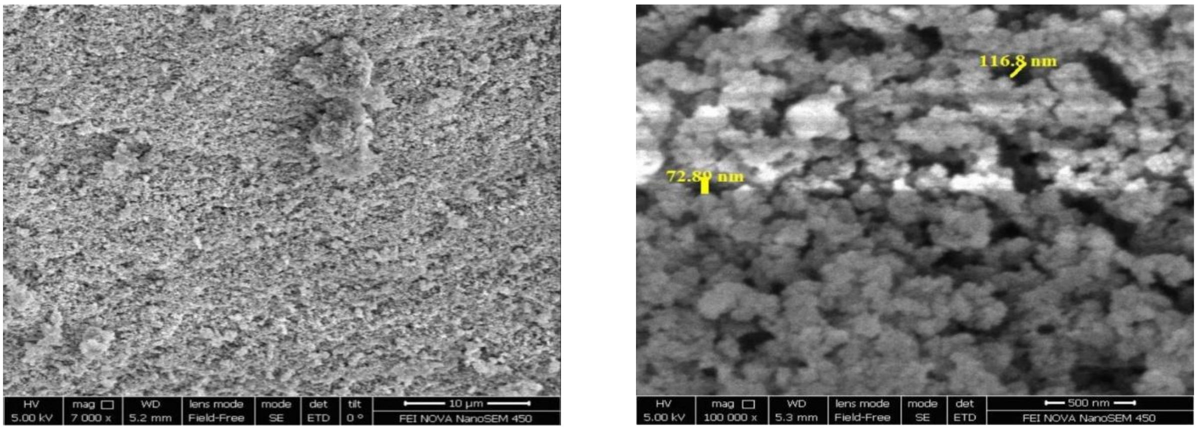
solution for 30 minutes to remove oxygen from it, and the solution was placed in a water path at 65°C. When the reaction was complete, the molecularly imprinted polymer became hard, and, after the polymerization process, the polymer was dried and crushed to obtain it as particles. Finally, these particles was sonicated in CHCL3/ CH3OH / CH3COOH (7 : 2 : 1)(v/ v/v) to remove the template from the MIP. The particles size of LEV- MIP (125 μm).

The preparation of non-molecularly imprinted polymers was carried out using the same method, using the same compounds and under the same conditions as in LEV-MIPpreparation, but without levofloxacin. A PVC tube (1-2 cm long) was flattened and polished by placing it on a glass plate and soaking it with THF. Similar to the actual diameter of the PVC tubing, the membrane was then sliced and pasted onto the polished end. The other end of that was attached to an electrode of Ag-AgCl.

Scanning Electron Microscope (SEM)

The SEM is used to get an understanding of the pore 's membrane thickness, composition, and surface distribution. SEM analysis showed that molecular impressed polymer has a strongly ordered and normal pore structure in surface and cross-section which serves as interface sites. Several papers have shown that due to the shape and function of the porous structures, the amolecular impressed membrane of this type recognizes that the molecule of the template is quickly transported with good efficacy.

The morphology of MIP and non- imprinted polymer NIP membranes before and after washing showed by electron microscope in (Figure2).



(A) (B)

Figure (2): SEM photograph of the surface of MIP, a) before washing b) after washing.

Construction of Ion-Selective Electrodes

Construction of Ion-Selective Electrodes As shown by **Mahajan*et al.* (2007)**, electrode body building and immobilization have been achieved. The solution of Levofloxacin 0.1 M was filled as an internal solution in the glass tube. Membrane was preferred tobe immersed in a standard solution of 0.1M levofloxacin for at least three hours before measurements representing membrane electrode stipulations.

Preparation of Pharmaceutical Samples

The drug tablets were ground to powder by using pestle and mortar. Subsequently, a required weight of the powder was used to prepare 100 mL solutions. Here, a certain amount of powder was dissolved in methanol (CH3OH) and stirred by magnetic stirrer for 30 minutes to completely dissolve the powder. The solution was completed to 100 mL by methanol to prepare 1×10-3 M and 1×10-4 M levofloxacin solutions.

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RESULTS AND DISCUSSION

MIP based liquid electrodes, their concentrations range and slopes response to Nernstian equation has been investigated. The membranes of MIP made of the monomer styrene with a PVC matrix using two plasticizers DMA and AOPH. The internal solution was used 0.1M aqueous standard solution of drug for all liquid electrodes. Experimental results of synthesis of molecularly imprinted (MIP) and non-imprinted polymers (NIP) based on monomer Styrene indicate that monomer can be used for the preparation of effective MIP for Levofloxacin. The plasticizer is an essential part of the sensing membrane which have important role as a solvent for the different components and determines the mobility of the analyte in membrane. Both of the plasticizers that are used, DMA and AOPH, are suitable for the fabrication of MIP-based LEV electrodes. (Table 1) show the parameters of the fabricated and tested electrodes, Two membranes of the different compositions were prepared using two different plasticizers Di methyl adepate (DMA)and acetophenone (AOPH). The results of electrode specification were obtained from the calibration curves that listed in (Table 1). The slopes of the electrodes ranged between -21.96 – -19.38 mV/decade (Figure 3). In generally the preparation electrodes have a short response time (about 60 second) mostly at high concentrations.

Table(1): Levofloxacin-MIP electrode properties dependent on various functional monomers and plasticizers.

Membrane compostion	LEV-MIP (DMA)	LEV-MIP (AOPH)
Slop (MV/decade)	-21.96	-19.38
correlation coefficients	0.9819	0.9872
detection limit (M)	2×10^{-4}	4×10^{-4}
range of linearity(M)	5×10^{-5}-1×10^{-1}	5×10^{-5}-1×10^{-1}
lifetime (day)	13days	14days

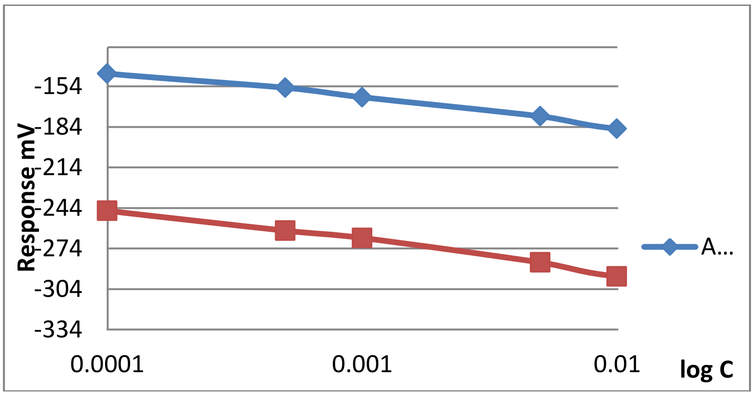


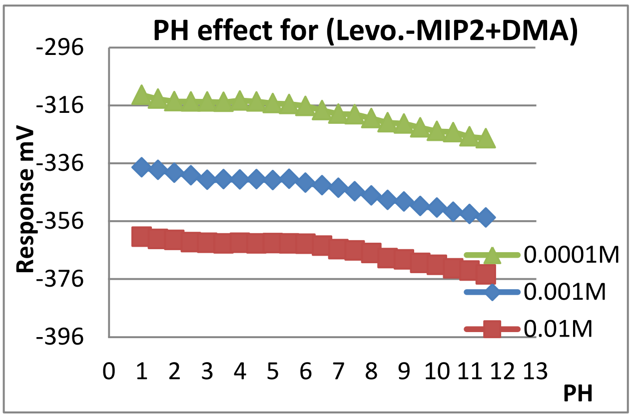
Figure (3): Calibration curve for Lev-MIP membrane electrodes.

Effect of pH on electrode response

The pH effect of the two electrode potential values for pH varied from 2.5 to 10 was studied and the pH effect was modified by adding drops of 0.1 N HCl and 0.1 M NaOH to aqueous drug solutions and then the potentials obtained for each value were recorded. With three concentrations of standard drug solutions 1×10^{-2}, 1×10^{-3} and 1×10^{-4} M, the pH effect on the electrode potential has been reported The results obtained are shown in (Table 2) and the typical pattern of electrode potential versus pH for electrode M1 and M2 as seen in (Figure 4).

Table(2): Working pH range for levofloxacin selective electrode.

Number and composition of MIPs	Membranes	Composition of the membrane	pH range		
			1×10^{-2}	1×10^{-3}	1×10^{-4}
MIP Lev+STY+N,NMDAM	M1	Lev-MIP+DMA	2.5-6.0	3.0-5.5	2.0-4.5
	M2	Lev-MIP+AOPH	6.5-9.5	8.0-10	7.5-10



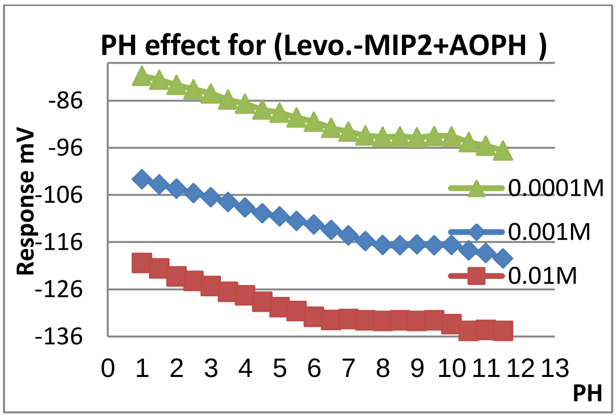


Figure (4): Effect of pH on levofloxacin (Lev-MIP+DMA(M1))and(Lev-MIP+AOPH(M2)) at 1×10^{-2}, 1×10^{-3} and 1×10^{-4} concentrations.

Response time and life time

Response time for both MIP.DMA and MIP.AOPH electrodes was obtained from dynamic potential reaction at range of concentration 5×10^{-5} – 1 $\times10^{-1}$ M by calculating the time needed to achieve 95 percent of the equilibrium potential. The findings show that the electrode reaction time was approximately 15 seconds for the solution of levofloxacin at a high concentration of 10^{-1} M and approximately 46 seconds at a low concentration of 10^{-5}M. The electrode lifetime was obtained by measuring the slope periodically from calibration curves for Lev. MIP. short life time was noticed for electrodes M1 and M2 (Table-1)

Interference Studies

The separate Solution Method (SSM) has been used to test potentiometric sensor selectivity coefficients for different species. In the SSM, two separate solutions are used to evaluate the potential of a cell comprising an active electrode and a reference electrode: one containing drug ions, E1, and the other containing interference ion potential (E2), respectively. The coefficient of selectivity was determined using the following equation:

$$\mathbf{Log\ K_{pot} = (E_2 - E_1) Z_1 F / 2.303RT (1 - Z_1/Z_2) \log a_1.}$$

E1, E1; z1, z2; and a1, represents the potentials, charge numbers, and activities for the primary 1 and interfering 2 ions, respectively at a1=a2. Selectivity coefficient of the electrodes L1 and L2 were studied toward several different ions like (K^{+},Ca^{+2} ,Al^{+3}). (Table3 and 4) (Figure5 and

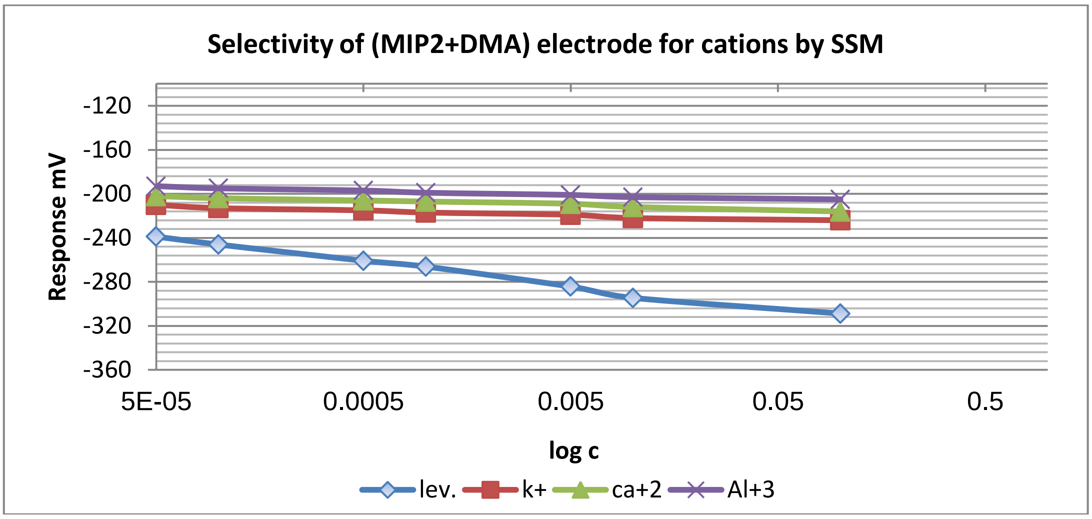
6) have provided both values for selectivity coefficients.

Table (3): Selectivity coefficients for (lev –MIP +DMA) electrode at different concentrations of levofloxacin.

Con.	Concentrations of levofloxacin(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}	-224	1.3754×10^{-4}	-216	1.8799×10^{-5}	-205	4.0413×10^{-6}
10^{-2}	-222	4.9429×10^{-4}	-212	1.7323×10^{-5}	-203	3.1288×10^{-6}
5×10^{-3}	-219	1.0627×10^{-3}	-209	2.6366×10^{-5}	-201	4.7069×10^{-6}
1×10^{-3}	-217	5.7069×10^{-3}	-207	6.3707×10^{-5}	-199	8.7074×10^{-6}
5×10^{-4}	-215	8.2109×10^{-3}	-206	7.1541×10^{-5}	-197	7.8292×10^{-6}
1×10^{-4}	-213	3.1097×10^{-2}	-204	1.2103×10^{-3}	-195	1.0147×10^{-5}
5×10^{-5}	-210	4.8303×10^{-2}	-202	1.4776×10^{-4}	-193	1.1029×10^{-5}

Table(4): Selectivity coefficients for (lev– MIP+ AOPH) electrodeat differen tconcentration soflevofloxacin.

Con.	Concentrations of levofloxacin (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}	-122.8	1.0764×10^{-4}	-110.8	8.1808×10^{-5}	-98.7	1.3236×10^{-6}
10^{-2}	-121.5	5.0441×10^{-4}	-108.7	1.1023×10^{-5}	-96.3	1.1724×10^{-6}
5×10^{-3}	-119.7	1.2151×10^{-3}	-105.5	1.5918×10^{-5}	-95.7	2.0552×10^{-6}
1×10^{-3}	-117.6	5.0563×10^{-3}	-104.6	3.4121×10^{-5}	-93.2	2.7848×10^{-6}
5×10^{-4}	-115.4	8.9433×10^{-3}	-103.5	4.8692×10^{-5}	-91.5	3.2905×10^{-6}
1×10^{-4}	-112.5	2.2062×10^{-2}	-102.1	6.4124×10^{-3}	-89.8	3.2036×10^{-5}
5×10^{-5}	-110.3	4.2915×10^{-2}	-100.9	9.9443×10^{-4}	-88.6	4.4218×10^{-5}



Figure(5): Selectivity of (Lev-MIP + DMA) electrodes with ions via separation solution method.

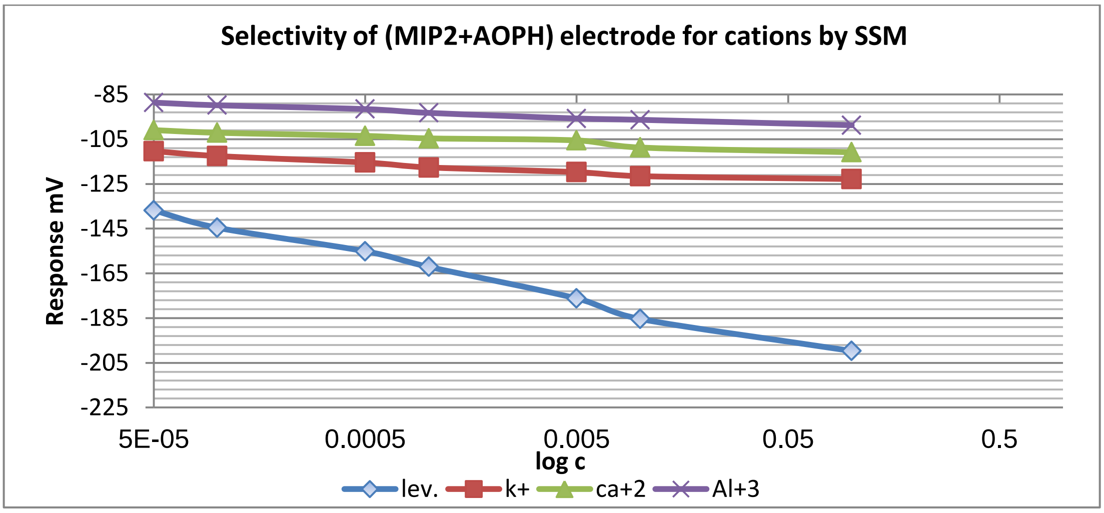


Figure (6): Selectivity of (Lev-MIP + AOPH) electrodes with ions via separation solution method.

Calculation using the Multiple Standard Addition Method (MSA)

The concentrations used in this process (1×10^{-3}& 1×10^{-4}) for two solutions of levofloxacin for plotting the antilog E / S (Y-) against the amount of regular levofloxacin (X-). (Figure 7 and 8) reflects the effects of the concentrations of levofloxacin determined by means of electrodes centered on Lev-MIP+ DMA, Lev-MIP+AOPH.

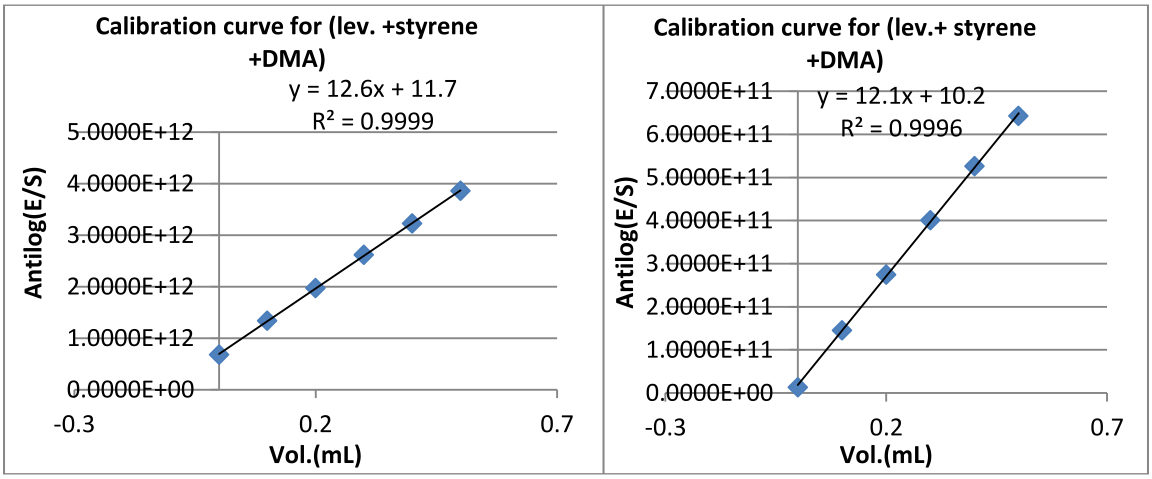


Figure (7): Antilog(E/S)againstthevolumeoftheaddedstandardforthedeterminationofLevofloxacin solution(1×10^{-3}and1×10^{-4}) by MSAusing(Lev–MIP+DMA)electrode.

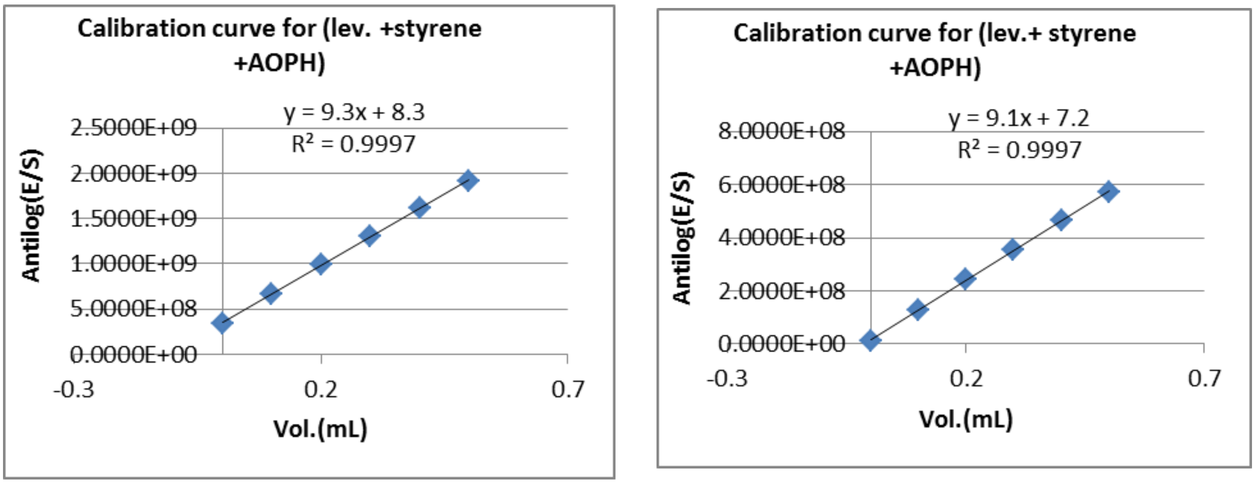


Figure (8): Antilog(E/S)againstthevolumeoftheaddedstandardforthedeterminationofLevofloxacin solution(1×10^{-3}and1×10^{-4})by MSAusing(Lev–MIP+AOPH)electrode.

Titration Methods (Titrimetry)

These methods relied on the identification of the end point of the titration. Such techniques have been using volumetric analysis between the concentrations and the reactants often make certain shifts slowly, resulting in a significant shift in the electrode reaction. Titration between the levofloxacin and ligand phosphomolybic acid (PMA). The findings for parameters RSD percent, RC percent and RE percent for all electrodes are shown in (Table 5).

Table (5): Levofloxacin sample analyses by using titration method for Lev electrodes.

Electrode NO.	Concentration (M) Measured using PMA as titrant		
	Parameter	**DMA**	**AOPH**
Pure (LEV)	**$1\times10^{--3}$**	1.0198×10^{-3}	1.012×10^{-3}
	RSD%	2.74	2.96
	RC%	101.98	102.14
	RE%	1.98	2.14
	1×10^{-4}	1.0208×10^{-4}	1.022×10^{-4}
	RSD%	2.89	3.11
	RC%	102.08	102.25
	RE%	2.08	2.25
ILFLOX(ILKO- TURKEY)	**1×10^{-3}**	1.0302×10^{-3}	1.025×10^{-3}
	RSD%	3.8	3.48
	RC%	103.02	102.52
	RE%	3.02	2.52
	1×10^{-4}	1.0230×10^{-4}	1.027×10^{-4}
	RSD%	3.18	3.78
	RC%	102.30	102.74
	RE%	2.30	2.74

Applications of pharmaceuticals

Ion sensitive electrodes based on molecularly imprinted polymers have been used for the determination of levofloxacin in pharmaceuticals. This ISE tests including: direct, standard addition, multiple standard and Gran plot. Levofloxacin preparation solutions at concentrations of 1×10^{-3} and 1×10^{-4}M.The RE percent, RC percent and RSDpercent were measured for Levofloxacin in pharmaceuticals. The results obtained represented in the (Table6 and 7).

Table (6): Determinationofleofloxacinsamplesbyionselectiveelectrodes(ISEs)techniquesbasedonPVC membranes.

Electrode NO. and composition	Measurement by using ISEs methods				
LEV-MIP+ DMA (I)	**Standard sample 1×10^{-3}**				
	Parameter	**RSD%**	**RC%**	**RE%**	**Con. found**
	Direct	1.64	101.70	1.70	1.0169×10^{-3}
	SAM	1.05	101.40	1.40	1.003×10^{-3}
	MSA	-	100.71	0.71	1.007×10^{-3}
	Standard sample 1×10^{-4}				
	Parameter	**RSD%**	**%RC**	**RE%**	**Con. found**
	Direct	0.43	101.62	1.62	1.016×10^{-4}
	SAM	1.07	101.55	1.55	1.0046×10^{-4}
	MSA	-	100.80	0.80	1.0080×10^{-4}
LEV-MIP + AOPH (II)	**Standard sample 1×10^{-3}**				
	Parameter	**RSD%**	**RC%**	**RE%**	**Con. found**
	Direct	2.8	101.60	1.60	1.01598×10^{-3}
	SAM	1.49	101.75	1.75	1.0024×10^{-3}

MSA	-	100.84	0.84	1.0084×10^{-3}
Standard sample 1×10^{-4}				
Parameter	**%RSD**	**%RC**	**%RE**	**Con. found**
Direct	1.2	101.93	1.93	1.019×10^{-4}
SAM	1.22	101.55	1.55	1.0031×10^{-4}
MSA	-	100.80	0.80	1.0080×10^{-4}

Table (7): Sample analysis of pharmaceuticals Levofloxacin by using ISE.

Membrane composition	**LEV-MIP+DMA**		
Pharmaceutical	**(ILFLOX -TURKEY)**		
	D M	**SA M**	**MSA M**
Concentration (prepared) M	**1×10-3**		
Value founded	1.0294×10^{-3}	1.0055×10^{-3}	1.0236×10^{-3}
Recovery %	102.94	101.98	101.23
RE%	2.94	1.98	1.23
RSD%	1.37	1.41	_
Concentration (prepared) M	**1×10-4**		
Value founded	1.019×10^{-4}	1.0276×10^{-4}	1.0147×10^{-4}
Recovery %	101.85	101.64	101.47
RE%	1.85	1.64	1.47
RSD%	0.73	1.10	_
Membrane composition	**LEV-MIP+AOPH**		
Pharmaceutical	**(ILFLOX - TURKEY)**		
Concentration (prepared) M	**1×10-3**		
Value founded	1.0229×10^{-3}	1.0174×10^{-3}	1.0146×10^{-3}
Recovery %	102.29	101.75	101.46
RE%	2.29	1.75	1.46
RSD%	3.1	1.49	_
Concentration (prepared) M	**1×10-4**		
Value founded	1.023×10^{-4}	1.0031×10^{-4}	1.0129×10^{-4}
Recovery %	102.27	101.88	101.29
RE%	2.27	1.88	1.29
RSD%	3.7	1.34	_-

***Each calculation was repeated three times.**

CONCLUSION

Installation of molecularly imprinted electrode sensors (MIP) use levofloxacin as a template and Styrene as a monomer in various plasticizers. Excellent MIP tests with high sensitivity, reasonable selectivity, strong static reaction, long-term stability and applicability over a wide pH range have been obtained by using a DMA and AOPH plasticizer based electrode. The purpose of the construction electrodes to be used for the determination of Levofloxacin in the pharmaceutical analysis.

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