REVIEW ARTICLE

Determination of Amoxicillin in Pharmaceutical Preparations by Molecularly Imprinted Polymer in Polyvinyl Chloride Matrix Membrane

Huda J. Hussein[1], Yehya K. Al-Bayati[2]*

[1]*Market Research and Consumer Protection Center, University of Baghdad, Baghdad, Iraq*
[2]*Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq*

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ABSTRACT

This study was based on synthesizing four electrodes based on molecularly imprinted polymers (MIPs). Using amoxicillin sodium (AMX-Na) as the template, 1-vinyl imidazole(VIZ) and vinyl acetate (VA) as monomer, and N, N-methylene bis acrylamide (MBAA) as cross-linkers and benzoyl peroxide as the initiator, two MIPs were prepared. In the preparation of non-impressed polymers (NIPs), the same composition was used without the template of amoxicillin sodium. Numerous plasticizers, such as tri-oly phosphate (TOP) and di-octyl phthalate (DOP), were used in the PVC matrix for the preparation of membranes. Slop, detection limit, lifetime, and linearity range of AMX-MIPs electrodes are the characteristics studied. There's no interaction with the drug Amoxicillin sodium in the results obtained from selectivity measurements on interfering cations (K+, Ca+2, Al+3) and certain pharmaceutical additives such as methylparaben propylparaben and trisodium citrate. The preparation electrodes have been shown good response, including testing pharmaceutical analysis.

Keywords: Amoxicillin sodium, Different plasticizers, Molecularly imprinted polymers, Potentiometric method, (MBAA) Cross-linkers.

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INTRODUCTION

Amoxicillin sodium (AMX), di-amino-p-hydroxy benzylpenicillin trihydrate (Figure 1a) is one of the most frequently used lactam antibiotics worlds and it is employed to treat humans and animals. Like many lactam antibiotics, there's also a lactam ring structure responsible for antibacterial activity and variable side chains that account for the significant differences in their chemical and pharmacological properties. Despite a high clinical success level, a significant resistance mechanism developed that involved a high dose regimen and a new pharmacokinetic combination. AMX is one of the more important antibiotics used in the treatment of bacterial infections and its determination.[1-3] However, the usage of antibiotics in food-producing animals, can lead to the presence of residues in food and the environment,[4] which can cause some side effects such as hypersensitivity in humans.[5] Various analytical methods have been developed to determine amoxicillin, such as chromatography,[6-8] electrochemical methods,[9-11] surface plasmon resonance,[9] and spectrophotometry.[10-12] Among these methods, fluorescence spectroscopy is an interesting alternative method because it has a short analysis time, is relatively simple to use, uses low-cost equipment and requires small sample amounts and minimal consumption of organic solvents.[11,13]

The molecular imprinting technique was first reported by Nishide *et al*.[14] Molecular imprint is a widely emerging method to make the polymers with different molecular properties for a given drug. Its analogs, or an enantiomer.[15,16] MIPs are prepared by combining a template molecule with functional

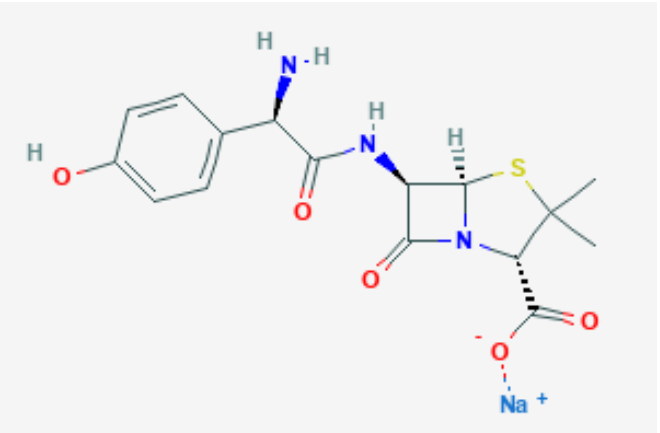

Figure 1a: The chemical structure of AMX-Na.

*Author for Correspondence: yahyaalbayti@yahoo.com

monomers, a cross-linker, and initiator in the appropriate solvent, mostly, polar and un-polar solvent. So after the polymerization, an extraction template molecule exposes the recognition cavities that complement the form, size, and chemical functionality of the template molecule, allowing the resulting polymers to selectively rebind the template molecule from a mix of closely related compounds.[17,18] In this analysis amoxicillin used a templet and select functional monomer of vinyl imidazol and MBAA a cross-linker for the preparation MIPs. Interactions between template and monomer have been studied through spectral and computer simulation research.

Several techniques has been used for the determination drugs and pharmaceuticals. The selective electrodes technique is used to determine phenylephrine hydrochloride because this technique has many characteristics like fast response time, ease used, rapid, low cost, and selectivity. The potentiometric sensors techniques based on PVC membrane electrodes are widely available for the analysis of drugs and ionic species.[19-21] MIPs were used the phenylephrine hydrochloride as the template. In contrast, the monomer, which was used in Vinyl acetate (VA) as well as 1-vinyl imidazole (VIZ) and MBAA as cross-linkers, respectively and benzoyl peroxide as an initiator to achieved the polymerization process. A variety of ion-selective electrode-determined drugs depended on MIP_S as recognition membranes like diclofenac sodium,[22] warfarin,[23] phenytoins,[24] and metronidazole benzoate.[25] This study used different plasticizers for the construction of membrane electrodes based on AMX-MIP_S, such as Tri-oly phosphate (TOP) and di-octyl phthalate (DOP).

MATERIALS AND METHODS

Preparation of MIP and NIP

For preparation, first amoxicillin molecularly imprinted polymer (AMX-MIP_1), 0.5 mmol (0.193 g) from amoxecilline sodium then mixed with 3 mmol (0.28 g) 1-vinyl imidazole (VIZ) as the monomer, after that added 15 mmol (2.313 g) N, N-methylene bisacrylamide (MBAA) to the solution as the cross-linker, followed that added (0.32 g) benzoyl peroxide as the initiator. All these materials were dissolved in 5 ± mL methanol (CH_3OH) except the initiator have dissolved in 3 ml chloroform. While the second amoxecilline molecularly imprinted polymer (AMX-MIP_5) were achieved by mixed 0.5 mmol (0.1937 g) from amoxecilline as the template, 3 mmol (0.258 g) Vinyl acetate (VA) as the monomer, 15 mmol (2.313 g) N,N-methylene bisacrylamide (MBAA) as the cross-linker and (0.3 g) benzoyl peroxide as the initiator which dissolved in 5 ± mL of methanol (CH_3OH). For obtaining a homogeneous solution, the mixture was stirred for 5 minutes. N_2 passes for 30 minutes on the mixture to remove oxygen from the solution. After that, the solution was put in a water bath. When the reaction completes, the molecularly imprinted polymer became hardened, after the polymerization process, the polymer was drying and crashed to obtain a polymer particle. These particles were sonicated in methanol/CH_3COOH (18:2 v/v) to remove the template from MIP. The polymer was dried for 106 hours for MIP_1 and 61 hours for MIP_5 at room temperature, crushed and ground the polymers by morter and sieve 125 µm particle size (using 125 µm mesh sieve); after dried completely at room temp., was used as an active substance in the selective sensors membrane. The particle size of AMX-MIP1 and AMX-MIP2 were between 43–60 µm and 75-125 µm, respectively. The preparation of non-MIPs using the same substances and conditions that formed AMX-MIP1 and AMX-MIP2 but without the amoxecillin sodium (template). The same composition was used in the preparation of NIPs, but without the template (amoxecillin sodium).

Instruments

Ion analyzer used in this work (WTW model, Germany), a pH meter (WTW model pH 720, Germany), and a saturated calomel electrode (Gallenkamp, USA). The electrode PPH-MIP used was constructed in the laboratory, and all potentiometric measurements were made at room temperature. The phenylephrine hydrochloride-MIP electrode combined with the Ag-AgCl electrode and the reference electrode was 0.1 M internal solution of amoxecillin sodium. The PVC tube (1–4 cm long) was flattened and polished by putting it on a glass plate and soaking with THF. The membrane was cut similar to the PVC tubing's external diameter and pasted on the polished end. The other direction of the PVC tubing was then linked to the electrode body. To make the electrodes more sensitive was by soaking in 0.1 M amoxicillin sodium solution for at least 2–3 hours before the use of the electrodes.

Materials and Chemicals

- Standard amoxecillin sodium obtained from industries of pharmaceuticals (IRAQ-SDI -Samarra). Global pharma Asanofi Company, UAE
- Amoxecilline capsules 500 mg, and Amoxecilline capsules 250mg Ap Ajanta pharma limited, Indea were purchased from local pharmacies.
- Plasticizers, TOP (99.5% purity),and DOP (98.0% purity) were purchased from Sigma Aldrich. Other chemicals and reagent materials were obtained from Fluka, BDH and Sigma Aldrich.

Preparing of Standard Solutions

For preparing a standard solution of 0.1 M amoxicillin sodium by dissolving 3.87 g of standard amoxicillin sodium in methanol and completed to 100 mL in the volumetric flask. The other solutions were prepared in 25 mL at the ranged from 10^{-6}-10^{-1} M in the same procedure.

The stock standard solution of 1×10^{-3} M, 1×10^{-4} M, phosphor molybdic acid was prepared by dissolving 0.225 g, 0.022 g, respectively in distilled water and completed to 100 mL.

All interfering cations (K^+, Ca^{+2}, Al^{+3}) and some pharmaceutical additives such as methyl paraben, propyl paraben, tri sodium citrate 0.1 M stock solution prepared at ranged from 10^{-6}–10^{-1} M which present the interfering ions were prepared and diluted to 100 mL.

Synthesis of Membrane MIPs Electrode

Amoxicillin sodium membrane was immobilized into the PVC tube, as portrayed by Rafela and Felismina.[26] AMX-MIP of 0.036g was mixed with different of plasticizers 0.4 g used in this work such as DOP (electrode A1), TOP (electrode A2). Then added 0.20g of PVC powder was scattered on 7 ± mL of tetrahydrofuran with stirring until a clear, viscous solution was acquired. Later the solutions mixed with stirring until the mixture became homogeneous. The mixture was cast into a glass ring 30–35 mm diameter and unwind on a glass plate and a ribbon of filter was placed on top of the glass. The solvent was then allowed to evaporate according to room temperature for more than 48 hours, at least. The thickness of the membrane obtained was different of the membrane to others; the thickness was about 0.4–0.7 mm. That size of the membrane was adequate to prepare electrodes.

Scanning Electron Microscope (SEM)

In scanning electron microscopy, a fine beam of electrons scans the membrane surface. This causes several kinds of interactions generating different signals, also used in image formation. The SEM can be used to get an idea about the size, geometry, and distribution of the membranes' pore surface. SEM analysis showed the highly ordered and regular pore structure of the molecular imprinted polymer surface and the cross-section. Several papers showed that the imprinted molecular membranes recognized the template molecule effectively and transported it with good efficiency due to the molecularly imprinted polymer's porous structures. The ordered porous and cross-section on the surface shows the sites of interaction, and MIP showed the highest transport rate towered the template molecule. The morphology of MIP before and after washing showed by electron microscope in Figure (2a,b) and Figure (3a,b). Microemulsion polymerization gives very small particles size around (1.100–1.400) Mm and (0.900–1.200) Mm for 1-Vinyl imidazole polymer in both MIP_S can be distinguished in the related image.

The morphology of the prepared membrane using the PPHMIP1 before washing is shown in Figure 2a, and after washing is shown in Figure 2b. Figure 2a (before washing) reveals that the particles of the complex are formed in a regular spherical shape with an average of about µm in diameter. On the other hand, Figure 2b (after washing) shows that the formed particles look like a colloidal particle growing in a solution; this might take place due to the presence of an excess of DFS that form ionic atmosphere surrounding the complex and create the formation of electric double layers.

Construction of Ion-selective Electrodes

The building of the electrode body and the immobilization were achieved as portrayed by Mahajan *et al.* [22] amoxecillin solution (0.1) M was filled in the glass tube as an internal solution, preferred immersing the membrane in a standard solution of (0.1) M of phenylephrine hydrochloride for at least (3) hours before measurements, which represents stipulations of membrane electrode.

Preparation of Pharmaceutical Samples

The contents of two bottles of amoxicillin capsules from to company glumox and apmox, each type of capsules contain 500 mg and 250 mg of amoxicillin sodium, (respectively). A specific amount of these capsules, which was equivalent to a stock solution with a concentration of about 10^{-3} M, was transferred into a 50 mL calibrated flask and completed to the volume with distilled water.

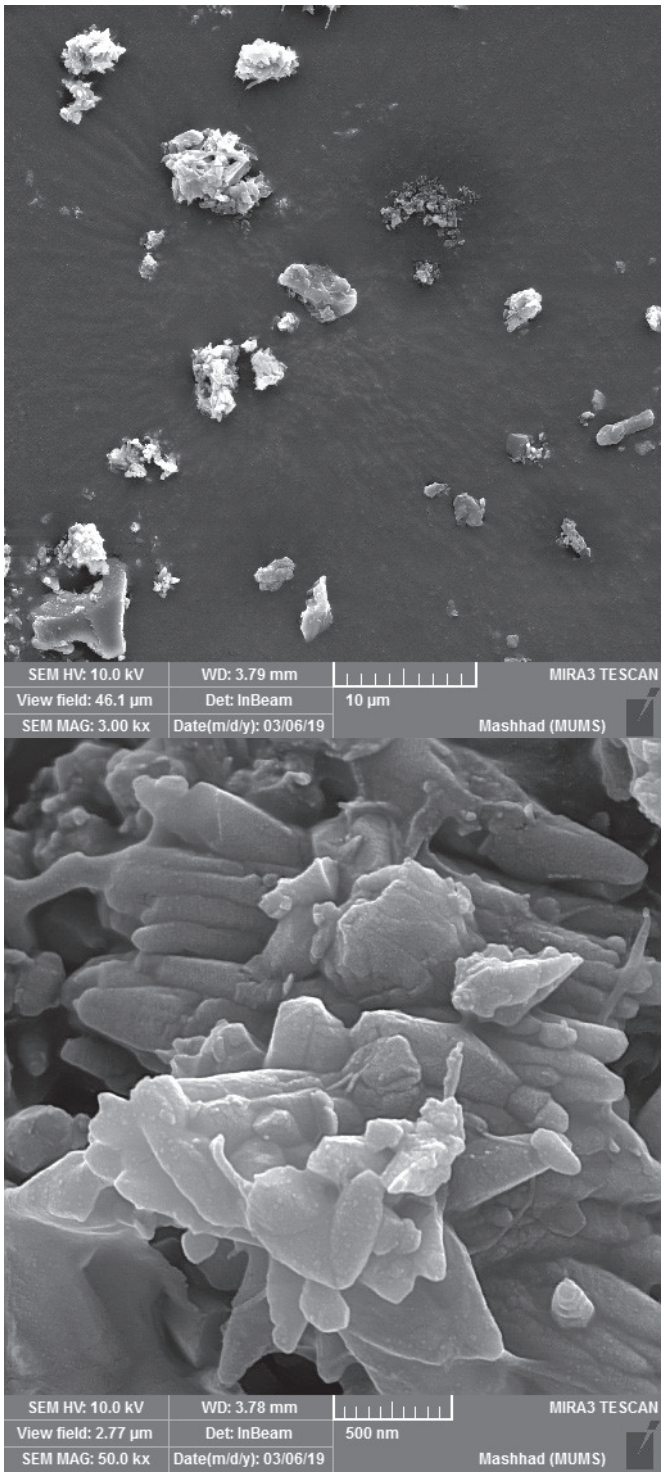

Figure 2a: SEM for the MIP1 before washing

Table 1: Characteristics of the amoxicillin sodium

Membrane composition	AMX-MIP1 + DOP (A1)	AMX-MIP1 +TOP (A2)	AMX-MIP5 +DOP (B1)	AMX-MIP5 +TOP (B2)
Slop (mV/decade)	-17.64	-19.36	-20.70	-19.02
Linearity range (M)	1×10^{-5}-1×10^{-1}	1×10^{-5}-1×10^{-1}	5×10^{-5}-1×10^{-1}	5×10^{-5}-1×10^{-1}
Correlation coefficient	0.9973	0.9989	0.9956	0.9903
Detection limit (M)	8×10^{-1}	9×10^{-1}	7.8×10^{-1}	6.3×10^{-1}
Life time (day)	11	9	11	10

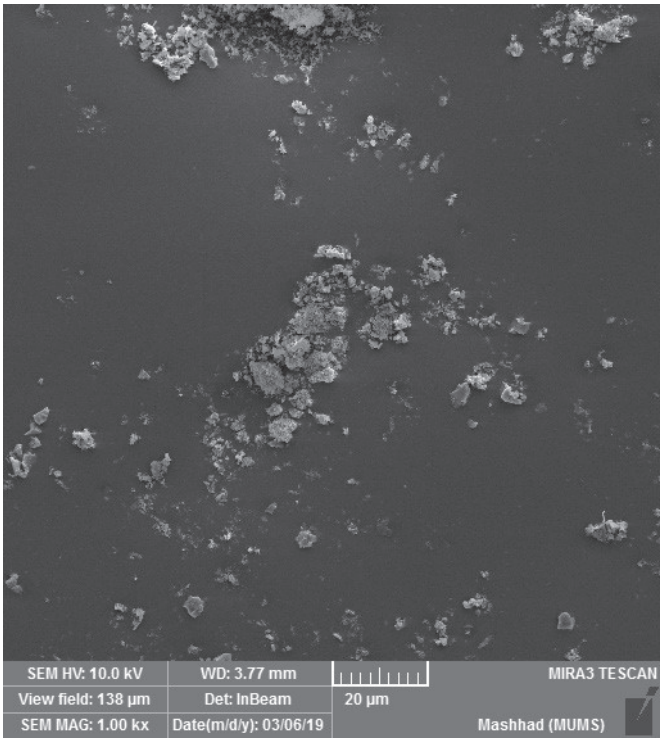

Figure 3a: SEM for the MIP2 before washing

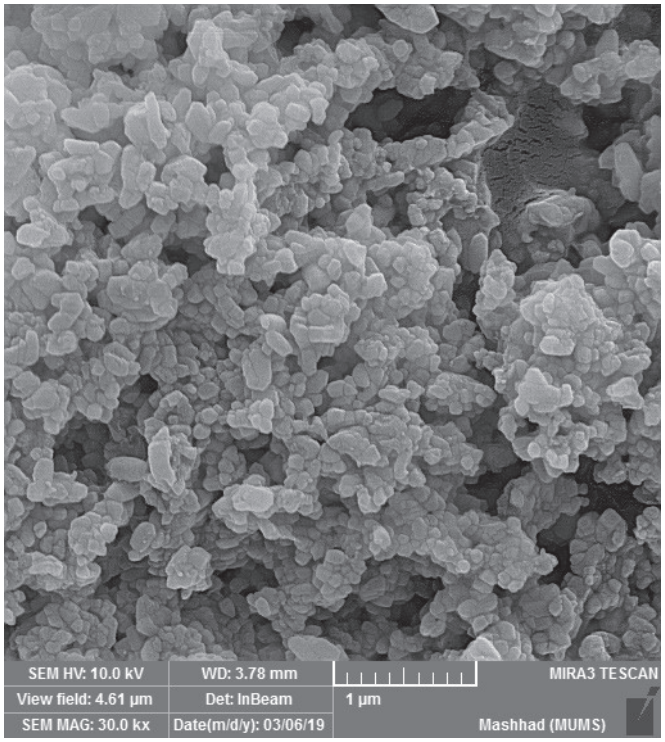

Figure 3b: Shows the SEM for MIP2 after washing

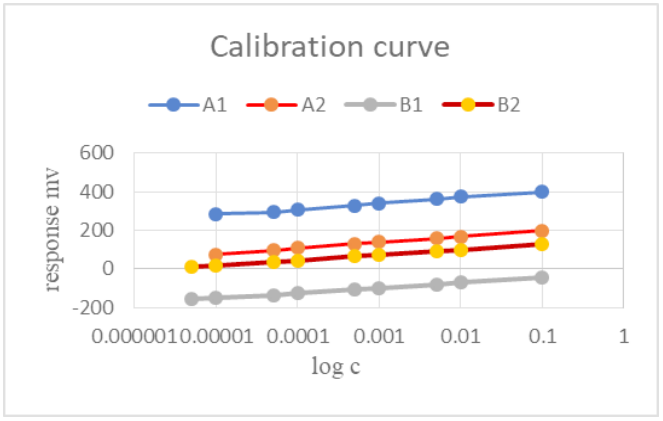

Figure 5: Calibration curve for AMX-MIP1 and AMX-MIP5 membranes electrodes.

Two MIPs have been prepared by using the amoxicillin sodium (AMX) as the template, vinyl imidazole (VIZ), and Vinyl acetate (VA) as monomers as well as N, N-methylene bis acrylamide (MBAA) as cross-linker and benzoyl peroxide as initiator. A plasticizer is an important component in an ISE membrane. Compatibility with the polymer and other membrane constituents provides a homogeneous environment for membrane when the plasticizers using as a solvent for the membrane practical use of ISE membrane should be avoided leaching of the plasticizer; otherwise, it would affect the electrode performance over time. Four electrodes have been constructed based on the PVC matrix, these plasticizers, such as tri-oly phosphate (TOP), and di-octyl phthalate (DOP). The characteristics were studied for all electrodes based on AMX-MIP1 (A1, A2 membranes) and AMX-MIP5 (B1, B2 membranes), which included linearity range, correlation coefficients, detection limit (M), and lifetime (day), respectively. The results obtained showed in Table 1 and Figure 5.

Effect of pH on Electrodes response

The study of pH effected on AMX membranes electrodes by various prepared concentrations of AMX (1×10-2, 1×10-3, and 1×10-4) M. To measurement the selective pH at ranged (1-11) by using the hydrochloric acid (0.1 M,1 M) and/or sodium hydroxide (0.1 M,1 M) for pH studies. The results were obtained by adding an appropriate volume of HCl/NaOH, as shown in Table 2 and Figure 6. The change in potentials at differential pH values may be due to the composition of electrodes. This composition also affects the response and lifetime for electrodes.

Table 2: Working pH range for AMX sodium Selective electrode

			pH range		
Number and composition of MIPs	*Membranes*	*Membrane composition*	*1×10^{-2}M*	*1×10^{-3}M*	*1×10^{-4}M*
MIP1	A1	AMX-MIP1 +DOP	2.5-8.5	3.5-8.0	3.5-9.0
AMX+1-VI+ MBAA MIP5	A2	AMX-MIP1 +TOP	3.5-9.0	3.0-6.5	4.0-9.0
AMX+ VA+	B1	AMX-MIP5+DOP	5.-9	7-9	6.5-9
MBAA	B2	AMX-MIP5 +TOP	6.5-9	6-9.5	7.5-9

Table 3: Sample analysis of AMX sodium by using ISE.

	Glumox, AMX 500 mg (Indea) by MIP5+DOP			
Pharmaceutical	*MSA*	*SAM*	*Direct method*	*Titration Method*
Concentration prepared	1×10^{-3}	1×10^{-3}	1×10^{-3}	1×10^{-3}
found	1.0095×10^{-3}	1.0120×10^{-3}	1.0158×10^{-3}	1.0192×10^{-3}
RC%	100.95	101.20	101.57	101.92
RSD%	……	1.62	2.71	4.60
RE%	0.95	1.20	1.57	1.92
Concentration prepared	1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Found	1.0122×10^{-4}	1.0146×10^{-4}	1.01243×10^{-4}	1.0291×10^{-4}
RSD%	…..	2.33	3.12	4
RC%	101.22	101.46	102.43	102.91
RE%	1.22	1.46	2.43	2.91

Table 4: Sample Analysis of AMX sodium by using ISE.

	Apmox AMX 250 mg (Indea) by MIP5+DOP			
Pharmaceutical	*MSA*	*SAM*	*Direct method*	*Titration method*
Concentration prepared	1×10^{-3}	1×10^{-3}	1×10^{-3}	1×10^{-3}
found	1.0119×10^{-3}	1.0143×10^{-3}	1.0174×10^{-3}	1.0266×10^{-3}
RC%	101.19	101.43	101.74	102.66
RSD%	……	1.55	1.93	4.08
RE%	1.19	1.43	1.74	2.66
Concentration prepared	1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Found	1.0141×10^{-4}	1.0164×10^{-4}	1.0245×10^{-4}	1.0355×10^{-4}
RSD%	…..	1.22	3.26	3.21
RC%	101.41	101.64	102.45	103.58
RE%	1.41	1.64	2.45	3.58

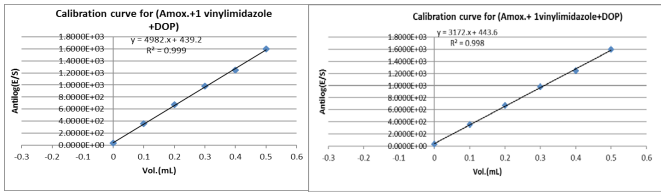

Figure 6: Antilog (E/S) against the volume of the added standard for the determination of amoxicillin sodium solution (1×10^{-3} and 1×10^{-4}) by MSA using (AMX–MIP1 + DOP) electrode

Calculation by Multiple Standard Addition Method (MSA)

The concentrations used for applied in this method (1×10^{-3} and 1×10^{-4}) for two solutions of amoxicillin sodium for plotting the antilog E/S (Y-axis) against a volume of standard Amoxicillin sodium (X-axis). Figure 6 represents the results of amoxicillin sodium concentrations calculated via the electrodes based on AMXMIP1+ DOP, AMX-MIP5+DOP.

Applications of Pharmaceuticals

Ion-selective electrodes based on MIPs were used for the determination of Amoxecillin sodium in pharmaceuticals. Preparation solutions of Amoxecillin sodium at concentrations $1\times10^{-3}$and 1×10^{-4} M. The RE, RC, and RSD% were calculated of Amoxecillin sodium in pharmaceuticals. The results obtained represented in Table 3 and 4.

CONCLUSION

By mixing with different plasticizers, selective electrodes can be constructed with Amoxecillin sodium membranes. These DOP and TOP plasticizers were used in the preparation of PVC-based Amoxecillin sodium membrane electrodes. As well as being applied to normal and pharmaceutical solutions, the results obtained for all electrodes were excellent. The purpose of design electrodes for use in the pharmaceutical analysis of amoxicillin sodium determination.

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