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وحماية المستهلك

SYNTHSIS A HIGHLY SENSITIVE MOLECULARLY IMPRINTEND POLYMER AS AN ELECTROCHEMICAL SENSOR FOR THE DETERMINATION OF AMLODIPINE IN PHARMACEUTICAL SAMPLES

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ABSTRACT

This paper demonstrates the synthesizing and storage of molecularly- imprinted polymers (MIP) at room temperature using bulk polymerization of amlodipine (AD) is characterized by high sensitivity, low costs and high stability. The research used 0.99:6:20 mmol ratios of template, monomer, and cross-linking agents for the polymerization in order to ensure an appropriate adsorption capacity. A functional monomer tripolyphosphate with cross-linking ethylene glycol dimethyl acrylate was attained by creating MIP for amlodipine as AD-MIP that could be characterized using a UV-VIS spectrophotometer at 238 nm, Fourier-transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). Mass spectrometric (MS) detection may use tritolylephosphate to determine amlodipine levels in pharmaceutical preparations. The GC/MS methods developed in this study are accurate, sensitive, and precise and can be easily applied to (AMADAY/India, NORVASC/U.K.) tablets in pharmaceutical preparation the elution process was applied to the template (AD) from the AD-MIP developed cavities caused by using pyrogenic solutions of methanol, chloroform, and acetic acid (70:20:10, v/v). The maximum adsorption capacity of AD-MIP was 0.263 µmol/g, and the ratio of template to monomer was 1:1 in adherence to the Langmuir isotherm model. A solid-phase extraction (SPE) syringe packed with molecularly imprinted polymers (MIPs) was used to selectively separate and pre-concentrate AD. from aqueous solutions and estimations of Amlodipine.

Keywords: Molecularly imprinted polymer, Amlodipine, Isothermal process.

[*]**The article is taken from the doctoral thesis of the first researcher.**

تصنيع بوليمرات مطبوعة جزيئيًا عالي التحسس بالمستشعر الكهروكيميائي لتقدير الاملوديبين في المستحضرات الصيدلانية

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الخلاصة

يوضح هذا البحث تركيب وتخزين البوليمرات الجزيئية المطبوعة (MIP) في درجة حرارة الغرفة باستخدام البلمرة السائبة للأملوديبين (AD) الذي يتميز بحساسية عالية وتكاليف منخفضة وثبات عالي. استخدم البحث ٠,٩٩ : ٦ : ٢٠ مليمول نسب من القوالب والمونومر وعوامل الربط المتبادل للبلمرة من أجل ضمان قدرة امتصاص مناسبة. تم الحصول على مونومر تراي توليل فوسفيت وظيفي مع إيثيلين جلايكول ثنائي ميثيل أكريليت متقاطع من خلال إنشاء MIP للأملوديبين مثل AD-MIP الذي يمكن تمييزه باستخدام مقياس الطيف الضوئي UV-VIS عند 238 نانومتر ، مطيافية الأشعة تحت الحمراء بتحويل فورييه (FTIR) والمسح المجهري الإلكتروني (SEM). قد يستخدم الكشف عن مقياس الطيف الكتلي (MS) تراي توليل فوسفيت لتحديد مستويات الأملوديبين في المستحضرات الصيدلانية. طرق GC / MS المطورة في هذه الدراسة دقيقة وحساسة ودقيقة ويمكن تطبيقها بسهولة على أقراص (AMADAY/ India، NORVASC/ UK). في التحضير الصيدلاني تم تطبيق عملية الشطف على القالب (AD) من التجاويف المطورة لـ AD-MIP الناتجة عن استخدام محاليل مسامية من الميثانول والكلوروفورم وحمض الخليك (١٠:٢٠:٧٠، على التوالي). كانت السعة القصوى لامتصاص AD-MIP 0.263 ميكرو مول / جم ، وكانت نسبة القالب إلى المونومر ١ : ١ في الالتزام بنموذج متساوي الحرارة Langmuir. تم استخدام حقنة استخلاص ذات المرحلة الصلبة (SPE) معبأة بالبوليمرات الجزيئية المطبوعة (MIPs) لفصلAD شكل انتقائي وتركيزه مسبقًا. من المحاليل المائية وتقديرات أملوديبين.

الكلمات المفتاحية: عملية الايزوثيرم ,الاملوديبين,بوليمرات الطبعة الجزيئية.

INTRODUCTION

Amlodipine is a synthetic dihydropyridine and a calcium channel blocker with antihypertensive and antianginal properties. Amlodipine inhibits the influx of extracellular calcium ions into myocardial and peripheral vascular smooth muscle cells, thereby preventing vascular and myocardial contraction. This results in a dilatation of the main coronary and systemic arteries, decreased myocardial contractility, increased blood flow, oxygen delivery to the myocardial tissue, and decreased total peripheral resistance. This agent may also modulate multi-drug resistance (MDR) activity through inhibition of the p-glycoprotein efflux pump **(Civantos *et al.*, 2004; Coseberg, *et al.*, 1997).**

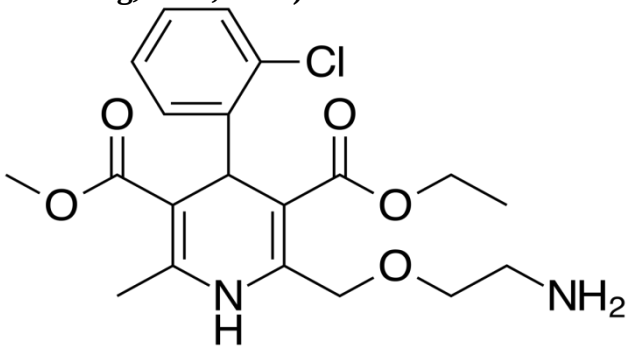


Figure (1): Structure of Amlodipine.

A molecularly imprinted solid phase (MI-SPE) preparation method is currently being developed which has so far shown a good level of selectivity. Molecular imprinting polymer is a technique for preparing polymer materials that have pre-ordered structures and specific molecular recognition capabilities. In this study, the selection of functional monomers was important in order to produce molecular-specific cavities of templates. tritolylephosphate is a functional monomer that can act as a hydrogen bond acceptor to its template. Previous research has been conducted on MISPE for amlodipine (**Bodoki *etal*., 2018 ,Y. Al-Bayati & E. Hadi.**et ***al*., 2022)**, with several GC–MS studies specifically investigating amlodipine as well **(Alsamarrai , *et al.*, 2017,Chaturvedi, *et al* ., 2005)**. Forsdahl et al. reported a method for the sensitive detection of isopropyl substituted b-blocking agents in human urine. Their sample-preparation phase involved enzymatic hydrolysis; solid-phase extraction; and derivatization with N-methyl-N-trimethylsilyl trifluoroacetamide. GC–MS was then used to detect atenolol as its bis, tris, and tetra-TMS derivatives. Angier and their co-workers **(E. A. Hadi & Y. K. Al-Bayati. 2022)**. Following this study, the use of mass selective detectors with a capillary GC coupled to MS has considerably increased **(Aljabari & Al-Bayati. 2023).** This development has led to the improvement of gas chromatographic properties of both the compounds and yield compounds, with mass spectra containing high relative intensity and high-mass fragments suitable for selected ions.

Initially, the important molecule of a molecular imprinted polymer (MIP), forms a complex of the actual monomers. Following the polymerization cycle, as is shown in Figure 2, the functional groups are kept in place by a highly cross-linking polymeric structure **(Al-Bayati,*et al.*, 2017)**. In addition, the steric configuration of all of these connections based around a given substratum and template is really an important characteristic for the formation of binding sites providing additional shape, size and flexibility to promote selective identification followed by a high target affinity. As a result, the process of recognition in MIPs can be characterized by resemblance to enzyme-proven mechanisms.The substratum- complex is formed like the (lock/ key) model **(Al-Bayati & F. I. Aljabari. 2016).**

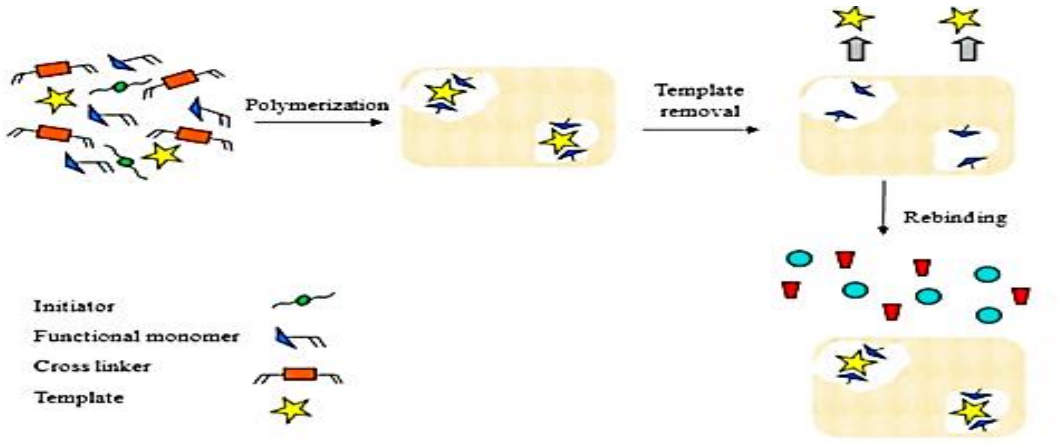


Figure (2): Molecular imprinted polymer cycle **(M. A. Sandoval Riofrio. 2017)**

Gas chromatography-mass spectroscopy (GC/MS) is a useful technique, a gas chromatograph (GC) coupled to a mass spectrometer (MS), used in the separation and quantification of complex mixtures of chemicals. It is injected into the GC inlet and, after vaporization, is forced into the column by a carrier gas (usually helium). The sample flows through the column and the constituent compounds of the respective mixture will be separated by virtue of their relative interaction with the column coating (stationary phase) and carrier gas (mobile phase). The latter passes from the column through a heated transmission line and ends at the inlet of the ion source where compounds separated from the column are converted into ions **(Karasek, *et al.*, 2012).**

EXPERIMENTAL PART

MATERIALS AND METHODS

Amlodipine from Samarra/Iraq was provided; tripolyphosphate, ethylene glycol dimethyl acrylate, and benzoyl peroxide were purchase from Sigma Aldrich (USA); methanol; and nitrogen gas (99.99) was supplied by the Al-Watan factory (Al-Nahda street/ Baghdad/Iraq); chloroform and acetic acid were purchased from Merck (Germany); and sulphuric acid of 98% purity was purchased from the CDH (***Central Drug House)***.

Preparation and Processing:

High-purity grade chemicals were used for the preparation process:
AD-MIP was prepared by stirring to dissolve 0.9977 mmol of amlodipine 0.408 g, in 4 mL of methanol; 6 mmol of tritolylephosphate, 1.473 g, was then added and was left for a few seconds at room temperature to dissolve. 20 mmol cross-linker ethylene glycol dimethyl acrylate, 4g, was then dissolved in the solution, followed by the addition of 0.3g, of benzoyl peroxide dissolved chloroform to act as an initiator. The solution was then shacked and bubbled for 20 min with pure nitrogen to remove the dissolved oxygen from the monomer solution, after which the tube was sealed with a rubber stopper. The stoppered solution was left in a water bath overnight at 60 ºC, following which the polymerization process 0.99:6:20 of AD-MIP was completed. The solution presented as a white- colored polymer with a rigid structure, and the formation of fine particles could be observed with the naked eye. The solution was, left to dry at room temperature overnight. AD- MIP was synthesized through the self-assembly (non-covalent) technique of bulk polymerization. Soxhlet solid liquid phase extraction for the template was performs to remove it from MIP by using pyrogenic solvent v/v (acetic acid, chloroform and methanol, at a ratio of 10:20:70,v/v respectively) performed successfully by repeatedly washing for 18-24 hours. The polymer was dried at room temperature, then crushed with a mortar and sieved to a particle size of 125µm.

A 3ml solid phase extraction vacuum through a plastic syringe (column) was used, and each syringe was packed with 0.1 g of AD-MIP and a flow rate of 70ml/min of standard solution amlodipine.

A series of standard solutions of amlodipine (0.1;0.08;0.06;0.04;0.02; and 0.01 mmol/ml) was prepared by dissolving 0.0368g of AD. In a methanol volumetric flask of 100 ml as a stock solution. A calibration curve between an x-axis describing the concentration of amlodipine and a y-axis describing its absorption A, was achieved using a 238 nm UV-VIS

instrument.The pharmaceutical samples were prepared by taking the average weight of the powder of amlodipine tablets (as is shown in Table 1) and dissolving it in 100 mL of methanol solution,before filtering it through cellulose filter paper of 0.07µm in order to obtain concentrations from the calibration curve 0.4×10^{-4}mmol/mL(0.4µmol/ml) of amlodipine drugs (AMADAY/India, NORVASC/U.K.) which have the lowest standard addition (SD) value. These were then used with MIP in a solid phase extraction (SPE) column,by which MIP-SPE was prepared.

Table (1): Pharmaceutical drugs prepared for treatment with AD-MIP polymer.

No. of samples	Commercial name, Country Content 100mg	Average weight for 10 of tablets (g)	Weight of sample equivalent to 0.012g (0.4×10^{-4}) mmol/mL of the active ingredient
1	AMADAY/India	1.783	0.2916
2	NORVASC/U.K.	3.99	0.6384

RESULTS AND DISCUSSION

After passing the solution of atenolol through a syringe packed with Ate-MIP, the residue with the least absorption was measured by UV-VIS.This indicated that a lower concentration during the final process had been a good expressive example of the advantages of the use of impressed polymers in SPE in the quantification of an amlodipine,as shown in Figures 4& and 5.

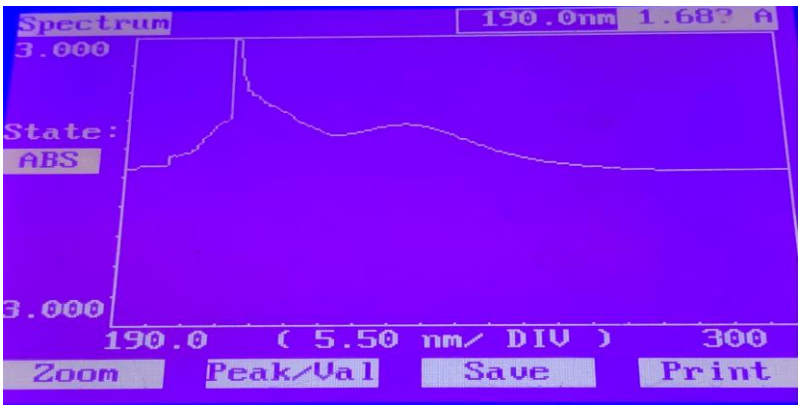


Figure (3): the absorption at 238 nm of the concentration amlodipine standard.

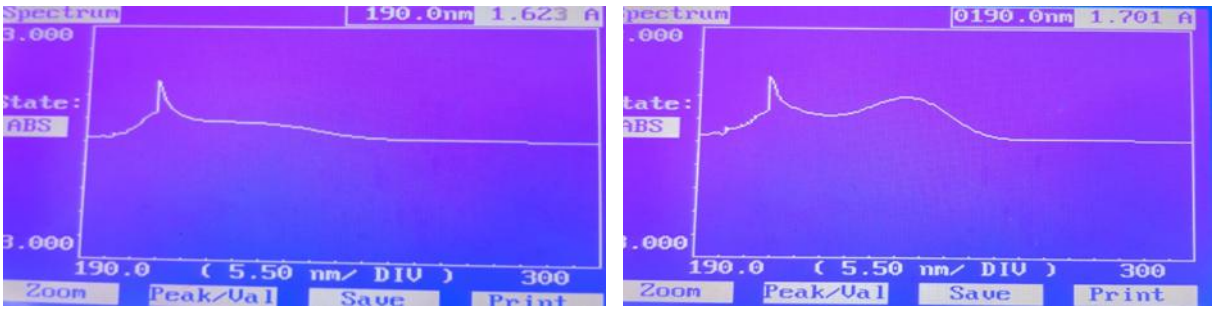


Figure (4): A, B the absorption at 238 nm of the concentration of Amlodipine drug (AMADAY/India) at 0.4×10^{-4} mmol/mL (0.4 µmol/ml) before & after passing through MIP column.

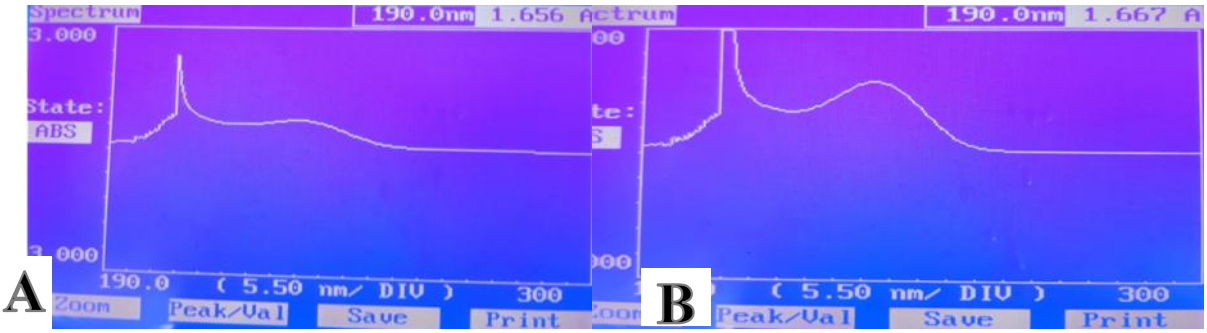


Figure (5): A, B the absorption at238 nm of the concentration of Amlodipine drug (NORVASC/U.K.) at 0.4×10^{-4} mmol/mL (0.4 µmol/ml) before & after passing through MIP column.

Transform Infrared Spectroscopy (FTIR) analysis:

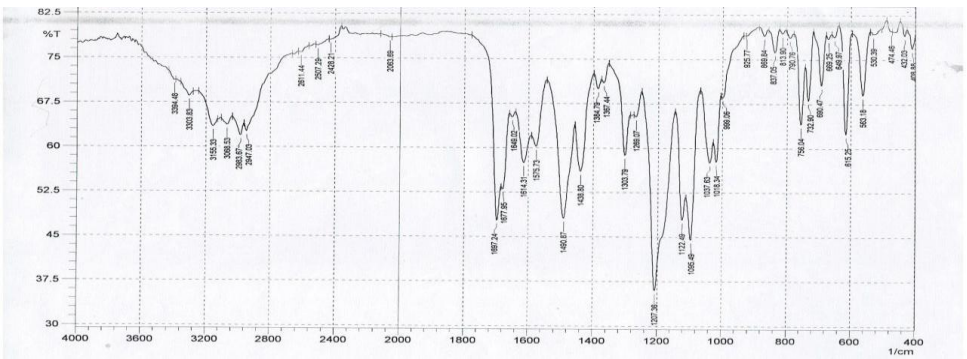


Figure (6): FTIR spectra of Amlodipine standard.

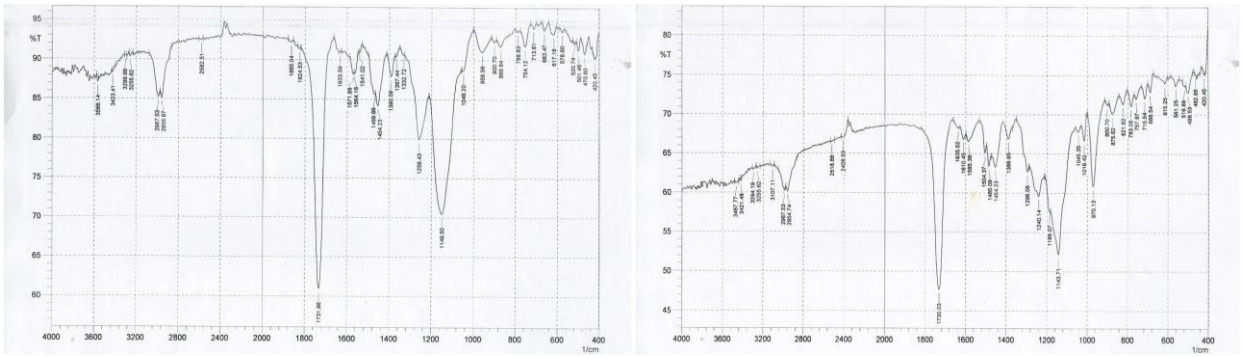


Figure (7): A, B FTIR spectrum of AD-MIP before and after extraction (after removal of the template amlodipine).

The MIP of AD was synthesized via a non-covalent bulk polymerization method. Functional monomers played an important role in studying the interactions that occur with the template. The monomer tritolylephosphate was used for the synthesization of MIP and NIP. FTIR analysis an important chemical characterization method to detect the functional groups present in a compound was also employed with the FTIR spectra found amongst different MIP_s and NIP_s shown in Table 2, and Figures 6 and 7.

Table (2): The structures of the main three compositions of AD-MIP and the bands indicate MIP before &after the removal template.

Template (Atenolol)	**Monomer (Allyl chloride)**	**Cross linker (Ethylene glycol di methacrylate)**	
Band	**Drug(Template)**	**MIP before extraction**	**MIP after extraction**
N-H$_{str.}$	3155	3294	-
NH$_2$ str.	3394-3303	3921 3467	-
O-C=O	1697	1635	1633
C-H$_{str.Aromatic}$	3068	_	_
C-H$_{STR.Aliph}$	2983,2947	2987 2954	2987 2956
O-P=O	_	1240	1259
P-O	_	1143	1149
CH2=CHCOOH	_	1730	1731

The Fourier transmission infrared spectrometry spectra of the leached and unleached amlodipine (AD) imprinted polymer MIP and NIP were recorded in the range of 400–4000 cm^{-1} by the KBr pellet method (Tabl 1).Within this table, the FTIR spectrum of the AD showed the following bands:3394;3303; 3155; 3068; 2983;2947and 1697 cm^{-1} for N-H$_2$ stretching;N-H

stretching; C-H stretching aromatic ;C-H stretching aliphatic and O-C=O respectively. The FTIR spectrum of atenolol MIP-(AD) before template removal showed the following bands :3421; 3467;3294;2987;2954;1635;1730;1240 and 1143 for cm^{-1} for N-H_2 stretching;N-H stretching; C-H stretching aliphatic; O-C=O;CH2=CHCOOH;O-P=O and P-O, respectively. The FTIR spectrum of the MIP(AD) after template removal demonstrated the absence of N-H stretching, $NH_{2\ stretching}$ O-C=O and CH stretching, which excise in the template (AD) spectrum and indicate the extraction of the drug from the template. When using the tritolylephosphate as a monomer for the synthesis of other MIPs for amlodipine, an FTIR spectrum was produced for MIPs both before and after template removal and NIP, which may be found in Table.The band's values **(Huang, *et al.*, 2018).**

The process of seizing the drug in the solid phase of the prepared molecular polymer may indicate the successful formation of the molecular polymer. In order to ensure the entry of the drug and the formation of the cavity, a spectrum GS/MS was measured for the prepared molecular polymer, with the structure of amlodipine shown in Figure 8.

From the injection of amlodipine as a liquid the spectrum of amlodipine with a molecular weight of 408.9 g.mol-1 begins to dip, though several peaks were confirmed using GS/MS. One such peak occurred at m/z 304 in the mass spectrum of amlodipine. The ionic fragment (m/z 97) observed in the MS/MS experiment was C_5H_8NO+, generated by the loss of the alcohol group from the precursor ions (m/z 97).

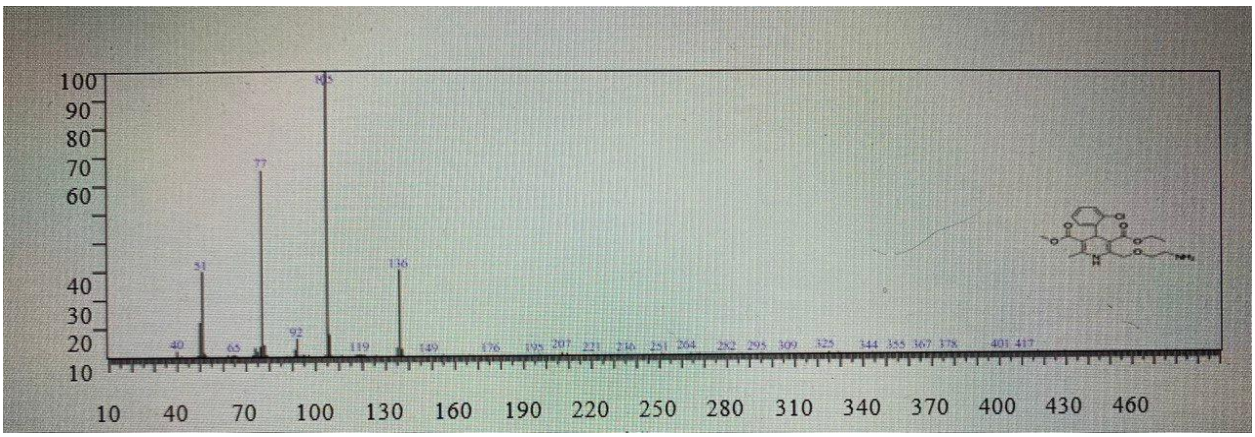


Figure (8): GC/MS structure of amlodipine.

Scanning electron microscope (SEM)

The morphological evaluation is critical to the appreciation of certain morphological traits, as well as the cavity sizes and surface configurations of MIPs both prior to and following the amlodipine template removal. SEM images were used to analyze the morphology of the AD-MIPs, as shown in Figure 8 (A, B).

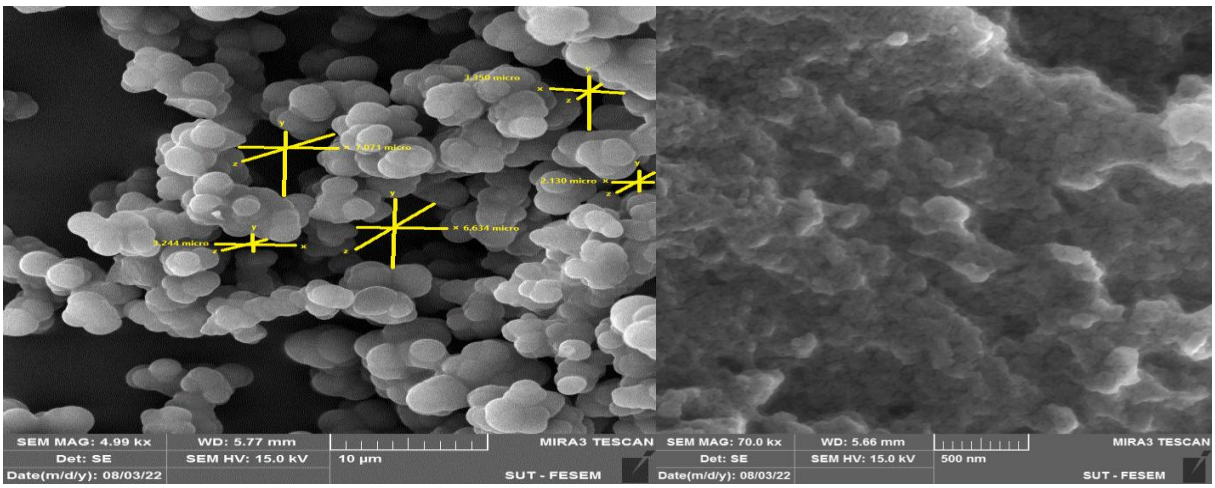


Figure (9): A, B surface morphologies of the particles before and after elution for AD- MIP respectively, and three dimensions of cavities with their areas.

show the surface morphologies of the particles before and after elution for Amlodipine–MIP and the relative cavities calculation table 3.

Table (3): Calculated mean, angle and lengths of some cavities (selected six of them) and their areas using image j program.

Area	Mean	Min- Max	Angle	Length
0.379	6488.741	1238.72-50153.79	6.911	7.071
0.356	6944.732	2445.17-23692.88	12.031	6.634
0.175	4392.59	2549-13038	0.939	3.244
0.116	2417.001	935.2-3722	2.862	2.13
0.181	2767.781	477-32673	0	3.35

Through Figure 9 and Table 3 the 3D of Cavities between min = 2417.001 (2.417001µm) to max = 6944.732nm (6.944732µm) we notice that the holes vary in diameter range between (2417.001-6944.732) nm and most of the holes are large, which leads to the retention of large quantities of the drug and this is consistent with the high value of the capacity in isotherm.

Relation between initial concentration and capacity

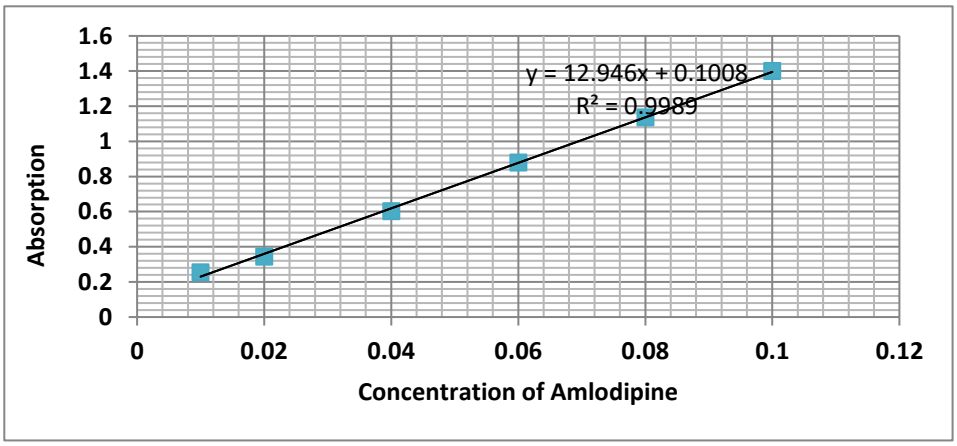


Figure (10): Calibration curve between concentrations of Amlodipine standard µmol/ml and its absorptions.

Adsorption capacity and pre-concentration:

A series of absorption achievements for different initial concentrations of AD-MIP ranging from 0.01 to 0.1 µmol/ml on adsorption capacity µmol/g was studied using the following equation **(Abass, *et al.*, 2010)**

Q = (Ci - Cf) (µmol/ml)* the concentrations from (0.1-0.01) µmol/ml consume (3-7) ml range of volumes when using 0.1g weight of AD-MIP,Table4.

Table (4): The optimal synthesis conditions for the molecularly imprinted polymer for Amlodipine developed in

W/ MIP (g)	Ci (µmol/ml)	Cf (µmol/ml)	Vol (ml)
0.1	0.1	0.0965	3
	0.08	0.0721	3
	0.06	0.0516	3
	0.04	0.0328	3
	0.02	0.0169	5
	0.01	0.0079	7

The relation between initial concentration Ci (µmol/ml) and capacity Q (µmol/g)

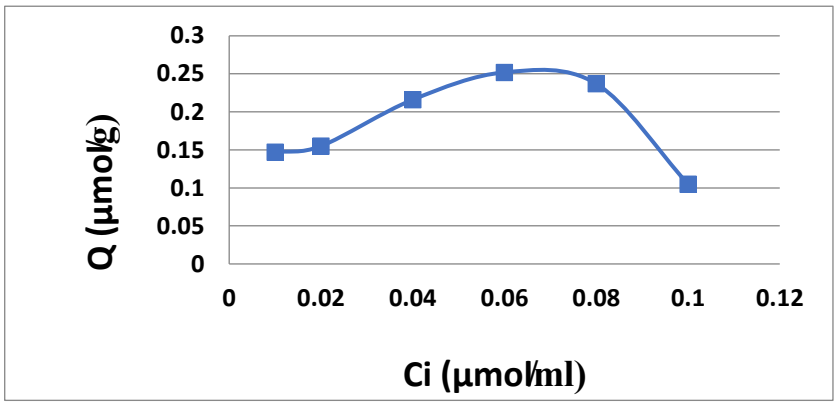
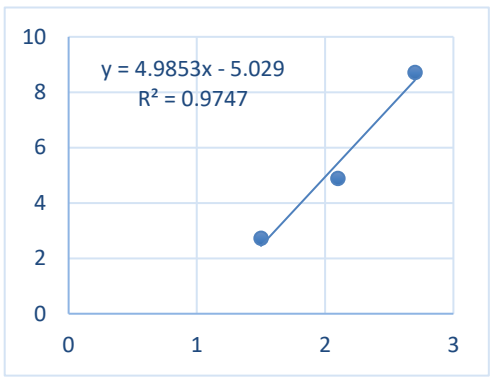
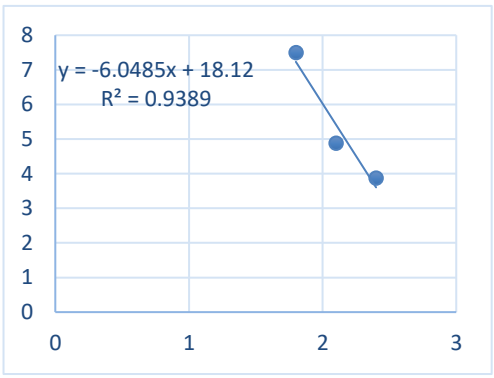


Figure (11): Illustrate the Langmuir isotherm model.

The relation between capacity Q (µmol/g) and Q/Cf (ml/g):





Slope = -1/kd
-124.36= -1/ kd Kd= 0.008
Intercept = 32.928 Intersept = Qmax/ kd
Qmax =32.928 * 0.008 = 0.263 µmol /g
That mean there was one capacities for AD-Mip equal 0.263 µmol/g it follow Langmuir isotherm model which has scattered value and one slope.

Table (5): Precision and accuracy of the analysis of pharmaceutical drugs in uv-vis spectrophotometry instrument before and after the isotherm process.

Drug name 100mg	MIP	Concentration Ci µmol/ml	Absorption before isotherm process	Absorption after isotherm process	Concentration Cf µmol/ml	Vol ml	Q µmol/g	RSD% =(δn-1/Mean) *100 Precision	Rec. % = (practical value/True value)*100 Accuracy	Re%= 100-Rec
AMADAY/India	MIP 0.1g	0.04	0.602	0.501	0.033	3	0.21	0.1661	99.717	0.16
NORVASC/U.K.		0.04	0.6036	0.511	0.0338	3	0.186	0.016	100.082	-0.0829

* For n=5 drugs were absorbed before the isotherm process (passing through MIP column). * The true value is the absorption at 0.04 µmol/ml in the calibration curve of amlodipine.
Isotherm adsorption of amlodipine MIP based on tripolyphosphate monomer was the same pattern which shows one sites connection of amlodipine with the polymer with a covalent bond. Scatchard plot showed only one equilibrium dissociation constant Kd and apparent maximum amount Qmax for the high affinity sites were calculated This behavior indicated that the adsorption was Langmuir isotherm and the binding was homogenies.

CONCLUSION

A novel bulk polymer was created by using different functional groups as monomers, with tritolylephosphate and crosslinked ethylene glycol dimethyl acrylate used to create AD-MIP.A variety of analytical approaches and experiments were used to reach selective molecular imprinted polymers by preparing and optimizing the required monomers; cross-linking through suitable solvents; applying pyrogen solvents for template removal, and adhering to optimal molar ratios of template (Amlodipine) to monomer for cross-linking. The irregularly three dimensional network structure of the polymer can be seen via SEM both before and after template removal, with FTIR, GC, and isotherm processing all improving the accuracy of this work. One slope gain when studied the capacity of adsorption of AD-MIP which follows the Langmuir isotherm model with scatter values (heterogeneous structure) and the ratio of template to monomer is 1:1. The maximum adsorption capacity of AD-MIP was 0.263 µmol/g.

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