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Development of a Molecularly Imprinted Polymer for Determination of Atenolol Based on Selective Solid Phase Extraction and Application in Pharmaceutical Samples

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Abstract

This paper demonstrates the synthesis and storage of molecular-imprinted polymers (MIP) at room temperature using bulk polymerization of atenolol (Ate), which 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. By making MIP for atenolol as Ate-MIP, which could be looked at with a UV-VIS spectrophotometer at 276 nm, Fourier- transform infrared spectroscopy (FT-IR), and scanning electron microscopy (SEM), a functional monomer of allyl chloride with cross-linking ethylene glycol dimethyl acrylate was made. Mass spectrometric (MS) detection may use allyl chloride to determine atenolol levels in pharmaceutical preparations. The GC/MS methods developed in this study are accurate, sensitive, and precise and can be easily applied to (NOVATEN/India and ATENOIOI/U.K.) tablets in pharmaceutical preparation. The elution process was applied to the template (Ate) from the Ate-MIP, which developed cavities, caused by using porogenic solutions of methanol, chloroform, and acetic acid (70:20:10, respectively). The maximum adsorption capacity of Ate-MIP was 2.9957 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 molecular imprinted polymers (MIPs) was used to selectively separate and pre-concentrate Ate from aqueous solutions and estimations of atenolol.

Keywords: Molecular imprinted polymer (MIP), Atenolol, Isotherm process, GC-MS.

تحضير وتحديد البوليمرات المطبوعة جزيئيًا لعقار أتينولول في استخلاص الطور الصلب بواسطة كروموتغرافيا الغاز – مطيافية الكتلة

همسه شاكر عميش* , يحيى كمال البياتي
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الخلاصة

يوضح هذا البحث تركيب وتخزين البوليمرات الجزيئية المطبوعة (MIP) في درجة حرارة الغرفة باستخدام البلمرة السائبة للأتينولول (Ate) الذي يتميز بحساسية عالية وتكاليف منخفضة وثبات عالي. استخدم البحث 0.99: 6: 20 مليمول نسب من القوالب والمونومر وعوامل الربط المتبادل للبلمرة من أجل ضمان قدرة امتصاص

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مناسبة. باستخدام اليل كلورايد كمونمر وظيفي مع إيثيلين جلايكول ثنائي ميثيل أكريليت كرابط تشابك تم إنشاء MIP للأتينولول Ate–MIP الذي يمكن تمييزه باستخدام مقياس الطيف الضوئي UV–VIS عند 276 نانومتر، مطيافية الأشعة تحت الحمراء بتحويل فوريه (FTIR) و المسح المجهري الإلكتروني (SEM). قد يستخدم الكشف عن مقياس الطيف الكتلي (MS) كلوريد الأليل لتحديد مستويات الأتينولول في المستحضرات الصيدلانية. استخدمت تقنية GC / MS المطورة في هذه الدراسة الدقيقة والحساسة والتي يمكن تطبيقها بسهولة على أقراص (ATENOIOI / UK ،NOVATEN / India) في التحضير الصيدلاني تم تطبيق عملية الشطف على القالب (Ate) من التجاويف المطورة لـ Ate–MIP الناتجة عن استخدام محاليل مسامية من الميثانول و الكلوروفورم و حمض الخليك (70:20:10 ، على التوالي). كانت السعة القصوى لامتصاص Ate–MIP 2.9957 ميكرو مول / جم، وكانت نسبة القالب إلى المونومر 1:1 في عملية الايزوثيرم Langmuir موديل. تم استخدام حقنة استخلاص ذات المرحلة الصلبة (SPE) معبأة بالبوليمرات الجزيئية المطبوعة (MIPs) لفصل Ate بشكل انتقائي وتقديره وتركيزه في المحاليل المائية للمستحضرات الصيدلانية.

1. Introduction

Atenolol 2-(*p*-(2-Hydroxy-3-(isopropylamino)propoxy)phenyl)acetamide shown in Figure 1 is useful in the treatment of cardiovascular diseases and conditions such as hypertension, coronary heart disease, arrhythmias, and angina (chest-pain) [1].

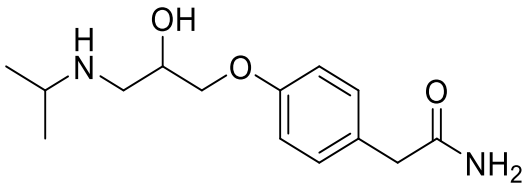

Figure 1: Structure of Atenolol [2]

A molecularly imprinted solid phase (MI-SPE) preparation method is currently being developed and has so far shown a good level of selectivity. Molecular imprinting polymer is a technique for preparing polymeric materials that have pre-ordered structures and specific molecular recognition capabilities [3]. In this study, the selection of functional monomers was important in order to produce molecular-specific cavities in templates. Allyl chloride is a functional monomer that can act as a hydrogen bond acceptor for its template [4]. Previous research has been conducted on MISPE for atenolol [5-7], and several GC-MS studies specifically investigating atenolol [8-11] 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*-trimethylsilyltrifluoroacetamide. GC-MS was then used to detect atenolol and its bis, tris, and tetra-TMS derivatives. Because no medical history existed with which to confirm the use of both drugs in these cases, atenolol, metoprolol, and propranolol, with their possible metabolites, were re-extracted from the selected case specimens and, derivatised with pentafluoropropionic anhydride (PFPA). Following this study, the use of mass-selective detectors with a capillary GC coupled to MS has considerably increased [12,13]. This development has led to the improvement of the gas chromatographic properties of both the compounds and yield compounds, with mass spectra containing high relative intensities and high-mass fragments suitable for selected ions. Initially, the important molecule of a molecularly imprinted polymer (MIP) forms a complex with the actual monomers. Following the polymerization cycle, as shown in Figure 2, the functional groups are kept in place by a highly cross-linking polymeric structure [14]. 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 its resemblance to enzyme-proven mechanisms. The substratum-complex is formed like the lock and key model [15-18].

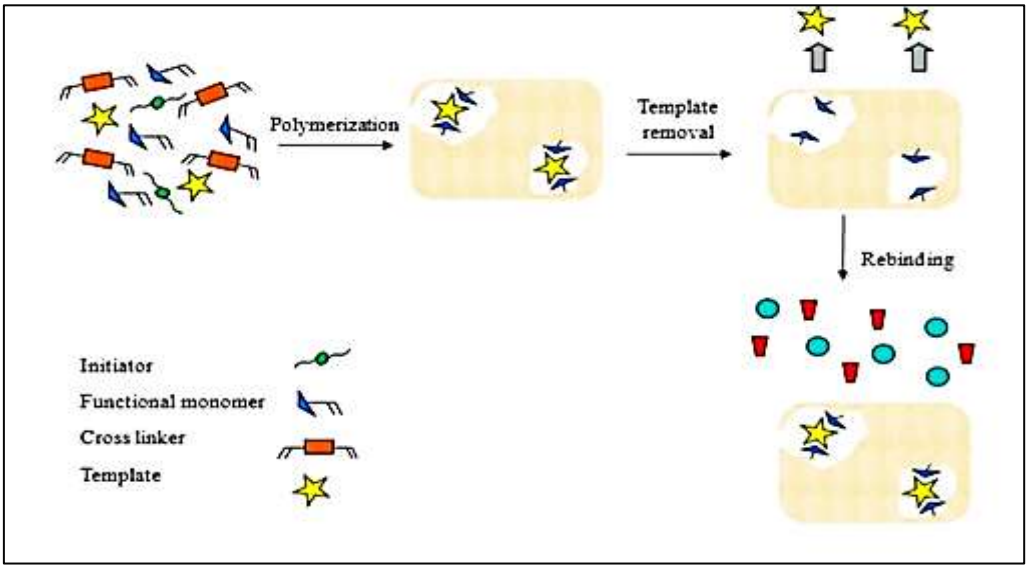

Figure 2: Molecular imprinted polymer cycle [19]

Gas chromatography-mass spectroscopy (GC/MS) is a useful technique that uses a gas chromatograph (GC) coupled to a mass spectrometer (MS), for 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 interactions 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 [20,21].

2. Experimental part

2.1. Materials and method

Atenolol was supplied from Samarra Pharmaceutical Company, Iraq; allyl chloride, ethylene glycol dimethyl acrylate, and benzoyl peroxide were purchased from Sigma Aldrich (USA); methanol and nitrogen gas (99.99%) were supplied by the Al-Watan factory (Al-Nahda Street, Baghdad, Iraq); chloroform and acetic acid were purchased from Merck (Germany); and sulfuric acid of 98% purity was purchased from the CDH (*Central Drug House)*.

2.2 Preparation and Processing

Ultra
-high-purity grade Chemicals was used for preparation process and bought from Sigma – Aldrich (St.
Louis, MO, USA). The solutions of Clopidogrel 30, 60, 90,120,150 ppm were prepared by dissolving 0.0015, 0.003,
0.0045, 0.006, and 0.0075 gm of Clopidogrel in 50 ml of methanol, respectively, at pH 8 by using volumetric flasks

The solutions were passed through the column at a flow rate of 70 rpm. The extraction column was cleaned twice by

using 2 mL of methanol in order to remove the interference from the matrix and then separated from MIP.

In general, 1mmol of Clopidogrel (CLO) was dissolved in 9 mL of porogen (methanol), then 4 mmol of acrylic

acid (AA) was added, sonicated for 5 minutes at 35 MHz at room temperature. In addition, 15 mmol cross-linker

(EGDMA) and 0.32 mg initiator (benzoyl peroxide) were added to the above solution. The solution was bubbled for

20 min with nitrogen and used as a pre-polymer solution, then, the rubber sealed the tube. Solution was left in a

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High-purity chemicals were used for the preparation process: Ate-MIP was prepared by dissolving atenolol (0.266 g, 0.99 mmol) in methanol (4 mL) before slowly adding allyl chloride (0.46 g, 6 mmol). This mixture was stirred for a few seconds at room temperature. The cross-linker ethylene glycol dimethyl acrylate (4 g, 20 mmol) was then dissolved in the solution, followed by the addition of a solution of benzoyl peroxide (0.3 g, 1.238 mmol) in chloroform to act as an initiator. The solution was then shacked and bubbled for 20 minutes 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 Ate-MIP was completed. The solution presented as a white-coloured 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. Ate-MIP was synthesized through the self-assembly (non-covalent) technique of bulk polymerization. Soxhlet solid liquid phase extraction for the template was performed to remove it from MIP using porogenic solvent v/v (acetic acid, chloroform, and methanol, at a ratio of 10:20:70, respectively), which was 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 Ate-MIP and a flow rate of 70mL/min of standard solution atenolol. A series of standard solutions of atenolol (0.7, 0.6, 0.5,

0.4, 0.3, and 0.2 mmol/mL) were prepared by dissolving 0.033 g of Ate in a 100-mL volumetric flask of methanol as a stock solution. A calibration curve between an x axis describing the concentration of atenolol and a y axis describing its absorption A was achieved using a 276 nm UV-VIS instrument. The pharmaceutical samples were prepared by taking the average weight of powder of atenolol tablets (as 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 of 0.4×10^{-4} mmol/mL (0.4 µmol/mL) of atenolol drugs (NOVATEN/India, ATENOIOI/U.K.) which have the lowest standard addition (SD) value. These were then used with MIP in a solid phase extraction (SPE) column, from which MIP-SPE was prepared.

Table 1: Pharmaceutical drugs prepared for treatment with Ate-MIP polymer

No. of samples	Commercial name, Country Content 100 mg	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	NOVATEN/India	3.954	0.474
2	ATENOIOI/U.K.	4.42	0.5304

3. 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 spectroscopy. 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 atenolol, as shown in Figures 3 and 4.

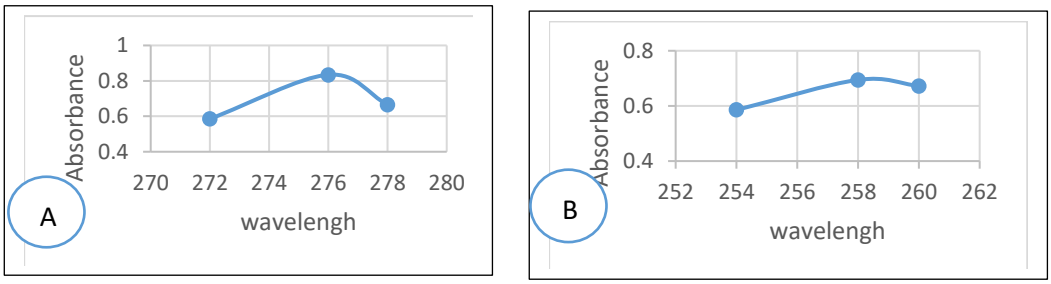


Figure 3: A and B, the absorption at 276 nm of the concentration of atenolol drug (NOVATEN/India) at 0.4×10^{-4} mmol/mL (0.4 µmol/mL) before and after passing through the MIP column.

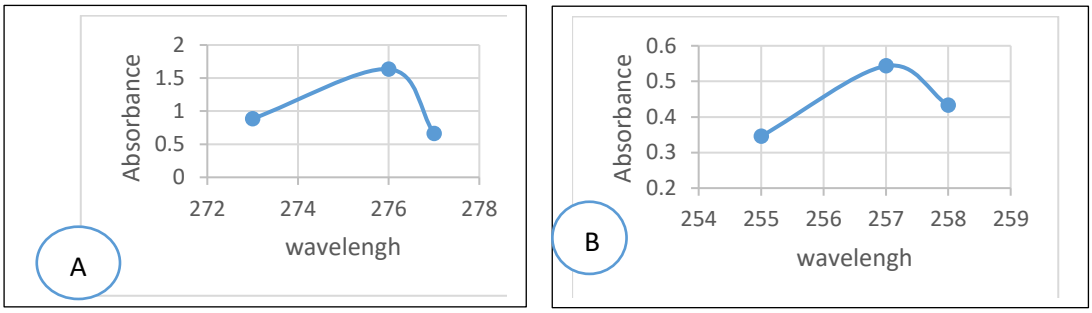


Figure 4: A and B, the absorption at 276 nm of the concentration of atenolol drug (ATENOIOI/U.K.) at 0.4×10^{-4} mmol/mL (0.4 µmol/mL) before and after passing through the MIP column

Through Figures 3 and 4, we noticed that the maximum wave length of atenolol was at 276 nm after passing 0.4×10^{-4} mmol/mL (0.4 µmol/mL) of the commercial atenolol solutions

through the MIP column. The wavelength of the atenolol disappearance and this is an indication that the atenolol has been captured in the column.

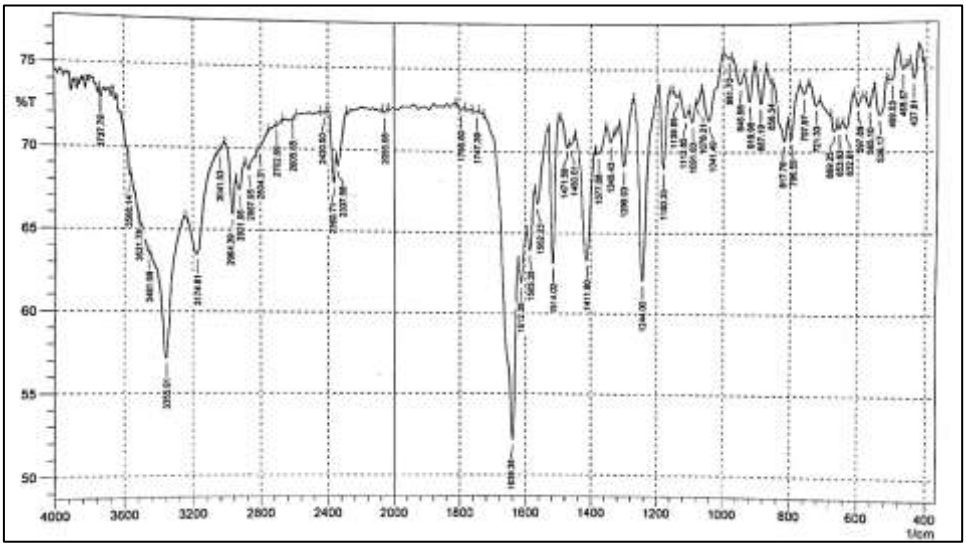


Figure 5: FT-IR spectrum of atenolol standard

The figure shows the active groups of atenolol, as shown in Table 2, which will be used in the identification and formation of the molecularly imprinted polymer for atenolol.

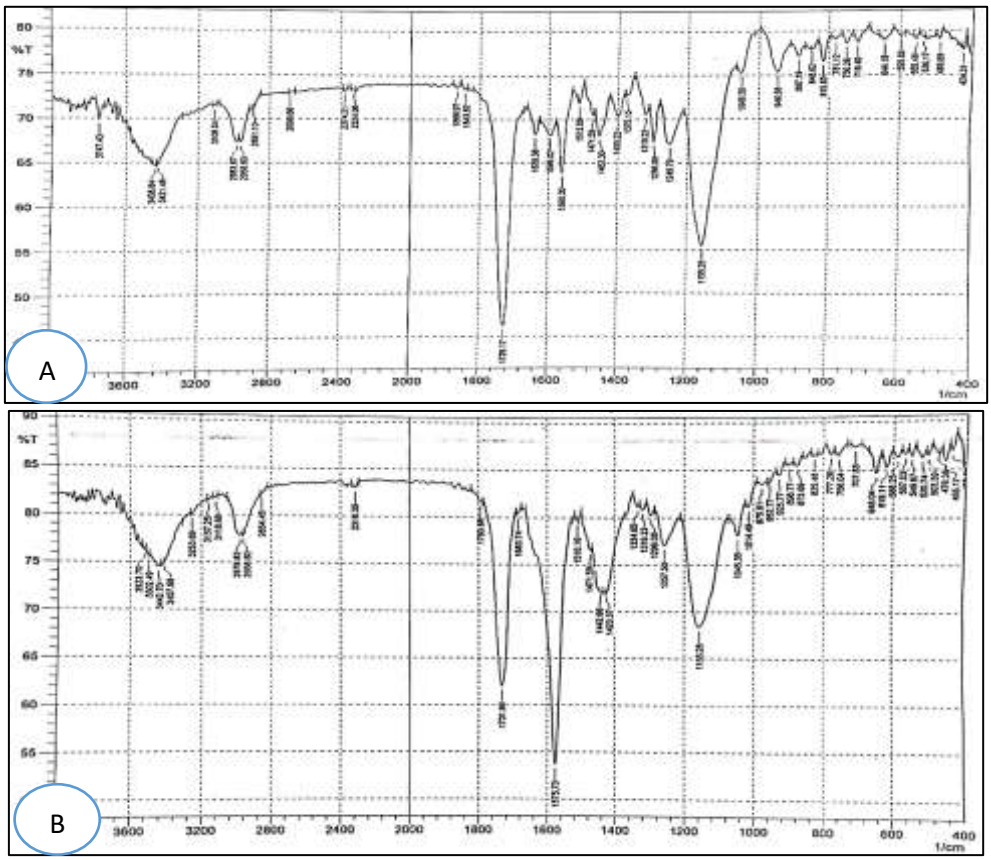


Figure 6: A and B, FT-IR spectra of Ate-MIP before and after extraction (after removal of the template atenolol)

The MIP of Ate 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 allyl chloride was used for the synthesis of MIP and NIP. FT-IR analysis, an important chemical characterization method to detect the functional groups present in a compound, was also employed, with the FT-IR spectra found amongst different MIP_s and NIP_s shown in Table 2 and Figures 5 and 6.

Table 2: The structures of the main three compositions of Met-MIP and the bands indicate MIP before and after removal of the template

Template (Atenolol)	**Monomer (Allyl chloride)**	**Cross linker (Ethylene glycol dimethacrylate)**	
Band	**Drug(Template)**	**MIP before extraction**	**MIP after extraction**
N-$H_{2str.}$	3461,3355	3438,3421	-
O=C-$N_{str.}$	1639	1639	-
C-$H_{aliph.}$	2964,2867	2983,2891	2979,2854
O-$H_{str.}$	3174	3109	-

The Fourier transmission infrared spectrometry spectra of the leached and unleached atenolol (Ate) imprinted polymers MIP and NIP were recorded in the range of 400-4000 cm^{-1} by the KBr pellet method (Table 1). Within this table, the FTIR spectrum of the Ate showed the following bands: 3461, 3355, 2964; 2867, 1639, and 3174 cm^{-1} for NH_2 stretching; C-H aliphatic; N-C=O stretching; and H-O stretching, respectively. The FTIR spectrum of atenolol MIP-(Ate) before template removal showed the following bands: 3438, 3421, 2983, 2891, 1639, and 3109 cm^{-1} for N-H_2 stretching; C-H aliphatic; O-H stretching of carboxylic acid; N-C=O stretching, and H-O stretching, respectively. The FT-IR spectrum of the MIP (Ate) after template removal demonstrated the absence of NH_2 stretching, N-C=O stretching and H-O stretching, which are excised in the template (Ate) spectrum and indicate the extraction of the drug from the template. When using allyl chloride as a monomer for the synthesis of other MIPs for atenolol, an FT-IR spectrum was produced for MIPs both before and after template removal and NIP, which may be found in Table 2. The process of seizing the drug in the solid phase of the prepared molecular polymer may indicate the successful formation of the molecular polymer [22]. In order to ensure the entry of the drug and the formation of the cavity, a spectrum of GS/MS was measured for the prepared molecular polymer, with the structure of atenolol shown in Figure 7. From the injection of atenolol as a liquid, the spectrum of atenolol, with a molecular weight of 266.341 $g.mol^{-1}$ begins to dip, though several peaks were confirmed using GS/MS. One such peak occurred at m/z 304 in the mass spectrum of atenolol. 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).

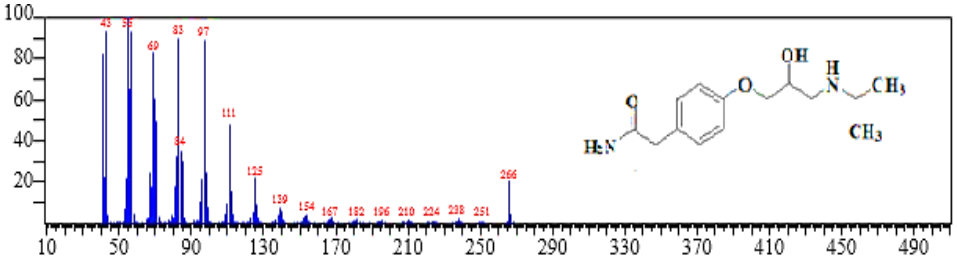


Figure 7: GC/MS structure of atenolol

Scanning electron microscopy SEM: Atenolol: 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 atenolol template removal. SEM images were used to analyze the morphology of the Ate-MIPs, as shown in Figure 8 (A and B) and Table 3.

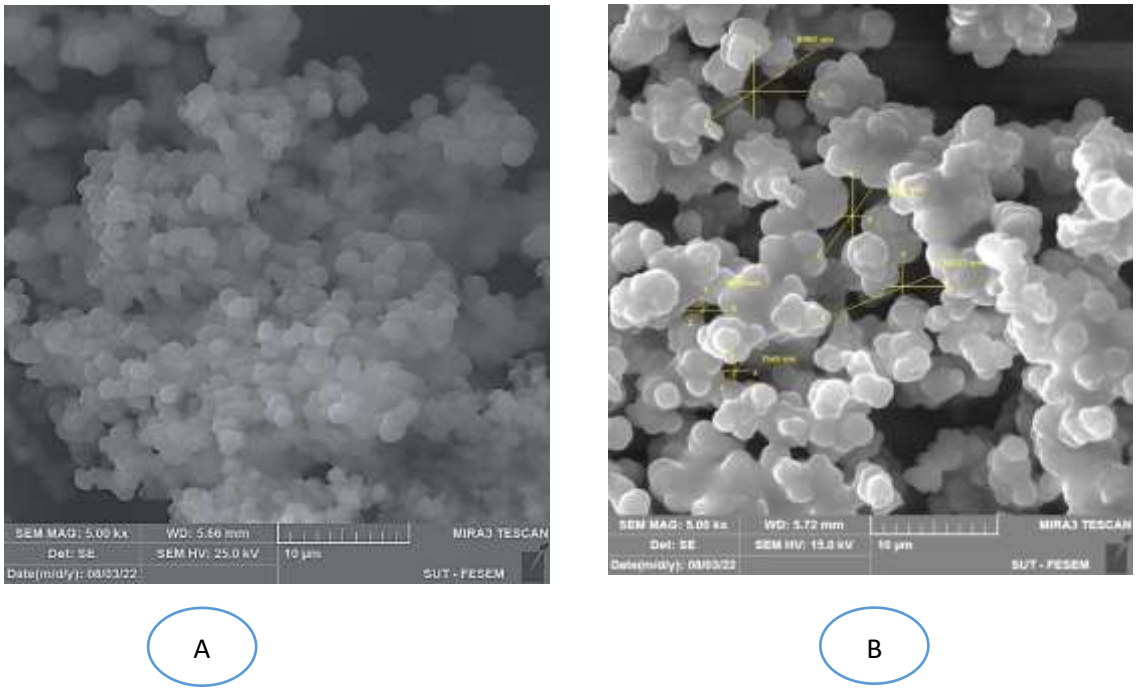


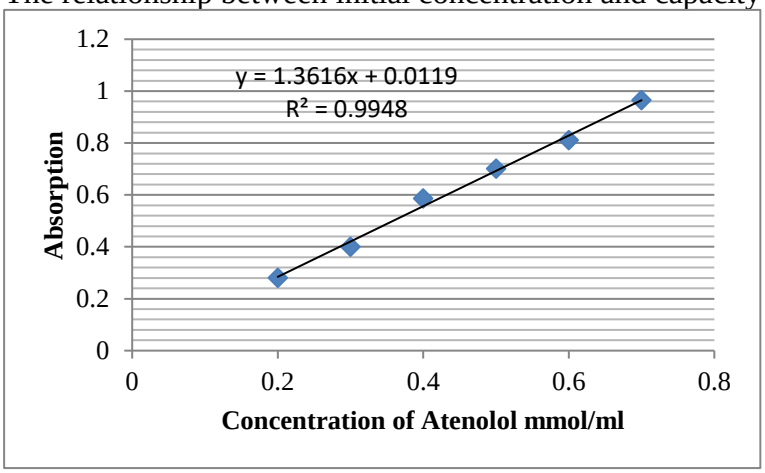
Figure 8: A and B, surface morphologies of the particles before and after elution for Ate-MIP respectively, and three dimensions of cavities with their areas

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

No.		Area	Mean	Min- Max	Angle	Length
1		0.011	7476.767	3952.256-37629.000	57.319	1.149
2		0.012	6960.400	3499.241-22602.000	38.720	1.357
3		0.012	10717.387	3941.503-47379.277	21.727	1.306
4		0.004	5673.481	4597.143-8012.000	14.323	0.443
5		0.003	7569.840	4522.000-24486.000	26.565	0.326
6	Total Mean	0.008	7679.575	4102.429-28021.655	31.731	0.916
7	SD	0.004	1858.972	456.362-15077.122	16.833	0.493
8	Total Min-Max	0.003-0.012	5673.481-10717.387	3499.241-8012.000	14.323-57.319	0.326-1.357

Through Figure 8 and Table 3, the 3D of cavities between min = 5673.481nm (5.673481µm) and max = 10717.387 nm (10.717387µm) we notice that the holes vary in diameter range between 5673.481 and 10717.387 nm, and most of the holes are large, which leads to the retention of large quantities of the drug, which is consistent with the high value of the capacity in isotherm.

The relationship between initial concentration and capacity



Concentration of Atenolol µmol /ml	Absorption
0.2	0.2814
0.3	0.4011
0.4	0.5867
0.5	0.7019
0.6	0.8112
0.7	0.9654

Figure 9: Calibration curve between concentrations of the atenolol standard (µmol/mL) and its absorptionsAdsorption capacity and pre-concentration: A series of absorption achievements for different initial concentrations of Ate-MIP ranging from 0.7 to 0.2 µmol/mL on adsorption capacity µmol/g were studied using the following equation [23]:

Q = (Ci - Cf)(µmol/ml)$*vol(ml)\ /\ W\ of\ Mip(g)$

Q is calculated according to the following equation:

$Q = [(C_i - C_f)\ V_s * 1000] / M_{MIP}$

C_i = Initial drug concentration (µmol/mL).

C_f = Final drug concentration (µmol/mL).

V_s = Volume of solution tested (mL).

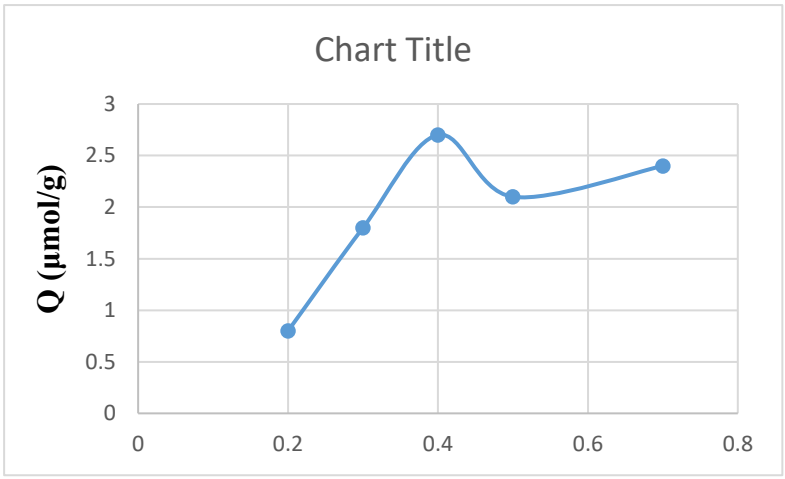
M_{MIP} = Mass of dried polymer (mg).

The concentrations from 0.7 to 0.2 µmol/mL consume a 3-4 mL range of volumes when using 0.1g of weight of Ate-MIP (Table 4).

Table 4: The optimal synthesis conditions for the molecularly imprinted polymer for the developed atenolol

W/ MIP (g)	Ci (ppm)	Ci (µmol/mL)	Cf (µmol/mL)	Vol (mL)
0.1	186.431	0.7	0.62	3
	159.798	0.6	0.55	3
	133.165	0.5	0.43	3
	106.532	0.4	0.31	3
	79.899	0.3	0.24	3
	53.266	0.2	0.18	4

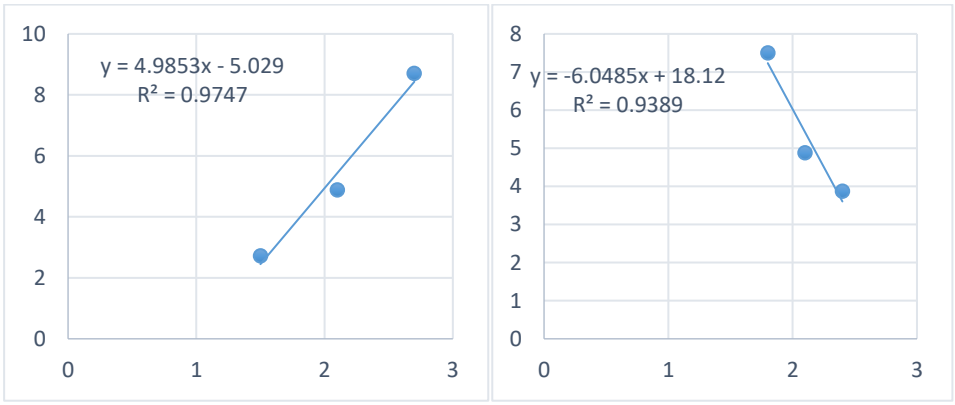
The relationship between initial concentration Ci (µmol/ml) and capacity Q (µmol/g)



Ci (µmol/mL)	Q (µmol/g)
0.7	2.4
0.6	1.5
0.5	2.1
0.4	2.7
0.3	1.8
0.2	0.8

Figure 10 : Illustrate the Langmuir isotherm model

In this model, a single layer, or monolayer, forms when adsorbate particles adhere to specific sites on the surface. Figure 10 shows that the maximum capacity can be obtained when concentrating 0.4 (µmol/mL) the use of a weight of 0.1 gm. The relationship between capacity Q (µmol/g) and Q/Cf (mL/g):



Q µmol/g	Q/Cf ml/g
2.4	3.8709
1.5	2.7272
2.1	4.8837
2.7	8.7096
1.8	7.500
0.8	4.4444

Slope = -1/kd
-6.0485 = -1/ kd Kd = 0.16533
Intersept = 18.12 Intersept = Qmax/ kd
Qmax =18.12 * 0.16533 = 2.9957 µmol/g
That means there was one capacity for Ate-Mip equal to 2.9957 µmol/g it follows the Langmuir isotherm model, which has scattered values and one slope.

Table 5: Precision and accuracy of the analysis of pharmaceutical drugs in UV-Vis spectrophotometry instruments before and after the isotherm process

Drug name (100 mg)	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% = Rec-100
NOVATEN/India	MIP 0.1 g	0.4	0.6100	0.5210	0.3416	3	1.752	0.0800	103.97	3.97
ATENOIOI/U.K.		0.4	0.5923	0.5207	0.3516	3	1.452	0.0277	100.95	0.95

* For n = 5, drugs were absorbed before the isotherm process (passing through the MIP column). *The true value is the absorption at 0.4 µmol/mL in the calibration curve of atenolol. Table 5 shows the statistical values obtained on the success of the process of capturing the atenolol and then separating and estimating it. The statistical values were acceptable, which indicates the optimal choice of conditions for capturing, separating, and estimating the atenolol in pharmaceutical preparations.

4. Conclusion

A novel bulk polymer was created by using different functional groups as monomers, with allyl chloride and cross-linked ethylene glycol dimethyl acrylate used to create Ate-MIP. Several analytical methods and experiments were used to make selective molecularly imprinted polymers. This was done by preparing and optimizing the needed monomers, cross-linking with the right solvents, using porogenic solvents, to remove the template, and sticking to the best molar ratios of template (atenolol) to monomer for cross-linking. The irregularly shaped three-dimensional network structure of the polymer can be seen *via* SEM both before and after template removal, with FT-IR, GC, and isotherm processing all improving the accuracy of this work. One slop gains when studying the capacity of adsorption of Ate-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 Ate-MIP was 2.9957 µmol/g.

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