CONSTRUCTION OF A NEW ELECTROCHEMICAL SENSOR BASED ON A NEW MOLECULARLY IMPRINTED POLYMERS(MIPS) FOR HIGHLY SELECTIVE AND SENSITIVE DETERMINATION OF CLEBOPRIDE (CBD) IN PHARMACEUTICAL COMMERCIAL SAMPLES

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ABSTRACT

Clebopride (CBD) selective molecularly imprinted polymers(MIPs) were based on ion-pair by prepared four polymers(MIPs) using CBD as the template a well as (Acryl amide) (AAM), 2-Acrylamido-2-Methyl-1-Propane sulphonic Acid (2-AAMMPSA as monomer, used N,N-ethylenebismethacrylamide (EBMAA) ,ethylene glycol dimethacrylate ethylene glycol(EGDMAC), N, N-methylene bisacrylamide (NNMBAAM)) as cross linker and used benzoyl peroxide as initiator . NIPs prepared by using the same composition of MIPs except the template (CBD). The MIPs were prepared using variation ratio of monomer and cross linker .These MIPs applicate as solid phase extraction for determination CBD in pharmaceutical preparation used UV as detector .the results gave good response, where the reconstruction percentage (Rec%) value of CBD drug took the range (99- 101%), and the relative standard deviation (RSD%) value took the range (0.27% - 0.93 %) for standard solution and Rec% took values of (98- 99) %, and RSD% took values of (0.86 – 1.62) % of CBD drug for the Clebopride pharmaceutical.

Keywords: New monomer, Cross linker, Initiator, Clebopride determination.

مجلة العلوم الزراعية العراقية -2021 :52 (2):367-376 البياتي

بناء متحسسات كهروكيميائي جديد يعتمد على بوليمرات جديدة مطبوعة جزيئيًا (MIPs) لتقدير انتقائي وحساس للغاية لـ Clebopride (CBD) في العينات الصيدلانية

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المستخلص

استندت البوليمرات المختارة جزيئيًا كليبوبرايد(CBD) اعتمدت إلى زوج الأيونات بواسطة أربعة بوليمرات محضرة (MIPs) باستخدام CBD كقالب وكذلك (أكريل أميد2– (AAM) (أكريلاميدو–2–ميثيل –1– حمض البروبان سلفونيك (– 2 AAMMPSA) كمونومر ، يستعمل N،N–ethylenebismethacrylamide (EBMAA) , إيثيلين جلايكول ثنائي ميثاكريلات الإيثيلين جلايكول (EGDMAC) و N –Nميثيلين بيساكريلاميد ((NNMBAAM) كروابط متقاطعة و البنزويل بيروكسايد (BPO) كبادئ. أعدت NIPs باستعمال نفس تركيبة MIPs باستثناء القالب (CBD) . تم تحضير MIPs باستعمال نسبة التباين بين المونومر والرابط المتقاطع. يتم تطبيق هذه MIPs كاستخراج طور صلب لتقدير CBD في المستحضرات الصيدلانية باستعمال الأشعة فوق البنفسجية ككاشف. أعطت النتائج استجابة جيدة ، حيث كانت قيمة (Rec ٪) لعقارCBD (99– 101٪)، وأخذت قيمة الانحراف المعياري النسبي(RSD٪) القيمة (0.27 ٪ –0.93٪) للمحلول القياسي وأخذت Rec ٪ قيمًا (98–99)٪ ، وأخذتRSD ٪ قيمًا من (0.86– 1.62)٪ من عقار الكانابيديول لمستحضرات الصيدلانية كليبوبرايد

الكلمات الرئيسية: مونومر جديد ، رابط متقاطع ، بادئ ، تحديد كليبوبريد..

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INTRODUCTION

Molecular imprinting is a technique which creates recognition sites specific to a target molecule, called a template, within a synthetic polymer and has been widely used for analytical purposes for the selective adsorption of drugs and their metabolites[11]Comparable to immunosorbents, the different binding sites are allocated to the particular interactions within the polymer network between the template and the functional groups, working similarly to an antigen-antibody system[9]. The synthesis of an MIP involves first the complexation in solution of a template with a functional monomer (FM) by non-covalent or covalent interactions, followed by the polymerization of these monomers around the template in the presence of a cross-linker, a radical initiator and a suitable solvent. Following polymerization, the template is removed from the polymer network, leaving its imprint and the cavities complementary to the template in the polymer structure with size shape and chemical functionality[5-8]

Clebopride, 4-amino-N-(1-benzylpiperidin-4-yl)-5-chloro- 2-methoxybenzamide (Figure 1), is a dopamine antagonist drug with antiemetic and prokinetic properties used to treat functional gastrointestinal disorders. Detailed investigation at several centres has demonstrated its encouraging antiemetic, gastrokinetic and anxiolytic properties[12-13]. Literature survey reveals that the drug can be estimated by thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC).[9-18] gas chromatography-mass spectrometry (GC-MS) and radioimmunoassay (RIA) in both animals and man [17-19] .There are a variety of ion selective electrode determined drugs that depended on MIPs as ecognition membranes like ibuprofen[1] , warfarin[2] ,phenytoin[3] and metronidazole benzoate [4] .No spectrophotometric method has been reported in the literature for the assay of clebopride[20] . This communication describes a simple and sensitive spectrophotometric method for the determination of clebopride in bulk and drug formulations ,the study was aimed to determination of clebopride (CBD) selective molecularly imprinted polymers.

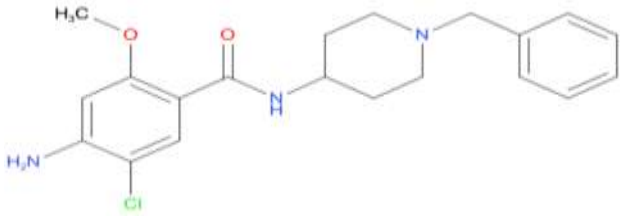


Figure 1. Structure of clebopride

MATERIALS AND METHODS

Reagents and chemicals: (Acryl amide) (AAM), 2-Acrylamido-2-Methyl-1-Propane Sulphonic Acid (2-AAMMPSA), Ethylene Glycol Dimethacrylate ethylene glycol(EGDMAC), N, N-Methylene Bisacrylamide (NNMBAAM)) and benzoyl peroxide were purchased from Sigma–Aldrich (St. Louis, MO, USA, www.sigma-aldrich.com), methanol were purchased from Merck (LiChrosolv, Merck KGaA, Darmstadt, Germany, www.merck.com).) Clebopride (CBD) was provided from Mahi BRAWN, Haryana –India, Park-Davis Company, Germany .Sodium hydroxide were purchased from Analar – Germany, nitrogen gas bottle (99.99) from Arab gulf factory Baghdad.

Instrumentation

Monitoring of the analyses was performed using UV-Vis (SHIMADZU UV -Visible Spectrophotometer 1800 pc using the (1cm) quartz cells and Scanning Electron Microscopy (SEM) (JSM.6390A) and SHIMADZU IRAffinity-1S (FTIR) - 8000 ,heating/stirring.During the polymerization process, pure Clebopride shows absorption band at 263 nm, this band can be used to ensure that all Clebopride was removed after washing, then it measured by using UV-Vis spectrophotometer An Ultrasonic Sensitive

Water Bath from (SONERX) was used for stirring the polymer solution.

Preparing of standard solutions

preparing of standard solution (100 µg/ml) Clebopride by dissolving (0.01 gm)of standard Clebopride in the methanol and completed to(100 mL) in the volumetric flask .The other solutions were prepared in100 mL at the ranged from (10-100 µg/ml) in the same procedure.

Synthesis of the imprinted polymer

CBD-(MIP_1-AAM): Unbreakable glass tube (50 ml) was utilized, and 0.45 mmol from the mold material CBD was added to the tube. CBD was dissolved in 7 ml of methanol. Furthermore. An amount of (5.8 mmol) of Acrylamide (AAM) was added to the mixture. Further, the combination was stirred via the ultrasonic waves for 5 minutes. Later, cross linkers of Ethylene Glycol Dimethacrylate (EGDMAC) (10.6 mmol) and Benzoyl Peroxide (0.21 mmol) (BPO), which acts as a starting point for polymerization, were added to the glass tube. Bubbles in liquid were moved out by using high-purified Nitrogen for 15 minutes. Immediately thereafter, a rubber cap tightly locked the tube orifice, and the resulting liquid was placed in a water bath at 45 C^o for two days without moving. After polymerization finishes, the mold was removed by frequent washing of the polymer using a combination of (15%) (v/v) of Acidic acid/Methanol utilizing the extractor (Soxhlet) for 48 hours. Following mold removal, it was necessary to guarantee that there were no reactive materials by checking it, following the process of frequent washing and drying at 40 C^o for one hour. After drying, the material was smashed into powder using a grinder of Granit and a steel sieve whose porosity is 75µm. For evaluating the extracted material, a plastic syringe (5 ml) was exploited by filling it with a polymer material. Furthermore, a standard liquid, which lies within the calibration curve, was prepared and permitted to pass through the plastic syringe. Finally, the liquid was removed from the plastic syringe by a washing solution and under a pressure of 10 pa.

Synthesis of the imprinted polymer

CBD- (MIP_2-2-AAMMPSA): Unbreakable glass tube (50 ml) was utilized, and 0.63 mmol from the mold material CBD was added to it. CBD was dissolved in 10 ml of methanol. In addition. An amount of 4.5 mmol of 2-Acrylamido-2-Methyl-1-Propane Sulphonic Acid (2-AAMMPSA) was added to the blend. Further, the combination was stirred via the ultrasonic waves for 10 minutes. Later, cross linkers of N, N-Methylene Bisacrylamide (NNMBAAM) (15 mmol) and Benzoyl Peroxide (0.35 mmol) (BPO), which represents a beginning point for polymerization, were added to the glass tube. Bubbles in the liquid were moved out using high-purified Nitrogen for 20 minutes. Directly thereafter, a rubber lid tightly locked the tube outlet, and the resulting liquid was placed in a water bath at 55 C^o for two days without moving. After polymerization finishes, the mold was removed by frequent washing of the polymer using a combination of (15%) (v/v) of Acidic acid/Methanol and utilizing the extractor (Soxhlet) for 48 hours. Succeeding mold removal, It was necessary to be certain that there were no reactive ingredients by checking it following the process of frequent washing and drying at 40 C^o for one hour. After drying, the material was smashed into powder using a grinder of Granit and a steel sieve whose porosity is 75µm. For evaluating the extracted material, a plastic syringe (5 ml) was exploited through filling it with the polymer material. Furthermore, a standard liquid, which lies within the calibration curve, was prepared and permitted to pass through the plastic syringe. Finally, the liquid was removed from the plastic syringe by a washing solution and under a pressure of 10 pa.

Preparation of pharmaceutical

CBD solutions: The pharmaceutical form, which is available in local markets and contains CBD, has tablets shape and is produced by the company "The Gulf Jilfar for medical industry" in UAE. Ten tablets of pharmaceutical form, which have 0.5 mg of the effective material, were weighed to get an average weight of 1.905 g. The collection was smashed and well mixed using a ceramic grinder. Then, an average of one tablet weight (0. 10905 g) was considered and dissolved in a volumetric vial (100 ml) using Methanol as a solvent. Following the process of placing in a water bath to dissolve by ultrasonic waves, the liquid was filtered through an infiltration paper

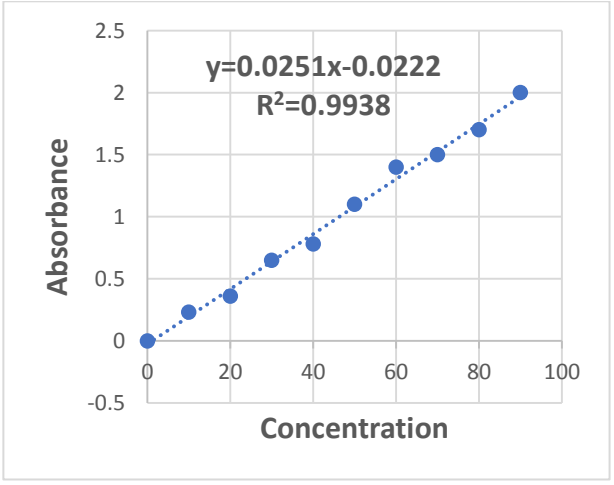
(Whatman No. 42) to get rid of any undissolved materials. Additionally, the leachate, containing 50 µg/ml of the effective material CBD, was obtained and applied in tests.

Procedure of CBD standard solution

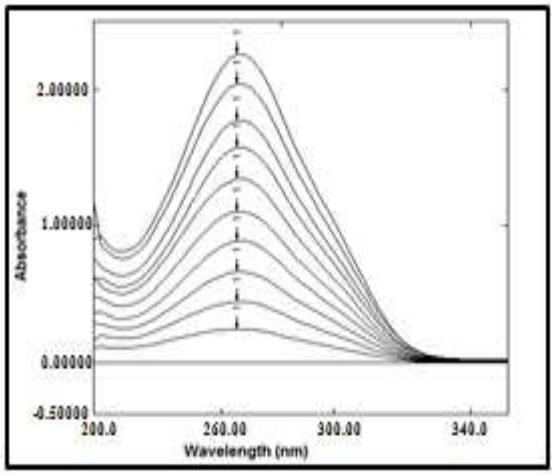
Different quantities of (1 – 10) ml of the standard liquid CBD, whose concentration is 100 µg/ml , were moved to a collection of volumetric bottles having 10 ml each, and were slaked up to the mark of this solvent. Then, the UV ray device scanned the wavelength (190 nm– 400 nm) of the combination to plot the zero spectrum and the absorption spectrum record (for each bottle) to calculate the range of concentrations that were consistent with Pier – Lambert law. The study showed that the maximum absorption was at 263 nm.

RESULTS AND DISCUSSION

Absorption spectra: Absorption of Clebopride versus its photo liquid was measured. Consequently, CBD showed a maximum absorption at 263 nm, as in Fig. 1.a. Then, a calibration curve for CBD drug was organized by plotting absorption versus concentration, as in Fig. 1.b. The linearity of CBD drug was in the range (10 – 100) µg.ml^{-1}, the gradient coefficient of CBD (R^2) was 0.9999, the molar absorption coefficient with Sandal indication of CBD were 11722.28 L.mol^{-1}.cm^{-1} and 0.044053 µg/cm respectively, and the identification limit with the estimation limit of CBD were 0.002985 µg/ml and 0.009949 µg/ml respectively. This method depicted satisfying accuracy and harmony, where the reconstruction percentage (Rec%) value of CBD drug took the range (99-101%), and the relative standard deviation (RSD%) value took the range (0.27% - 0.93 %).



(b)



(a)

Fig. 2. a. zero-order spectra of CBD at 263 nm and b. calibration curve of CBD with concentrations (10 – 100) µg/ml

Accuracy and precision

Accuracy and consistency of the method were computed through Rec% and RSD% for two concentrations within the calibration curve, where Table (1) Shows the obtained results. Rec% value took a range of (99.2 – 101.23 %), and RSD% took the range (0.86 - 1.62%) for CBD drug.

Table 1. accuracy and consistency of CBD drug

Sample	Drug conc (µg/ml)		Rec %	RSD %
	Taken	Found		
CBD	30	30.37	101.23	0.27
	60	59.52	99.2	0.93

Synthesis of MIPs for Clebopride (CBD)

Two MIPs of Clebopride were prepared via polymerization. In addition, polymerization method requires the drug as a mold, and requires choosing monomers that have a great role in reacting with mold and forming molecular printed polymers. Two types of monomers were utilized, which were Acrylamide (AAM) and 2-Acrylamido-2-methyl-1-propane Sulphonic Acid (2-

AAMMPSA) that supports checking of the printing process. The molecular printed polymers needed appropriate type and quantity of cross linkers to complete polymerization to become a hard and a high selective polymer. Many attempts to prepare molecular printed polymers were conducted, and they included finding the perfect ratios of (monomer: cross: linker drug) to prepare NIPs and MIPs. The prepared NIPs and MIPs included convenient properties regarding their performance, as shown in Table (2)

Table 2. the various ratios (D: M: C) that were used to prepare NIPs and MIPs for BMSP

No.MIP	Ratio	Drug CBD	Monomer AAM	Cross linker EGDMAC	Initiator BPO	Solvent	Result
MIP1	%	2.26	37.59	60.15	1.24	10ml CH3OH	White suspensions
	mmol	0.30	5.00	8.00	0.21		
MIP1	%	3.22	34.94	61.82	1.24	10ml CH3OH	White suspensions
	mmol	0.6	6.5	11.5	0.21		
MIP1	%	2.67	34.42	62.90	1.24	10ml CH3OH	White hard powder
	mmol	0.45	5.8	10.6	0.21		
NIP1	%		34.42	62.90	1.24	10ml CH3OH	White hard powder
	mmol		5.8	10.6	0.21		
No.MIP		**Drug CBD**	**Monomer 2-AAMMPSA**	**Cross linker NNMBAAM**	**Initiator BPO**	**Solvent**	**Result**
MIP2	%	1.92	11.54	86.54	1.73	10ml CH3OH	White suspensions
	mmol	0.5	3	22.5	0.35		
MIP2	%	2.18	16.05	81.75	1.73	10ml CH3OH	White suspensions
	mmol	0.75	5.5	28	0.35		
MIP2	%	3.12	22.35	74.51	1.73	10ml CH3OH	White hard powder
	mmol	0.63	4.5	15	0.35		
NIP2	%		22.35	74.51	1.73	10ml CH3OH	White hard powder
	mmol		4.5	15	0.35		

All ratios of MIPs and NIPs were prepared employing a water bath at (45 – 55) C^o

FTIR analysis

FTIR spectra of CBD drug appear at forming MIPs that stand on the monomer Acrylamide and 2-Acrylamido-2-methyl-1-propane Sulphonic acid. Before and after drug removing, basic functional groups perform, as shown in Figs. (2 – 6).

Table 3. demonstrates the most recognized peaks in FTIR spectra of the molecular printed polymer of BMSP using AAM as a functional monomer

No.	Functional Group	CBD	CBD-(MIP_1-AAM) before template removal	CBD-(MIP_1-AAM) after template removal
1	N-H str.	---	3444	3448
2	O-H str.	3406	3367	---
3	C-H aliphatic.	2987, 2945	2956 , 2866	2995 , 2958
4	C=O str.ester.	---	1670	1728
5	C=O str.Carbonyl	1722	---	---
6	C=O str.α.β.unsaturated	1662	1728	---
7	C=O str.amid	---	1631	1676
8	C=C str.exocyclic	1606	---	---
9	C-H bending	1454	1454	1456
10	C-O str. asymm.	1174	1149	1145
11	C-O str. symm.	1099	1047	1049

FTIR spectra of pure Clebopride were measured. The same operation occurred to the molecular printed polymers (before and after removing the mold) through scanning within the range (400 – 4000) cm^{-1} utilizing the solid tablets method (KBr).Through FTIR spectra, a wide band of OH group was observed. The frequency band of this group became less than its previous value, because of the linkage between OH of CBD drug with atoms existing within the monomer (AAM) via hydrogen bonds. Consequently, the hydrogen bonds drag the (O-H) bond and change the dynamics of this bond. Furthermore, we can observe that Carbonyl group (C=O) disappeared after the process of removing the mold molecule finished. In addition, groups (C=O amid) and (N-H) that belong to monomer AAM appeared. In spite of conducting the process of removing the mold molecule, the groups did not disappear. This verifies that washing and removing actions were effective.

Table 4. Shows the most recognized peaks within FTIR spectra of the molecular printed polymer of CBD using 2-AAMMPSA as a functional monomer

No.	Functional Group	CBD	CBD-(MIP_2-2-AAMMPSA) before template removal	CBD-(MIP_2-2-AAMMPSA) after template removal
1	O-H str.	3406	3523, 3409	3438
2	C-H aromatic.	---	3068	3076
3	C-H aliphatic.	2987, 2945	2945	2933
4	C=O str.Carbonyl	1722	---	---
5	C=O str.α.β.unsaturated	1662	---	---
6	C=O str.amid	---	1656	1654
7	C=C str.exocyclic	1606	---	---
8	C-H bending	1454	1452	1452
9	C-O str. asymm.	1174	1114	1114
10	C-O str. symm.	1099	1064	1039

FTIR referred to the existing of a wideband of OH group having frequencies that became higher than its preceding value, because the new band represents a summation of OH frequencies of CBD drug and the frequencies existing in 2-AAMMPSA monomer. Moreover, we observed that the Carbonyl groups (C=O) disappeared after the operation of removing the mold molecule. In addition, the groups (C=O amid), which belongs to the monomer, appeared during the formation of MIPs and did not disappear after removing the mold molecule. The operation proves that the frequent washing using a combination of 10 % (v/v) of Acetic acid/Methanol and mold molecule removal was effective.

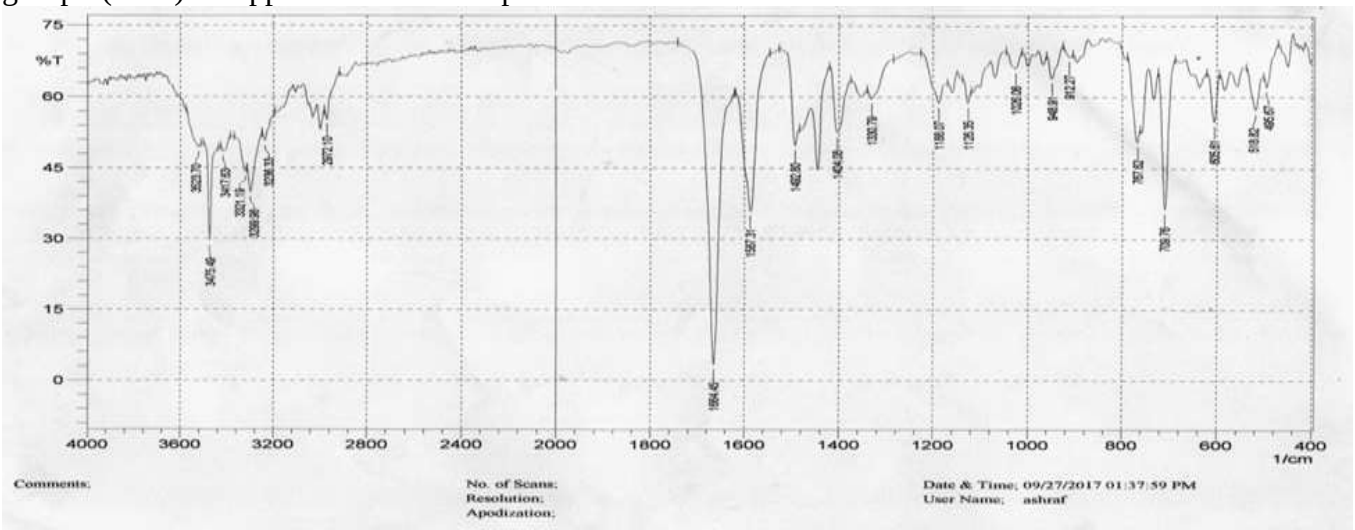


Figure 3. FTIR of (CBD) drug

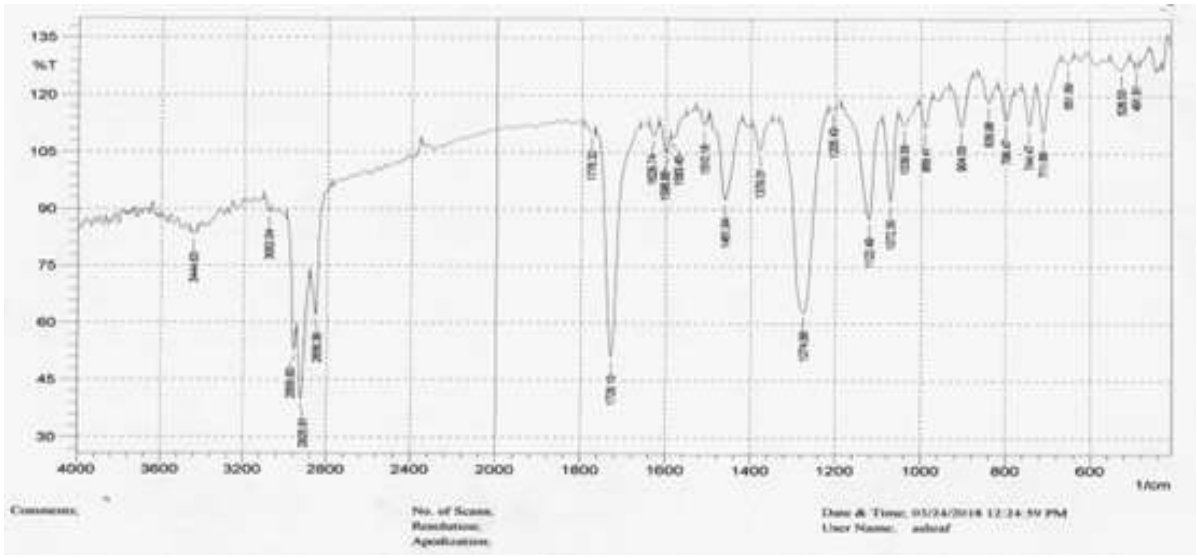


Figure 4. FTIR CBD-MIP$_1$-AAM before the removal of (CBD)

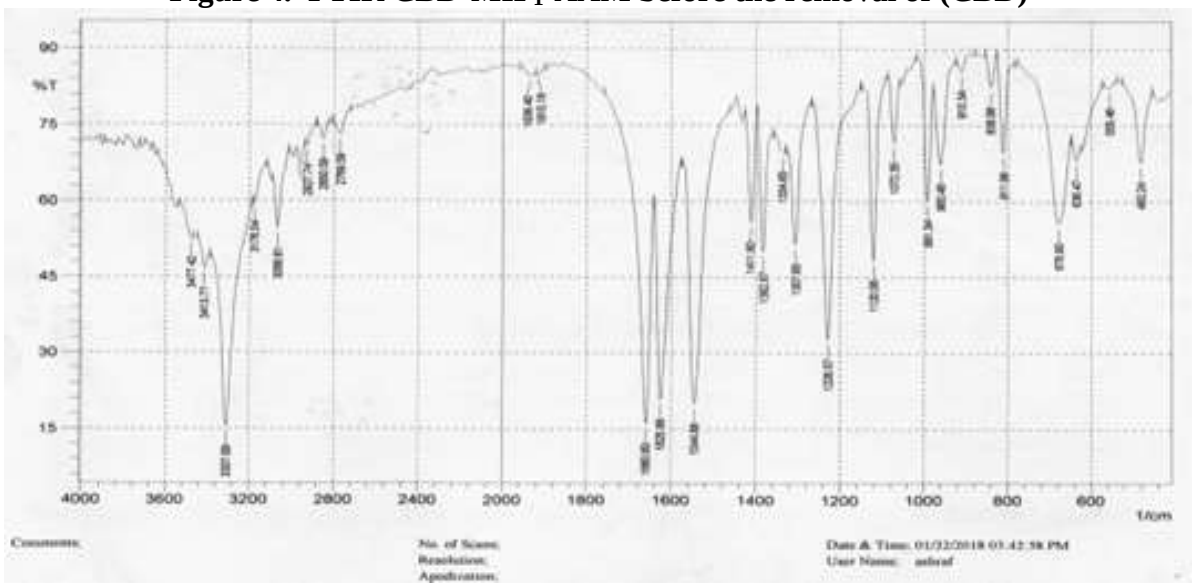


Figure 5. FTIR CBD-MIP1-AAM after the removal of (CBD)

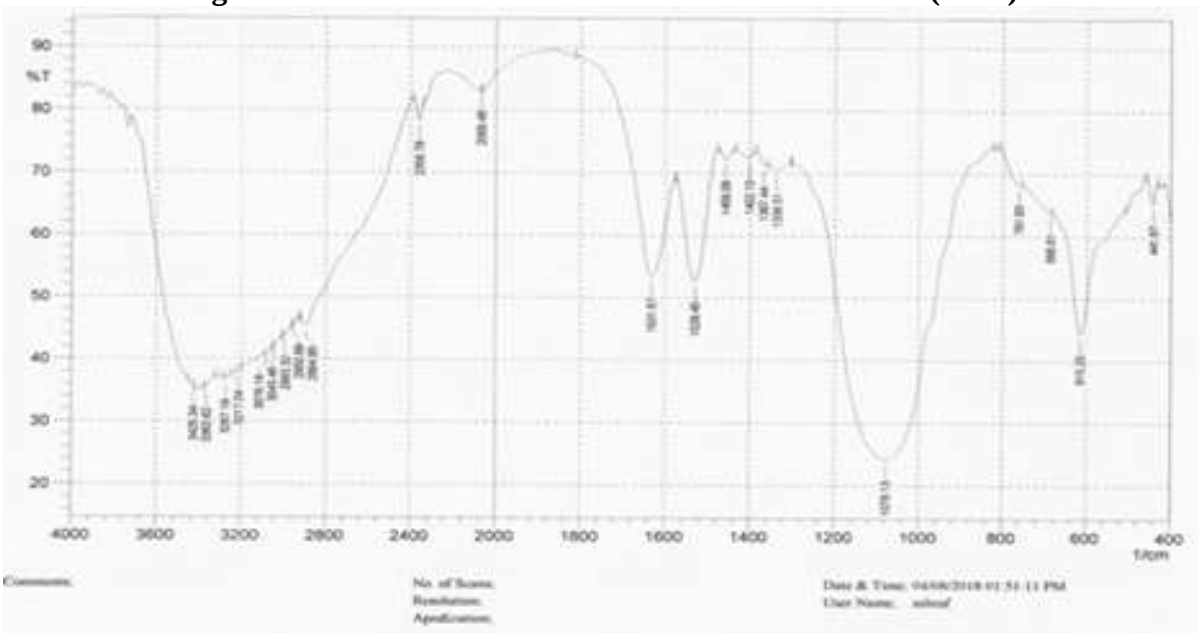


Figure 6. FTIR CBD-MIP2-2-AAMMPSA before the removal of (CBD)

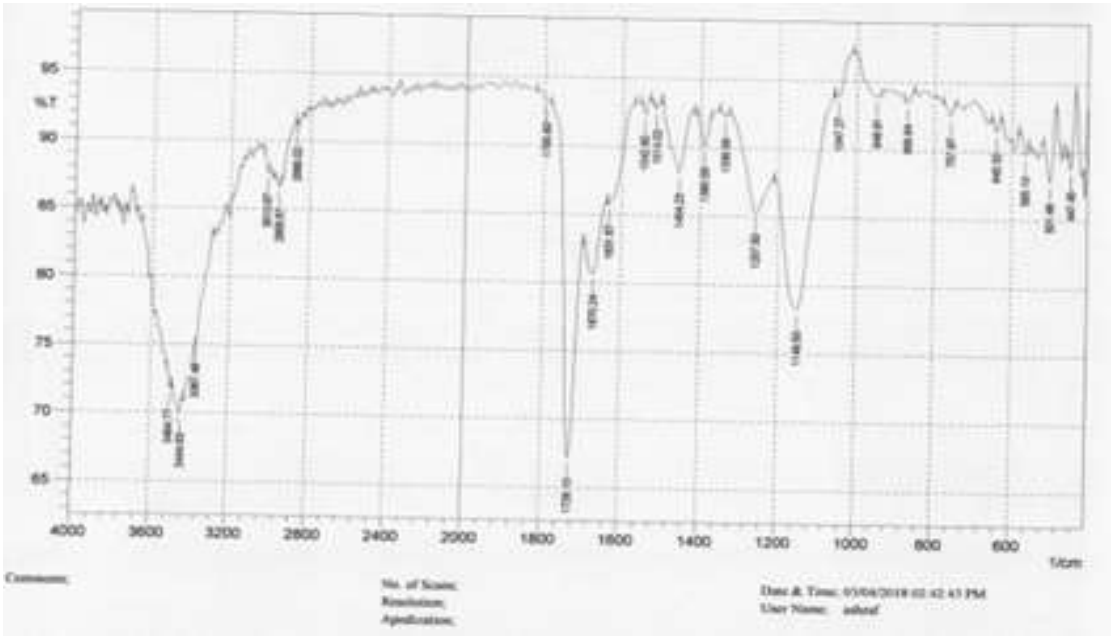
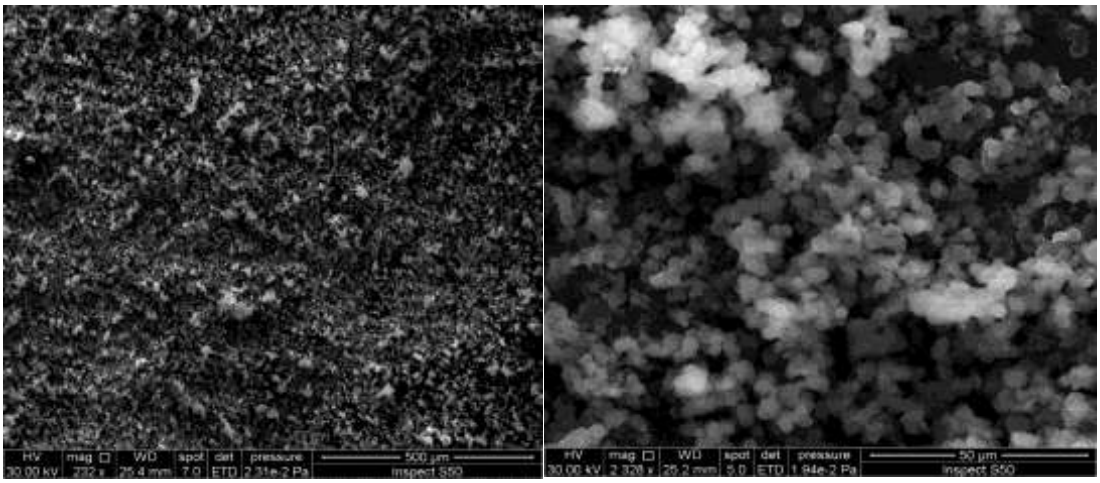


Figure 7. FTIR CBD-MIP2-2-AAMMPSA after the removal of (CBD)

Morphological characterization

Morphological analysis is very important for clarifying the particles design and their volumes before and after the mold (CBD) molecule removal of the polymer occurs. Structural analysis of molecules shows an existence of very small particles, which are polymeric spherical particles having tiny volumes CBD-MIP_2-2-AAMMPSA (0.85µm - 0.56 µm) before the mold (CBD) molecule removal happens. The other set of volumes (0.61 µm - 0.42 µm) of CBD-MIP_2-2-AAMMPS comes after the mold (CBD) molecule removal, where the wholes becomes obvious.



(a) **(b)**

Figure 8. SEM photograph of the surface of CBD-MIP2 - 2-AAMMPSA, a) before CBD removal b) after MAMP removal

Application of CBD

The aforementioned method was applied utilizing Solid Phase Extraction and was conducted for two concentrations (within the calibration curve) that are (30 and 60) $\mu g.ml^{-1}$ for two materials. The materials are CBD (the standard material) and Clebopride pharmaceutical and have the same concentrations for three repetitions for every measurement process. Then, a scan with wavelengths of (200 – 400) nm for the prepared combinations was carried out; hence, the results exhibited efficient accuracy and consistency. Moreover, Rec% took values of (98- 99) %, and RSD% took values of (0.86 - 1.62) % of CBD drug for the Clebopride pharmaceutical, as depicted in Tables (5) and Tables (6).

Table 5. Results of applying the method on CBD-MIP_1-AAM and CBD-MIP_2-2-AAMMPSA that were prepared using Solid Phase Extraction for the concentrations (30 and 60) µg/ml in their pure form

Sample	Method	conc (µg/mL) Taken	Found	Rec %	RSD %
Standard solutions (CBD)	CBD-MIP_1-AAM.	30	29.69	98.96	0.27
		60	59.58	99.3	0.78
Standard solutions (CBD)	CBD-MIP_2-2-AAMMPSA.	30	29.85	99.5	0.83
		60	59.20	98.66	0.93

Table 6. Results of applying the method on CBD-MIP_1-AAM and CBD-MIP_2-2-AAMMPSA that were prepared using Solid Phase Extraction for the concentrations (30 and 60) µg/ml for Clebopride pharmaceutical

Sample	Method	conc (µg/mL) Taken	Found	Rec %	RSD %
Clebopride Tablet (Haryana -India)0.5mg	CBD-MIP_1-AAM.	30	30.30	101	1.93
		60	59.41	99.01	2.37
Clebopride Tablet(Haryana – India) 0.5mg	CBD- MIP_2-2-AAMMPSA.	30	29.14	97.13	1.25
		60	59.81	99.68	1.99

Table 7. Results of applying the method on CBD-MIP_1-AAM and CBD-MIP_2-2-AAMMPSA that were prepared using Solid Phase Extraction for the concentrations (30 and 60) µg/ml for Clebopride pharmaceutical.(Germany)

Sample	Method	conc (µg/mL) Taken	Found	Rec %	RSD %
Clebopride Tablet (Haryana -India Park-Davis, Germany)0.5mg	CBD-MIP_1-AAM.	30	30.05	101.66	0.82
		60	60.11	100.18	1.52
Clebopride Tablet(Park-Davis, Germany) 0.5mg	CBD- MIP_2-2-AAMMPSA.	30	29.04	96.80	2.16
		60	59.45	99.08	1.74

Conclusion

The research includes the preparation of chemi cal sensors using different monomers with cros slinker to give the appropriate geometric shape to obtain the molecularly imprinted polymers (MIP),On the basis of small concentrations an d multiple mixtures, the drug can thus be estim ated. Preparation of clebopride molecularly im pressed polymers included:The first step was t o prepare molecular printing and the second to obtain a low dose concentration drug using s olid state extraction, thus obtaining a concent ration and estimation process in one step.

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