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Preparation and characterized study of new molecularly imprinted polymers for determination Cocaine by GC-Mass based on different Functional Monomers

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Abstract

Molecularly imprinted polymers (MIP) Showing high selectivity and affinity with major increasing analysis is now seen in the predetermined molecule (template) Furthermore, it is difficult to refine imprinted items due to the fact that there are multiple variables to worry about, Any or all of this could have a likely effect on the chemical, Properties of the imprinted components in morphological and molecular identification, it is a rapidly emerging technique for the preparation of polymers having unique molecular recognition properties for a given compound MIP synthesis is a relatively easy and inexpensive process, either for its analogues or for a single enantiomer. For the selective extraction of cocaine and benzoylecgonine from urine samples, newly synthesized molecularly imprinted polymer sorbents were proposed in this report. using a functional monomer which to build a monolithic solid-phase micro extraction (SPME) fiber, styrene and allyl chloride are used, as well as ethylene glycol methacrylate (EGDMA) as a suitable cross-linker and Cocaine as a template.a non-imprinted polymer was created by preparing a polymer without selective binding sites (NIP). all of these analytical procedures were utilized to extract, preconcentrate, and selectively determine Cocaine and its derivatives (SPME) with gas chromatography and mass spectrometry (GC/MS). sturdiness, the manufactured fiber's basic and vital role in SPME is due to its stability and durability. The samples were taken from a suspected cocaine abuser who was donated by the medico-legal directorate (Baghdad, Iraq). The analytes were monitored using a (GC MS), UV-Vis, scanning electron microscopy (SEM)and FTIR (Fourier –transform infrared spectroscopy) The relative standard deviations (RSD percent) for two patients' repeated studies for three measurements vary from (1.587-4.545) percent (at 20-100 ppm of Cocaine). Cocaine relative recoveries in human urine samples spiked with the drug are in the range of (102-105).

Keywords: Cocaine/Molecularly imprinted polymer / GC / MS

1. Introduction

Cocaine is still the most often used illicit stimulant drug in Europe, and it is no longer regarded a Belite drug due to its recent notoriety. Cocaine abuse is a serious problem. Numerous health issues, including respiratory disorders, neurological insufficiency, social problems, and mortality, are linked to smoking. [1, 2]. Urine tests are commonly tested for the purpose of human function forensic toxicology in drivers and in workplace substance monitoring programs [3]. The defined methods of sample preparation for the detection and quantification of cocaine in urine specimens mainly involve the commonly used solid-phase methods (SPE) [4–8]. and liquid-liquid extraction (LLE) [9–12] procedures, while molecularly imprinted polymers (MIPs) Often used were [13] more recently. Preparation is the latest trend in sample downsizing, which may be owing to the large volumes of solvents and samples required by more traditional approaches (which are also more time-consuming). Microextraction with packed sorbent (MEPS) is a downsized SPE that minimizes running volumes, sample size, and costs. Sample processing time, the screening of cocaine and metabolites has been successfully extended [14, 15], However, costly technology that is not required for regular research in most laboratories is used. This approach has been widely introduced in the area of clinical and forensic toxicology [16] Other miniaturized SPE approaches include for instance µSPE procedures; Although both can be regarded as miniaturized versions of the widely used SPE, presenting their comparatively low cost, reduced solvent use, and compatibility with various analyte

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separation and detection systems as benefits, μSPE has a variety of disadvantages, including the restricted range of availability of stationary phases and the probability of carryover. Moreover, MEPS often entails greater time and sample volume reductions needed for target analytes to be pre-concentrated. But the huge benefit is that the sorbent can be reused many times, greatly lowering the expense of the whole process. Gas chromatography combined with mass spectrometry (GCMS) is widely used for cocaine identification in forensic toxicology laboratories. [17–21], Despite the method of derivatization, which typically takes time to evaluate the main metabolites, [22]. Polymers have also been manufactured in the same way, and their selectivity has been demonstrated to them when used as high-precision films [23]. And since this method is characterized by high selection and economics in consuming biological samples. This method was used in the estimation of other narcotic substances in forensic medicine laboratories such as amphetamine [24-25]. The goal of this work is to employ new MIPs as solid-phase recovery and mass-spectrometry (GC-Ms) as a detector to identify Cocaine.

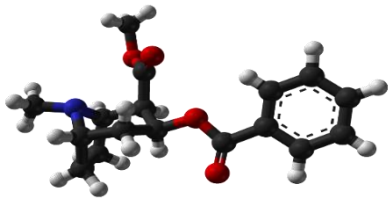

Fig.1: Structure of Cocaine

2. Experimental Reagents and Chemicals

Methanol, chloroform, and acetic acid were acquired from Merck (Darmstadt, Germany, www.merck.com), and were acquired from Sigma–Aldrich (St. Louis, MO, USA, www.sigma-aldrich.com). The medico-legal institution provided the cocaine (Baghdad, Iraq). nitrogen gas (99.99%) from a Baghdad facility in the Arab Gulf.

2.1. Instrumentation

GC MS (Agilent chnologies (7890A) (United States of America) and UV (Shimadzu uv spectrophotometer 1800 pc) and scanning electron microscopy (SEM) were used for the control (JSM.6390A). Heating / series FTIR Shimadzu (FTIR) - 8000 (Japan). Chromatography is the process of separating a mixture of substances into separate components, which is then calculated using GC in three stages.

1. Injecting a sample into the GC.
2. Separate the sample into individual components.
3. Detection of compounds in the sample.

Messages from the Agilent 7890A GC are shown during this operation, and user modifications to parameter settings may be made via the operator panel. Pure Cocaine uptake of 273 nm was measured using ultraviolet light. It was then utilized to quantify MIP-Cocaine absorption, following which it was pre-washed to verify that all Cocaine had been eliminated. The prepolymer solution was stirred up with Sonerx (W. GERMANY).

2.2. MIP procedure

1 mmol of template (Cocaine) was dissolved in 2 ml porogen (methanol) and 0.416 mmol and 0.428 of (styrene) and (allyl chloride) respectively then added and using ultrasonically for stirring the solution for 5 min, 5.94 mmol of cross linker (EGDMA) for both and 0.32 mg initiator (benzoyl peroxide) was added to the mixture. Passing the N2 gas 20 min to the solution for prepolymerization step sealed the tube by the stopper. Then the tubs were left in the water bath at 60◦c overnight. During that period the processes of polymerization have been completed and Cocaine-MIPs were formed. The non-molecular imprinted polymer NIP was synthesized exactly in the same method of synthesizing MIP but without the Cocaine. Washed the mixture of MIP and NIP in the soxhlet using excess amount of solvent methanol/acetic acid (32:8, v/v) for extraction the template and removing all the non-reacted compounds followed by dried the results in vacuum for 1 h. The synthesized MIP and NIP prepared was left for 1 h at 30 in a drying oven After that, crushed and grounded the mixture using mortar and pestle to get 75μm particles size. Before extraction, of the sampling device and used as extraction needles. The plastic syringe (Column) was packed with prepared (MIP) by using of a plastic syringe. The solution (urine or standard solution) was poured from top of the column; the movement of the solution was by vacuum at 75 rpm.

2.3. Sampling Procedure

Prepare a stock solution of Cocaine at pH 8 with a concentration of (20, 40, 60, 80, 100 ppm) and a flow rate of 75 rpm via Colum. To eliminate matrix interference, the column was rinsed twice with 2 mL distilled water and then removed from the MIP.

2.4. The Sampling Device

A 3 ml plastic syringe was utilized, and each syringe was filled with varied weights of MIP that had been previously ground and sifted (0.75 microns).

2.5. Real Sample

Urine samples of suspected cocaine were collected and forwarded to forensic medicine at the judge's order (Baghdad, Iraq). To remove any precipitated material, the centrifuge sample was spun at 5000 rpm for 10 minutes. Cocaine was immediately impregnated in the urine supernatant, and the non-pointed and squid samples were extracted by Colom.

2.6. Extraction Procedure

A MIP Cocaine solid phase extraction (SPE) column was used to extract cocaine from the urine. A 3 ml plastic syringe was previously filled with MIP to make this column (0.2 g). The supernatant from the centrifuged urine sample was poured into the space above the packing of the SPE column at a flow rate of 1 mL/min (75 rpm). After then 1ml of distilled water and 1ml of methanol/acetic acid (32:8, v/v) were added to the column and the eluent was collected in a small beaker. The eluent was dried for 10 min, and 1 ml (1:100, v/v) acetic acid: methanol was added and the eluent was also collected in the same beaker, and the residue was dried again in water bath at 50°C. Later the solution was cooled to room temperature and evaporated the solvent to dryness under stream of nitrogen followed by adding 1ml of methanol to residues and the sample to be ready to inject in the GC/ MS.

3. Results and discussion

3.1. Synthesis of MIPs for Cocaine

Self-assembly(non-covalent) bulk polymerization was used to install two MIPS of Cocaine. Two monomers, styrene and allyl chloride, were employed to synthesis the MIPs and NIPs and were essential in analyzing interactions with the template.

3.2. FTIR Analysis

To detect the functional groups, present in a compound, FTIR is an important chemical characterization process. The FTIR spectrum of various MIPs and NIPs shown in Table-1.

The KBr pellet approach was used to record the Fourier transmission infrared spectrometer spectra of leached and unleached Cocaine imprinted polymers MIP and NIP in the region of 400–4000 cm-1 (Table 1) the FTIR spectrum of the Cocaine showed the following bands (3419, 2962and 2842, 1730, 3024, 1598, 1269, 730 and 752) cm-1 for OH (H2O) stretching, C-H aliphatic stretching, C=O ester stretching, Ar-H stretching, C=C vinyl stretching, C-O stretching, $C=CH_2$ stretching C=C alken stretching and out of plane bending for mono substituted ring. The FTIR spectrum of the Cocaine –MIP(Styrene) before template removal shows the following bands 3446 cm^{-1} for OH (H_2O) stretching ,2952 and 2873 cm^{-1} for C-H aliphatic stretching, 3064 cm^{-1} for Ar-H stretching, 1583cm-1 for C=C aliphatic stretching, 1228 cm-1 for C-O stretching, 1620 cm^{-1} for $C=CH_2$ stretching,1535 cm^{-1} for C=C stretching, and 723, 678 cm^{-1} out of plan bending for mono substituted ring. The FTIR spectrum of the MIP (Styrene) after template removal shows the absence of C=O ester stretching, and out of plan bending for mono substituted ring which in template (Cocaine) spectrum which indicate the extracted of drug from template see fig2&3&4.

Table 1: The most identified peaks of FT-IR spectra for Cocaine-imprinted polymer and NIP using Styrene as a functional monomer

	Functional Group	Cocaine	Cocaine-MIP Styrene before template removal	Cocaine-MIP Styrene after template removal
1	OH(H_2O)	3419	3446	3467
2	CH-aliphatic.(cm^1)	2962,2842	2952,2873	2948,2867
3	C=O ester.(cm^{-1})	1730		
4	Ar-H.(cm^{-1})	3024	3064	3080
5	C=C aliphatic.(cm^1)	1598	1583	1556
6	C-O .(cm^{-1})	1269	1228	1259
7	$C=CH_2$.(cm^{-1})		1620	1637
8	C=C alkene .(cm^{-1})		1535	1529
9	Out-of plane-mono-sub	730,752	756,763	

When using the allyl Chloride as monomer for synthesis of another MIPs for Cocaine, the FTIR spectra of MIPs before and after template removal and NIP are shown in Table (2).

From Table (1,2) the FTIR spectrum of the Cocaine showed the following bands (3419, 2962 and 2842, 1730, 3024, 1598, 1269, 730 and 752) cm^{-1} for OH (H2O) stretching, C-H aliphatic stretching, C=O ester stretching, Ar-H stretching, C=C aliphatic stretching, C=O ester stretching, Ar-H Stretching C=C aliphatic stretching C-O Stretching $C=CH_2$, C-Cl stretching and out of plane bending for mono

substituted ring. The FTIR spectrum of the Cocaine – MIP (allyl chloride) before template removal shows the following bands 3460 cm^{-1} for OH (H_2O) stretching ,2956 and 2837 cm^{-1} for C-H aliphatic stretching ,1728 cm^{-1} for C=O ester stretching, 3066 cm^{-1} for Ar-H stretching, 1539 cm^{-1} for C=C, 1259 cm^{-1} C-O stretching, 1637 cm^{-1} for C=CH_2 stretching, 1620 cm^{-1} for C-Cl stretching, and 754, 705 cm^{-1} out of plan bending for mono substituted ring. The FTIR spectrum of the MIP (allyl Chloride) after template removal shows the absence of C=O ester stretching, AR-H stretching=C aliphatic and out of plan bending for mono substituted ring which excise in template (Cocaine) spectrum which indicate the extracted of drug from template see fig5&6

Several experiments were carried out using different ratios (Cocaine: Monomer: Cross linker) to reach the optimum ratio for the preparation of MIPs (Cocaine). Among these experiments of the molar ratios (Cocaine: Monomer: Cross linker) of (4.5:6.244:89.252), (4.504: 6.34: 89.16) for Cocaine - MIPs have produced polymers suitable characteristics

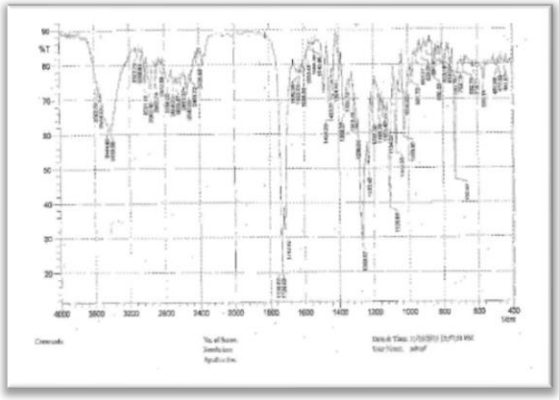

fig2: FTIR spectrum of standard cocaine

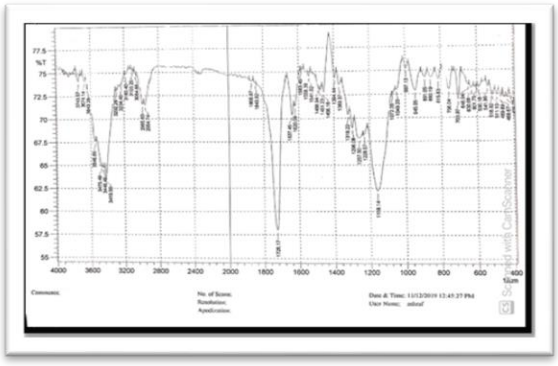

Fig3: FTIR spectrum of cocaine-MIP(styrene)before the removal of (cocaine)

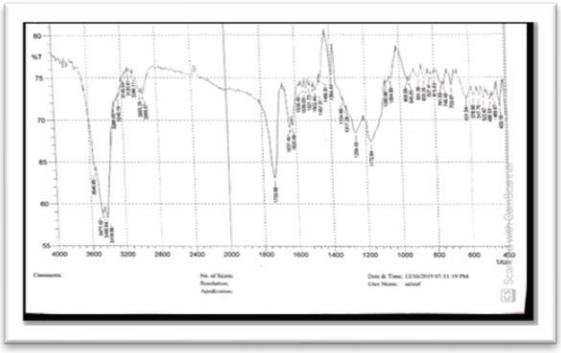

Fig4: FTIR spectrum of cocaine-MIP(styrene)after the removal of (cocaine)

Table 2: The most identified peaks of FT-IR spectra for Cocaine-imprinted polymer and NIP using Allyl Chloride as a functional monomer

	Functional Group	**Cocaine**	**Cocaine-MIP Allyl Chloride before template removal**	**Cocaine-MIP Allyl Chloride after template removal**
1	OH (H_2O)	3419	3460	3452
2	CH-aliphatic.(cm^1)	2962,2842	2956,2837	2991,2958
3	C=O ester.(cm^{-1})	1730	1728	
4	Ar-H.(cm^{-1})	3024	3066	
5	C=C aliphatic.(cm^1)	1598	1539	
6	C-O .(cm^{-1})	1269	1259	1259
7	C=CH_2 .(cm^{-1})		1637	1731
8	C-Cl .(cm^{-1})		1620	1639
9	Out-of plane-mono-sub	730,752	754,705	

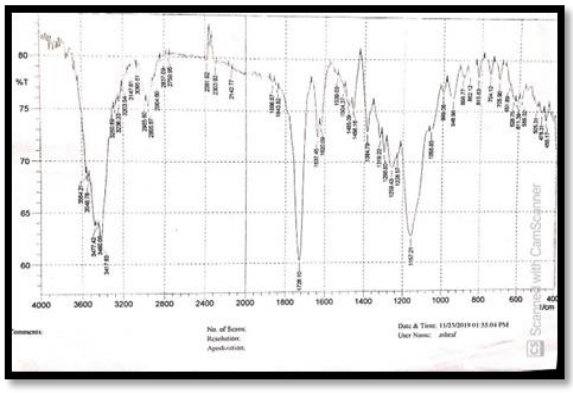

Fig5: FTIR spectrum of cocaine-MIP (allyl chloride) before the removal of (cocaine)

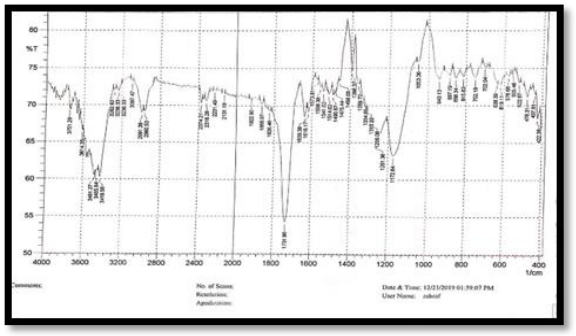

Fig6: FTIR spectrum of cocaine-MIP (allyl chloride) after the removal of (cocaine)

3.3. Morphological Characterization:

The technology of molecular imprinting allowed the preparation of synthetic polymers with specific binding sites for a target molecule. Throughout the polymerization process, the target was present, thus it acted as a molecular template. Monomers that carried certain functional groups were arranged around the template through either noncovalent or covalent interactions. Following polymerization with a high degree of crosslinking, the functional groups were held in position by the polymer network. Following the removal of the template by solvent extraction or chemical cleavage left complementary cavities to the template in shape, size, and arrangement of functional groups.

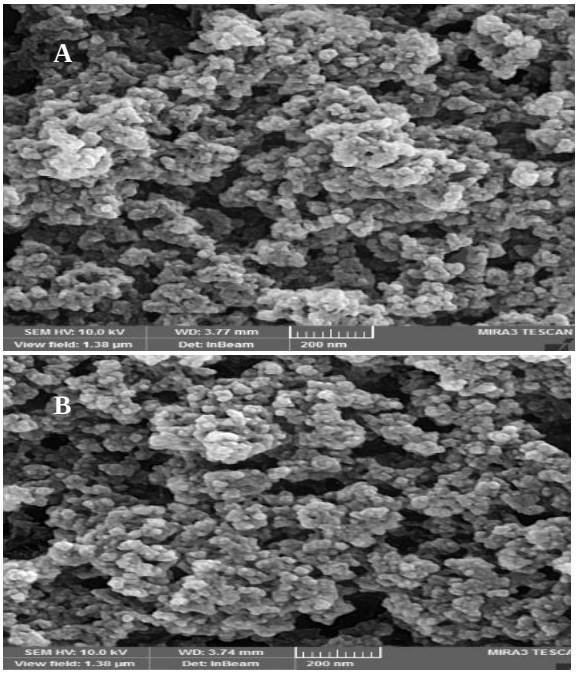

Fig7: SEM photograph of the surface of Cocaine-MIP (styrene), (a) before) Cocaine removal, (b) after) Cocaine removal

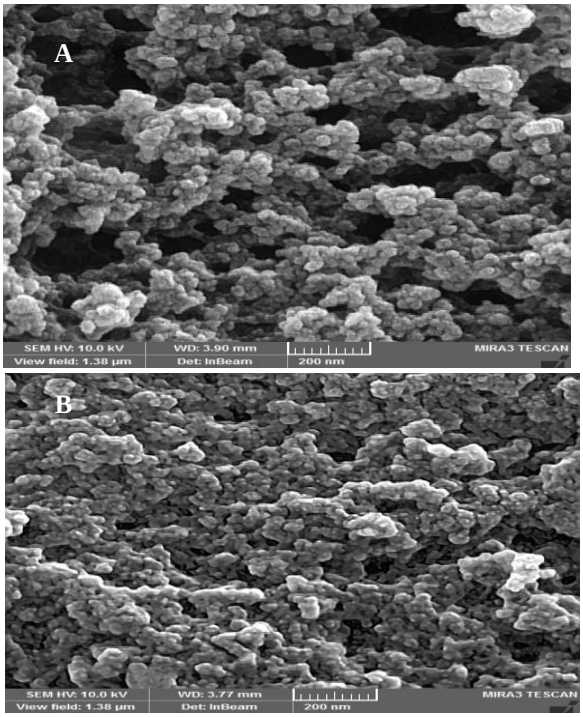

Fig8: SEM photograph of the surface of Cocaine-MIP (allyl chloride), (a) before) Cocaine removal, (b) after) Cocaine removal

3.4. Adsorption condition

Adsorption isotherm is useful in understanding the adsorption mechanism of the adsorption template on a polymer surface. The data obtained from the equilibrium of adsorption isotherm were analyzed to show the model of isotherm Langmuir or Freundlich models show fig (10,11)

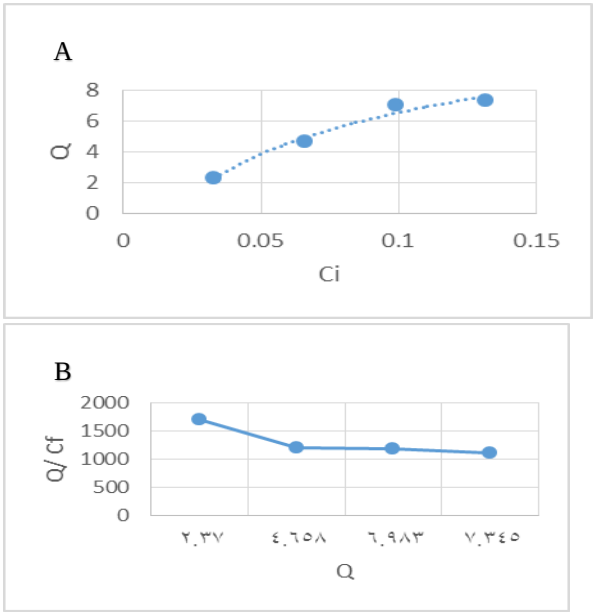

Fig 9: plots of styrene at MIP =0.2g (a,b)

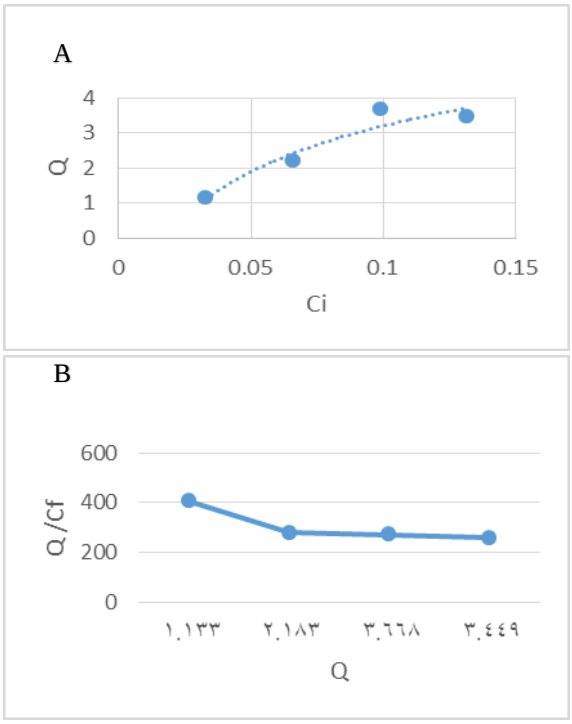

Fig10: plots of styrene at MIP =0.4g (a, b)

This was accomplished by plotting the ability of binding (Q) against free concentration of the drug, Q is calculated according to the following equation:

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

Ci = initial drug concentration (µmol / ml).

Cf = final drug concentration (µmol / ml).

Vs = volume of solution tested (ml).

MMIP = mass of dried polymer (mg).

Than measuring binding parameter

MIP/drug binding could be calculated by Scatchard analysis using the fallowing equation:

$Q/C_f = (Q_{max} - Q) / K_d$

Q_{max} = maximum capacity.

K_d = dissociation constant at binding side.

Table 3: Values of absorbance at different concentrations (20- 100) ppm Cocaine

concentration	Absorbance
20	0.076
40	0.144
60	0.196
80	0.259
100	0.325

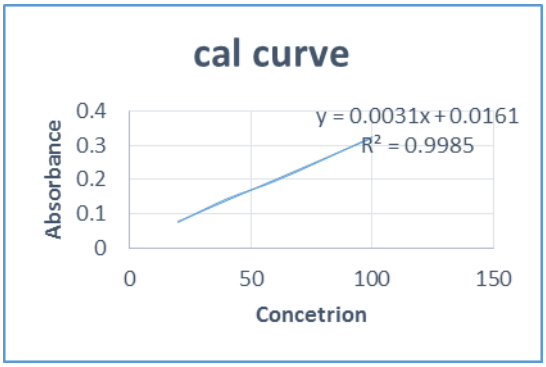

Figure 9: Calibration curve of Cocaine standard solution at different concentration (20-100) ppm used UV-Vis.

Isotherm adsorption of cocaine MIP based on styrene monomer were shows two sites connection of cocaine with the polymer with a covalent bond. While the cocaine MIP based on allyl chloride showed only one straight line by plotting Q/Cf and Q gave only one site connection of cocaine with polymer. 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 Freundlich . The variation ratios of [D:M:C] and progeny used in the preparation of MIPs and NIPs for Cocaine show table 5

Table4: Rebinding Values of (cocaine) using cocaine _MIP particle based on (styrene + EGDMA) depended on UV-Vis

Cocaine_ MIP(Styrene)						
Mass of MIP g	Constriction ppm	Ci mM	C_{free} mM	Q µMole /g	Q/C_{free} L/g	T: P (templet: polymer)
0.2	10	0.033	0.0014	2.370	1692.9	1:4
	20	0.066	0.0039	4.658	1194.2	1:14
	30	0.099	0.0059	6.983	1183.5	1:14
	40	0.132	0.0067	7.345	1100.4	1:14
0.4	10	0.033	0.0028	1.133	404.5	1:4
	20	0.066	0.0078	2.183	279.8	1:14
	30	0.099	0.012	3.668	271.9	1:14
	40	0.132	0.014	3.449	257.6	1:14

Isotherm adsorption of cocaine MIP based on styrene monomer were shows two sites connection of cocaine with the polymer with a covalent bond. While the cocaine MIP based on allyl chloride showed only one straight line by plotting Q/Cf and Q gave only one site connection of cocaine with polymer. 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 Freundlich . The variation ratios of [D:M:C] and progeny used in the preparation of MIPs and NIPs for Cocaine show in tabe 5

On the other hand, the control NIPs and MIPs after the removal of template have the similar spectra indicating the similarity in the backbone structure and prove that washing the MIP particles with 70% methanol solution used a Soxhlet extraction system is an efficient way to remove the template molecule leaving specific recognition binding sites in the polymer structure.

3.5. Urine Samples Analysis

To detect Cocaine in urine samples, MIP-styrene was administered homogeneously and MIP-Allyl chloride was administered using the Freundlich isotherm under ideal circumstances. The first stage was to extract the urine sample matrix, and the second step was to wash the sample matrix.. The washing step can be realized by allowing the solution of the carrier,and solution flow through the plastic syringe using peristaltic pump. The washing process is supposed to eliminate the components that suck weakly into a homogenous column. The matrix peaks were noticeably decreased by increasing the washing duration from 70 seconds to 3 minutes. Extraction of an empty urine sample with a 3-minute wash stage can indicate this. The use of the same washing method to the urine sample rose resulted in good Cocaine results: there was no change in the amount of cocaine discovered. Under ideal conditions, a plastic syringe containing 0.2-0.4 g of MIP (styrene), MIP (allyl chloride), and passing varied concentrations of Cocaine in urine samples was effectively achieved in a range of 20-100 ppm. Table 7 summarizes the findings.

Table 5: Rebinding Values of (cocaine) using cocaine_MIP particle based on (Allyl chloride +EGDMA) depended on UV-Vis

Cocaine_MIP(Allyl Chloride)						
Mass of MIP g	Constriction ppm	Ci mM	C_{free} mM	Q µMole /g	Q/C_{free} L/g	T: P (templet:polymer)
0.2	10	0.033	0.00074	2.42	3270.3	1:10
	20	0.066	0.0017	4.82	2835.3	1:5
	30	0.099	0.0026	7.23	2780.8	1:5
	40	0.132	0.0023	6.31	2731.5	1:5
0.4	10	0.033	0.0015	1.18	786.7	1:10
	20	0.066	0.0035	2.34	668.6	1:5
	30	0.099	0.0053	3.51	662.3	1:5
	40	0.132	0.0050	3.29	659.2	1:5

Table 5:

		Drug Cocaine	Monomer Styrene	Cross linker EGDMA	Initiator	Solvent	Result
MIP3	%	6.55	4.36	88.908	0.3	6 ml	Pale
	mmole	0.45	0.30	0.12	0.32	CH_3OH	yellow
MIP3	%	6.82	8.93	84.3	0.3	6 ml	Pale
	m mole	0.40	0.52	4.94	0.32	CH_3OH	yellow
MIP3	%	4.5	6.244	89.252	0.3	6 ml	Pale
	mmole	0.30	0.416	5.946	0.32	CH_3OH	yellow
NIP3	%	------	6.244	89.252	0.3	6 ml	Pale
	mmole		0.416	5.946	0.32	CH_3OH	yellow
		Drug Cocaine	Monomer AIlyI Chlorid	Cross linker EGDMA	Initiator	Solvent	Result
MIP4	%	6.21	11.69	82.089	0.3	6 ml	Pale
	mmole	0.25	0.47	3.30	0.32	CH_3OH	yellow
MIP4	%	5.99	6.33	87.76	0.3	6 ml	Pale
	mmole	0.35	0.37	5.12	0.32	CH_3OH	yellow
MIP4	%	4.504	6.34	89.18	0.3	6 ml	Pale
	mmole	0.30	0.42	5.94	0.32	CH_3OH	yellow
NIP4	%	-------	6.34	89.18	0.3	6 ml	Pale
	mmole		0.42	5.94	0.32	CH_3OH	yellow

Table 7: Standard addition method for drug determination using imprinted polymer method solid phase extraction By GC-MC

Wt. of MIP(g)	Type of MIP	NO.of patient	Conc. Taken (ppm)	Conc. Found (ppm)	% Recovery	RSD%	RE%
0.2	MIP1 Styrene	1	60	62	103	2.437	3.33
		2	20	21	105	4.545	5
0.2	MIP2 Allyl chloride	1	80	82	102	1.86	2.5
		2	60	62	103	1.587	3.33

4. Conclusion

Cocaine was extracted from urine samples in this investigation using the MIP Cocaine solid phase extraction (SPE) Colum. The creation of chemical sensors using various monomers and cross-linkers to offer the proper geometric form to generate molecularly imprinted polymers (MIP), as well as knowledge of the capacity of each imprinted created for the application. Cocaine and its derivatives. styrene and allyl chloride were used as monomers. small concentrations and different combinations can be used to estimate the medication. The initial stage was to develop Cocaine molecularly imprinted polymers, which can be concentrated. and estimate small percentages of the drug and at different times for the metabolism of the drug. The second step was to obtain a concentration using solid phase extraction, thus the combination of a molecularly-imprinted polymer with solid-phase micro extraction (SPME) obtaining a pre- concentration and estimation process in one step for better precision, sensitivity and selectivity. Using gas chromatography-mass spectrometry (GC-MS), the results of the extraction parameters such as flow rate and sample volume on the extraction performance of the fiber to C0caine were studied. The time decrease as the flow rate increase and we fixed the flow rate of 75 rpm in which the time was 5 minutes. The volumes less than 10 mL for Cocaine should be selected, exhibited good reproducibility and was considered suitable for the determination of trace levels. The data obtained from the equilibrium of isotherm adsorption were analyzed to show the type of isotherm Langmuir or Freundlich models. The binding capacity increase with increasing the concentration of the drug. Very lower detection limits were achieved in range of 0.8–1.2 ng mL−1.Finally, the MIP fibers were successfully applied for selective extraction of Cocaine in urine samples with the relative recoveries ranging from (102-105).

5. References

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