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Construction, identification, and description of molecularly imprinted polymers based on solid-phase microextraction-UV for determination of ciprofloxacin in pharmaceutical samples

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Abstract

Ciprofloxacin it as one of the most widely used antibiotics, making it essential to study its incorporation in pharmaceutical formulations. This study utilized a molecularly imprinted polymer (MIP) composed of styrene and ethylene glycol dimethyl acrylate to optimize the sorbent for ciprofloxacin solid-phase extraction (MISPµE). The MIP generated a maximum adsorption capacity of 6.5247 µmol/g, demonstrating high selectivity sorbent for its template molecule. Calibration curve analysis indicated a concentration value of 30 µmol/mL. The MIP-SPE method was applied to pharmaceutical samples, achieving a detection limit of 0.21 µmol/mL. Drug recovery varied between 91.28 and 96.57 % by employing this method., These outcomes proved the viability of this optimized MIP-SPµE.

Keywords: Ciprofloxacin, Molecularly imprinted polymer, optimization, (CIP-SPµE) Micro-solid phase extraction.

أساس الاستخلاص الدقيق في الطور تخليق وتشخيص ووصف البوليمرات المطبوعة جزيئيًا على الصلب – الأشعة فوق البنفسجية لتحديد السيبروفلوكساسين في العينات الصيدلانية

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الخلاصة

يُعدّ السيبروفلوكساسين من أكثر المضادات الحيوية استخدامًا، مما يجعل دراسة دمجه في المستحضرات الصيدلانية أمرًا ضروريًا. استخدمت هذه الدراسة بوليمرًا مطبوعًا جزيئيًا (MIP) مكونًا من ستايرين وإيثيلين جليكول ثنائي ميثيل أكريلات، لتحسين المادة الماصة لاستخلاص السيبروفلوكساسين في الطور الصلب (MISPµE). وقد أنتجت MIP قدرة امتصاص قصوى تبلغ 6.5247 ميكرومول/جم، مما يُظهر انتقائية

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عالية للمادة الماصة لجزيء القالب. أشار تحليل منحنى المعايرة إلى قيمة تركيز 30 ميكرومول/مل. طُبّقت طريقة MIP-SPE على عينات صيدلانية، محققةً حد كشف قدره 0.21 ميكرومول/مل. تراوحت نسبة استرداد الدواء باستخدام هذه الطريقة بين 91.28% و96.57%. أثبتت هذه النتائج جدوى MIP-SPµE المُحسّن.

1. Introduction

Ciprofloxacin (CIP), a widely used antibiotic, is classified as a second-generation fluoroquinolone. It was added to the WHO Model List of Essential Medicines, which sets minimum drug requirements for an essential healthcare system that includes the most efficient, safe, and economical medicines, and was added to the CIP in 2015 [1]. This antibiotic is employed to treat various bacterial infections, including those affecting infections and gastrointestinal, respiratory, and urinary tract infections [2]. MIP is a class of synthetic materials typically manufactured by copolymerizing a functional monomer and a cross-linker. Once polymerization is complete, the template is eliminated by extraction or dissolution, exposing binding sites similar in size and shape to the template [3, 4]. Lab-made receptors known as molecularly imprinted polymers (MIPs) have recognition sites pre-selected to match the template molecules [5]. Because they are so good at sticking to and recognizing targets in complex systems, MIPs have made big steps forward in SPE [6-8], chemical sensors [9, 10], biomimetic catalysts[11, 12], and other areas.

Solid-phase extraction (SPE) has been a key component in chemical sample preparation with its simplicity, adaptability, and minimal solvent consumption[13]. Recent studies have demonstrated the effectiveness of molecularly imprinted polymer-based solid-phase extraction (SPE). MIPs are a productive method for removing contaminants and pre-concentrated analyses from complex sample matrices [14].

High-performance liquid chromatography (HPLC) is a widely used technique for ciprofloxacin analysis, offering high levels of detection. To ensure accurate results,[15, 16], was used in coupled with UV detector. [17] or fluorescent detector [18]. Several analytical methods, such as spectrophotometry[19] and mass spectrometry[20], In this work the drug was evaluated in pharmaceutical preparations. In this paper, a new MIP material was synthesized and applied as a new MISPµE adsorbent in pure drugs and commercial drugs, and the results were evaluated by spectrophotometric measurements. To obtain the best performance of the imprinting and optimize various parameters, the adsorption properties of CIP on MIP and non-imprinted polymer (NIP) were performed. Lastly, CIP-MIP was used as an adsorbent to selectively extract CIP in commercial drugs.

2.Experimental

2.1 Materials and Methods

Ciprofloxacin was purchased for the General Company for the Industry and Healthcare Equipment (Iraq-Samarra). Styrene, EGDMA and benzoyl peroxide (99.99%) were supplied from Sigma-Aldrich, while nitrogen gas (99.7%) was supplied from Al-Watan factory (Al-Nahda Street/Baghdad/Iraq), 2-propanol from Fulka, chloroform, ethanol, and acetic acid were purchased from Merck (Darmstadt, Germany) as solvents.

2.2 Instruments

Several instruments were utilized in this study, including a UV-VIS spectrophotometer equipped with 1 ml quartz cells from a Shimadzu 1800pc UV spectrophotometer (Japan), a SEM scanning electron microscope (JMS.6390a) from Tokyo, Japan, and a sensitive balance ± 0.0001 g electronic balance ACS120-4 Kern &Sohn GmbH, Germany. Additional equipment comprised a hotplate heater/motor (Germany), Shimadzu-8000 Fourier Transform Infrared Spectroscopy (FTIR) (Japan), Nitrogen gas system from Al-Watan plant in Baghdad, Soxhlet device from SONERX (West Germany), Water bath from Germany /Memmert-854.Shaker-Maix Mix Plus from Thermolyne Vortex Mixer 125 µm sieve (Germany).

2.4 Preparation of MIP - SPμE columns

To prepare the solid phase cartridge with a capacity of 3 ml, various amounts of MIP (0.05, 0.06, and 0.07 g) were dried, ground, and sieved before being packed into the column. The cartridge is filled and prepared by rinsing it with ethanol. Subsequently, 0.2 ml of the standard solution is added at a flow rate. 68 rpm on MIP-SPμE cartridge. The absorbance of the eluted solutions is measured by a UV-VIS spectrophotometer absorbance at 278nm

2.5 preparation of drugs

A 500 µmol/mL ciprofloxacin standard solution was prepared by dissolving the appropriate amount in a 50 mL volumetric flask. Pharmaceutical samples were prepared by weighing an average weight of ciprofloxacin tablet powder, dissolved in 50 ml of ethanol solution with a few drops of HCl, and filtered through 0.07 µm cellulose filter paper to obtain the concentration from a calibration curve. $3x10^{-5}$, mmol/ml (30 µmol/ml) of the drugs (Cipro-Denk 10 tablets 500 mg from (Germany), Ciprofloxacin10 tablets 500 mg from (Berkhamsted, UK), Cipropharm10 tablets 500 mg from (Jordan).

3. Results and Discussion

3.1 Characterization

3.1.1 Uv-vis spectroscopy characterization

UV spectroscopy is a rapid analysis technique used to conduct extraction studies of before and after extraction of CIP and CIP-MIP processes at a wavelength of 278 nm, as shown in Fig.[22].

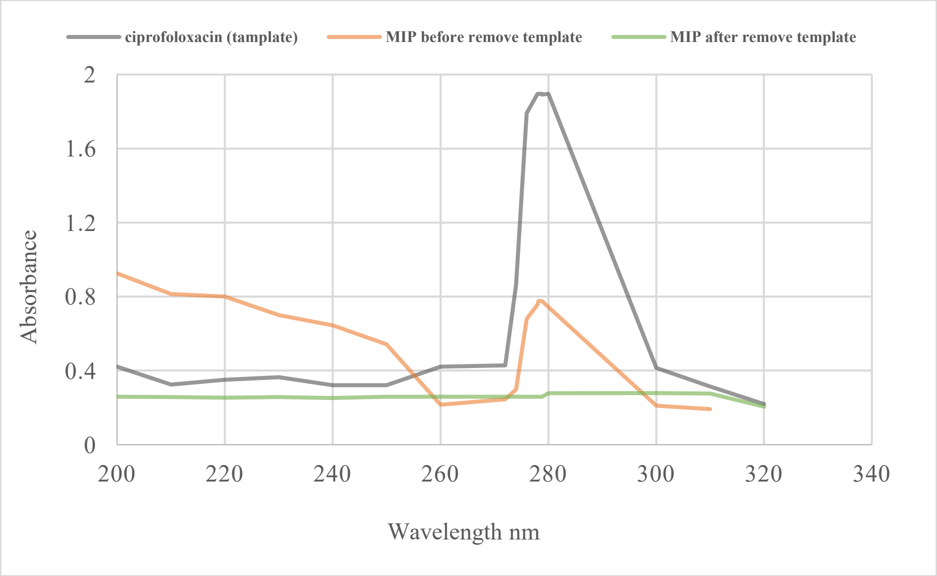

Figure 1: Absorption curves of CIP, CIP- MIP before and after extraction

3.1.2 Scanning electron microscope (SEM)

Using a concentrated electron beam, scanning electron microscopes examine a material's surface to produce high-resolution images. Surface composition is displayed in images produced by SEM. The MIP of CIP is shown in the image both before and after washing. Using Soxhlet extraction, additionally demonstrates the extractor's hole, as illustrated in Figure 2. Very tiny balls with sizes ranging from 72.16 to 111.11 nm were formed as the resultant holes[23]. Morphological evaluation is a crucial step in understanding the structural features of CIP-MIPs, including cavity size and surface configurations. This analysis helps determine how effectively the imprinted polymer interacts with ciprofloxacin, both before and after the removal of the ciprofloxacin template. In this study, scanning electron microscope (SEM) images were used to analyze the morphology of CIP-MIP. Figure 2(A) shows the surface morphology of the particles before removal of the ciprofloxacin template: Cavities or pits are visible on the surface of the polymer particles. These cavities are essential features that make the polymer able to selectively capture ciprofloxacin. Before elution, these cavities can be occupied by ciprofloxacin molecules that were immobilized within the polymer structure during the molding process. The surface of the particles also shows a complex and cohesive texture, indicating the formation of a well-cross-linked polymer that provides the appropriate environment for molecular entrapment. Figure 2(B): shows the morphology of the surface of the particles after removing the ciprofloxacin template: After the elution process (removal of ciprofloxacin), the shape of the cavities on the surface changes, with two empty cavities or empty spaces appearing in the polymer particles. This change confirms the removal of the ciprofloxacin molecules that were occupying those cavities. Despite the removal of the template, the overall structure of the polymer maintains its basic shape, indicating that the printed polymer network is still stable and able to selectively capture other molecules when needed the templet.

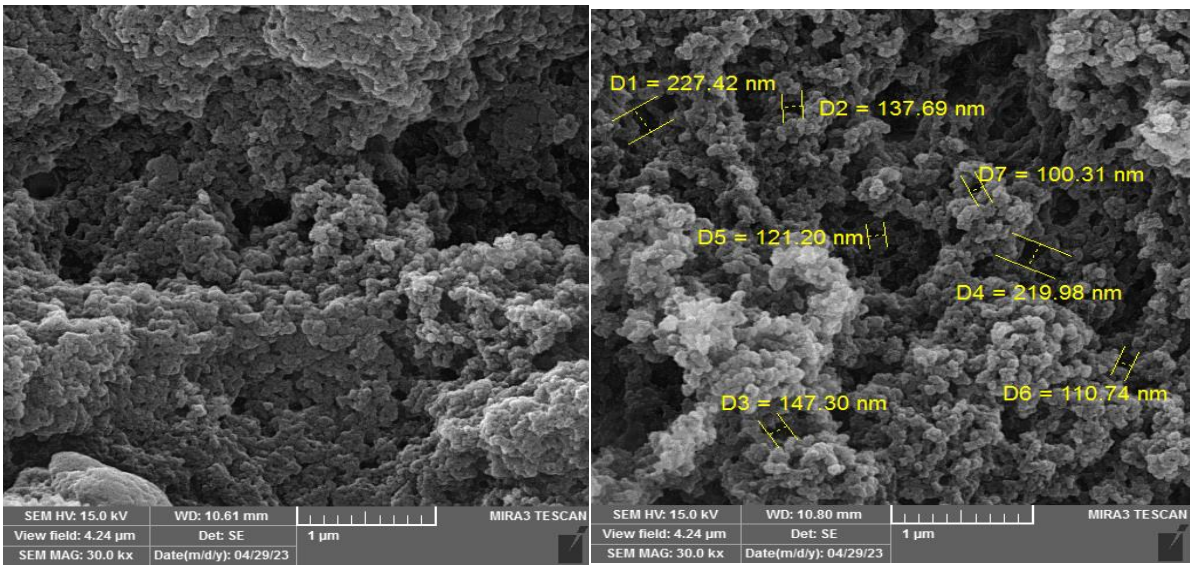

Figure 2: The SEM of Ciprofloxacin MIP (A) before washing the templet, (B) after washing

3.2.3 Fourier Transmission Infrared Spectrometry (FTIR)

Using a Fourier transform spectrometer (Bruker Optic GmbH Vertex 70, Germany), Fourier transform infrared (FTIR) analyses were performed at resolutions between 4000 and 400 cm^{-1}, employing the conventional method (KBr tablet). Where both the pre-and post-extraction CIP and CIP-MIP infrared spectra (Figure 3) were acquired.

Table 1 shows the FTIR spectra of CIP and CIP-MIP, revealing bands at 3377 and 3332 cm^{-1} corresponding to COOH stretching expansion, which disappeared after extraction. Bands were also observed at 1625 and 1629 cm^{-1} for (O=C-C=C) stretching, at 3533 and 3467 cm^{-1} for (N-H) stretching, at 1708,1710 cm^{-1} (C=O) stretching, their disappearance was observed after extraction respectively. These changes confirm the formation of a template and the drug was removed from the polymer[24, 25].

Table 1: shows the main FTIR compositions and spectra of imprinted polymers (CIP-MIP) both before and after the template was removed

Template (ciprofloxacin)	**Monomer Styrene**	**Cross linker Ethylene glycol dimethylacrylate**	
Band	**Drug(Template)**	**MIP before extraction**	**MIP after extraction**
C-H aliph. str.	2839,2929	2985,2948	2987,2952
C-H aromatic str.	3085	3080	3024
O=C-C=C- str.	1625	1629	-
O=C-O str.	-	1730	1731
N-H str.	3533	3467	-
COOH str.	3377	3332	-
CH=CH2- str.	-	1610	1635
C=O str.	1708	1710	-
C=C str.	1552	1600	1606

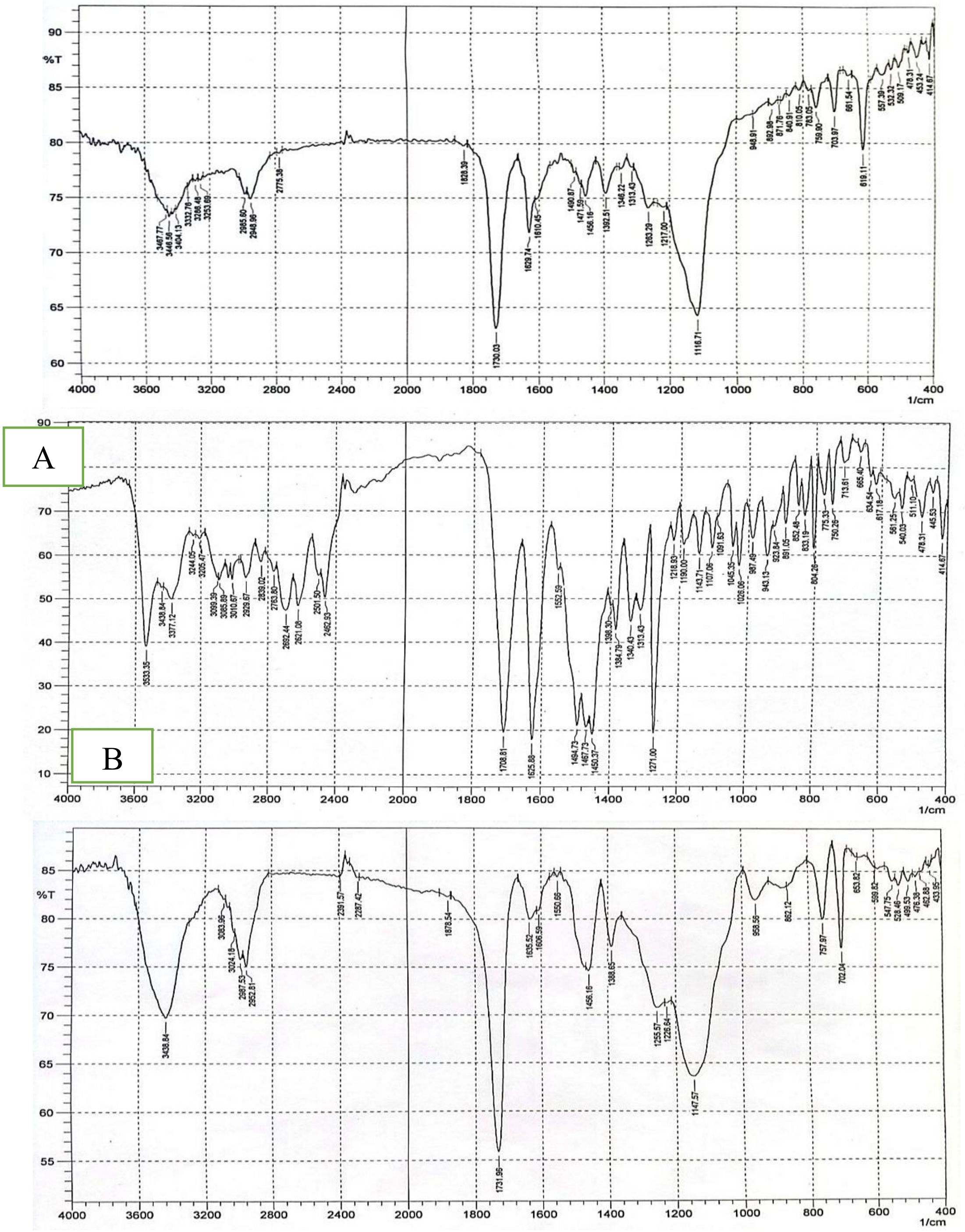

Figure 3: FTIR of the Ciprofloxacin (CIP), (A) CIP-MIP before extraction of the template and (B) CIP-MIP after extraction of template

3.2 Optimization of the MIP- SPµE Method

The present study employed MIP- SPµE combined with UV-Vis spectroscopy to extract and quantify CIP in commercial drugs. Absorbance at 278 nm was measured. Various factors were investigated, and their influence (MIP mass, drug solution volume, drug solution flow rate through peristaltic pump, elution solvent, and elution volume) on the efficiency of MIP-SPµE was studied. The result showed that the suitable weight of MIP was 0.05 g, the suitable volume was 0.2 ml, and the flow rate was 68 rpm to obtain stable recovery rates. Different elution solvents ethanol, methanol, 2-propanol, and chloroform, were studied. The highest recovery rates of CIP were obtained by using 0.2 ml of CIP and 0.4 ml of ethanol as elution solvent, which can help to absorb CIP almost. The parameters are shown in the figures below.

3.2.1 Influence of adsorbent material mass

The initial step in developing the MIP-SPE method involved optimizing the amount of MIP. To facilitate easier handling during experiments, different quantities of MIP (0.05, 0.06 and 0.07 g) were examined. These amounts were added to the pipette tips. Ethanol was used to activate and filter the cartridges. The findings demonstrated that when the MIP amount grew from 0.06 and 0.07g, CIP recoveries gradually declined. As indicated in Figure 4, 0.05 g MIP was chosen since is more effective for the recovery of ciprofloxacin.

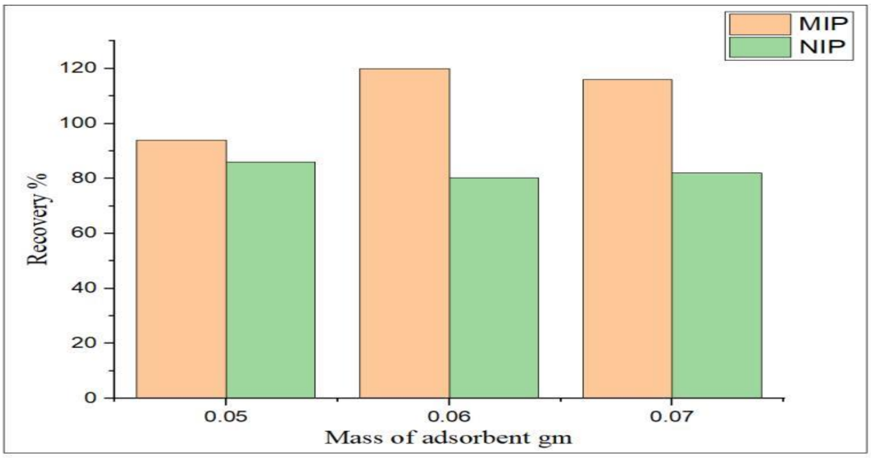

Figure 4: CIP recovery from MIP-SPE when using different weights for MIP & NIP

3.2.2 The influence of flow rate

The flow rate of the sample solution is a critical element as it determines the overall analysis time. The analyzer must be successfully maintained at a sufficiently low flow rate. The effect of the sample loading rate on recovery was examined at three different speeds of 68, 70, and 72 rpm to evaluate how the contact time between the MIP and the sample solution influences the recovery, as shown in Figure 5. The results indicated that as the flow speed increased, the recovery of the CIP decreased; the best retention value and also indicated the highest recovery were obtained at 68 rpm. The speed of 68 was selected and used as the best speed for the optimal sample flow test.

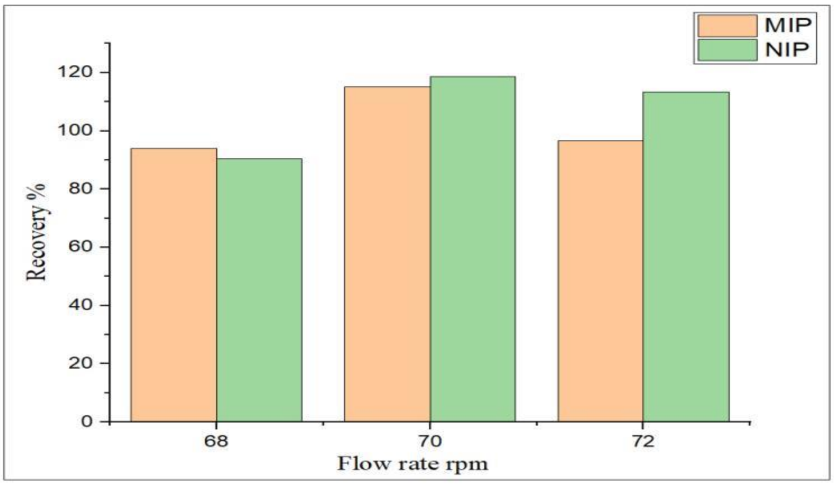

Figure 5: shows the CIP recovery based on SPμE for the Influence of flow rate for MIP and NIP

3.2.3 The influence of sample volume

The evaluation of three sample volumes 0.1, 0.2, and 0.3 mL is illustrated in Figure 6. The findings indicated that at sample sizes of 0.1 and 0.3, analyte recovery becomes lower. 0.2 ml of drug solution volume indicated higher recovery, a sample volume of 0.2 mL was used for examining the future parameters.

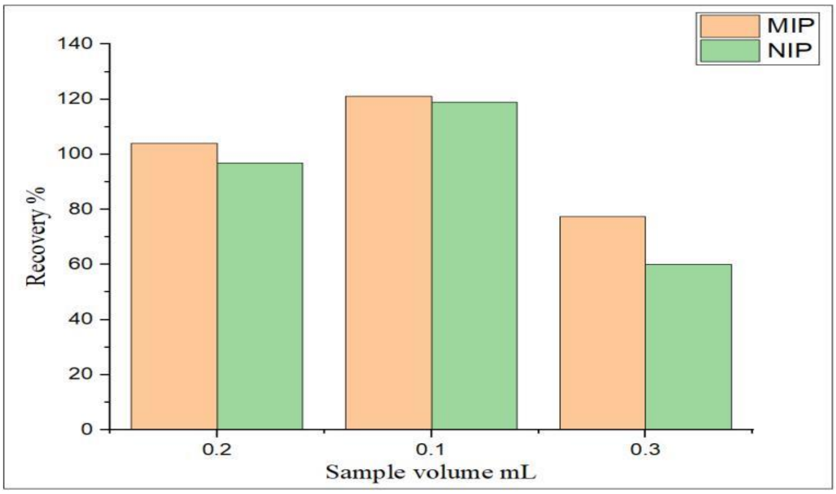

Figure 6: shows the CIP recovery based on SPμE for the influence of sample volume for MIP and NIP

3.2.4 influence of different types of eluent solvents

When preparing a sample using MIP-SPμE, selecting the appropriate elution solvent for the analytes retained in the cartridge is crucial. The elution solvent must be compatible with the sorbent based on its properties. To achieve effective elution of ciprofloxacin, several different polar solvents were evaluated in this study, including ethanol, methanol, 2-propanol, and chloroform. The results showed that ciprofloxacin recoveries were well achieved using ethanol, as shown in Figure 7A. Ethanol was chosen as the ideal elution solvent.

3.2.5 Eluent volume's influence

Eluent volume's effect as indicated by the results in Figure 7B, the influence of eluent volume was determined by changing the volumes of 0.2, 0.4, 0.6, and 0.8 mL of ethanol. The results showed that 0.4, 0.6, and 0.8 mL of eluent were unable to extract a significant amount of analytes ciprofloxacin removed it very effectively in 0.2 mL.

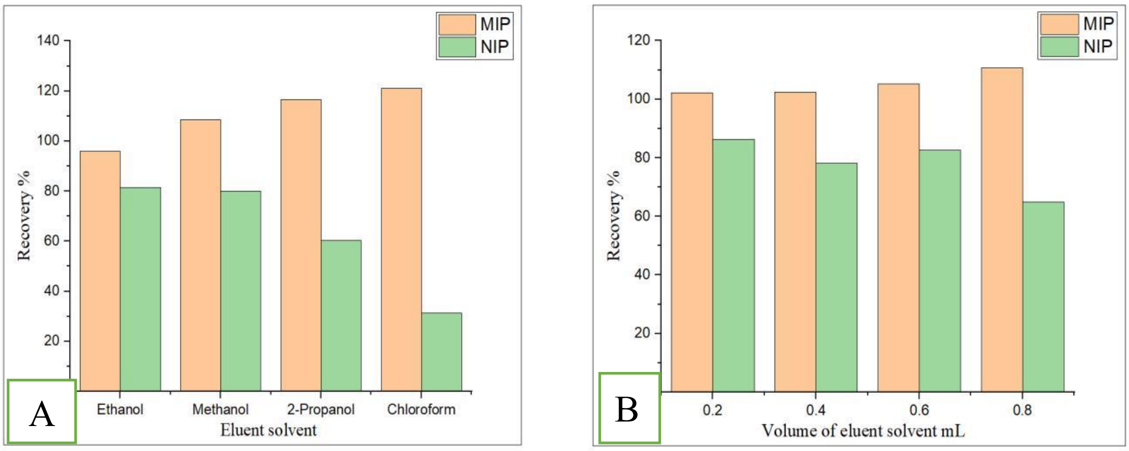

Figure 7: (A) shows the CIP recoveries based on MIP-SPµE for various eluting solvents for MIP and NIP (B) volume mL of eluent solvent for MIP and NIP by using (0.05 gm of MIP)

3.3 Method Validation

Tables 2,4 and 5 present the confirmed results for the suggested approach in terms of linearity and sensitivity, quantification and detection limits, recovery and precision.

3.4 Linearity of calibration curve

A calibration curve was generated by performing duplicate analyses at each SPE concentration (5–70 µmol/mL). Recovery and reproducibility were evaluated at a concentration level of 30 µmol/mL. The following formulas were used to calculate the limits of detection (LOD) and quantification (LOQ) according to the guidelines: LOQ = 10 S/b and LOD = 3.3 S/b, where S is the standard deviation of the blank absorbance readings and b is the slope of the calibration plot. Relative standard deviation values were calculated for all analytes. Excellent recovery rates of the target compounds were achieved in terms of recoveries. Validation data from the technique are summarized in Table 2. The results show excellent sensitivity and precision for the pharmaceutical samples in Tables 4 and 5 which were tested under different method parameters.

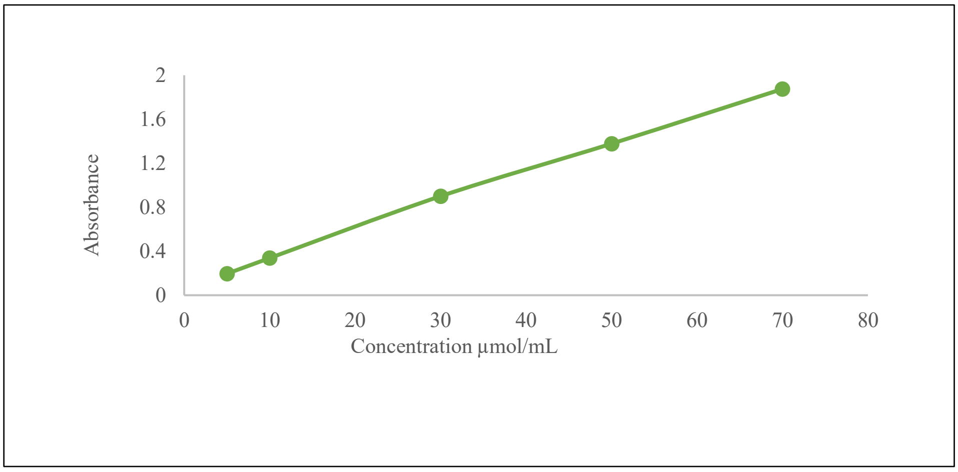

Figure 8: calibration curve of Ciprofloxacin

Table 2: Calibration curve data

Parameter	**value**
Lambda Max(nm)	278
Linear Range, µmol/mL	5 - 70
Limit of Detection (LOD), µmol/mL	0.21
Limit of Quantification (LOQ), µmol/mL	0.62
Intercept (a)	0.0861
Slope (b)	0.0258
Correlation Coefficient (r)	0.9994

3.5 Adsorption capacity

By dispersing MIP and NIP (0.05 g) from many solutions of CIP with varying initial concentrations (5-70 µmol/mL) at 25 °C, an adsorption test was conducted. After activation, UV was employed to analyze the CIP content. The remaining CIP was also evaluated using UV. The following equation was used to determine the adsorption capabilities of CIP bound to both imprinted and non-imprinted materials[23].

$$\mathbf{Q = (C_i - C_f) * V * 1000 / M} \qquad \dots\dots\dots (1)$$

where C_i and C_f (µmol/mL) are the initial and final concentrations of the CIP solution, respectively; V (mL) is the volume of the CIP solution; M (g) is the mass of MIP or NIP; and Q (µmol/g) is the equilibrium adsorption capacity of CIP shown in Figure 9.

$$\mathbf{Q/C_f = (Q_{max} - Q)/Kd} \qquad \dots\dots\dots (2)$$

A binding site dissociation constant (Kd) and maximum capacity (Q_{max}) are defined. The experimental data is shown in Table 3 and Figure 10.

Table 3: Rebinding value of CIP-MIP and CIP-NIP based on (STY) as monomer and (EGDMA) as cross-link:

M of MIP(g)	**C_i (µmol/ mL)**	**C_f (µmol/mL)**	**Vol. (mL)**	**Q (µmol/g)**	**Q/C_f (mL/g)**
0.05	5	2.24	0.2	11.04	4.9285
	10	0.863	0.2	36.548	42.3499
	30	0.782	0.2	116.872	149.4527
	50	1.19	0.2	195.24	164.0672
	70	1.71	0.2	273.16	159.7427
M of NIP(g)	**C_i (µmol/ mL**	**C_f (µmol/mL)**	**Vol. (mL)**	**Q (µmol/g)**	**Q/C_f (mL/g)**
0.05	5	4.89	0.2	0.44	0.0899
	10	6.115	0.2	15.54	2.5412
	30	12.305	0.2	70.78	5.7521
	50	17.38	0.2	130.48	7.507
	70	9.875	0.2	240.5	24.3544

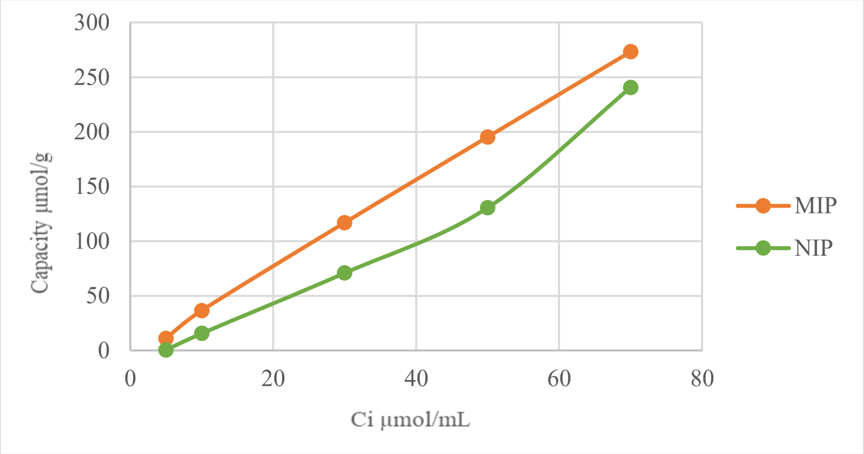

Figure 9: The linear isotherm model was determined by the relationship between the initial concentration C_i and the capacity Q of MIP and NIP

3.6 Performances of MIP-SPµE

The cartridge capacity, recovery rate, and MIP-SPµE performance were verified under optimum conditions. The MIP cartridge was able to adsorb 6.5247 µmol/g of CIP, with a recovery rate of 100.62%. NIP was also tested as mentioned above to confirm whether the cartridge captured CIP due to non-specific adsorption. Figure 9 shows that the MIP cartridge showed a high retention rate of CIP, while the NIP cartridge showed a very poor retention when compared to MIP. These results suggest that the recognition of a specific molecule enabled the developed MIP-SPµE cartridge to capture CIP.

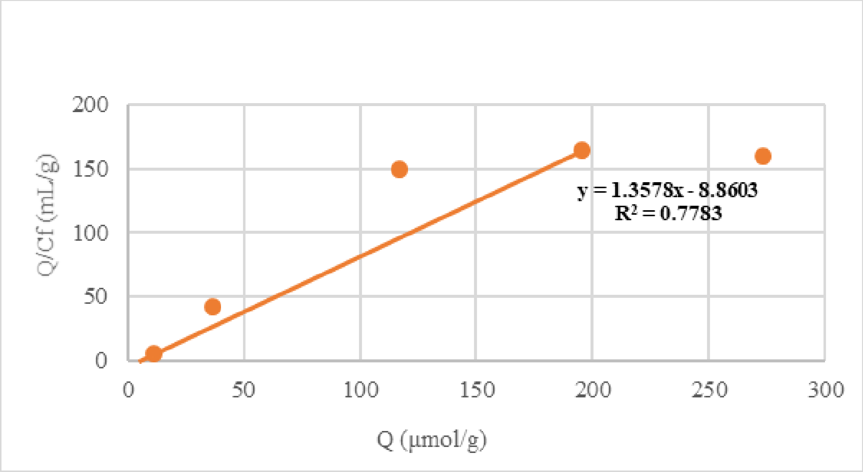

Figure 10: Plot showing the relation between Q (µmol/g) and Q/C_f (mL/g) for CIP-MIP

MIP illustrated a greater affinity for CIP than NIP, suggesting that specific binding to a small number of binding sites within the polymer network, as opposed to non-specific adsorption, was the cause of the binding of CIP to MIP. The findings indicate that MIP had a maximum adsorption capacity that was approximately 2 times more than NIP and that MIP had a much greater number of recognition sites and CIP bound to their surface. Static equilibrium adsorption was used to illustrate the binding characteristics of MIP to CIP, and linear heat equation models were fitted to the equilibrium data. Figure 9. Its plot demonstrates

how the binding capacity rises with increasing drug concentration. The linear figure, which shows homogeneous binding sides between the template and monomer, demonstrates one kind of isotherm adsorption. In Figure 10 of Q/C_f against Q, there is only one line that displays a greater affinity binding site. The values of Kd and Q_{max} are, respectively: -0.7364 and 6.5247 µmol/g.
From slope equation:

$$\mathbf{Slope = -1/Kd} \qquad \text{……} \ \mathbf{(3)}$$

Kd = -1/1.3578 = -0.7364

$$\mathbf{Intercept = Q_{max}/\ Kd} \qquad \text{……} \ \mathbf{(4)}$$

Intercept = -8.8603
Q_{max} = -8.8603 * -0.7364 = 6.5247 µmol/g
for MIP by using (0.05 g)

Table 4: Estimation of the precision, recovery and capacity of the Ciprofloxacin standard

Drug	CIP Taken µmol/mL	CIP Found µmol/mL	Retained conc.%	Vol. (mL)	Q	RSD%	REC%
Ciprofloxacin standard MIP	30	29.1	92.15	0.2	107.92	0.01	100.62

3.7 Procedures for the preparation and estimation of ciprofloxacin in commercial pharmaceuticals

The contents of ten tablets from each commercial product were individually weighed and ground into a fine powder. A precisely measured part of the powder was thereafter moved to 50 ml calibrated vials, where it was dissolved in 5 ml of ethanol (30 µmol/mL), diluted with ethanol to volume, vigorously shaken for 10 minutes, and the mixtures were filtered through a membrane filter with a pore size of 10 µm. Commercial CIP solutions were prepared in this manner, the phase extraction method was effectively used to evaluate CIP in pharmaceutical preparations. The test was performed three times to determine the concentration of ciprofloxacin in ethanol (30 µmol/mL) to evaluate the accuracy of the method. A statistical comparison was made between the reference UV method and the results obtained (Table 6). The absorbance of the extracted drug was measured at a wavelength of 278 nm.

Table 5: Estimation of the precision, recovery and capacity of the pharmaceutical samples

Company	CIP Taken µmol/mL	CIP Found µmol/mL	Retained conc.%	Vol. (mL)	Q	RSD%	REC %
Cipropharm (Jordan)	30	27.4	86.16	0.2	109.04	0.02	91.28
Ciprofloxacin(Berkhamsted,U)	30	28.8	89.50	0.2	108.48	0.01	95.88
Cipro-Denk(Germany)	30	29.0	91.57	0.2	108.40	0.01	96.57

Table 6: Comparative data of the proposed method with previous studies for the determination of ciprofloxacin

Sample	Extraction method	Detection method	Linear range ($\mu g\ L^{-1}$)	LOD ($\mu g\ L^{-1}$)	LOQ ($\mu g\ L^{-1}$)	RSD %	Ref.
Pharmaceutical	SPE	Spectrophotometry	50-300	12	36	1.11	[26]
Pharmaceutical	-	Spectrophotometry	2000-10000	400	1200	1.86	[27]
Seawater, human plasma and tablet	MIP PT-SPµE	Spectrophotometry	5-150	1.5	4.5	7.0	[28]
pharmaceutical	MIP	Potentiometric	1325-662600	106	318	1.1	[29]
pharmaceutical	MIP -SPµE	Spectrophotometry	1.65 - 23.19	0.21	0.62	0.01	proposed method

Conclusion

This study employed the synthesis of a new MIP for CIP-based solid-phase micro extraction of several pharmaceutical dosage forms. The suggested approach showed excellent analyte extraction capacity and selectivity. According to experimental data, the technique shows minimal consumption of organic solvent, good extraction efficiency, and linearity across a broad range of concentration. Time, energy, and chemicals are saved because the procedure is sensitive, straightforward, and repeatable, producing a high number of parameters from a comparatively small number of tests. In this method, the drug was concentrated by using the preparation (MIP) which uses (SPE) and thus through this the method has lower LOD, it led to an increase in the sensitivity of the method in addition to its being an easy and inexpensive method and this (MIP) can be used several times after the removal process (MIP).

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