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Design Molecular Imprinting Polymer Coupled with Spectrophotometric Detection for the Determination of Tramadol Hydrochloride in Pure and Pharmaceutical Formulations

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ABSTRACT

This research describes a new method for estimating tramadol hydrochloride in pharmaceutical formulations using Molecularly Imprinted Solid-Phase Extraction (MISPE) as a sample extraction technique. Acrylamide was used as the functional monomer, trimethylolpropane Trimethacrylate as the cross-linker, and tramadol hydrochloride as the template molecule to make Molecularly Imprinted Polymer (MIP). The new molecularly imprinted polymer was characterized using UV-Vis spectroscopy, Fourier transform infrared spectroscopy, and a scanning electron microscope. The adsorption isotherm of the prepared polymer was determined under the optimum conditions using spectrophotometry at a wavelength of 272 nm. The method's linear dynamic range was found to be 5–140 µg/mL, and the limits of detection (LOD) and quantification (LOQ) were 0.62 and 1.87 µg/mL, respectively. Relative Standard Deviation (RSD%) was less than 2% five times in intra-day and inter-day. This method was successfully utilized to determine tramadol hydrochloride in pharmaceutical formulations with recoveries in the 93.04–104.3% range.

Keywords: Tramadol hydrochloride, Molecular imprinted polymer, Solid-phase extraction, Acrylamide, and Trimethylolpropane Trimethacrylate.

1. INTRODUCTION

Trans-(±)-2-[(dimethylamino)methyl]-1-(hydroxyphenyl) -Cyclohexanol hydrochloride (TMH) is the format of tramadol hydrochloride. THM is a synthetic analgesic (see **Fig. 1**). Tramadol's analgesic effect seems to stem from its binding to the opioid receptors in the brain, akin to morphine, which inhibits the reuptake of norepinephrine and serotonin **(Al Samarrai et al., 2019)**. TMH is an effective and well-tolerated medication that treats chronic pain of malignant or nonmalignant origin, particularly neuropathic pain, as well as pain from trauma, biliary colic or renal, and labor **(Yoon et al., 2023)**. Since 1977, it has been the world's

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most widely distributed opioid analgesic medication used to treat severe physicalpain. In addition to its analgesic and anti-hyperalgesic properties, tramadol plays antidepressantanxiolytic and anti-shivering functions in pain management **(Barakat, 2019)**. Ortho-McNeil Pharmaceutical (OMP) markets Ultram® in the United State **(Subedi et al., 2019)**.

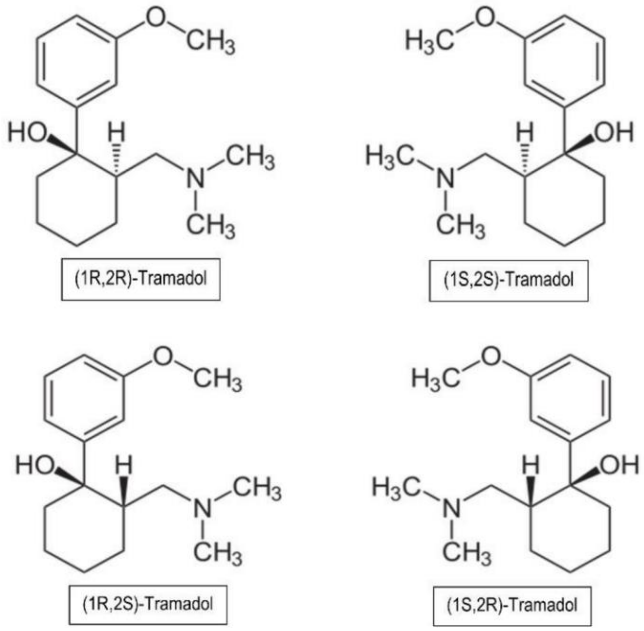


Figure 1. Isomers of Tramadol HCl

Due to its widespread use, numerous techniques have been developed to determine TMH in pharmaceutical products, including High-Performance Liquid Chromatography **(Pereira et al., 2021; Hemant et al., 2019)**, Thin-Layer Chromatography Densitometry **(Naveen et al., 2020; Kumar et al., 2020)**, Capillary Isotachophoresis **(Sarkany et al., 2019)**, Ion-Selective Electrode-Based Potentiometry **(Pourhakkak et al., 2022; Isildak and Özbek, 2021; Al-Safi and Al-Bayati, 2018)**, adsorptive stripping voltammetry**(Saichanapan et al., 2021; Pallavi et al., 2023)**, square-wave voltammetry **(Jahromi et al., 2020)**, UV spectrophotometry **(Akula et al., 2021; Nakhla et al., 2021)** and flow injection Chemiluminescence Spectrophotometer **(Al Samarrai et al., 2019)**.

The aforementioned approaches lack ease of use, affordability, and simplicity. An essential step in analyzing compounds found in real samples is preparing the sample. Traditional sorbents are typically inefficient at separating analytes in complex biological or natural samples due to their low selectivity. Solid-phase extraction (SPE) is the most widely used clean-up technique because it is affordable, easy to use, simple, and time-saving. Nowadays SPE is the most widely used sample pretreatment approach. Molecularly imprinted polymers (MIPs) have emerged as a relatively new development in the field of SPE for sample clearing up **(Khatibi et al., 2021; Hadi and Al-Bayati, 2022)**. Halfa century ago **(Parisi et al., 2020)**, first described the effective technique of molecular imprinting to add particular recognition sites to a matrix of polymers. Modern molecularly imprinted polymer (MIP) technology is based on providing high affinity binding sites for a variety of molecules, including organic, inorganic, and even biological molecules or ions **(Al-Bayati, 2018)**. Additionally, it utilizes materials with high selectivity toward analytical molecules, which are formed at specific sites of recognition within the polymer matrix through analytical presence synthesis as a particle printing method. Employing the

copolymerization of a monomer in the presence of a template molecule can produce a cross-linked synthetic polymer. Washing removes both the polymer and the template, leaving behind specific locations that serve as recognition sites. The shape, size, and chemical functionality of these sites and the template molecules complement one another. The MIP demonstrates selective rebinding with the template and its derivatives **(Toudeshki et al., 2019)**.

The objective of this study is to design a new molecular imprinting polymer that serves as a selective sorbent for the solid-phase extraction of tramadol hydrochloride, subsequently enabling its detection through spectrophotometry. The spectrophotometric technique was effectively combined with the designed MIP to extract and detect tramadol hydrochloride in pharmaceutical formulation samples. To analyze the performance of the proposed controller, a comparison with previous studies is made.

3. EXPERIMENTAL Work

3.1 Materials and Chemicals

Tramadol hydrochloride (TMH) standard was supplied from (KIMADIA,IRAQ). Tramadol hydrochloride ampoules: 50 µg/2mL (Gland Pharma Limited, India), and 100 µg/2mL (Telangana. Hemopharm A.D., Serbia), both from Hospital Madain. Acrylamide (AA) as a monomer (≥99%), trimethylolpropane trimethacrylate (TPT) as a cross-linker (95%), and benzoyl peroxide (BP) as the initiator from (Sigma Aldrich, America). Methanol (≥99.8%) from (CHEM-LAB ,Belgium.), and acetic acid (>98%) from (Fluka ,Germany) as solvents .

3.2 Instruments and Tools

- Fourier-transform infrared spectrophotometer (FTIR) and UV-VIS spectrophotometer with a1 cm quartz cell from Shimadzu 1800PC, Japan
- Scanning Electron Microscopy (SEM) JMS-6390A from Tokyo, Japan
- Sensitive balance (±0.0001 g) from ACS120-4, Kern & Sohn GmbH, Germany
- Heater/stirrer hot plate
- Centrifuge
- Water bath
- Shaker - Maxi Mix Plus from Thermolyne Vortex mixer
- Sieve (250 µm), Germany
- Nitrogen gas system from Arab Gulf Factory, Baghdad
- Micropipette (1000 µL) from Dragon MED, China
- Soxhlet apparatus from SONERX, Germany

3.3 Preparation of Stock Solutions

Accurately weighed, 0.1 g of pure tramadol hydrochloride was dissolved in and diluted to mark in a 100 mL of standard flask with methanol (the final concentration of TMH was 1000 µg/mL) and used to prepare a series of solutions with different concentrations

3.4 Preparation of MIP

To prepare the tramadol hydrochloride molecular imprinted polymer (TMH-MIP), (0.682 mmol, 0.179 g) of tramadol HCl was combined with (4.999 mmol, 0.471 g) of acrylamide as the monomer and (12.50 mmol, 4.230 g) of trimethylolpropane trimethacrylate was added to the solution as a cross-linker, followed by 0.07 g of benzoyl peroxide as an initiator. Each of these

materials was then dissolved in 5 mL of methanol. The solution was then stirred for 5 minutes with a vortex mixer to obtain a homogeneous solution. After that, the nitrogen gas (N_2) was passed through the solution for 20 minutes to eliminate the oxygen, and the solution was placed in a 70°C ,water bath. After the reaction was completed, the molecularly imprinted polymer was solidified and it was then dried, crushed into fine particles, and sieved to 250 µm. Finally, the template was removed by using a Soxhlet with a mixture of solvent of methanol and acetic acid with a ratio of 9:1. The extraction continued until the tramadol hydrochloride was not detected spectrophotometrically at 272 nm

3.5 Preparation Process of MISPE Cartridge

In order to prepare the MISPE cartridge, 0.05 g of imprinted polymer was weighed and packed into a 3 mL empty polypropylene SPE cartridge with organic frit at the top and bottom to avoid the leakage of MIP. The polymer was conditioned with 5 ml methanol. After that, different concentrations of the standard solution of 1 ml volume were added at a flow rate of 7 rpm on the MIP-SPE cartridge. Following that, the absorbance of the resulting solutions is measured by a UV-VIS spectrophotometer

3.6 Rebinding Experiments

Column adsorption experiments were utilized to evaluate the binding affinity of the imprinted polymer, as previously reported. The overall procedure for tramadol HCl adsorption by the MIP was as follows: 0.05 g of polymer particles were packed into a 3 ml .cartridge, and tramadol HCl solutions of varying concentrations (5–140 µg/ml) were added After passing through the SPE column, the solution was collected using a peristaltic pump at 7 rpm. The unbound concentration of tramadol HCl after adsorption was measured using a UV-VIS spectrophotometer at 272 nm .

3.7 Pharmaceutical Sample Analysis

Two ampules of tramadol HCl with concentrations of (50 µg/2 mL) and (100 µg/2 mL) (Gland Pharma Limited, India and Hemopharm A.D., Serbia, respectively) were gated and stored at 20°C. A stock solution of 1000 µg/mL was prepared, and series concentrations of 20, 60, and 100 µg/mL were prepared by diluting the stock solution with methanol using a 25 mL volumetric flask.

4. RESULTS AND DISCUSSIONS

4.1 UV- visible Spectroscopy Analysis

UV-visible spectroscopy is a quick analytical method for finding out the absorbance **(Passos and Saraiva, 2019)** . The absorbance of the TMH and TMH-MIP was taken before and after extraction;this is shown in **Fig .2 .** Before extraction, UV absorption spectra of tramadol HCl and ;tramadol MIP in methanol medium revealed a single, clearly defined maximum peak at 272 nm .this peak disappears once the drug is extracted

↓

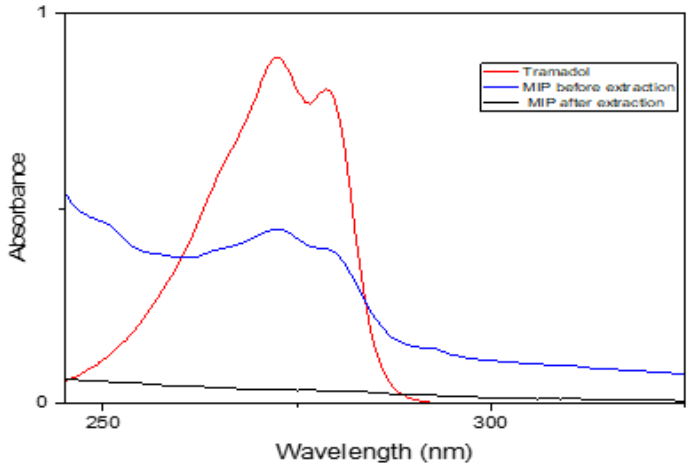
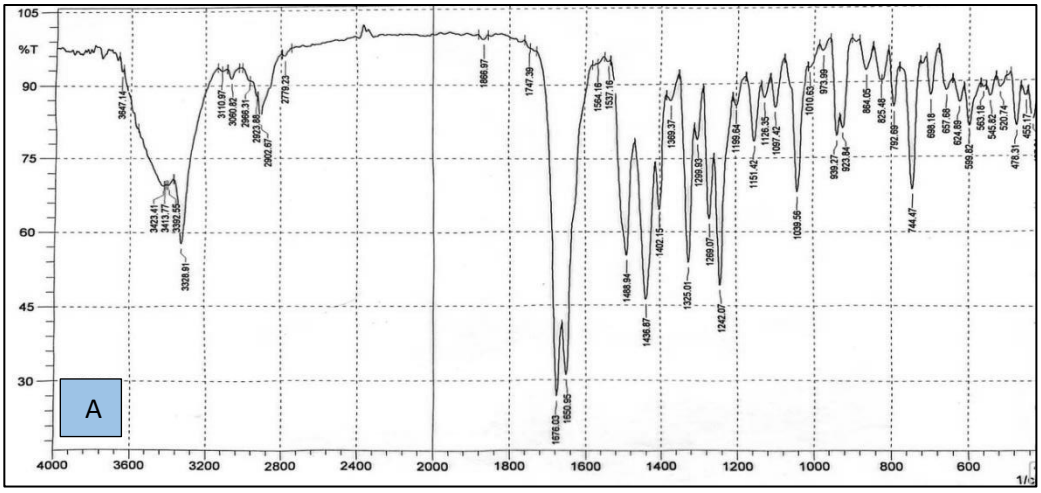


Figure 2. UV spectrum of tramadol HCl standard and tramadol MIP before and after extraction at 272 nm

4.2 Fourier Transmission Infrared (FTIR) Analysis

FT-IR spectroscopy was employed to characterize the functional groups in TMH and MIP within the 400-4000 cm^{-1} range. The FTIR pattern for the template (TMH) and MIP was recorded in **Fig. 3**. The template pattern exhibits intensity bands at 3326 and 2968 cm^{-1}, corresponding to the hydroxyl groups and (CH-aliphatic) groups in the template, and at 3060 cm^{-1}, associated with the aromatic ring in the drug structure. A pronounced increase at 1571 cm^{-1} corresponds to C = C. A weak peak at 1151 cm^{-1} is attributed to the C=O bond. A comparable peak for TMH-MIP, with small shifts at 3112, 3112, 2960, 3068, and 1584 cm^{-1}, is ascribed to TMH molecules, while these peaks disappear and shift to 2975 cm^{-1} for CH-aliphatic after the template is removed. The peaks at 3444 and 1730 cm^{-1} correspond to amine and C=O ester groups in the cross-linker (**Table 1**). These results indicate that the polymerization process was satisfactory



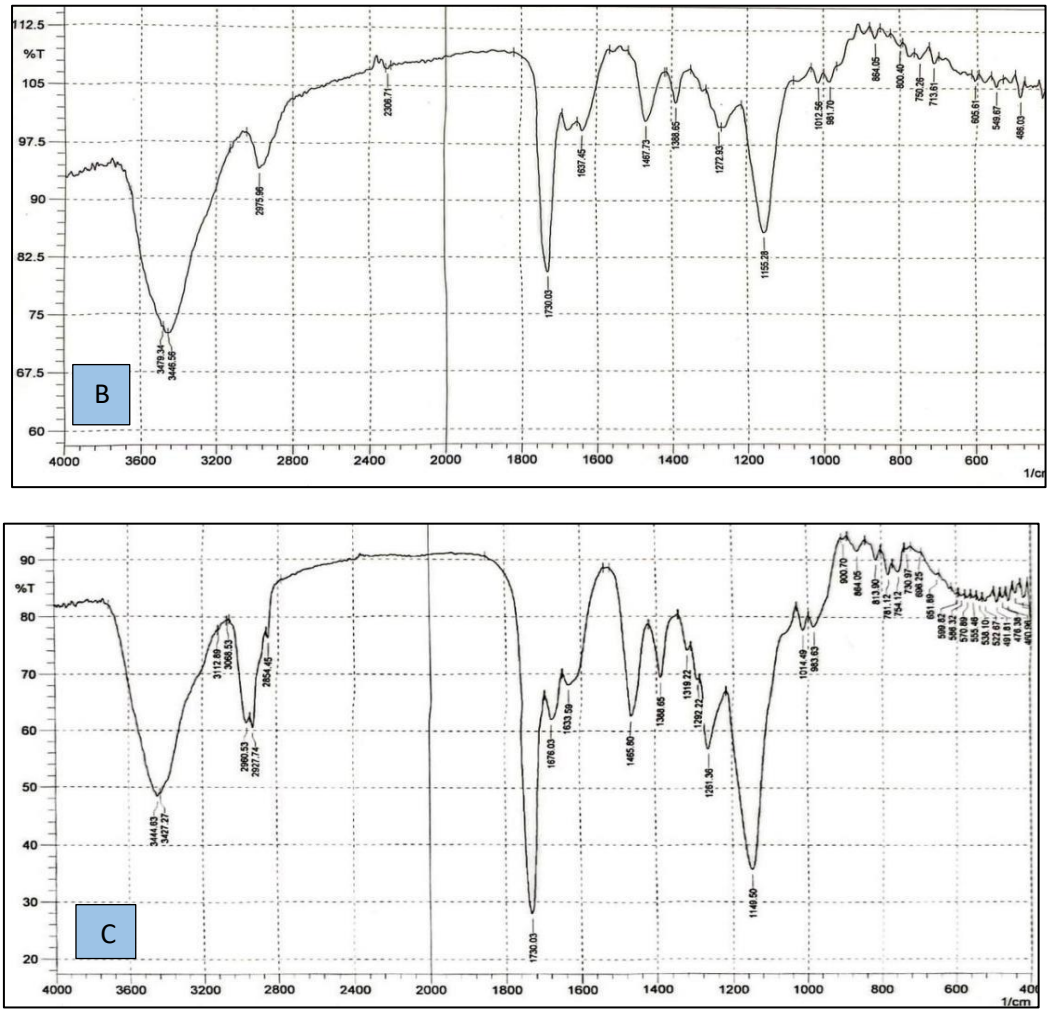


Figure3. FT-IR of the (A) Tramadol Hydrochloride (TMH) Standard **(Mali et al., 2017)** and .(B,C) TMH-MIP before and after extraction of templet, respectively

Table 1. The most identified FT-IR spectra peaks for the TMH-imprinted polymer

No.	Functional Group	TMH standard	TMH-MIP before template removal	TMH-MIP After template removal
1	-OH str.(cm^{-1})	3326	3112	\
2	-CH aromatic	3060	3068	\
3	-CH-aliphatic.(cm^{-1})	2968,2904	2960,2921	2975
4	C=C str. (cm^{-1})	1571	1584	\
5	C-O str.(cm^{-1})	1242,1151	1149	1155
6	O-C=O str.ester (cm^{-1})	\	1730	1730
7	NH_2- str.(cm^{-1})	\	3444,3427	3479,3446
8	H-C=C str.(cm^{-1})	\	1633	1637

4.3 Scanning Electron Microscope Analysis (SEM)

The SEM can be used to determine the size, geometry, and distribution of pore surfaces in membranes **(Hao et al., 2020, Hussein and Al-Bayati, 2021)** and analyze the surface and

topography of TMH-MIP .SEM analysis shows that the molecularly imprinted polymer had an extremely regular and ordered pore structure on the surface and in cross-section **(Aljabari and Al-Bayati, 2021)** which served as interaction sites. Several papers have , shown that a molecularly imprinted membrane of this type recognizes and transports the template molecule effectively and efficiently due to the type and quality of the porous structures **(Rydz et al., 2019)** The morphology of MIP is shown in **Fig. 4** both before and after extraction, as demonstrated by SEM. It can be seen that microemulsion polymerization .produces very small particles (133.50–327.50 µm) for this MIP

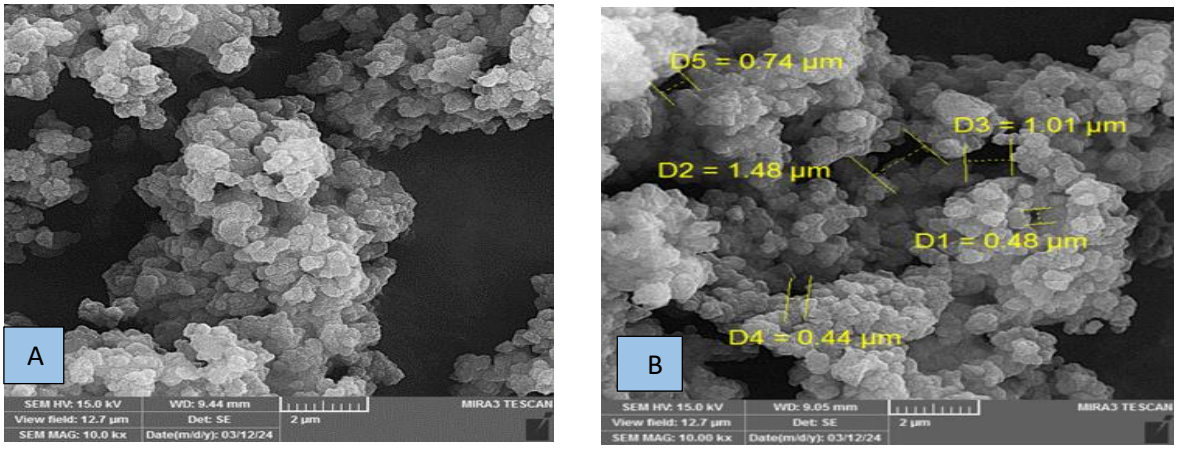


Figure 4. The SEM images of tramadol HCl MIP (A)before extraction of the template (B) after extraction of the template

4.4. Optimization of the MIP-SPE Method

A multivariate screening approach was applied to obtain efficient extraction of tramadol from MIP . Two factors were looked at in order to determine the variables and the ways in which they interact that have a significant effect. The variables were (1) mass of MIP (g) used in the MISPE cartridges and (2) flow rate. The specifics of the experimental design are displayed in **Fig. 5.** At the weight of the MIP (0.05 g) and flow rate (7 rpm), the best amount of TMH was retained.

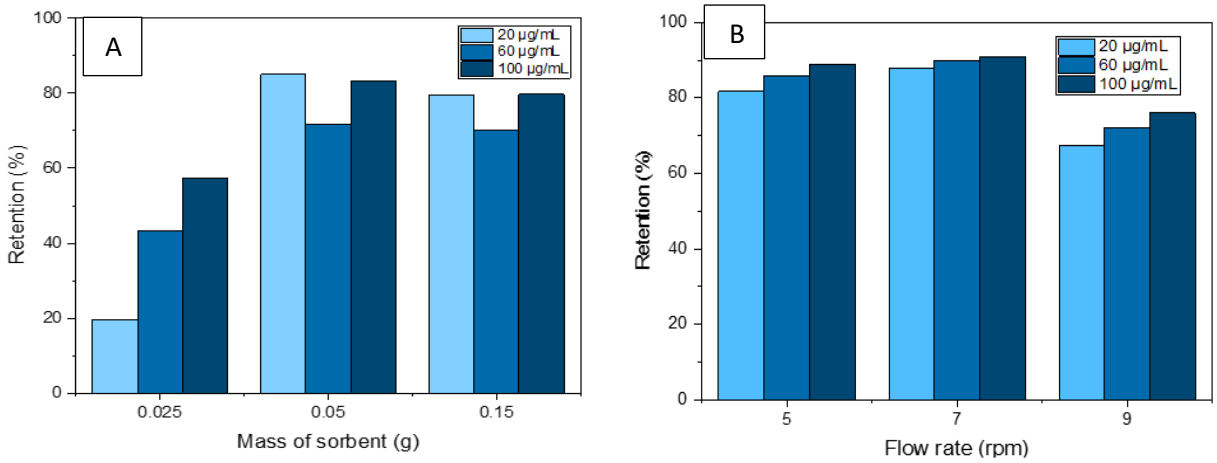


Figure 5. (A) Effect of sorbent mass. (B) Effect of flow rate

4.5 Adsorption Capacity

Isotherm adsorption can be used to better understand the mechanism of adsorption between an adsorption template and the polymer surface. Data from the isothermal adsorption equilibrium were analyzed **(Rahman et al., 2021)** to illustrate the different types of isotherm linear models. This was ascertained by plotting the drug's bind-to-free concentration (Q), which can be calculated by applying the equation that follows:

$$\mathbf{Q} = \frac{\mathbf{C_i - C_f}}{\mathbf{M}}\ \mathbf{v} \quad (1)$$

Where V (mL) is the solution volume, M (g) is the weight of the sorbent, Q (µg/g) is the amount of analyte retained by the sorbent, and Ci (µg/mL) and Cf (µg/mL) are the initial and final concentrations of tramadol HCl in the solution, respectively **(Ndunda, 2020)**.The MIP/drug binding was computed using the equation after the binding parameter was measured.

$$\frac{Q}{C_f} = \frac{Q_{max} - Q}{K_d} \quad (2)$$

Maximum capacity (Q_{max}) and binding side dissociation constant (K_d) are defined **(Quinto et al., 2020)**. **Table 2** offers experimental data for the regrouping experiments.

Table 2. Rebinding value of TMH-MIP based on (AA) as monomer and (TPT) as cross linker

Mass of MIP* g	Ci ** µg /mL	Cf ** µg /mL	Q µg /mL	Q/Cf
0.05	5	3.689	15.720	4.260
	20	9.369	127.574	13.617
	40	9.813	301.870	30.762
	60	7.003	529.965	75.671
	80	6.969	730.312	104.798
	100	8.546	914.535	107.008
	120	8.727	890.185	102.005
	140	28.744	890.045	30.964

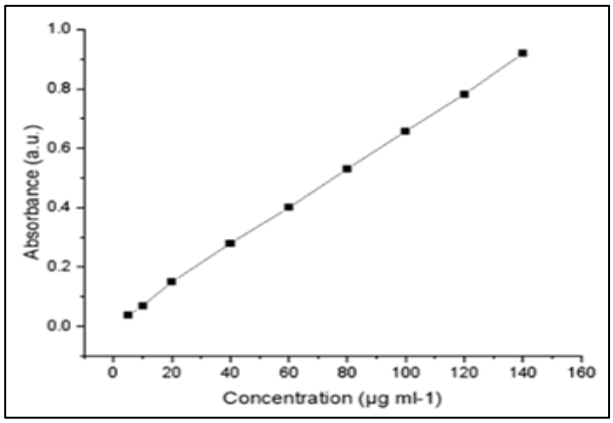
*molecular imprinted polymer, ** the initial and final concentrations

4.6. Method Validation

According to **Table 3**, the suggested approach has been verified for linearity and sensitivity, quantification and detection limits, accuracy, and precision.

4.7. Linearity of Calibration Curves

For UV determination, a range of standard tramadol hydrochloride concentrations was measured. The absorbance vs. concentration was plotted over a three-day period to create the standard calibration curves for TMH (see **Fig. 6**). A simple linear regression model (y = mx + b) with the least-squares method was used to analyze and average the data. There was good linearity in the concentration range of (5–140 µg/mL). The calibration curve mean regression equation, complete with the correlation coefficient and all data, is displayed in **Table 3.**



Conc. µg/ml	Abs.
5	0.0377
10	0.0684
20	0.149
40	0.28
60	0.4
80	0.531
100	0.658
120	0.782
140	0.92

Figure 6. Calibration curve of tramadol HCl

Table 3. The regression and sensitivity parameters.

Parameter	Value
Maximum wavelength (nm)	272
Linear Range, µg /mL	5-140
Limit of Detection (LOD), µg /mL	0.62
Limit of Quantification (LOQ), µg /mL	1.87
Intercept (a)	0.0115
Slope (b)	0.0065
Correlation Coefficient	0.9996

The International Conference on Harmonisation (ICH) guidelines were followed in the calculation of the Limits of Detection (LOD) and Quantification (LOQ) **(Gu et al., 2021)**, which were determined utilizing the subsequent formulas: LOQ = 10 S/b and LOD = 3.3 S/b, where b is the slope of the calibration plot and S is the standard deviation of the blank absorbance values.

4.8. Accuracy and Precision

Five replicated measurements for each concentration of the analyte were used to assess the precision and recovery of this method at three different concentration levels. The high repeatability and precision of the developed methods are demonstrated by the average (X), standard deviation (SD), and percentage relative standard deviation (RSD%) with good recovery between (93.04-104.3%). These values are shown in **Tables 3 and 4**.
The plot in **Fig. 7** shows that the binding capacity increases as the drug's concentration rises. One type of isotherm adsorption is indicated by the linear plot, which indicates homogeneous binding sites. There is only one line showing a higher affinity binding site in **Fig. 5** of Q/Cf against Q. Kd is (-6.596 µg/g) and Qmax is (25.699 µg/g), in that order.

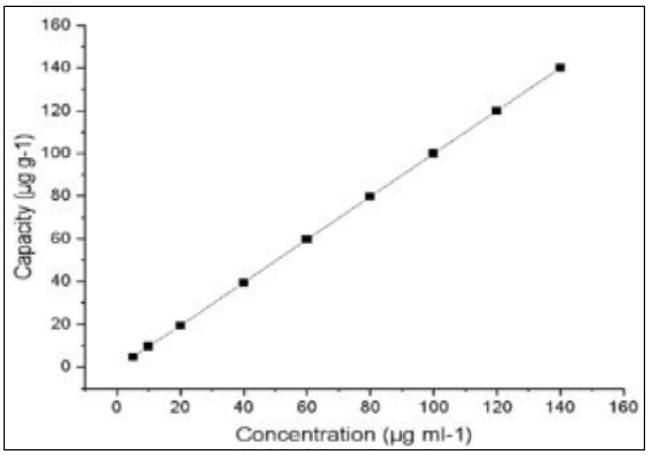


Figure 7. The linear isotherm model was determined by the relationship between the initial concentration Ci and the capacity Q.

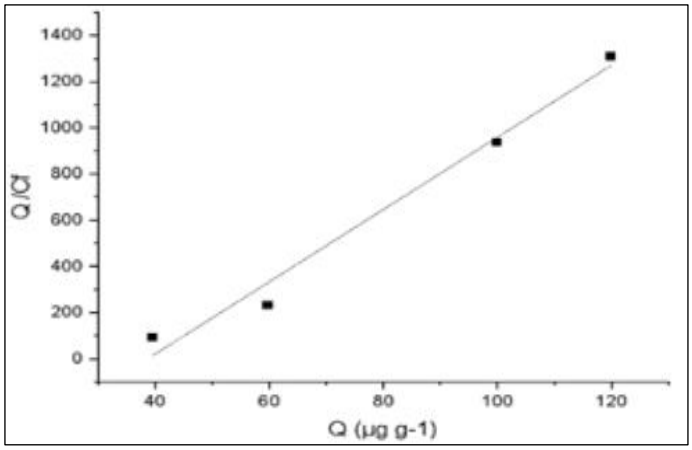


Figure 8. The relationship between Q/Cf and adsorption capacity to calculate the maximum adsorption capacity and equilibrium dissociation constant for TMH-MIP.

Table 4. Assessment of the intra- and inter-day recovery and precision of the tramadol HCl standard

TMH taken µg /mL	Intra-day (n=5)				Inter –day (n=5)			
	TMH Found µg /mL	$\bar{X}$	RSD%	REC.%	TMH Found µg /mL	$\bar{X}$	RSD%	REC.%
20	10.63	0.307	1.602	94.7	9.17	0.306	0.149	93.2
60	52.99	0.406	0.016	96.4	54.93	0.297	0.306	94.5
100	91.45	0.489	0.022	103.5	88.02	0.587	0.075	98.9

X:(mean or average),RSD%: (percentage relative standard deviation),REC%.:(percentage recovery)

4.9 Analyzing the Pharmaceutical Preparation

TMH in its ampule formulation was successfully determined using the method outlined. To evaluate the precision and accuracy of this method, five replicate determinations were made for tramadol HCl in methanol at varying concentrations (20, 60, and 100 µg/ml). A statistical comparison was conducted between the obtained results (see **Table 5**) and the reference

UV methods. The procedure involved measuring the ampoule extract absorbance in methanol at a wavelength of 272 nm. The results of the proposed method were in good agreement with the reference methods, as shown in **Table 6**. Results were compared statistically with those of the reference methods using parameters for precision and accuracy. The results indicate that the values calculated by the suggested method are near those of the reference methods. Thus, based on the results, it is a good and accurate method.

Table 5. Assessment of the intra- and inter-day recovery and precision of the tramadol HCl ampoules

company	TMH taken µg/mL	Intra–day (n=5)				Inter –day (n=5)			
		TMH Found µg /mL	$\bar{X}$	RSD%	REC.%	TMH Found µg /mL	$\bar{X}$	RSD%	REC.%
(Hemopharm A.D),Serbia	20	9.78	0.167	0.089	103.5	6.14	0.168	0.029	102.9
	60	47.15	0.267	0.176	102	25.25	0.299	0.025	95.8
	100	76.90	0.426	0.521	100.1	30.05	0.408	1.230	104.3
(Gland Pharma limited), India	20	10.55	0.409	0.004	96.1	9.61	0.433	0.105	94.8
	60	53.94	1.277	0.016	93.4	47.95	1.269	1.210	93.5
	100	93.04	95.6	0.011	1.895	90.93	1.686	0.268	93.3

X:(mean or average),RSD%: (percentage relative standard deviation),REC.%:(percentage recovery)

Table 6. Comparison of the analytical parameters between various spectroscopic methods for the determination TMH

Method	analyte	Dynamic linear range µg/mL	R^2	LOD µg/mL	LOQ µg/mL	slope	RSD%	sample	Ref.
UV spectrophotometric method	TMH	10-50	0.998	0.296	0.888	0.0068	< 2.0	Pharmaceutical dosage form	**(Lakshmi et al., 2016)**
UV-Vis Spectroscopic Method	TMH	80-120	0.9964	3.621	80.24	1.00	< 2.0	medicines	**(Borive Amani and Marini Djang'Eing' A, 2021)**
UV spectrophotometric method	TMH	30-150	0.999	0.12	0.36	0.006	<0.02	bulk and tablet dosage form	**(Sayed et al., 2014)**
UV-Vis Spectroscopic Method	TMH	5-140	0.9996	0.62	1.87	0.0065	< 2.0	Pharmaceutical formulations	This work

TMH (tramadol hydrochloride), R^2 (correlation coefficient), LOQ (limit of detection), LOQ (limit of quantification), RSD% (percentage relative standard deviation

5. CONCLUSIONS

In this investigation, a straightforward protocol was effectively created and utilized for the extraction and quantification of TMH. The enhanced spectrophotometric technique demonstrated excellent repeatability and TMH sensitivity. Additionally, the developed spectrophotometric method in conjunction with the prepared MIP has shown its efficacy in selectively adsorbing TMH in various matrices, and it offers benefits in terms of TMH separation, adsorption, and determination in pharmaceutical samples. These incredibly positive findings open the horizons to the creation of novel spectrophotometric techniques linked to MIP for the effective adsorption and identification of a number of important compounds.

Credit Authorship Contribution Statement

Both authors conceived the idea and supervised the findings of this work. H.H.A. developed the theory, investigated the topic of the article, and performed the computations. Both authors verified the analytical methods, results discussion and the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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تصميم بوليمر جزيئي مطبوع مقترنًا بالكشف الطيفي الضوئي لتحديد هيدروكلوريد الترامادول في المستحضرات النقية والصيدلانية

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الخلاصة

يصف هذا البحث طريقة جديدة لتقدير هيدروكلوريد الترامادول في المستحضرات الصيدلانية باستخدام الاستخلاص بالطور الصلب المطبوع جزيئيًا (MISPE) كتقنية لاستخراج العينة. تم استخدام الأكريلاميد كمونيمر وظيفي، وثلاثي ميثيلول بروبان تريميثاكريلات كرابط متقاطع، وهيدروكلوريد الترامادول كجزيء قالب لصنع بوليمر مطبوع جزيئيًا. (MIP) تم وصف البوليمر المطبوع جزيئيًا الجديد باستخدام مطيافية الأشعة فوق البنفسجية والمرئية، ومطيافية الأشعة تحت الحمراء بتحويل فوريه، ومجهر مسح إلكتروني. تم تحديد درجة حرارة الامتزاز للبوليمر المحضر في ظل الظروف المثلى باستخدام مطيافية ضوئية بطول موجة 272 نانومتر. وجد أن النطاق الديناميكي الخطي للطريقة يتراوح بين 5 و140 ميكروجرام/مل، وكانت حدود الكشف (LOD) والقياس الكمي 0.62 (LOQ) و1.87 ميكروجرام/مل على التوالي. كان الانحراف المعياري النسبي (RSD%) أقل من 2% لخمس مرات خلال اليوم الواحد وبين الايام. وقد تم استخدام هذه الطريقة بنجاح لتحديد هيدروكلوريد الترامادول في المستحضرات الصيدلانية مع نسبة استرداد تتراوح بين 93.04% و104.3% .

الكلمات المفتاحية: هيدروكلوريد الترامادول، بوليمر مطبوع جزيئي، استخلاص في الطور الصلب، أكريلاميد، وثلاثي ميثيلول بروبان تريميثاكريلات.