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Drug Imprinted Solid Phase Extraction of Ciprpfloxacin from Aqueous Solutions

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Abstract: During the study of antibiotics of molecularly imprinted polymers (MIPs) using non covalent molecular imprinting technique, MIPs were synthesized for the exclusion of selected antibiotics from the aqueous solutions. For this purpose, polymerization of ciprofloxacin as a template was performed using Methacrylic acid (MAA) as monomer, (EGDMA) Ethyleneglycodimethacrylate cross-linker, the (AIBN) 2,2-azobisisobutyronitrile as an initiator and toluene as porogenic solvent. The template Ciprofloxacin was removed by leaching with 0.1 M HCl. The MIP particles were characterized by Infra-red spectroscopy and (SEM) scanning electron microscopy. The adsorption parameters i.e. pH, shaking time, doze optimization, effect of temperature and concentration have been studied. The optimized dozewascalculatedtobe0.005gm.,optimizedshakingtime30min,andatpH6maximum % adsorption was observed. The D-R models, Freundlich and Langmuir were applied to study the multilayer adsorption capacity, monolayer capacity of adsorption and mechanism of the adsorption. 1st order rate constant (k) and Rd (intra particle diffusion constant) have been calculated by using kinetics models. In thermodynamic studies, ΔG & ΔS, ΔH have been calculated.

Keywords: MIP; Ciprofloxacin; optimization, Multilayer; Monolayer; Thermodynamics; Kinetics

1. INTRODUCTION

Antibiotics are possibly the most effective family of drugs so far the improvement of human health. Antibiotics are also used to prevent and treat animal and plants infections as well as for endorsing growth in animal farming (Guilfoile *et al.*, 2007, Kinrys *et al.*, 2018). Antibiotics are not only the reason of food pollution, but also inflict pressure on ecosystem security and environmental health, as a significant quantity of anti-biotic is unconfined into aquatic environments through discarding of (medical wastes animal feces, and direct feeding). The main cause of pollution is human medication, which results from waste water treatment plants, presence of antibiotics in hospital seepage, municipal waste water, and sewage discharged from waste water treatment plants (Alrumman *et al.*, 2016; Briggs *et al.*, 2003). Ciprofloxacin is the one related to Fluoroquinolone group. Its presence in our food, body parts, blood stream and in aquatic environment causes so many side effects. The main side effects of ciprofloxacin are: Skin irritation, vomiting, Nausea, Anemia, respiratory disorders, Diarrhea, Rash and its increased doze may cause tendon rupture (Kinrys *et al.*, 2018). Extraction of Ciprofloxacin drug as pollutant from aqueous solutions depends on several pretreatment steps. But the most powerful, effective and less time consuming method is the solid phase extraction. For this purpose molecularly imprinted polymer technique (MIP) is one of the unique techniques used in different fields.

In fact molecular imprinting provides binding site for the target molecule in the structure of the polymer matrix. In polymerization process target (template) is capable to interact in the presence of cross-linker with monomer and a porous polymer is obtained by removing template. The imprinting in polymer to create cavities is of two types; covalent imprinting and non-covalent imprinting; which depend on the nature of interaction between monomer and template but the most versatile and easier imprinting is non-covalent in which hydrogen bonding, electrostatic or hydrophobic interactions and Vander Waals forces takes plac (Giuseppe, 2011). In recent years use of molecularly imprinted polymers is of great interest. Apart from advantages of high affinity and traditional MIPs, these can rapidly and easily be separated with high efficiency and low cost.

In present work the drug imprinted polymer is to be synthesized by bulk polymerization process using ciprofloxacin as a template, (MMA) as a monomer and(EGDMA) as a cross linking agent. The synthesized drug imprinted polymer is used to separate ciprofloxacin from contaminated water.

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2. MATERIA AND METHODS

2.1 Reagents and Chemicals:

All chemicals and reagents were analytical grade. The drug Ciprofloxacin (Novartis, Pakistan), MAA (Methacrylic acid), EGDMA (ethylene glycol dimethyl acrylate), AIBN (2, 2- aisobisisobutyronityle) and Toluene ((Merck, Germany) were used.

METHODS

2.2 Synthesis of molecularly imprinted polymer (MIP) and Non-imprinted polymer (NIP).

The Molecularly imprinted polymer of ciprofloxacin was synthesized by freeradicalpolymerization.The0.09gm.oftemplateciprofloxacinwastakeninatesttubeadded 0.25 ml MAA monomer, 1.12 ml EGDMA as cross-linker, 1.2 ml toluene as porogenic solventthen0.2mginitiatorABIN (Azobisisobutyronitrile) was added. The above chemical were put into a test tube and sonicated in a sonicater for one hour and then the reaction mixture was subjected for purging in the nitrogen atmosphere for 10 min. In the last, the reaction mixture was placed in an oven at 70 ^{0}C for 24 hour. As shown in Table 2.1and in fig: 2.1. The non-imprinted polymer (NIP) was synthesis in the absence of template ciprofloxacin by using same method as in MIP (Tan *et al.*, 2013; Qu *et al.*, 2010).

Table 2.1 Step-Wise Synthesis of Cipro-Mip

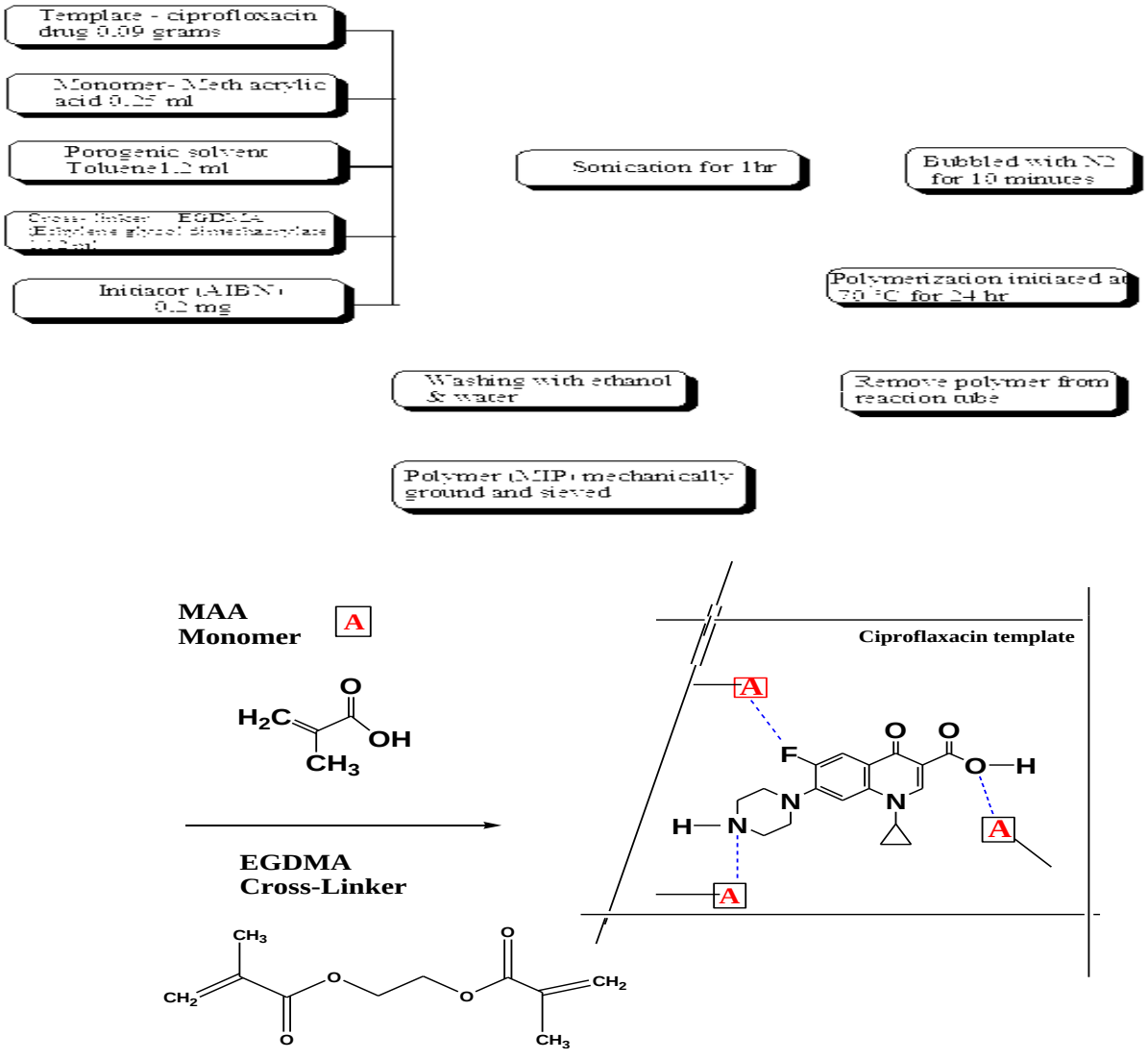
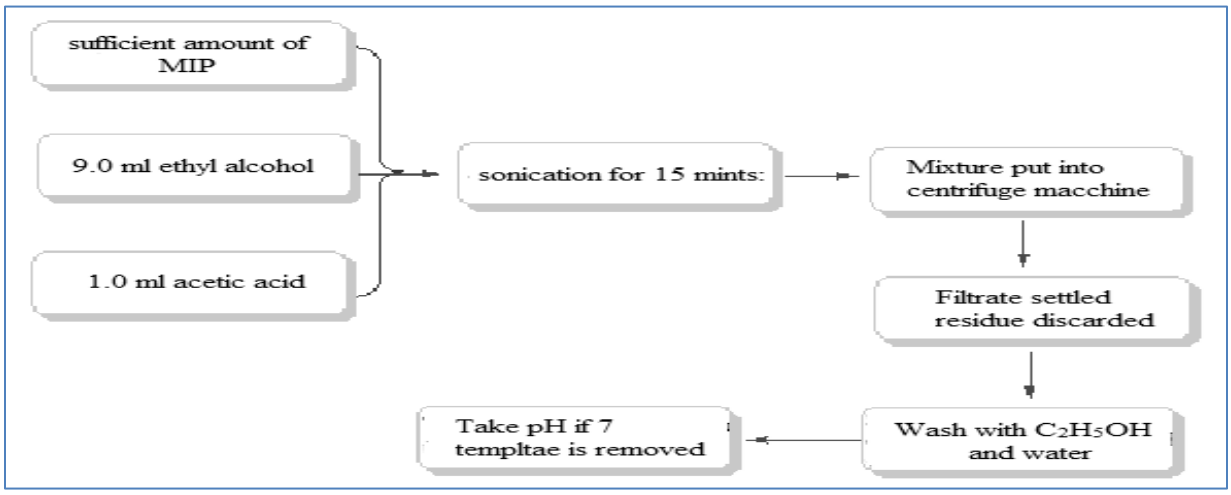


Fig. 2.1 Scheme of synthesis of molecularly imprinted polymer

2.3Extraction of template ciprofloxacin from the MIP

A sufficient amount of synthesized MIP was taken in a test tube, and then 9 ml of ethyl alcohol (C_2H_5OH) and 1ml of acetic acid (CH_3-COOH) were added in the test tube. Then the reaction mixture (MIP+ethyl alcohol +acetic acid) was subjected for sonication for15min.After sonication the reaction mixture was put in the centrifuge machine. When the filtrate is settled in the bottom of test tubetheresidue was discarded. In such a way the above process was repeated for three times. After this process the compound was washed with de-ionized water. For this purpose the MIP was carried into a filter paper kept in a funnel and rinsed/washed for several times. For the satisfaction of removal of template, either it is removed or not? The PH of rinsed water was checked. It was 7 so it was confirmed that there was no template as shown in Fig. 2.2. The mechanism of MIP synthesis and removal of template is illustrated in **(Table 2)**

Table 2.2.Removal of Template



2.4 Mechanism of Cipro-MIP.

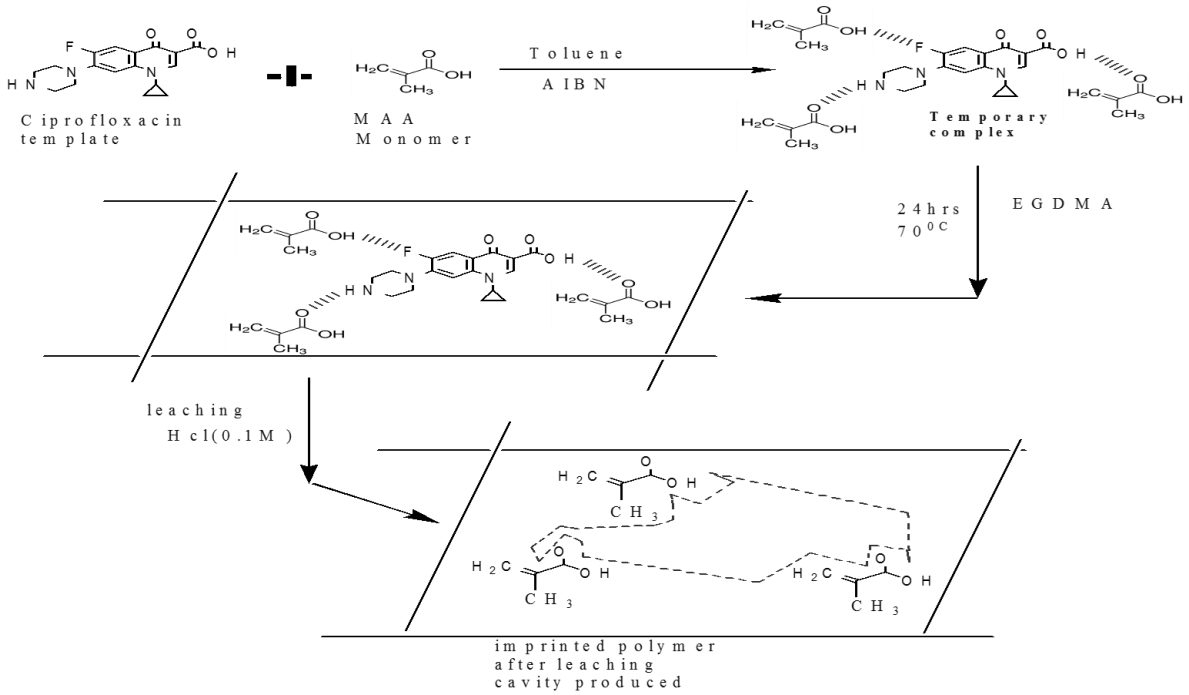


Fig. 2.2Schematic representation of synthesized imprinted polymer.

3. RESULT AND DISCUSSION

3.1 Characterization Of Cipro-Mip And Cipro-Nip

3.1.1 Fourier Transform Infrarespectroscopy (Ft-Ir) Of Cipro-Mip.

FTIR technique (Heller *et al.,* 2011) is a appropriate method to examine the types of bonds and functional groups present in MIP. Ciprofloxacin, NIP and monomer were used as an indication to verify the polymerization and interface with template that has occurred. The spectra for Ciprofloxacin, Methacrylic acid as monomer, Cipro-MIP, NIP and MAA and are represented in Fig. 5 and 6. N-H amine is a weak acid. Its peak for Cipro-MIP and MAA spectra can be observed at3425 cm^{-1} but in NIP and MAA spectra this peak (NH stretch) is absent. While in the presence of ciprofloxacin that peak occurs. The three spectra (C–H stretching at 3471 cm^{-1}), (the monomer Methacrylic acid 2355 cm^{-1}) and (Cipro- MIP and 3512 cm^{-1}) show a weak band. The two important peaks around (C=O stretching) at 1730 $cm^{-1}$and 1705 cm^{-1}supports the existence of cross-linker (EGDMA) in Cipro-MIP-MAA and NIP-MAA. This data confirms the success of Polymerization process. The following vibrational peaks in MIP appear at different wave numbers, this proves that majority of monomer units take part in polymerization process to synthesize an MIP. For NIP shown in the figure the characteristic signals are quite similar as in MIP, however there are two different points, first the intensity of MIP(3512$\mathbf{cm^{-1}}$> 3425$\mathbf{cm^{-1}}$) is higher than C-H stretching vibration peak and second the intensity –OH acid (2960 $\mathbf{cm^{-1}}$< 2991$\mathbf{cm^{-1}}$) is lower than MIP. Probably there are two reasons. One is polymerization of NIP being entirely lacking of template ciprofloxacin and other is the template ciprofloxacin is assembled with monomer Methacrylic acid by Hydrogen bonding, which is essential for monomer (MAA) and cross-linker (EGDMA)to polymerization. Consequently the stable imprinting cavities were formed by distribution of different functional groups containing –OH acid. This result confirms that ciprofloxacin MIP possess cavities as shown in Fig. 3.1

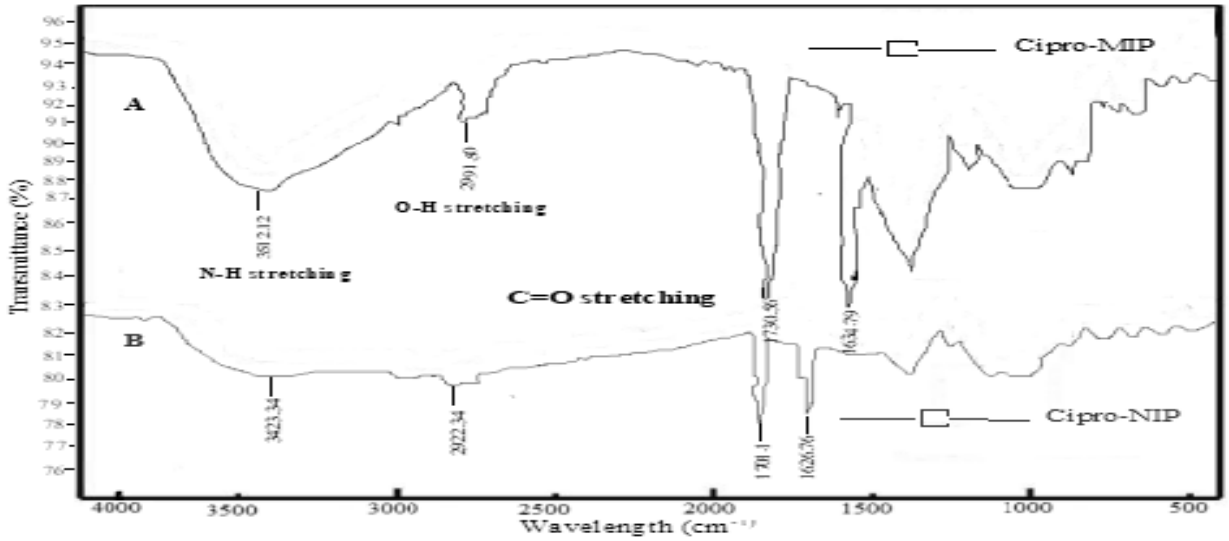
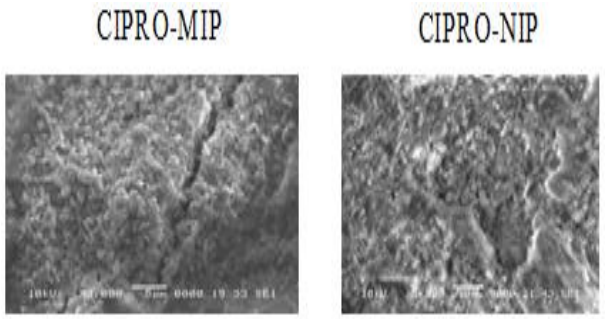


Fig. 3.1 FTIR spectrum of MIP &NIP of Cipro-MMIP

3.1.2 Scanning Electron Microscopic techniques (SEM)

The scanning electron microscope model JSM_ 6380L was used for the analysis of synthesized MIP. The learning of surface geography of solid materials is carried out by this technique. The all emitted secondary electrons are providing a nonstop image of geographical surface of material. The nonstop image of the real surface structure is virtually by electron micrograph. . The SEM instrument was operated at 10 KV to obtained framework and surface arrangement of the NIP and MIP (Bikiaris *et al.,* 2006). The SEM images of the Cipro-MIP-A and NIP-MAA under the amplification of 10KV X 1,500 10 are shown in Figure 7. The NIP- MAA particles are low porous denser and smooth while Cipro-MIP-MAA particles are globular. The NIP polymer contains no peculiar binding sites due to template ciprofloxacin therefore its morphology appears smooth .The porous and globular MIP has great adsorption capacity towards template (Ciprofloxacin) as compared to NIP, it is due to the porosity and high surface area. The high adsorption of ciprofloxacin towards MIP is actually by peculiar binding sites created by Cipro. The SEM images are shown in Fig. 3.2 a & b.



(a) (b)

Fig.3.2 SEM images (a) & (b) of MIP and NIP

3.2 Adsorption study

3.2.1 pH study of Cipro-MIP.

The effect of different pH viz: 2,4,6,8 and 10 pH helped to determine the most favorable pH of MIP towards adsorption capacity of Ciprofloxacin (Heller *et al.*, 2011). The adsorption capacity of template Ciprofloxacin by Cipro- MIP-MAA at different pH was calculated. The adsorption of Ciprofloxacin becomes high in the pH choice of 2.0–6.0 but becomes low ahead of this range. It was due to strong hydrogen bonding between amine group of ciprofloxacin and protonated Methacrylic acid. The Ciprofloxacin mainly becomes a neutral compound when pH is more than 6. The deprotonation of amino group in ciprofloxacin is responsible for weak interaction between polymer and hydrogen bonding. The adsorption capacity of Ciprofloxacin in MIP is higher than NIP as shown in Figure3.3.That's why NIP shows less adsorption capacity and MIP shows more adsorption capacity. In polymer matrix due to non- specific interaction of bonding and cavities no adsorption of Ciprofloxacin template takes place in NIP.

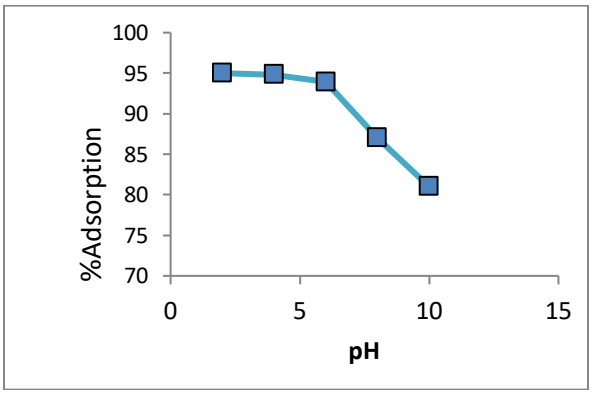


Fig: 3.3 Effect of pH on adsorption of (Cipro-MIP) using 10ml of 1.51× 10^{-5} mol.dm^{-3} ciprofloxacin at 303 K3.2.2 Dose study of Cipro-MIP.

The dose study of (Cipro-MIP-MAA) was calculated by changing the amount of adsorbents from 0.002 mg to 0.008 mg, whereas other specifications like, pH, concentration, and time were kept constant. When the MIP dose was increased, the removal percentage of ciprofloxacin also increased, as shown in Fig. 3.4. Because MIP dose provided more surface area and imprinting sites for adsorption of ciprofloxacin on the surface of MIP (Heller *et al.*, 2011).

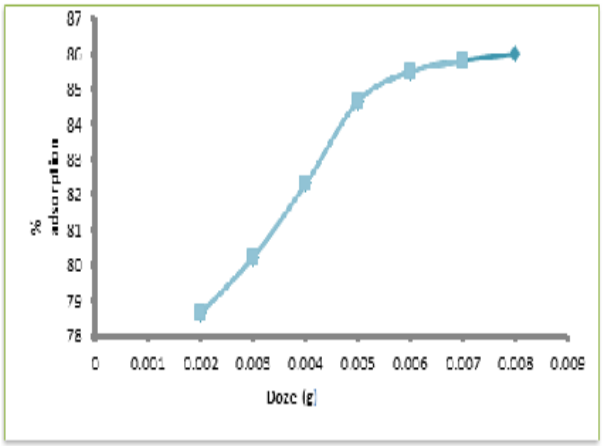


Fig. 3.4 Effect of dose on (Cipro-MIP)using 10ml of 1.51× 10^{-5} mol.dm^{-3} ciprofloxacin at 303 K and at pH 6

3.2.3 Shaking speed.

The adsorption capacity of an adsorbent can be analyzed by important parameter shaking speed. The range of shaking speed was fixed up to 25-150 rpm to study the adsorption of ciprofloxacin. It was observed that by increasing shaking speed the % adsorption increased and reached at maximum range of 88 at 70 rpm as cleared in Fig. 3.5. Therefore by using 70 rpm shaking speed maximum adsorption can be obtained.

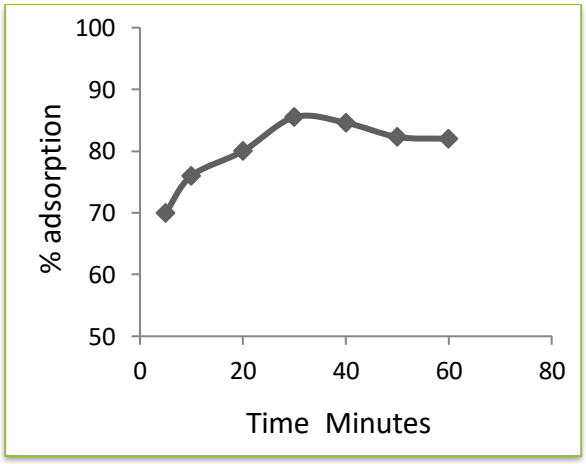


Fig: 3.5 Effect of Shaking Speed on (Cipro-MIP) using 10ml of 1.51× 10^{-5} mol.dm^{-3} ciprofloxacin at 303 K and at pH 6

3.3 Adsorption study.

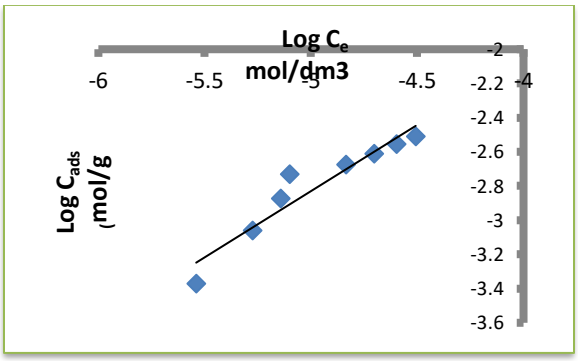
The study through graphs known as adsorption isotherm .It is represented by the graph between the surface of adsorbent and amounts of adsorbate. There aredifferenttypesofadsorptionisothermsi.e, Freundlich isotherm, Langmuir isotherm,(D-R) isotherm etc.

3.3.1 Freundlich isotherm:

Adsorption isotherm actually gives the extent of gas adsorbed on the surface of solid at lower values of pressure at constant temperature. It fails at high pressure. The Freundlich successfully explained the effect of pressure exerted on the surface of adsorbent. Freundlich isotherm shows a figuring relationship which explains exponential re-division of sites, multiplicity of surface and energies. Freundlich isotherm can be explained by the help equation as shown below (Yusof *et al.*, 2013).

$$\log C_{ads} = K_F + \frac{1}{n}\log C_e$$

In the above equation 1/n is the potency of adsorption, the amount adsorbed on urface is denoted by C_{ads}, and the concentration of adsorbate at equilibrium is represented by Ce and multilayer adsorption capacity of adsorbent is denotedby KF.(Omidietal.,2014). A plot between Log C_{ads} versus logs $C_e$shows a straight line having intercept log KF with a slope 1/n (Fig:3.6). The numerical value of 1/n is calculated to be 0.96 and adsorption capacity KF calculated is 2.09.



Fig/ 3.6 Freundlich isotherm plot for ciprofloxacin.

Table 3.1 Freundlich Parameters For ciprofloxacin adsorption

Adsorbent	Adsorbate	1/n	K_F (mmol/g)	R^2
MIP	ciprofloxacin	0.956	2.091	0.960

3.3.2 Langmuir isotherm:

Langmuir isothermis despicable on kinetic theory of gases. The assumptions on which this isotherm depends are: it is monolayer adsorption isotherm, the surface of adsorbent shows equivalency of each site and adsorption of a molecule is self-dependent of presence of another molecule on neighboring site. He also considered desorption and adsorption takes place simultaneously (Rao *et al.*, 2006). The Langmuir isotherm and its linear form can be represented by following equation.

$$\frac{C_e}{C_{ads}} = \frac{1}{K_L}b + \frac{C_e}{K_L}$$

Here constant for enthalpy of adsorption is b,the constant for adsorption capacity independent of temperature is KL,the amount of adsorbate is Cadsand equilibrium concentration is Ce.

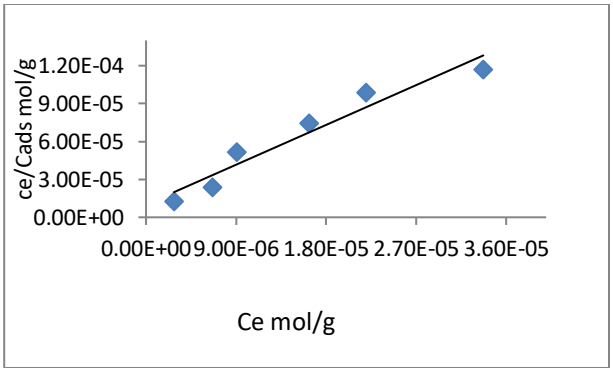


Fig. 3.7 Langmuir isotherm plot for ciprofloxacin.

Table 3.2 Langmuir parameters for Ciprofloxacin adsorption.

Adsorbate	b(dm^3/mol)	K_L(mmol/g)	R_L
CIPROFLOXACIN	285 ± 5.67	2.85 ± 0.002	0.654 – 0.0654

3.3.3 D-R adsorption isotherm:

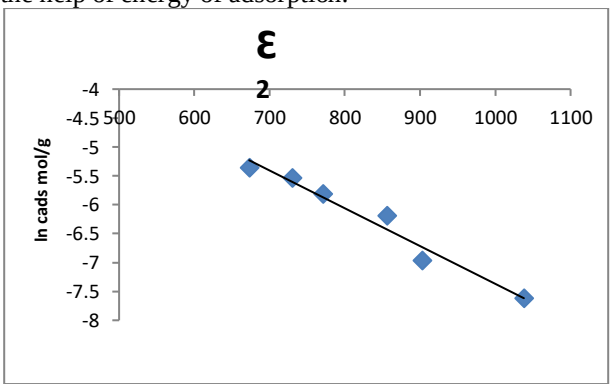
The (D-R) equation was initially put forward as an empirical variation. This basic equation numerically describes the adsorption of gases and vapors by micro porous sorbents have been derived from Polanyi theory of adsorption potential.It is more comprehensive form of isotherm than Langmuir adsorption isotherm, because it does not adopt surface identity or regular adsorption potential. The (D-R) model can be expressed in linear form of equation it is as under:

$$lnC_{ads} = \ln K_{D-R} - \beta\varepsilon$$

The (D-R) constant is KD-R .its value depends on adsorption capacity. The value of energy of adsorption E can be determined by the equation,

$$E = -\frac{1}{\sqrt{2\beta}}$$

The mechanism or type of adsorption can be guessed by the help of energy of adsorption.



Fig, 3.8 Dubinin-Radushkevich (D-R) Isotherm plot for ciprofloxacin.

Table 3.3 Dubinin-Radushkevich (D-R) parameters for Ciprofloxacin.

Adsorbent	Adsorbate	R_d (µmol.g^{-1}.min^{-1})	R^2
Mip	Ciprofloxacin	37.00	0.947

Table 3.4 Lagergren parameters for Ciprofloxacin Adsorption.

Adsorbent	Adsorbate	K_{D-R}(mmol/g)	E (kJ/mol)	R^2
MIP	ciprofloxacin	0.0065	9.132	0.965

3.4 Kinetics of adsorption.

Kinetics of adsorption demonstrates to the adsorbate-adsorbent interaction and system conditions (Rao *et al.*, 2006). It is applied in water pollution control. Two important points of energetic and kinetic adsorption process are reaction rate and mechanism. So many attempts were made to explain the energetic and kinetics for the liquid-solid adsorption system on solid surface. The following two models well explain the kinetics of adsorption.

3.4.1 Lagergren Model.

The Lagergren first order rate equation is used to calculate the order of the adsorption process. This kinetic relation depends on adsorption capacity of solid and concentration of solution. The most well-known form of Lagergren equation is:

$$\log(q_e - q_t) = \log q_e - \frac{kt}{2.303}$$

Here q_t and q_e (mg.g^{-1}) at equilibrium at time "t" are called adsorption capacities respectively. The Fig.11 is used to determine the rate constant **K** (min^{-1}) (Lagergren *et al.*, 1898).

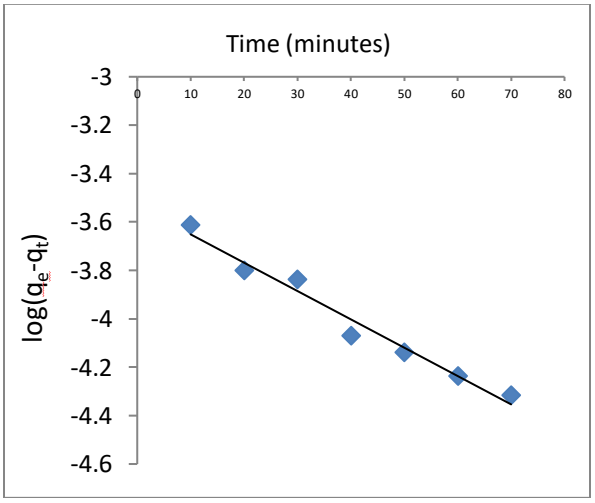


Fig. 3.9 Lagergren plot for ciprofloxacin

Table 3.5 Morris Weber Parameters for Ciprofloxacin:

Adsorbent	Adsorbate	K(min^{-1})	R^2
MIP	ciprofloxacin	0.053	0.971

3.4.2 Morris Weber Model:

The Morris Weber model or intra particle diffusion model was put forward by Morris and Weber in 1962. This model is applied to explain the competitive adsorption. In a solid-liquid system the fractional consumption of the solute on particle differs according to fraction of diffusion inside the particle. Here is r is the radius of particle. The following equation is used to calculate the value of intra particle diffusion constant.

$$q_t = Rd\sqrt{t}$$

Here concentration adsorbed in mol.g^{-1}.mint^{-1} at time t is denoted by qt. The intra-particle diffusion constant is denoted by Rd. (Lagergren *et al.*, 1898). The following figure 12 of Morris Weber plot shows a straight line appears for ciprofloxacin and value of **R_d** was calculated to be 37.00.

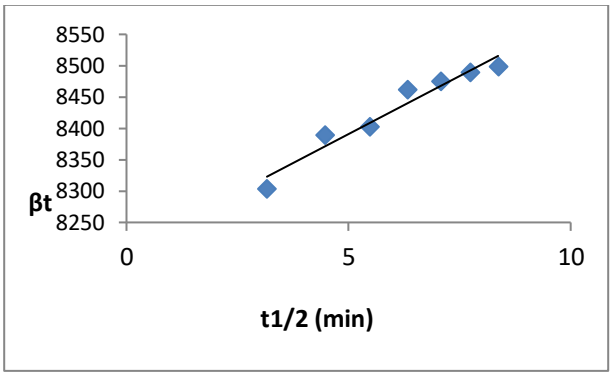


Fig. 3.10 Morris-Weber plot for ciprofloxacin adsorption.

3.5 Thermodynamics of adsorption

In the sketch of adsorption network, two types of thermodynamic characteristics are required namely the direct assessable characteristics like temperature (Balouch *et al.*, 2013) equilibrium constant and the properties which cannot be measured openly such as activation energy, and other thermal parameters (Chowdury *et al.*, 2011). These boundaries help to predict the machinery of adsorption separation process and are also for basic requirement for the description and optimization of an adsorption process (Jambulingam *et al.*, 2005).In thermodynamic following equation is used to calculate the activation parameters like ΔH, ΔS and ΔG.

$$lnKc = \frac{-\Delta H}{RT} + \frac{\Delta S}{R} \qquad Kc = \frac{F}{1-F}$$

$$F = \frac{\%\ sorption}{100} \qquad \Delta G = \Delta H - T\Delta S$$

In the above equation the Kc stands for equilibrium constant. From the value of slope and intercept of plot of ln Kc versus 1/T the value of **ΔG** (Gibb's free energy) **ΔH** and **ΔS** can be calculated.The calculated values are **ΔH = –5.3359** kJ.mol^{-1} and **ΔS = 0.0041** kJ.mol^{-1}K^{-1} using Figure 3.11 These values recommend that adsorption is exothermic and favorable in nature. The spontaneousity of the reaction is determined by the help of negative values of ΔG by varying the temperatures. The thermodynamic parameters are shown in Table 3.6&3.7

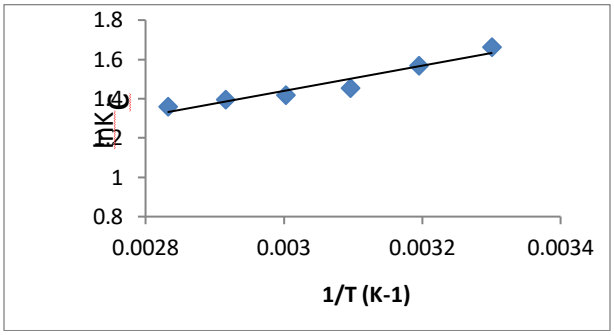


Fig. 3.11 Plot showing the effect of temperature on % adsorption of Cipro-Mip

Table 3.6 Thermodynamics parameters for Ciprofloxacin.

Adsorbent	Adsorbate	ΔH kJ.mol^{-1}	ΔS kJ.mol^{-1}.K^{-1}	R^2
MMIP	ciprofloxacin	-5.3359	-0.004032	0.932

Table 3.7 Thermodynamic values of Δ*G* for Ciprofloxacin:

Temperature (K)	303	313	323	333	343	353	363	373	383
ΔG (kJ.mol^{-1})	-211	-207	-203	-1.99	-1.95	-1.91	-1.87	-1.83	-1.79

3.6 COMPARISON WITH REPORTED METHODS:

Table 3.8 compares the adsorption capacity values calculated for the removal of Ciprofloxacin using MIP sorbent. The adsorption capacity of synthesized and modified MIP is comparable with most of the adsorbents, whereas its preparation is very simple.

Table 3.8 Comparisons of adsorption capacities of various sorbents for Ciprofloxacin;

Adsorbent	**Adsorption capacity**	**Ref:**
EU-PS @MIBA	2.13 mg g^{-1},	Li, Z *et al*., 2019
(MISPE) Jiaozhou Bay china.	2.96 mg g^{-1}	Lian, Z *et al*., 2016
MIP –H_2O for selective SPE	19.96 (mg/g)	Zhu, G., *et al.*, 2019
Multi-template SPE for FQs.	20.01 mg g^{-1}	Fan, Y., *et al.*, 2020
Micro Cipro-MIPs onto ZnS.	7.67 mg. g^{-1}	Zhang, Y., *et al*., 2012
CIPRO-MIP.	25.45 mg.g^{-1}	Present work

4. CONCLUSION

The synthesized MIPs are highly cross-linked specific in nature for binding certain targeted molecules; Therefore MIPs as sorbents can be used to remove a particular antibiotic drug like ciprofloxacin from contaminated water. The free-radical polymerization method was used to synthesize MIP for CIPRO-MIP-MAA. The categorization of MIP was carried out by FTIR and SEM techniques. The equilibrium condition was established within 70 minutes at pH 6 using 10 ml of ciprofloxacin. The (D-R) Dubinin-Radushkevich, Langmuir and Freundlich isotherms followed the adsorption data with 98% adsorption efficiency. Lagergren kinetics model suggests the pseudo first order kinetics of adsorption process with the k value of 0.053 min^{-1}. The adsorption process was exothermic (**ΔH**= -5.3359 kJ.mol^{-1}) and spontaneous in nature(**ΔG** = -211 kJ.mol^{-1}). The interaction between adsorbate and adsorbent are thermodynamically favorable (**ΔH = 0.0041** kJ.mol^{-1}K^{-1}. The kinetic study suggests that it is pseudo- first order reaction.

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