Yehya Kamal Al-Bayati /J. Pharm. Sci. & Res. Vol. 10(12), 2018, 3140-3145

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Determination of Metoclopramide based on Molecularly imprinted solid-phase used trimethoxysiane(TMS) and itaconic acid (ITC)as functional monomer

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Abstract:
A novel method characterized by high sensitivity, low cost and high stability was developed. This method based on a molecularly imprinted polymer(MIP) using a functional monomer which is trimethoxysiane(TMS) and itaconic acid (ITC), suitable cross-linker and the template which is Metoclopramide(MTPD) to fabricate a monolithic solid-phase micro extraction (SPME) fiber. A polymer was The molecularly imprinted fiber and the molecularly non-imprinted membranes were synthesized without selective binding sites this was referred to as a non-imprinted polymer (NIP). The new synthesis electrodes were successfully used for the analyte estimated in preparation pharmaceutical sample without any time consuming pretreatment steps. Monitoring of the analytes was performed using UV-vis and Scanning electron microscopy (SEM) and FTIR. The relative standard deviations (RSD%) for five Patients repeated experiments for three measurements is (2.48-3.26) %. The relative recoveries obtained for MTPD in spiked human urine samples are in the range of (94.83-98.36).

Keywords : Molecularly imprinted electrodes; Metoclopramide ; potentiometric method; (TMS) ; (ITC) monomers.

1.INTRODUCTION

Metoclopramide (MTPD) It is a drug that is mostly used for stomach and esophagus problems, figure 1. [2] It is usually used to treat and prevent nausea and vomiting, to help empty the stomach in people with delayed gastric emptying, gastroenteritis and to help with gastroesophageal reflux disease. [3] It is also used to treat migraines. [4] It is also used to treat the symptoms of gastropris.

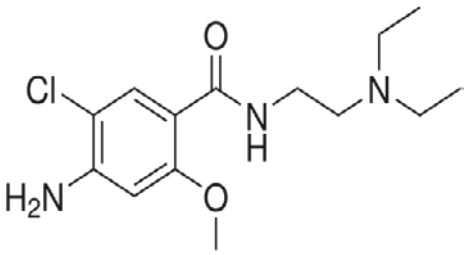


Fig. (1): Structure Metoclopramide(MTPD)

Common side effects include fatigue, diarrhea and anxiety. The most serious side effects include: Movement disorders such as delayed movement disorder, a condition called malignant syndrome of the psychosis, and depression. [5] People are rarely advised to take the drug for more than 12 weeks. [6] It is the pregnancy of category B in the US and category A in Australia, meaning that no evidence of the damage was found after many pregnant women took it. Belongs to a group of drugs known as dopamine receptor antagonists. [7]

Molecularly imprinted polymers (MIPs), generally behave as synthetic antibody snob, have been appear to be very promising candidates as highly selective adsorbents, because the advantages inherent such as reusability, physiochemical, molecular specificity, stability and applicability in harsh chemical media[8]. MIPs are mainly based on the polymerization of functional monomers in the presence of a template molecule. The template is leached out leaving behind cavities which are integral in shape, size and functionality to the template. Through the use of a common polymerization process for monomer, we can obtain cross-linked synthetic polymers, which are performed in the presence of a template molecule. Both the polymer and the mold are washed, and contain specific sites that are recognized as sites of recognition. .It was determination some drugs such as tramadol hydrochloride [9] and methamphetamine [10] based on molecularly imprinted polymer method. In this study imprinted polymer electrodes were prepared based on metoclopramide as a template in PVC matrix membrane and electrodes specification were studied.

2.EXPERIMENTAL

2-1. Chemicals

Metoclopramide standard was obtained from the State Company of Drug Industries (IRAQ-SDI –Samara) and Medical Appliances (Germany-actavis Ajanta Pharma, India). The Commercial Metoclopramide tablets obtained from local stores is 10 mg from active metrial .Trimethoxysiane(TMS) and itaconic acid (ITC), as well as metal salts were purchased from Sigma-Aldrich and were used as they were received. Pentaerythritoltriacrylate (PETRA) (99%),Trimethylpropane trimethacrylate (TMPTMA) (99%), and benzoyl peroxide (BPO) (78%) were purchased from Sigma-Aldrich. The chemicals used in the search were possesses high purity does not need to purify.

2-2. Apparatus

Potentiometric measurements were carried out with a digital voltmeter (HANA pH 211 instrument Microprocessor pH meter). pH measurements were made with a digital pH meter (wissenschaftlich-TechnischeWerkstätten GmbH WTW/pH meter in lab pH720-Germany), UV-Visible spectrophotometer double-beam model (UV-1800 PC) SHIMADZ (Japan), interfaced with computer via a SHIMADZU UV probe data system program (Version 1.10), using 1.00cm quartz cells, Infrared spectrophotometer SHIMADZU, FTIR-8000 (Japan), Scaning Electron Microscopy (SEM) [JSM-6390A] (Tokyo, Japan) and sensitive balance (Electronic balance ACS120-4 Kern &Sohn GmbH, Germany. The performance of the electrode was investigated by measuring the potential of Metoclopramide solutions at room temperature with a concentrations range from10^{-1} to 10^{-6} M. For the accuracy the potential of solutions were measured after the arrival of the internal and external solution to the equilibrium, then the potential recorded.

2-3. Synthesis of the imprinted polymer (MIP)

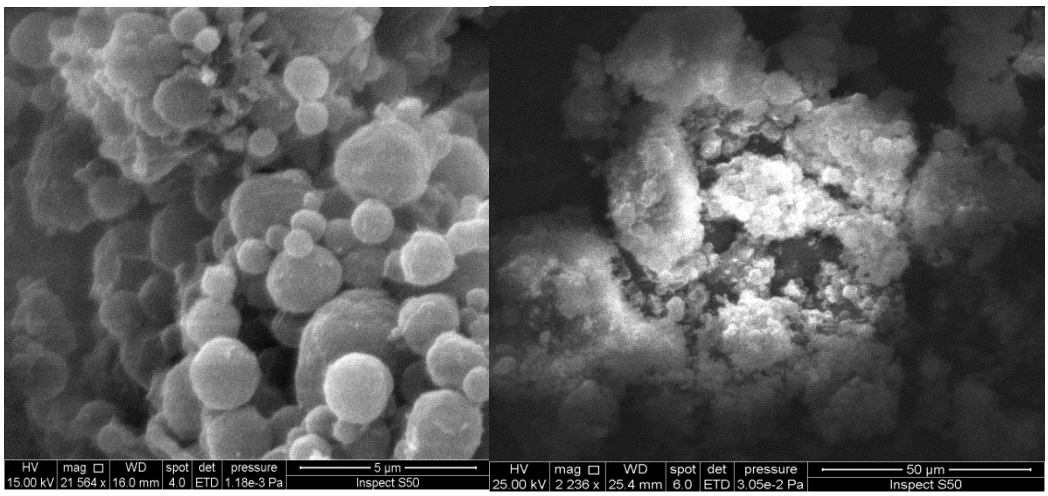
Bulk polymerization method was used for preparation of MIP. The template (MTPD) of 0.6mmol was dissolved in a thick walled glass tube (80 mL capacity) filled with 8 mL chloroform. Two monomers were used for preparation of MIP, 4 mmole of Trimethoxysiane(TMS) with 8 mmole pentaerythritoltriacrylate (PETRA) as a cross-linker, the second MIP based on 3.4mmol of itaconic acid (ITC) as a monomer with 9.99 mmole Trimethylpropane trimethacrylate (TMPTMA) as cross-linker. The initiator of 0.32 mmole BPO was used. The solution was mixed in ultrasonic water bath for a period of 25 minutes, during this time the nitrogen gas was purged the mixture. After 25

minutes seal the tube and put the tube in 55°C water bath to permit starting the reaction which continued for 72 h. The templates were removed by repeated washing the MIPs successively with 75 mL portions of acetic acid/ acetonitrile was added (1:100,v/v) solution by using soxhlet extraction. The polymer was dried at (35-45) ^{o}C for (24-48) hours, The polymers were then crushed and grounded using mortar and pestle and sieved to particles size 75 µm (using 100 mesh sieve); After the polymer was completely dried at ambient temperature, it was used as an active material in the selective sensor membrane. The non-printed polymer NIP was made at the same way but without the template drug. To prepare specific PVC membrane, high molecular weight PVC (0.18g) mixed together with the MIP (0.04g) and the plasticizer (0.42g) until the solution become homogenized, and then add THF (7-8 mL) and stirred. The solution was transferred to glass vessel based on glass board with 5cm dia. circular section to let this mixture evaporate for 24 hours. A glass tube contain a silver wire painted with silver chloride and filled with 0.1 M standard solution of Metoclopramide was connected to one end of the Tygon tube tightly while the second end of the tube was attached to 10 mm dia. circular disk of the PVC membrane by using a concentrated PVC/THF solution as a glue in purpose of producing the electrode.

2-4. Morphological Characterization

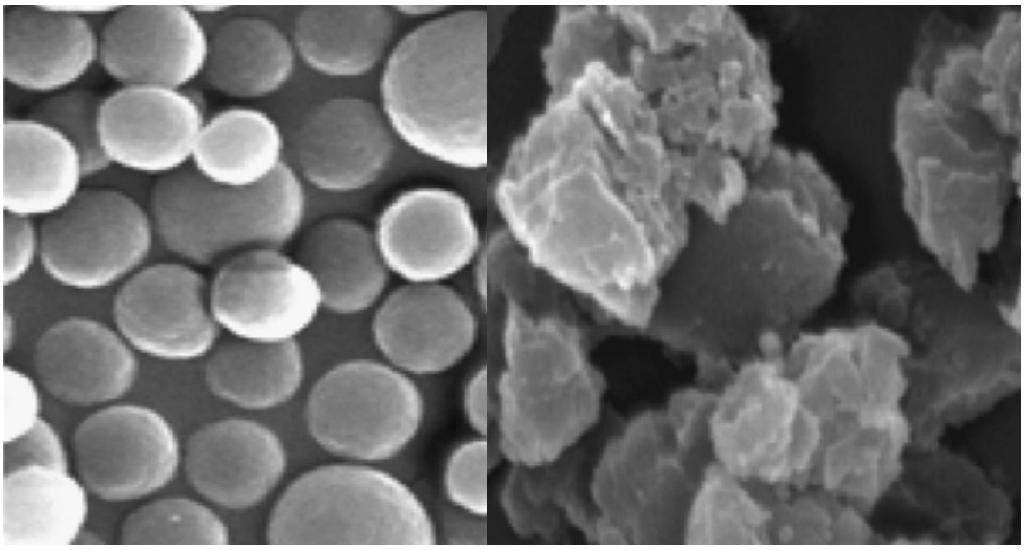
The technology of molecular imprinting allows the preparation of synthetic polymers with specific binding sites for a target molecule. Throughout the polymerization process, the target is present, thus it acts as a molecular template. Monomers that carry certain functional groups are arranged around the template through either noncovalent or covalent interactions. Following polymerization with a high degree of cross-linking, the functional groups are held in position by the polymer network. Following removal of the template by solvent extraction or chemical cleavage leaves complementary cavities to the template in shape, size, and arrangement of functional groups.

From the SEM images Figure (2 and 3) noticed that MTPD-MIP powders have been successfully hybridized into polymer membranes, while after the removal of the MTP, the printed membranes showed a smooth surface area. Morphological analysis also indicated that the MTPD –MIP (TMS) it has a more porous structure compared to a MTPD-MIP (ITC). SEM shows very small particles and spherically shaped polymeric particles with small sizes around (2.382-10.37) µm for TMS polymer and (1.62-3.25) µm for ITC polymer.



a **b**

Fig. (2): SEM photograph of the surface of MTPD-MIP(TMS) a) after washing b) before washing



a **b**

Fig. (3): SEM photograph of the surface of MTPD-MIP(ITC) a) after washing b) before washing

2-5.Preparation of Pharmaceutical Samples

Two types of tablets were used to determine the concentration of metoclopramide, 10 mg (actavis tablets) Germany and 10 mg Ajanta Pharma tablets) India were grinded (0.0599g) and dissolved in 1M (HCl) and completed in volumetric flask to (100ml).

3. RESULTS AND DISCUSSION

Several trails were performed using different ratios of (D:M:C)to find out the optimal ratio for the preparation of MIPs (MTP) . Among these trails the molar ratios (D: M: C) of (1.3:19.7:79) and (3.7:11.3:85) for MTP-MIPs has produced polymer with very suitable performance characteristics. These ratios are in consistence with some prepared MIPs found in literature. Table (1) summarize the optimum ratios used in the synthesis of MIPs and NIPs for (MTP) drug.

On the other hand, controlling NIPs and MIPs after removing the template have similar spectra indicating the similarities in the structure of the spine and prove that washing the MIP particles with 70% acetic acid solution uses the Soxhlet system is an effective method to remove the template molecule leaving specific recognition link locations in the structure Polymer.

3-1. Adsorption Isotherm

The absorption of isotherm An important characteristic is to know the size of the particles used in the separation and estimation process. The data obtained from isothermal equilibrium was analyzed to show the isochromatic type of LANGMUIR or Freundlich models [11].The binding capacity (Q) versus the free concentration of the drug is calculated according to the following equation:

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

C_i = initial drug concentration (µmol / mL)

C_f = final drug concentration (µmol / mL)

V_s = volume of solution tested (mL)

M_{MIP} = mass of dried polymer (mg)

Than measuring binding parameter

MIP/drug binding calculated by Scatchard analysis using the equation

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

Q_{max} = maximum capacity

K_d = dissociation constant at binding side.

To obtained Isotherm adsorption for different concentrations of MTPD, the synthesis particles were shaking for 2 hours in a thermal water bath at 25 ° C as given in in figure (4). Experimental data for regrouping experiments were included in Table (2).

Table(1) . The variation ratios of [D:M:C] and progeny used in the preparation of MIPs and NIPs for (MTP).

		Drug MAMP	Monomer (TMS)	Cross linker PETRA	Initiator	Solvent
IP1	%	1	16	27.28	0.686	5mLCHCOOH+5 mL $CHCl_3$
	Mmole	0.3	4.94	8.185	0.206	
IP1	%	1	4	20	0.4	5mLCHCOOH+5 mL $CHCl_3$
	mmole	0.5	2	10	0.2	
IP1	%	1.3	19.7	79	0.3	5mLCHCOOH+5 mL $CHCl_3$
	Mmole	2.00	30.00	120.00	0.32	
IP1	%	----	19.7	79	0.3	5mLCHCOOH+5 mL $CHCl_3$
	Mmole		3.00	120.00	0.32	
		Drug MBV Mmole	Monomer (ITC)	Cross linker TMPTMA	Initiator	Solvent
IP2	%	1	4	20	0.4	5mLCHCOOH+5 mL $CHCl_3$
	Mmole	0.5	2	10	0.2	
IP2	%	1	2.16	4.68	0.093	5mLCHCOOH+5 mL $CHCl_3$
	Mmole	2.133	4.61	10	0.2	
IP2	%	3.7	11.3	85	0.3	5mLCHCOOH+5 mL $CHCl_3$
	Mmole	2.00	6.00	45.00	0.32	
IP2	%	----	11.3	85	0.3	5mLCHCOOH+5 mL $CHCl_3$
	mole		6.00	45.00	0.32	

All ratio prepared in water bath at 60 C^0 .

Table (2). Rebinding values of (MTPD) using MTPD -MIP particles based on (TMS) and (ITC).

MTPD-MIP(TMS)					**MTPD-MIP(ITC)**			
Mass of MIP mg	**Ci mM**	**C_{free} mM**	**Q µMole /g**	**Q/Cfree L/g**	**Ci mM**	**C_{free} mM**	**Q µMole /g**	**Q/C_{free} L/g**
0.2	0.0100	0.0038	0.3100	81.5789	0.0100	0.0073	0.1350	18.4931
	0.0400	0.0275	0.6250	22.7272	0.0400	0.0093	1.5350	165.0537
	0.0800	0.0662	0.6900	10.4229	0.0800	0.0029	3.8550	1329.310
	0.1600	0.1537	0.7000	2.0490	0.1600	0.1500	3.9100	3.3333
0.4	0.0100	0.0045	0.1375	30.5555	0.0100	0.0063	0.0925	14.6825
	0.0400	0.0328	0.1800	5.4878	0.0400	0.0043	0.8925	207.5581
	0.0800	0.0714	0.2150	3.0112	0.0800	0.0041	1.8975	462.8048
	0.1600	0.1537	0.2300	1.0247	0.1600	0.0918	1.7050	18.5729

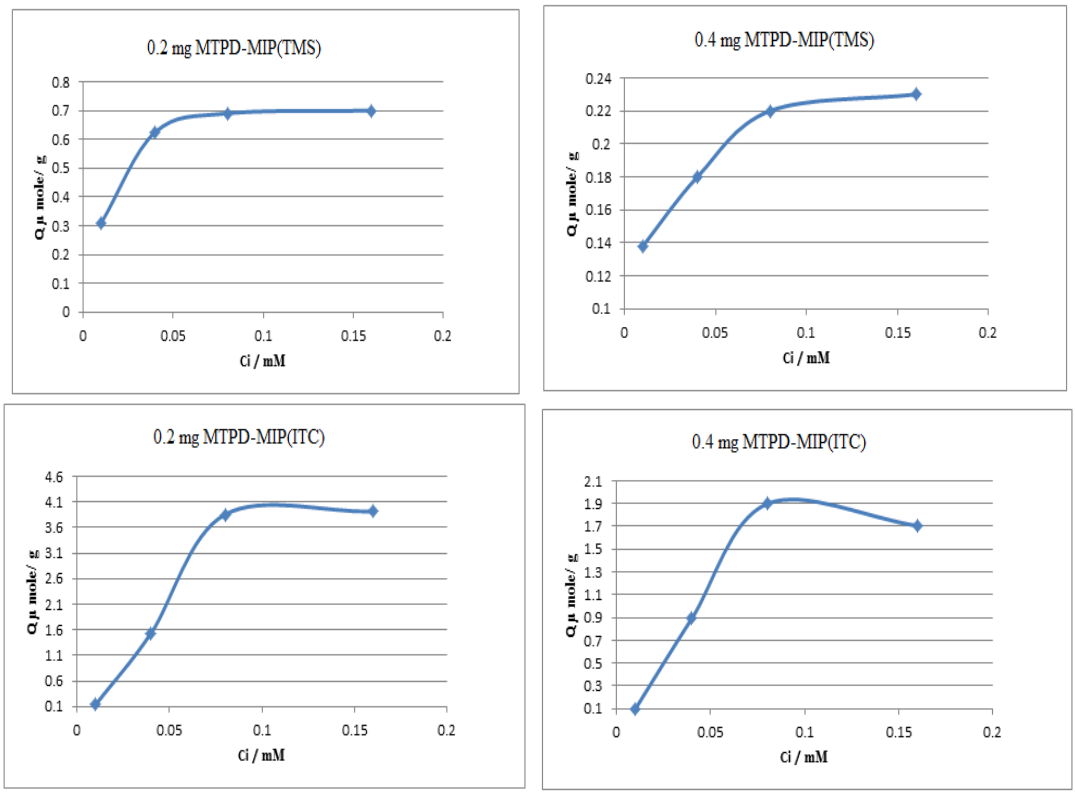


Fig. (4). Binding isotherm of TMS and ITC monomers by plotting Q/g against Ci

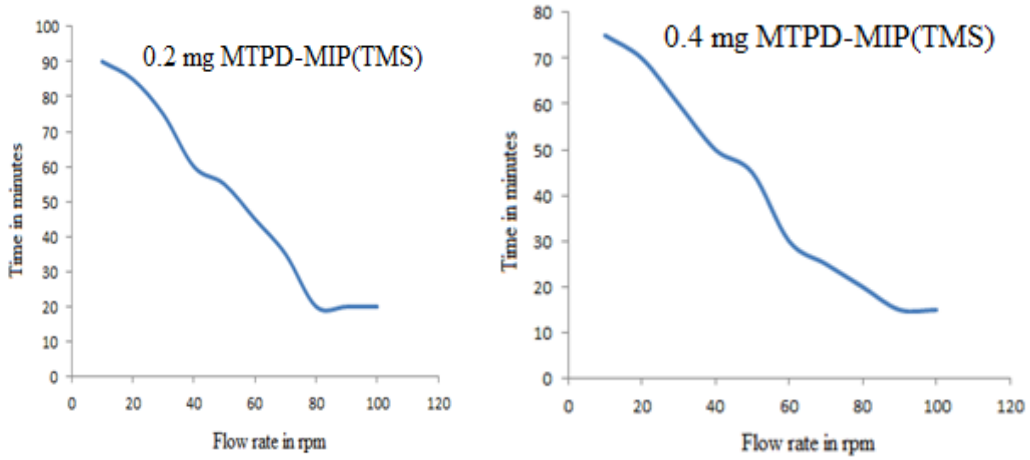


Fig. (5): Relationship between the flow rate and extraction time based on (0.2and 0.4)mg of MTPD-MIP(TMS) used 0.08 mM from MTPD

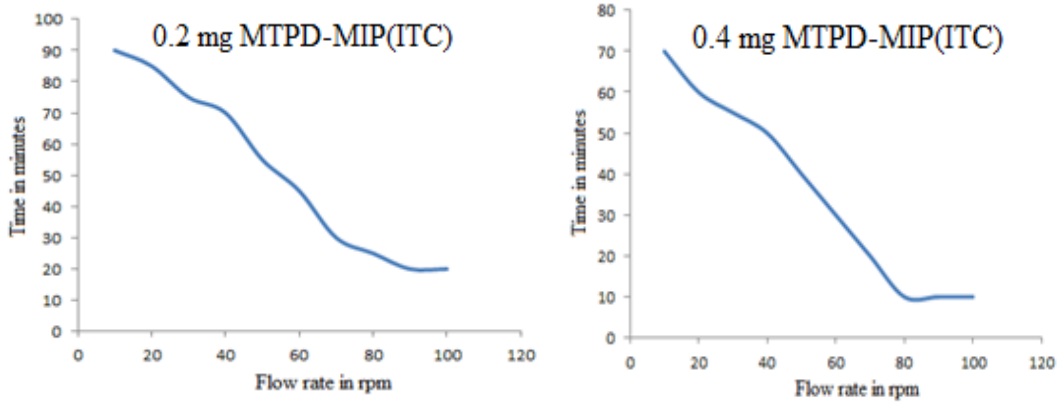


Fig. (6): Relationship between the flow rate and extraction time based on (0.2and 0.4) mg of MTPD-MIP(ITC) used 0.08 mM from MTPD

The isotherm adsorption can be calculated by interaction of the drug with the binding sites of the polymer as a solid adsorbent. The capacity factor increase with increase the concentration of the template until reach the equilibrium and in this study the binding capacity for MTPD-MIP (TMD) at two concentrations of drug are 0.70and 0.22 and for MTPD-MIP (ITC) are 4.1 and 2.0, respectively. The plots are shown in Figure (3). From the results of binding capacity the MIP based on ITC form a strong bonding to polymer than MIP (TMS).

3-2. Effect of flow rate

Flow rate one of the important factors that help to speed the analysis process through the solid phase extraction of the steel to remove the drug and know the time and sufficient size of the removal process. In the beginning, the (MTPD) is removed from the template by injecting 15 ml acetic acid/ acetonitrile was added (1:100,v/v) solution using the peristaltic pump. After the completion of the removal process, the standard solution is added in the form of batches until the (MTPD) complete reservation inside solid phase, the effect of the sample flow flow rate was studied in a range of 10-100 rpm figure (5and 6).

At first, the optimal conditions for the analysis are established, after which samples of the urine containing the MTPD are taken and treatment with solution of phosphate buffer, which carrier through the plastic syringe used for the perstic pump.

Table (3) Standard addition method for drug determination using imprinted polymer method solid phase extraction used MTPD-MIP(TMS).

Wt. of MIP (g)	Conc. of solution (ppm)	Synthetic solution		% Recovery	No. of Patients	*Drug conc. (Mm)	% Recovery	RSD%
		Conc. Taken (Mm)	Conc. Found (Mm)					
0.2	0.04	0.04	0.0401	100.25	1 2 3 4 5	0.0405 0.0391 0.0382 0.0412 0.0395	101.25 97.75 95.5 103 98.75	1.83 2.62 1.73 1.29 2.81 2.23
0.2	0.08	0.08	0.0803	100.37	1 2 3 4 5	0.0806 0.0798 0.0805 0.0809 0.0799	100.75 99.75 100.62 101.12 99.87	1.18 1.32 2.09 1.82 1.93
0.4	0.04	0.04	0.0409	102.25	1 2 3 4 5	0.0412 0.0391 0.0406 0.0409 0.0416	103 97.75 101.5 102.25 104	3.62 1.93 2.81 1.04 2.18
0.4	0.08	0.08	0.0808	101	1 2 3 4 5	0.0811 0.0809 0.0799 0.0789 0.0804	101.37 101.12 99.87 98.62 100.5	2.18 1.59 1.89 1.32 1.86

Average of three measurements

Table (4) Standard addition method for drug determination using imprinted polymer method solid phase extraction used of MTPD-MIP(ITC)

Wt. of MIP (g)	Conc. of solution (Mm)	Synthetic solution		% Recovery	No. of Patients	*Drug conc. (Mm)	% Relative error	RSD%
		Conc. Taken (Mm)	Conc. Found (Mm)					
0.2	0.04	0.04	0.0409	102.25	1 2 3 4 5	0.0404 0.0411 0.0399 0.0404 0.0414	101 102.75 99.75 101 103.5	1.08 1.93 1.02 1.71 2.85
0.2	0.08	0.08	0.0799	99.87	1 2 3 4 5	0.0792 0.0808 0.0791 0.0804 0.0811	99 101 98.87 100.5 101.37	1.67 1.34 1.29 1.55 1.98
0.4	0.04	0.04	0.0409	102.25	1 2 3 4 5	0.0392 0.0397 0.0409 0.0411 0.0406	98 99.25 102.25 102.75 101.5	1.24 1.91 2.81 1.48 2.15
0.4	0.08	0.08	0.0803	100.37	1 2 3 4 5	0.0809 0.0811 0.0802 0.0815 0.0802	100.74 101.37 100.25 101.87 100.25	2.93 1.28 1.61 1.35 2.92

Average of three measurements

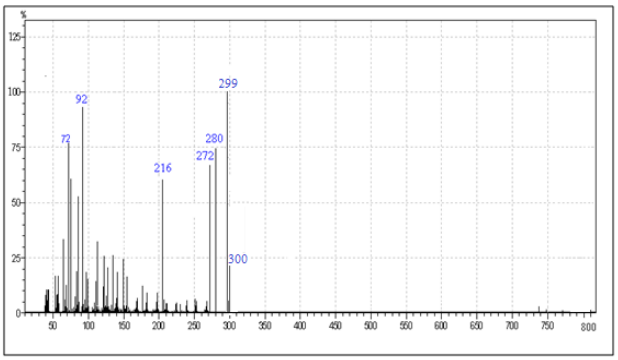


Fig.(7) structure of Metoclopramide.

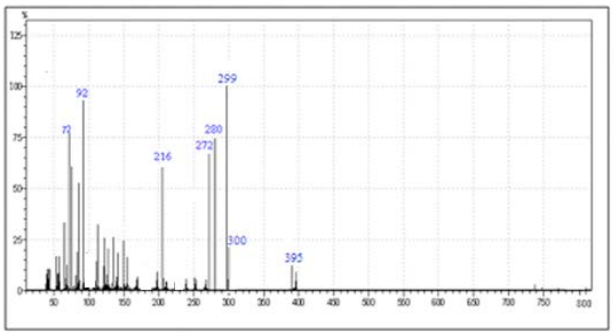


Fig.(8) structure of Metoclopramide sulfate.

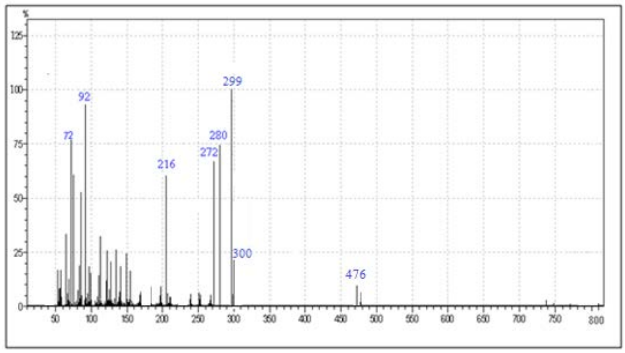


Fig.(9) structure of Metoclopramide N4-β-D-glucuronide.

When passing urine containing the MTPD will enter the gaps in the medicine on the solid phase .The components that suck weakly into a homogeneous column are expected to be removed by the washing step.

The washing process is repeated for three times and the washing time takes 3 minutes each time after which the solvent has been added for the complete removal of the MTPD.

The application of the same washing step to the urine sample rose, achieved satisfactory results of MTPD: no decrease was found in height of the analytes compared to those obtained by extracting standard samples.

That were taken plastic syringe contains (0.2-0.4) mg of MIP (TMS) and MIP (ITC) with passing different concentration of metoclopramide in urine samples was achieved in a range of 0.01-0.16 mM successfully under optimal conditions. The results are shown in table 5 and 6.

From the figures of GC-Mass we note the appearance of derivatives for MTPD due to the process of metabolism of MTPD in the body, which agree with the literature.

The results obtained from the tables (3 and 4) show a high possibility of estimating the MTPD using different types of MIP synthesis. The samples were measured by using GC-Mass. The analysis and evaluation of the MTPD are shown by the figures (7,8 and 9)..

CONCLUSION

The study included preparation molecularly imprinted polymers (MIPs) for Metoclopramide, by taking different monomers with appropriate cross-linker to and using a reaction initiator. The process included three steps of extracting, pre- concentration and then estimation. Samples taken from urine by extraction process was carried out initially and then the pre- concentration and estimation steps done where the MIPs preparation proved to have the ability to estimate small proportions Of the Metoclopramide in the human body at different times.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. All samples were measured using GC-Mass.

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