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Development and characterization of molecularly imprinted polymers for controlled release of citalopram

Majid Abdouss · Ebadullah Asadi · Saman Azodi-Deilami · Neda Beik-mohammadi · Saeed Amir Aslanzadeh

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Abstract In this work, the use of molecularly imprinted polymers (MIPs) for citalolpram as anti-depressant drug was studied. Imprinted polymers were prepared from methacrylic acid (MAA; functional monomer), ethylene glycol dimethacrylate (EGDMA; cross-linker), and citalopram (as a drug template) using bulk polymerization method. The polymeric devices were further characterized by FT-IR, thermogravimetric analysis, scanning electron microscopy, and binding experiments. The dissolution media employed in controlled release studies were hydrochloric acid at the pH level of 4.3 and phosphate buffers, at pH levels of 7.2 and 10.1, maintained at 37.0 and 25.0 ± 0.5°C. Results showed the ability of MIP polymers to control the release of citalopram. In all cases, the imprinted polymers showed a higher affinity for citalopram and a slower release rate than the nonimprinted polymers. At the pH level of 4.3 and at the temperature of 25°C, slower release of citalopram imprinted polymer occurred.

1 Introduction

Molecular imprinting technology can provide efficient polymer systems with the ability to recognize specific bioactive molecules and a sorption capacity dependent on the properties and template concentration of the solution [1, 2]. Among the different methods available for the preparation of molecularly imprinted polymers (MIPs), the so-called non-covalent approach, which uses only non-covalent interactions between the template and the functional monomers, is probably the most flexible regarding the selection of the functional monomers and the possible template molecules. For these reasons, the non-covalent approach has been the most widely adopted [2]. It is a process where functional and cross-linking monomers are co-polymerized in the presence of the template molecules [2–6]. The functional monomers initially form a complex with the imprint molecule which is then followed by a process of polymerization, consequently their functional groups are held in position by the highly cross-linked polymeric structure. The subsequent removal of the imprint molecule reveals the binding sites, which are complementary in size and shape to the template molecule. Thus, the MIPs can often be used as selective separation media for the template [6].

The applicability of the MIP has led to numerous reports such as sensors and biosensors [7, 8], as stationary phases for affinity chromatography [9], for membrane separation [10], as adsorbent for solid phase extraction [11], enzyme like catalysts [12], enantioseparation [13, 14], and pharmaceutical applications [15].

Polymer systems that allow the controlled-release of a drug are well-established. In most recent studies, MIPs, materials with artificially fabricated receptor structures, have been used to develop the design of drug delivery systems (DDS) [15–20]. The molecular imprinting technology can provide polymeric materials with the ability to recognize specific bioactive molecules with sorption and release behavior that can be made sensitive to the properties of the surrounding medium. The potential advantage of imprinted polymers capable of DDS is the longer presence of the drug

M. Abdouss (✉) · E. Asadi · S. Azodi-Deilami · N. Beik-mohammadi
Department of Chemistry, Amirkabir University of Technology, Tehran, Iran
e-mail: majidabdouss@yahoo.com

S. A. Aslanzadeh
Enghelab Islami Technical College, Yaftabad, Tehran, Iran

within body. This can be done by reducing the rate at which the drug is released. In cases where the drug has a narrow therapeutic index, MIP delivery vehicles might keep the concentration of the drug in the body below the concentration where adverse side effects become dominant.

Citalopram hydrobromide is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram HBr is a racemic bicyclic phthalane derivative designated (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1, 3-dihydroisobenzofuran-5-carbonitrile, Citalopram HBr occurs as a fine, white to off-white powder. Citalopram HBr is sparingly soluble in water and soluble in ethanol.

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). In vitro and in vivo studies in animals suggest that citalopram is a highly SSRI with minimal effects on norepinephrine (NE) and dopamine (DA) neuronal reuptake. Tolerance to the inhibition of 5-HT uptake is not induced by long-term (14-day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer.

Recently, we applied MIP as new carrier for controlled release of tramadol [21] and SPE of tramadol [22]. In this paper, first DDS based on MIPs is presented for the controlled release of citalopram and the key factors controlling recognition and release by imprinted polymer matrices are discussed.

2 Experimental part

2.1 Materials

2.1.1 Reagents

Methacrylic acid (MAA) obtained from *Merck* (Germany) was distilled in a vacuum prior to its usage in order to remove the stabilizers. Ethylene glycol dimethacrylate (EGDMA) and 2,2-azobisisobutyronitrile (AIBN) from *Sigma-Aldrich* (Germany) were of reagent grade and were used without any further purification. Citalopram hydrochloric acid, ambroxol hydrochloric acid, dextromethorphan hydrobromic acid, and diphenhydramine hydrochloric acid were obtained from the ministry of health and medical education (Tehran, Iran) and the degree of purity of all drugs were above 97%. The citalopram stock solutions as standard solution (1,000 μg l^{-1}) were prepared monthly in water and stored at 4°C. Intermediate standard solutions of 50 μg l^{-1} were prepared weekly by the dilution of stock solutions with water. Working standard solutions of different concentrations were prepared daily by diluting the intermediate standard solutions with mobile phase solutions. The phosphate buffer solutions were prepared in deionized water with a desired pH value. All solvents used in the analyses were HPLC grade and supplied by *Merck* (Germany).

2.1.2 MIP and NMIP preparation with bulk polymerization

The schematic representation of the imprinting and removal of citalopram from the imprinted polymer is shown in Fig. 1. The molecular imprinted polymers for citalopram were prepared from a reagent mixture obtained by mixing of citalopram and MAA in chloroform as Table 1. The solution was placed in room temperature for 5 h to prearrange template and monomer. EGDMA and AIBN were added to the solution and the mixture was uniformly dispersed by sonication. After sonication (5 min), it was purged with N_2 for 3 min and the glass tubes were sealed under N_2 atmosphere. It was, then, put into a water bath maintained at 60°C for 22 h. The produced polymer was filtered using a Whatman filter and washed with acetone and methanol before the template removal. The template was removed by washing the MIP successively in 50 ml of a methanol/acetic acid solution (9:1, v/v, of 98% methanol and pure acetic acid) for five times, each time for 1.5 h, and then four times in 100 ml of pure water for 1.5 h. The template extraction of the polymer created the cavities, leading to the specific sorption of the template. In addition, the removal of other materials from the polymer took place (e.g. residual monomers or oligomers and initiator fragments). NMIPs were also synthesized following exactly the same procedure, but excluding the template citalopram from the formulation.

2.2 Instrumentation

The HPLC system consisted a Waters 515 pump, a 486Waters UV/vis detector, *a model 7725i Rehodyne* injector with a 25 μl sample loop, and a micro-Bondapak *C18 column* of 4.6 mm × 150 mm HPLC column. HPLC data was acquired and processed using a PC and Millennium 2010 Chromatogram Manager software (Version 2.1 Waters). Water bath (*memmert WNB14*) was used to carry out the polymerization. Sonic bath (*EURONDA 4D*) with the power of 350 W and frequency of 50 Hz was used to disperse the mixture. A scanning electron microscope (SEM; *Philips XLC*) was used to study the morphology of the polymer particles. The pH levels of the solutions were

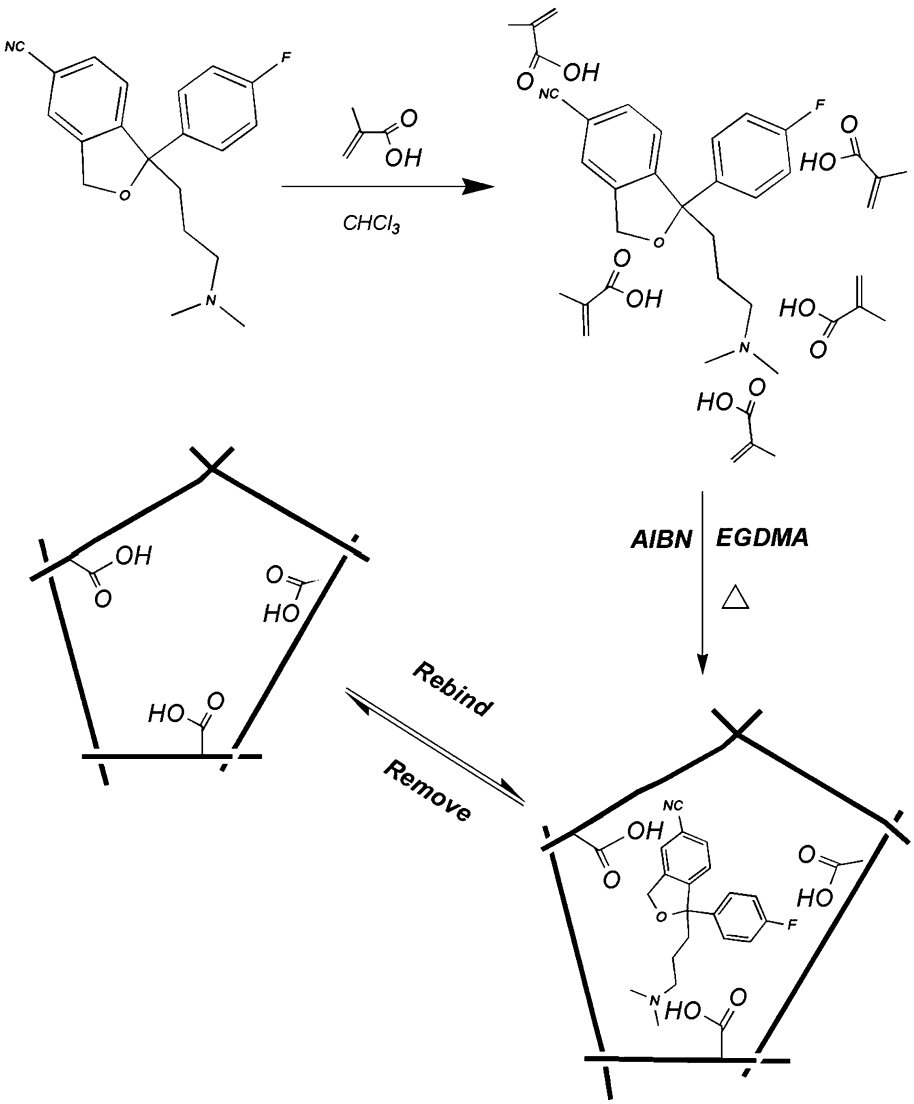

Fig. 1 Schematic representation of the MIP synthesis for citalopram

Table 1 Polymer compositions and the percentage of citalopram bound by each matrix

Polymer	Template: monomer	Citalopram (mmol)	MAA (mmol)	EGDMA (mmol)	Recovery (%)[a]
MIP_1	1:2	0.75	1.5	18	68 (±1.6)
MIP_2	1:3	0.5	1.5	18	73 (±2.0)
MIP_3	1:4	0.37	1.5	18	79 (±1.4)
MIP_4	1:5	0.3	1.5	18	86 (±1)
MIP_5	1:6	0.25	1.5	18	75 (±2.0)
NIP	–	–	1.5	18	12 (±1.7)

[a] Average of three determinations

adjusted using a *model 630 digital Metrohm* pH meter equipped with a combined glass-calomel electrode. The FT-IR spectra of the ground polymers was recorded (*Bruker model EQUINOX 55*). The thermal analysis of the polymers were carried out using a model *PL-STA-1500,* the thermo gravimetric analysis (TGA) was carried out on a *Perkin Elmer TGS-2* instrument at the maximum heating rate of 20°C min^{-1} in an oxygen atmosphere.

2.3 Procedures

2.3.1 Chromatographic conditions

The HPLC was carried out at room temperature. A degassed mixture of acetonitrile:phosphate buffer (0.01 mol l^{-1}, pH 3.0) (30:70) at a flow rate of 1.1 ml min^{-1} was selected as a mobile phase [23]. All of

the analyses were carried out at an operation wavelength of 239 nm and the results were recorded by *Millennium chromatography* software.

2.3.2 Batch rebinding experiment

For measuring of template binding, 50 mg of particles were suspended in 10 ml of 5–100 μg l^{-1} citalopram solution (pH 8.0). The solution was mixed for 1 h and then particles were filtrated on a paper filter (flow rate = 100 ml min^{-1} by applied vacuum). The supernatant was analyzed by HPLC-UV at 239 nm. The amount of citalopram bound to particles was calculated by subtraction of the free fraction from the total amount added. The same procedure was followed for NMIP particles.

2.3.3 Drug loading through soaking procedure

50 mg of powder polymers were suspended in 10 ml of citalopram solution (50 μg l^{-1}) and soaked for 30 min at room temperature. During this time, the mixture was continuously stirred and then the solvent was removed. Subsequently the MIP particles were dried under vacuum overnight at 40°C.

2.3.4 In vitro drug release studies

The release studies were carried out using the dissolution method [24]. Two parallel experiments for MIP_4 and NMIP matrices were performed. First, MIP_4 and NMIP particles (50 mg) loaded with citalopram, were dispersed in flasks containing various solutions (10 ml) such as phosphate buffer solution (pH 6.0 and 8.0) and hydrochloric acid pH 3.0 at 25.0 and 37.0 ± 0.5°C in a water bath under magnetic stirring (50 rpm). Samples (2 ml) were drawn from the solution at appropriate time intervals to determine the amount of drug released. Experiments were repeated three times.

3 Results and discussion

3.1 Characterization

The IR spectra of NMIP and the unleached and leached MIP_4 displayed similar characteristic peaks, indicating the similarity in the backbone structure of the different polymers. The IR spectra of the unleached and leached imprinted poly (MAA *co*-EGDMA) are shown in Fig. 2. As a result of the hydrogen binding with the –COOH group of MAA, the C=O stretching, the OH stretching, and the bending vibrations at 1710, 3457, and 1388 cm^{-1} in the unleached MIP_4 materials were shifted to 1722, 3473, and 1394 cm^{-1} in the corresponding leached MIP_4, respectively. Furthermore, there were two other distinct differences between the IR spectra of the unleached and leached MIPs. In the leached polymer, there were one sharp band with low relative intensity of 1522 cm^{-1} and one band with high relative intensity of 2965 cm^{-1} that was seen at 1538 and 2940 cm^{-1} in the corresponding unleached MIP_4, respectively. Other absorption peaks match those of MIP_4, as well as NMIP: 1252, 1129 cm^{-1} (symmetric and asymmetric ester C–O stretch bands), 1636 cm^{-1} (stretching vibration of residual vinylic C=C bonds), and 985 cm^{-1} (out-of-plane bending vibration of vinylic C–H bond).

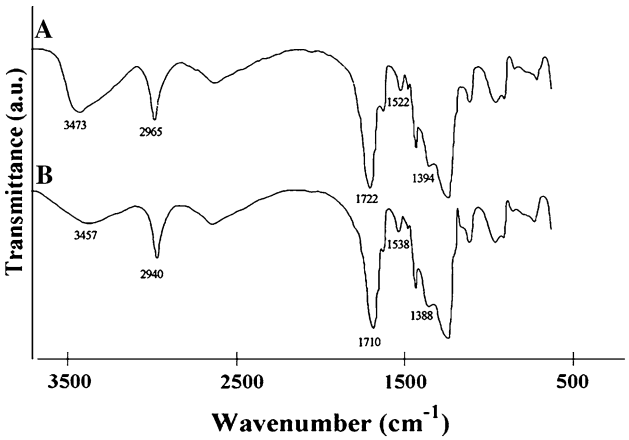

Fig. 2 Infrared plots of the leached (*a*) and unleached (*b*) MIP particles

Moreover, regarding the unleached MIP particles, TGA revealed two decomposition states: one mass loss between 100 and 180°C (10% weight loss), assigned to the decomposition of the free monomer and the cross-linker, and one starting at 186°C, related to the citalopram hydrobromide decomposition as the melting point of citalopram hydrobromide is 186°C [25]. All the materials were completely decomposed prior to reaching the temperature of 460°C. These observations indicated that the rigidity of the unleached and leached MIP_4 particles is more than blank materials, as the formers exhibits a decomposition above ~300°C; the latter starts its decomposition at ~250°C onwards. Also, the unleached and leached MIP particles have similar degradation patterns above 400°C. The complete decomposition of the polymeric matrix occurs for both at temperatures above 450°C.

3.2 Study of morphology

The morphology of the MIP_4 particles, determined by a SEM, is shown in Fig. 3a–c. These figures show unleached and leached MIP_4 and NMIP particles at the magnification of 5,000. As seen in Fig. 3, remarkable differences in the

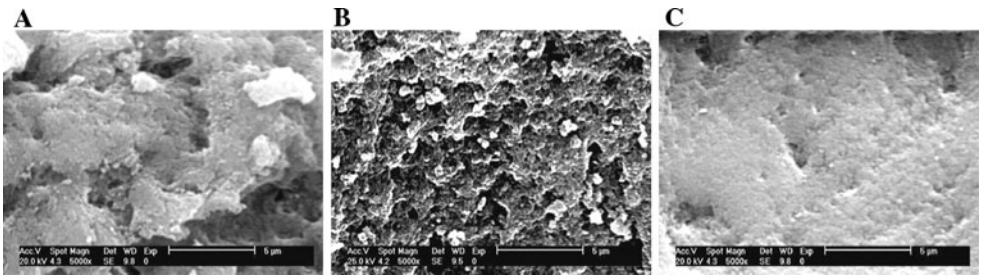

Fig. 3 Scanning electron micrographs: **a** unleached MIP, **b** leached MIP, **c** leached NMIP

morphologies of the polymers were considered and a porous surface could be manifestly observed for the MIP_4.

3.3 Optimal MIP formulation and progenic solvent

There are some variable parameters influencing the final characteristics of the obtained materials in terms of capacity, affinity, and selectivity for the target analyte, such as amount of monomer or the nature of the cross-linker and solvent. Solvent plays an important role in the formation of the porous structure of the MIPs, which are a subset of a larger class known as macroporous polymers [26, 27]. The morphological properties of porosity and surface area are determined by the type of solvent, referred to as "porogen," used in the polymerization. Porosity arises from the phase separation from the porogen and the growing polymer during polymerization. Porogens with a low solubility phase separate early and tend to form larger pores and materials with lower surface areas. Conversely, porogens with a higher solubility phase, separate later in the polymerization, which provides materials with smaller pore size distributions and greater surface area. It does not appear, however, that binding and selectivity in MIPs are dependent on a particular porosity. In fact, optimal results are often obtained when chloroform is used as the porogen [29].

As Table 2 shows, the primary experiment revealed that the imprinted polymer prepared in chloroform shows a better molecular recognition ability than acetonitrile (ACN) and dimethyl formaldehyde (DMF) in an aqueous environment. Thus, chloroform is chosen as a suitable solvent to optimize the functional monomer to template ratio in order to improve molecular recognition capabilities. Generally, proper mole ratios of functional monomer to template are very important to enhance specific polymers and a number of MIPs recognition sites. The pre-polymer complex can be increased by increasing the template concentration. This is an interesting prospect because in theory the template can be increased to very high concentrations without altering the composition of the monomers in the final polymer. This is because the template is not covalently incorporated into the final polymer and is removed at the end of the imprinting process [28]. On the other hand, a high ratio of functional monomers to templates results in high non specific affinity while low ratios cause less complication due to insufficient functional groups [29].

Table 2 Recoveries obtained using the MIP and NMIP polymers synthesized in different organic solvents

Solvents	Adsorption (%)	
	MIP_4	NMIP
$CHCl_3$	86 ± 1.0	12 ± 1.7
ACN	57 ± 2	24 ± 1.5
DMF	43 ± 1	20 ± 1

Batch experiments with 50 mg or polymer particles; sample volume 5 ml; pH 5.2; citalopram concentrations 50 μg l^{-1} (mean ± SD, $n = 3$)

As Table 1 depicts, different ratios of monomers MAA to the template were used in the experiment. The optimal ratio of the functional monomers to the template for citalopram by bulk polymerization was 5:1 which had the best specific affinity and the highest recovery of 86% while that of the corresponding NMIP was 12%. Excess of the functional monomer with respect to the template yielded higher non-specific affinity. Therefore, the typical 1:5:60 (template:monomer:cross linker mole) ratio was used for further studies.

3.4 Effect of pH on drug loading

Different polymers with different template to monomer ratios were synthesized and the pH effects were investigated on drug loading. The effect of pH on the sorption of citalopram was examined by varying the pH of solutions from 3.0 to 11.0. Several batch experiments were performed by equilibrating 50 mg of the imprinted particles with 5 ml of the solutions containing 50 μg l^{-1} of citalopram under the desired levels of pH. The results for different polymers (Fig. 4) displayed that pH has great effects

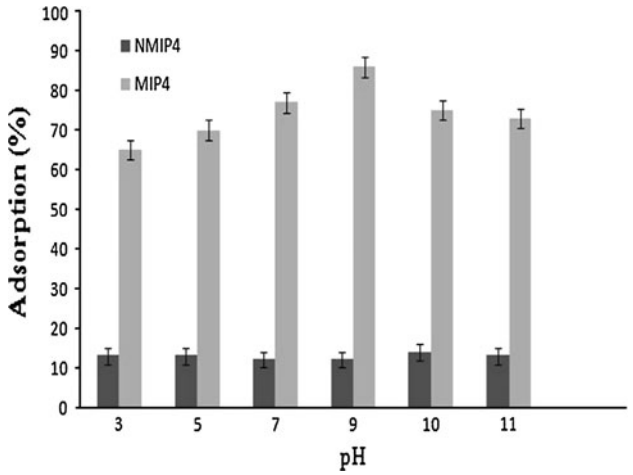

Fig. 4 Effect of pH on rebinding efficiency of citalopram. 50 mg of the imprinted polymers; sample volume 5 ml; citalopram concentration 50 μg l^{-1}; temperature 20°C (mean ± SD, $n = 3$)

on loading. The percentage of citalopram recovery increases up to 9.0 pH and then it decreases by further increase of pH. A difference of about 74% between MIP_4 and NMIP was seen at the pH level of 9.0. Lesser effects were observed at lower and higher pH values and which may have been attributed to the protonation of the functional group of citalopram and to the deprotonation of carboxyl groups of the polymer, respectively.

3.5 Choice of loading, washing, and eluent solution

Generally, the polymers have binding ability with both specific and non-specific interactions. The specific interactions originate mainly from the imprinting procedure, which creates selective recognition sites for the template. The non-specific interactions were assessed by measuring the binding of the non-imprinted polymer. In order to investigate the usefulness of the washing step, various aqueous media including ACN, acetone, tetrahydrofuran, and dimethyl formamide were assessed for obtaining the maximum recovery of the analytes. A citalopram solution was employed for the loading of MIP and NMIP cartridges, separately, followed by desorption with a washing solvent. The results showed that washing with tetrahydrofuran had no clear effect on the retention of citalopram on both MIP and NMIP cartridges. In contrast, polar organic solvents, such as ACN and dimethyl formamide had evidently large effects on the retention of citalopram on both MIP and NMIP cartridges. It was learned that acetone can elute interferences and was chosen as the washing solution (Table 3). For the recovery of strongly bound citalopram, the polymers were eluted with 3 × 1 ml of 10% (v/v) AcOH/MeOH. With acetone, the recovery of citalopram in the NMIP cartridge was decreased to 12% while the recovery of citalopram by the MIP cartridges was not reduced (86%).

Table 3 Recovery (%) obtained from after the loading of 50 mg of MIP and NMIP

Steps	Fractions	Recovery (%)	
		MIP	NMIP
1A	Washing, 1 ml, acetonitrile	14 ± 2[a]	15 ± 3
1B	Washing, 1 ml, acetone	7 ± 1	10 ± 3
1C	Washing, 1 ml, tetrahydrofuran	8 ± 2	10 ± 2
1D	Washing, 1 ml, dimethyl formamide	25 ± 3	33 ± 1
2	Elution (after step 1B), 3 × 1 ml, 10% (v/v) AcOH/MeOH	86 ± 1.0	12 ± 1.7

[a] Average of three determinations

3.6 Study of MIP selectivity

The chromatographic evaluation and equilibrium batch rebinding experiments are the methods most commonly used to investigate the selectivity of the imprinted materials [30]. For equilibrium batch rebinding experiments, a known mass of the template in solution is added to a vial containing a fixed mass of the polymer. Once the system has reached the equilibrium, the concentration of the free template in solution is measured and the mass of the template absorbed to the MIP is calculated [31, 32]. Diphenhydramine, Tramadol, and Chlorphenamine were selected to investigate the selectivity of the MIP. Their molecular structures are shown in Fig. 5. Solutions of all the compounds were prepared individually with the concentration of 50 μg l^{-1}. The extraction of the solvent was 10% (v/v) AcOH/MeOH. The extraction yields of the selected compounds with the MIP and NIP are shown in Table 4. Surprisingly, the extraction yields of the analogues with the MIP were much higher than that of the NMIP. It was revealed that the citalopram based-MIP possess better affinity to the template molecule. This affinity is mainly caused by the hydrogen bonding interaction between the functional groups possessed by all drugs and carboxylic groups in the MIP. A possible reason for the difference is the extractions of drugs were relative to their structural similarity with the template molecule of MIP.

3.7 Drug release profiles

Our release studies were carried out in three medias. MIP_4 matrices, which are the most effective on template recognition, were tested in vitro as devices for citalopram delivery and the results were compared with NMIP

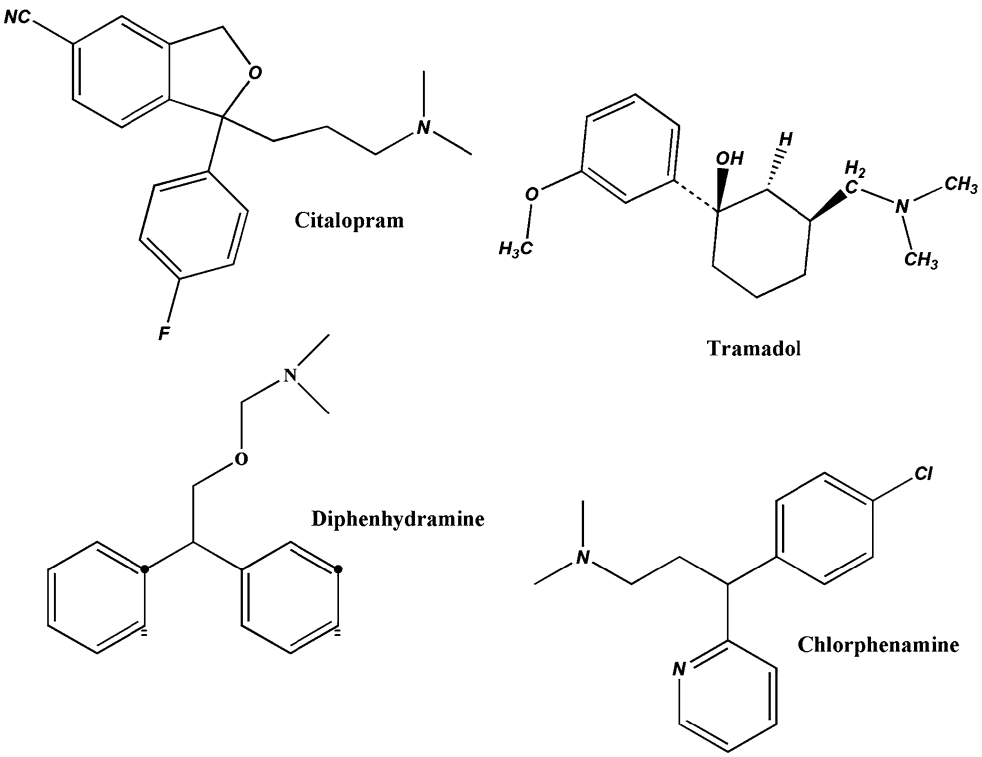

Fig. 5 Chemical structures of investigated drugs

Table 4 Adsorption of diphenhydramine, citalopram, tramadol, and chlorphenamine with MIP_4 and NMIP at 50 μg l^{-1} concentration

Compounds	Adsorption (%)	
	MIP_4	NMIP
Diphenhydramine	70 ± 1.2	20 ± 1.0
Citalopram	86 ± 1.0	12 ± 1.7
Tramadol	49 ± 1.0	21 ± 1.4
Chlorphenamine	61 ± 2	19 ± 1.1

$V = 5$ ml; pH 5.2 at 25°C (mean ± SD, $n = 3$)

particles. We studied the release of citalopram from polymer particles in hydrochloric acid (pH 4.3) and phosphate buffer (pH 7.2 and 10.1), respectively. The purpose of this study was to observe a considerable difference between the MIP and NMIP in drug release and the investigation of pH and the effects of temperature on release profiles.

3.7.1 Effect of pH

The release of citalopram from MIP_4 and NMIP was investigated as a function of the pH of the media (Fig. 6). At the pH level of 10.1, the release of both polymers was dramatically faster than at the pH levels of 7.2 and 4.3, with 100% of the release occurring within 3 h for NMIP and 6 h for MIP_4. However, the release of the polymers was delayed up to 7 h for NMIP and up to nearly 19 h for MIP_4 in the 7.2 pH buffer. The release of citalopram at the pH level of 4.3 was delayed more than other pH levels, 13 h for NMIP and nearly 40 h for MIP_4.

These results manifest the anionic properties and pH sensibility of these P(MAA-co-EGDMA) systems. The initial quick release of citalopram in NMIP and MIP_4 is related to physical adsorption and non-specific bonds. However, in this case we have a slower release rate for the MIP_4 because of specific binding sites, which interacted strongly with citalopram. Drug release was found to reduce with the decrease in pH. However, in all cases the release of MIP_4 was deferred for a longer time as compared to NMIP although at the pH level of 4.3 the difference in release was the highest. At pH values below the p*K*a of MAA, which was a value of approximately 4.66, the number of negative charges was very low. The carboxylic groups of the acrylate structures were hardly ionized. Then, the PEGDMA chains of the P(MAA-co-EGDMA) copolymers were able to interact with the non-ionized carboxylic groups via hydrogen bonding. Consequently, the controlled release of the drug improved compared to a higher pH level because the release of the polymers was slower and the matrices remained intact. As the pH of the release medium became more basic, the ionization of the carboxylic groups in the acrylate structure increased, resulting in an electrostatic repulsive interaction between the PEGDMA

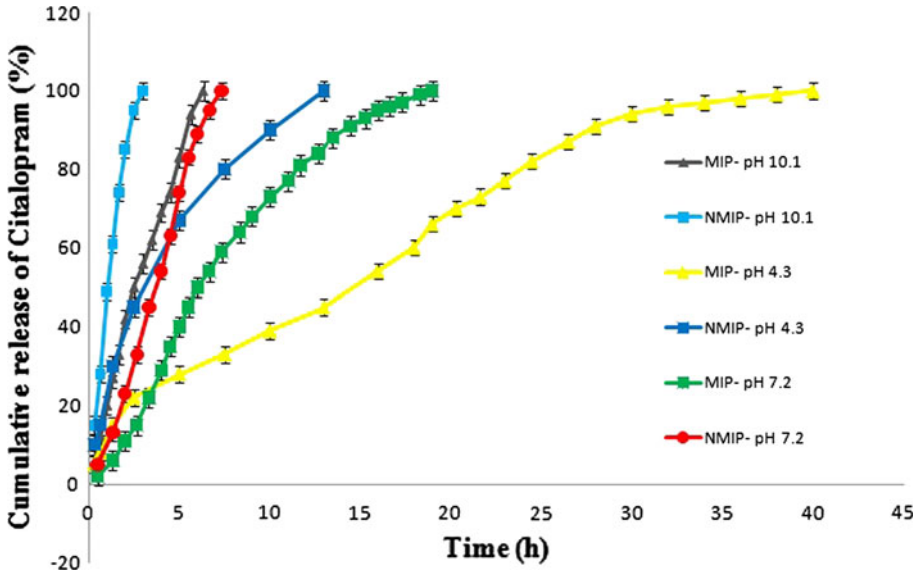

Fig. 6 Release profile of 50 mg citalopram imprinted polymer at 37°C and various pH levels of 4.3, 7.2, and 10.1. Media volume: 5 ml (mean ± SD, $n = 3$)

chains and the PMAA backbone, and also the subsequent rupture of the hydrogen bonds. This phenomenon led to decomplexation and the matrices could not control the release of citalopram, as a result, drug release occurred at a much faster rate.

3.7.2 *Effect of temperature*

The experiment proved that decreasing the temperature from 37 to 25°C did not affect the matrix in controlling the MIP and NMIP release. As seen, in Fig. 7 at room temperature (25°C) the slower release of citalopram occurred in both polymers. Nevertheless, the difference between MIP_4 and NMIP was still observed at 25°C.

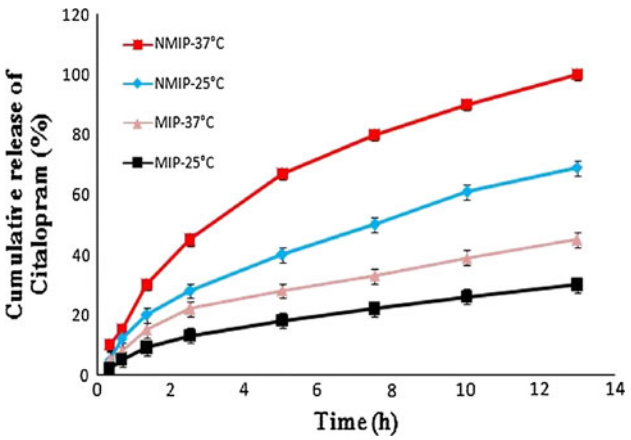

Fig. 7 The effect of temperature on the release profile of 50 mg citalopram imprinted polymer with the pH level of 3.0 (mean ± SD, $n = 3$)

4 Conclusion

Imprinted polymers are well-established as molecular recognition materials but are now being increasingly considered for active biomedical applications such as drug delivery. In this work, we developed uniformly sized MIPs as a sustained-release system for the delivery of citalopram. In this study, some highlights of new research into molecularly imprinted drug delivery and controlled release systems are presented. The key factors controlling recognition and release by imprinted polymer matrices included mole ratios of monomer to citalopram and medium nature and pH are discussed. In this case, the monomer/citalopram ratio of 5:1 showed the best specific affinity of 74% and because of the existence specific binding sites, we obtained proper release profiles compared with the controlled polymers. Changes in the release behavior are observed depending on both the temperature and pH of the releasing media. After drug loading, in vitro release experiments were performed, and the results showed the ability of MIP polymers to control the release of citalopram, supporting a release mechanism in which the release rate of the drug from the matrices depends on the selective interaction between the drug and imprinted cavities, and also the pH level and temperature of the dissolution medium. For this reason, the release rate was considerably different, and therefore MIP represents a very promising polymeric device for the selective and controlled release of citalopram related to non-imprinted polymers. After consideration of MIPs in all pH and temperature levels, at pH 4.3 and the temperature of 25°C, slower release and at pH 10.1 and 37°C faster release of citalopram imprinted polymer occurred.

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