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The Syntheses and Characterization of Molecularly Imprinted Polymers for the Controlled Release of Bromhexine

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Abstract Imprinted polymers are now being increasingly considered for active biomedical uses such as drug delivery. In this work, the use of molecularly imprinted polymers (MIPs) in designing new drug delivery devices was studied. Imprinted polymers were prepared from methacrylic acid (functional monomer), ethylene glycol dimethacrylate (cross-linker), and bromhexine (as a drug template) using bulk polymerization method. The influence of the template/functional monomer proportion and pH on the achievement of MIPs with pore cavities with a high enough affinity for the drug was investigated. The polymeric devices were further characterized by FT-IR, thermogravimetric analysis, scanning electron microscopy, and binding experiments. The imprinted polymers showed a higher affinity for bromhexine and a slower release rate than the non-imprinted polymers. The controlled release of bromhexine from the prepared imprinted polymers was investigated through in vitro dissolution tests by measuring absorbance at λ_{max} of 310 nm by HPLC-UV. The dissolution media employed were hydrochloric acid at the pH level of 3.0 and phosphate buffers, at pH levels of 6.0 and 8.0, maintained at 37.0 and 25.0±0.5 °C. Results from the analyses showed the ability of MIP polymers to control the release of bromhexine In all cases The imprinted polymers showed a higher affinity for bromhexine and a slower release rate than the non-imprinted polymers. At the pH level of 3.0 and at the temperature of 25 °C, slower release of bromhexine imprinted polymer occurred.

Keywords Molecularly imprinted polymer · Bromhexine · Bulk polymerization · Drug release · Biological systems

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

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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 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.

Bromhexine hydrochloride is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver. Its oral bioavailability is stated to be only about 20%. It is widely distributed to body tissues and is highly bound to plasma proteins. About 85% to 90% of a dose is excreted in the urine mainly as metabolites. It has a terminal elimination half-life of up to about 12 h. Bromhexine crosses the blood brain barrier and small amounts cross the placenta.

Bromhexine is an oral mucolytic agent with a low level of associated toxicity. Bromhexine acts on the mucus at the formative stages in the glands, within the mucus-secreting cells. Bromhexine disrupts the structure of acid mucopolysaccharide fibers in mucoid sputum and produces a less viscous mucus, which is easier to expectorate.

In this paper, first DDS based on molecularly imprinted polymers is presented for the controlled release of bromhexine and the key factors controlling recognition and release by imprinted polymer matrices are discussed.

Experimental Part

Materials

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-azobis isobutyronitrile (AIBN) from Sigma–Aldrich (Germany) were of reagent grade and were used without any further purification. Bromhexine 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 bromhexine stock solutions as standard solution (1,000 $\mu g L^{-1}$) were prepared monthly in water and stored at 4 °C. Intermediate standard solutions of 50 $\mu g L^{-1}$ 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 de-ionized water with a desired pH value. All solvents used in the analyses were high-performance liquid chromatography (HPLC) grade and supplied by Merck (Germany).

MIP and NMIP Preparation with Bulk Polymerization

The schematic representation of the imprinting and removal of bromhexine from the imprinted polymer is shown in Fig. 1. The molecular imprinted polymers for bromhexine were prepared from a reagent mixture obtained by mixing of bromhexine 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 bromhexine from the formulation.

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 4.6×150 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 (*Philips XLC*) was used to study the morphology of the polymer particles. The pH levels of the solutions were 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.

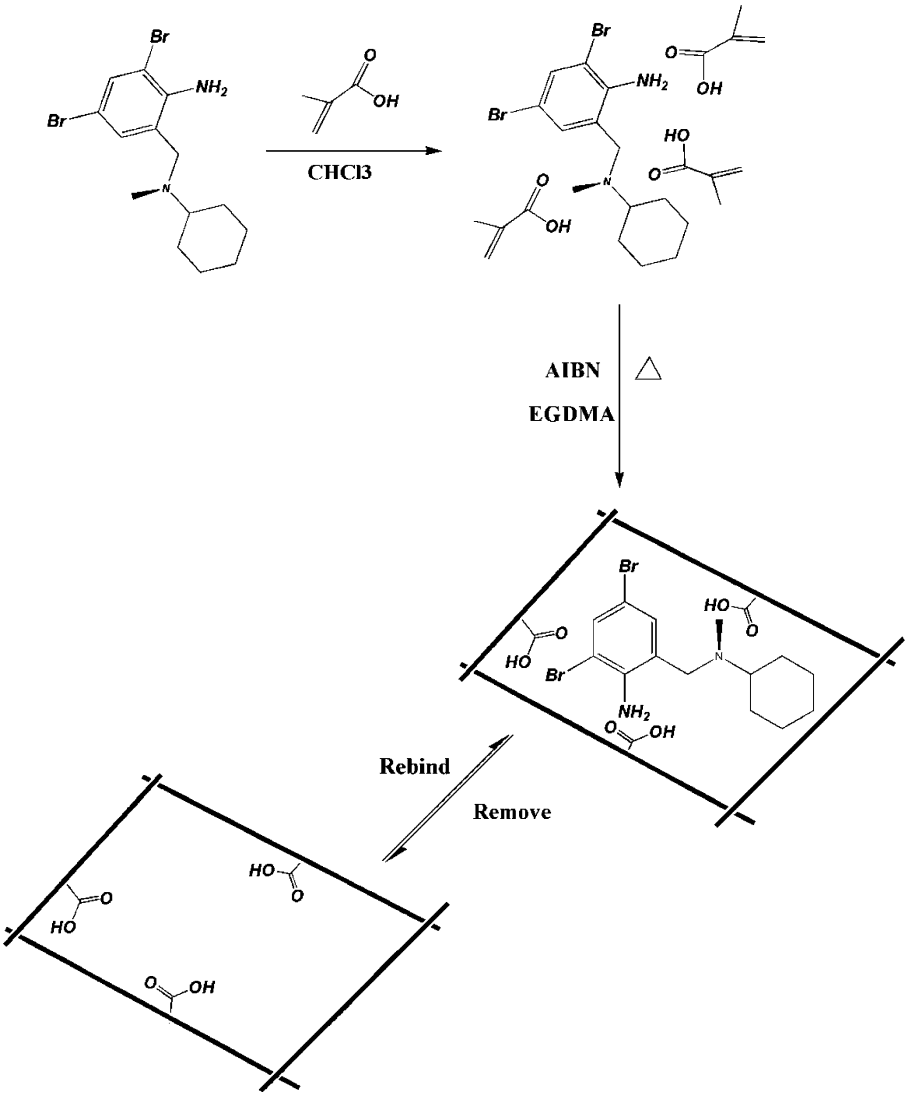

Fig. 1 Schematic representation of the MIP synthesis for bromhexine

Procedures

Chromatographic Conditions

The HPLC was carried out at room temperature. A degassed mixture of acetonitrile/phosphate buffer (0.01 $molL^{-1}$, pH 3.0; 30:70) at a flow rate of 1.1 $mLmin^{-1}$ was selected as a mobile phase [21]. All of the analyses were carried out at an operation wavelength of 310 nm, and the results were recorded by *Millennium chromatography* software.

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

Polymer	Template/Monomer	Bromhexine (mmol)	MAA (mmol)	EGDMA (mmol)	Recovery (%)[a]
MIP_1	1:2	0.82	1.85	18	45 (±1.8)
MIP_2	1:4	0.66	1.85	18	60 (±2.5)
MIP_3	1:6	0.27	1.85	18	65 (±1.2)
MIP_4	1:8	0.23	1.85	18	90 (±1.5)
MIP_5	1:10	0.16	1.85	18	72 (±1.9)
NIP	–	–	1.85	18	17 (±2.0)

[a] Average of three determinations

Batch Rebinding Experiment

For measuring of template binding, 50 mg of particles were suspended in 10 mL of 5–100 $\mu g L^{-1}$ DIP solution (pH 5.2). 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 310 nm. The amount of bromhexine bound to particles was calculated by subtraction of the free fraction from the total amount added. The same procedure was followed for NMIP particles.

Drug Loading Through Soaking Procedure

Fifty milligrams of polymers were suspended in 10 mL of bromhexine solution (50 $\mu g L^{-1}$) 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.

In Vitro Drug Release Studies

The release studies were carried out using the dissolution method [22]. Two parallel experiments for MIP_4 and NMIP matrices were performed. Firstly, MIP_4 and NMIP particles (50 mg) loaded with bromhexine, 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.

Results and Discussion

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

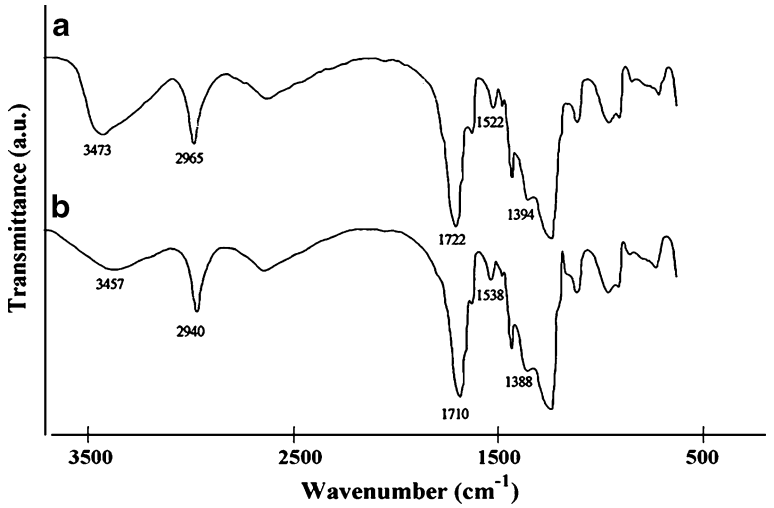

Fig. 2 Infrared plots of the leached (**a**) and unleached (**b**) MIP particles

1,710, 3,457, and 1,388 cm^{-1} in the unleached MIP_4 materials were shifted to 1,722, 3,473, and 1,394 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 1,522 cm^{-1} and one band with high relative intensity of 2,965 cm^{-1} that was seen at 1,538 and 2,940 cm^{-1} in the corresponding unleached MIP_4, respectively. Other absorption peaks match those of MIP_4, as well as NMIP: 1,252, 1,129 cm^{-1} (symmetric and asymmetric ester C–O stretch bands), 1,636 cm^{-1} (stretching vibration of residual vinylic C=C bonds), and 985 cm^{-1} (out-of-plane bending vibration of vinylic C–H bond).

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 235 °C, related to the bromhexine hydrochloride decomposition as the melting point of bromhexine hydrochloride is 235 °C [23]. 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.

Study of Morphology

The morphology of the MIP_4 particles, determined by a scanning electron microscope, 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 morphologies of the polymers were considered and a porous surface could be manifestly observed for the MIP_4.

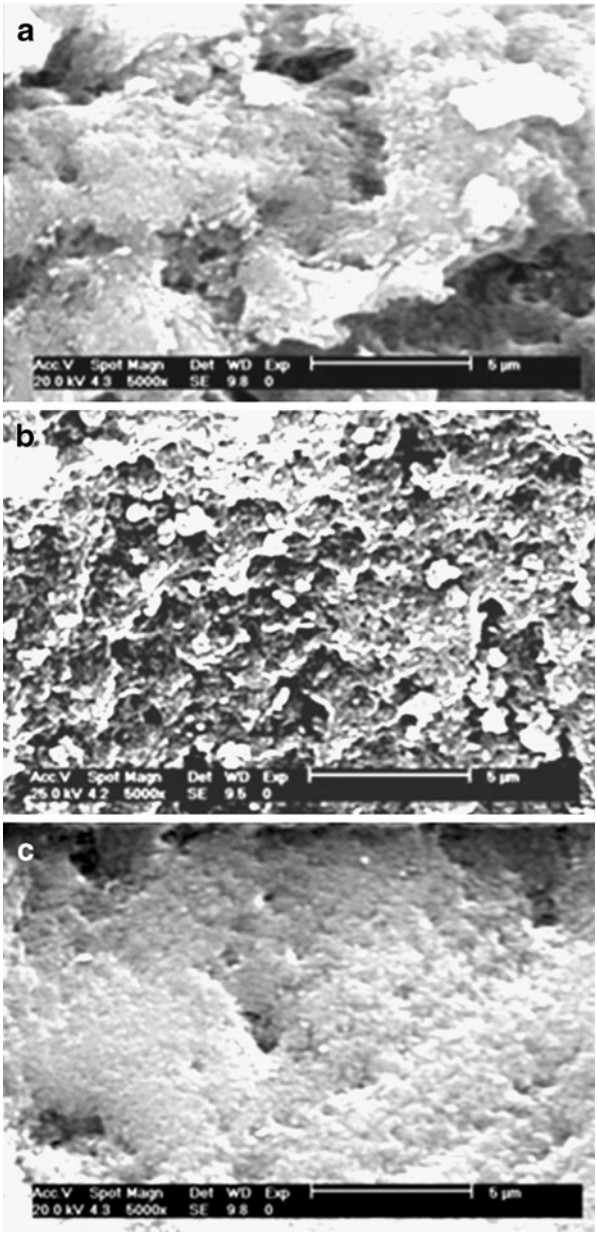

Fig. 3 Scanning electron micrographs: **a** unleached MIP; **b** leached MIP; **c** leached NMIP

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 [24, 25]. 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 [27].

As Table 2 shows, the primary experiment revealed that the imprinted polymer prepared in chloroform shows a better molecular recognition ability than acetonitrile and dimethyl formaldehyde 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 [26]. 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 [27].

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 bromhexine by bulk polymerization was 8:1 which had the best specific affinity and the highest recovery of 90% while that of the corresponding NMIP was 17%. Excess of the functional monomer with respect to the template yielded higher non-specific affinity. Therefore, the typical 1:8:80 (template/monomer/cross-linker mole) ratio was used for further studies.

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 bromhexine was examined by varying the pH of solutions from 2.2 to 6.6. Several batch experiments were performed by equilibrating 50 mg of the imprinted particles with 5 mL of the

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

Solvents	Adsorption (%)	
	MIP_4	NMIP
$CHCl_3$	90±1.5	17±2
ACN	50±2	20±1.5
DMF	40±1	25±1

Batch experiments with 50 mg or polymer particles; sample volume, 5 mL; pH 5.2; bromhexine concentrations, 50 μgL^{-1} (mean±SD, n=3)

ACN acetonitrile, *DMF* dimethyl formaldehyde

solutions containing 50 $\mu g L^{-1}$ of bromhexine under the desired levels of pH. The results for different polymers (Fig. 4) displayed that pH has great effects on loading. The percentage of bromhexine recovery increases up to pH 5.2 and then it decreases by further increase of pH. A difference of about 73% between MIP4 and NMIP was seen at the pH level of 5.2. Lesser effects were observed at lower and higher pH values and which may have been attributed to the protonation of the functional group of bromhexine and to the deprotonation of carboxyl groups of the polymer, respectively.

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 acetonitrile, acetone, tetrahydrofuran, and dimethyl formamide were assessed for obtaining the maximum recovery of the analytes. A bromhexine 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 bromhexine on both MIP and NMIP cartridges. In contrast, polar organic solvents, such as acetonitrileand dimethyl formamide had evidently large effects on the retention of bromhexine 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 bromhexine, the polymers were eluted with 3×1 ml of 10% (*v*/*v*) AcOH/MeOH. With acetone, the recovery of bromhexine in the NMIP cartridge was decreased to 17% while the recovery of bromhexine by the MIP cartridges was not reduced (90%).

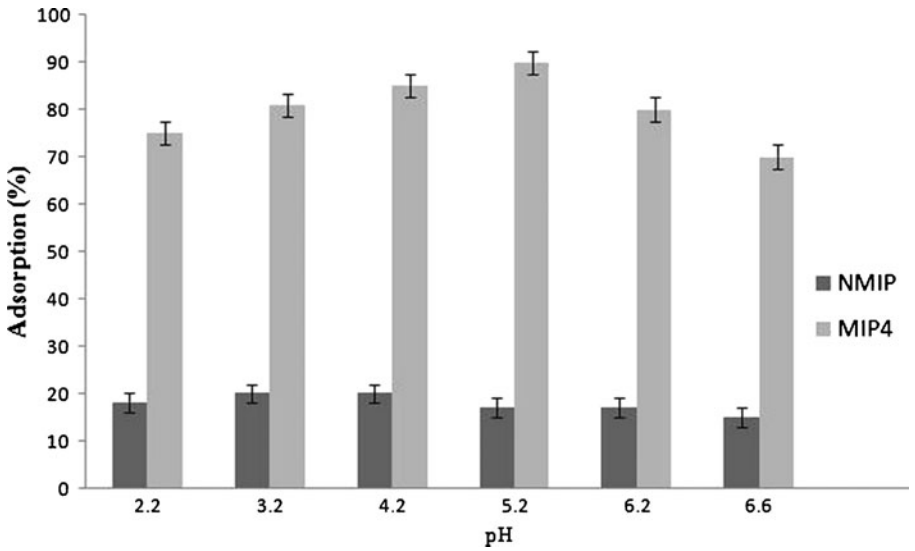

Fig. 4 Effect of pH on rebinding efficiency of bromhexine; 50 mg of the imprinted polymers; sample volume, 5 mL; bromhexine concentration, 50 $\mu g L^{-1}$; temperature 20 °C (mean±SD, n=3)

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	11±2[a]	14±3
1B	Washing, 1 ml, acetone	7±1	10±3
1C	Washing, 1 ml, tetrahydrofuran	3±2	6±2
1D	Washing, 1 ml, dimethyl formamide	21±3	27±1
2	Elution (after step 1B), 3×1 ml, 10% (*v*/*v*) AcOH/MeOH	90±1.5	17±2

[a] Average of three determinations

Capacity of Polymers

The capacity of the sorbent is an important factor that determines how much sorbent is required to remove a specific amount of drug from the solution quantitatively [28, 29]. In the measurement of the adsorption capacity of MIP_4 and NMIP absorbents, the absorbents (50 mg) were added into 10-mL bromhexine solutions at concentrations of 1–500 $\mu g L^{-1}$, and the suspensions were mechanically shaken at room temperature, followed by the removing of the absorbents centrifugally. The remained bromhexine in the supernatant was measured by HPLC-UV. The adsorption isotherm which is the number of milligrams adsorbed per gram of adsorbent (Q) versus the equilibrium concentration of bromhexine is shown in Fig. 5. According to these results, the maximum amount of bromhexine that can be absorbed by MIP_4 was found to be 78 $mg g^{-1}$ (180 $\mu mol g^{-1}$) at the pH level of 5.2. As all the accessible specific cavities of the MIP_4 are saturated, the retention of the analyte is only due to non-specific interactions, which can be approximately identical for MIP and NMIP polymers.

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, 31]. For equilibrium batch rebinding experiments, a known mass of the template in solution

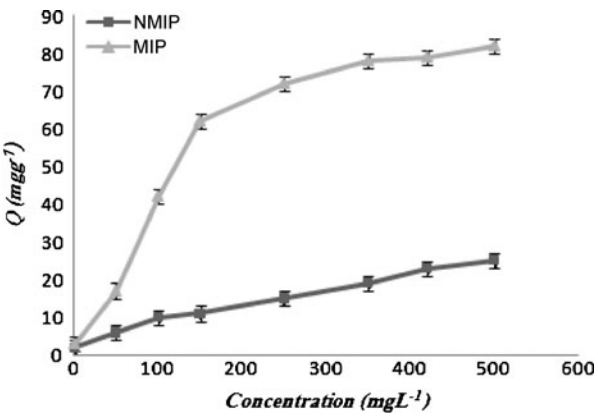

Fig. 5 Curve of capacity obtained after the loading of 5 mL aqueous solution spiked with increasing amounts of bromhexine onto the MIP particles (mean±SD, n=3)

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 [32, 33]. Dextromethorphan and diphenhydramine as antitussive (cough suppressant) drugs, ambroxol as an active metabolite of bromhexine, 2, 4-dibromo aniline, and dimethyl cyclohexzyl amine as structural analogs of bromhexine were selected to investigate the selectivity of the MIP. Their molecular structures are shown in Fig. 6. Solutions of all the compounds were prepared individually with the concentration of 50 $\mu g L^{-1}$. 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 analogs with the MIP were much higher than that of the NMIP. It was revealed that the bromhexine 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

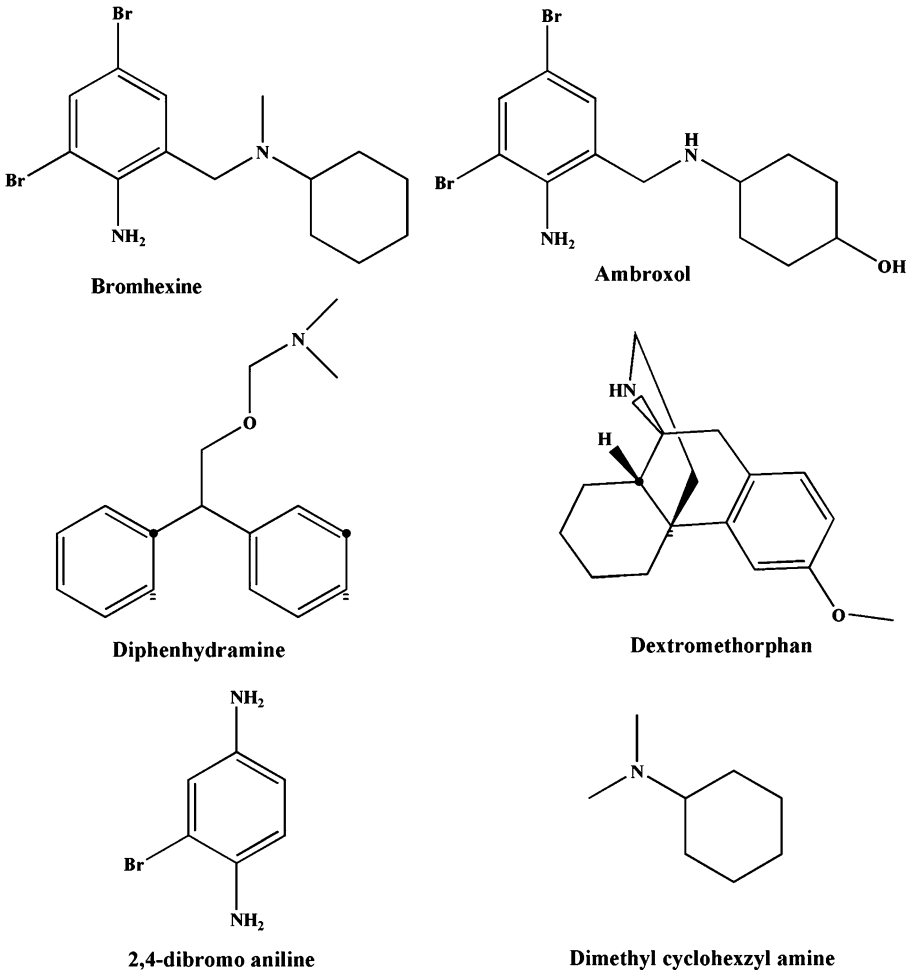

Fig. 6 Chemical structures of investigated drugs

Table 4 Adsorption of 2, 4-dibromo aniline, bromhexine, ambroxol, diphenhydramine, dextromethorphane, and dimethyl cyclohexzyl amine with MIP_4 and NMIP at 50 $\mu g L^{-1}$ concentration

Compounds	Adsorption (%)	
	MIP_4	NMIP
2, 4-dibromo aniline	33±2.5	17±1.5
Bromhexine	90±1.5	17±2
Ambroxol	60±2	16±2
Diphenhydramine	21±2	14±1.5
Dextromethorphane	16±1.5	14±1
Dimethyl cyclohexzyl amine	52±1	18±2.5

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

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.

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 bromhexine delivery and the results were compared with NMIP particles. We studied the release of bromhexine from polymer particles in hydrochloric acid (pH 3.0) and phosphate buffer (pH 6.0 and 8.0), 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.

Effect of pH

The release of bromhexine from MIP_4 and NMIP was investigated as a function of the pH of the media (Fig. 7). At the pH level of 8.0, the release of both polymers was dramatically faster than at the pH levels of 6.0 and 3.0, with 100% of the release occurring within 2 h for NMIP and 7 h for MIP_4. However, the release of the polymers was delayed up to 6 h for NMIP and up to nearly 17 h for MIP_4 in the 6.0 pH buffer. The release of bromhexine at the pH level of 3.0 was delayed more than other pH levels, 13 h for NMIP and nearly 36 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 bromhexine 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 bromhexine. 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 with NMIP although at the pH level of 3.0 the difference in release was the highest. At pH values below the pKa 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

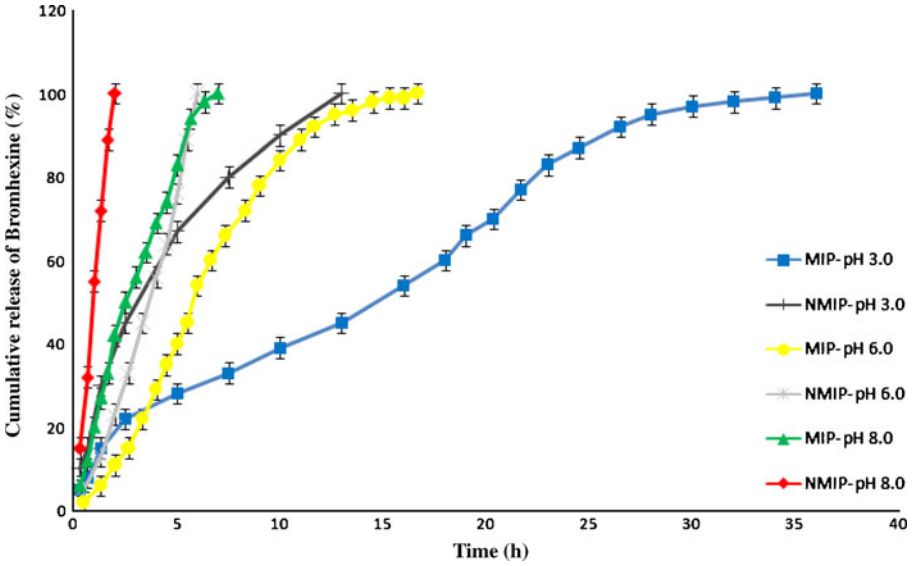

Fig. 7 Release profile of 50 mg bromhexine imprinted polymer at 37 °C and various pH levels of 3.0, 6.0, and 8.0. Media volume, 5 mL (mean±SD, n=3)

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 chains and the PMAA backbone, and also the subsequent rupture of the hydrogen bonds. This

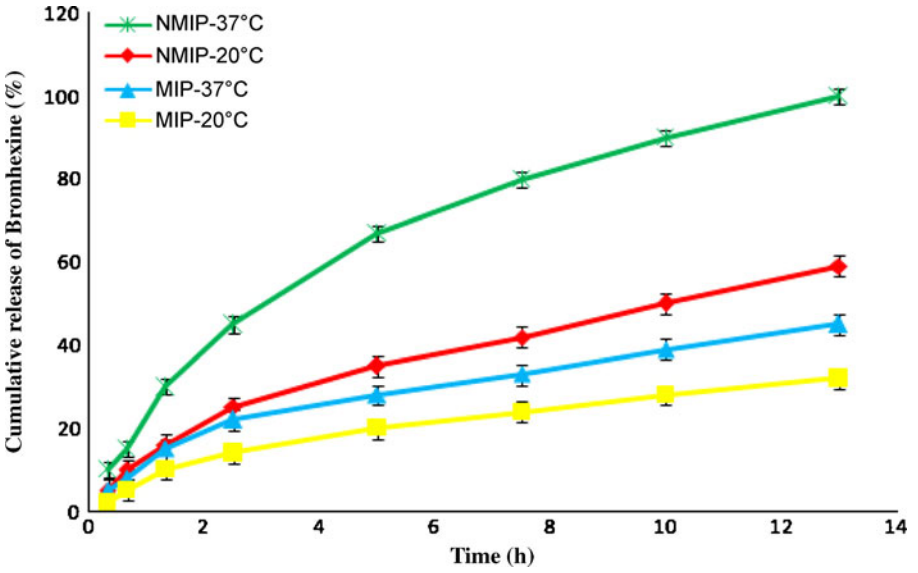

Fig. 8 The effect of temperature on the release profile of 50 mg bromhexine imprinted polymer with the pH level of 3.0 (mean±SD, n=3)

phenomenon led to decomplexation and the matrices could not control the release of bromhexine, as a result, drug release occurred at a much faster rate.

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. 8 at room temperature (25 °C) the slower release of bromhexine occurred in both polymers. Nevertheless, the difference between MIP_4 and NMIP was still obserat 25 °C.

Conclusions

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 bromhexine. 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 bromhexine and medium nature and pH are discussed. In this case, the monomer/bromhexine ratio of 8:1 showed the best specific affinity of 73% 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 bromhexine, 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 bromhexine related to non-imprinted polymers.

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