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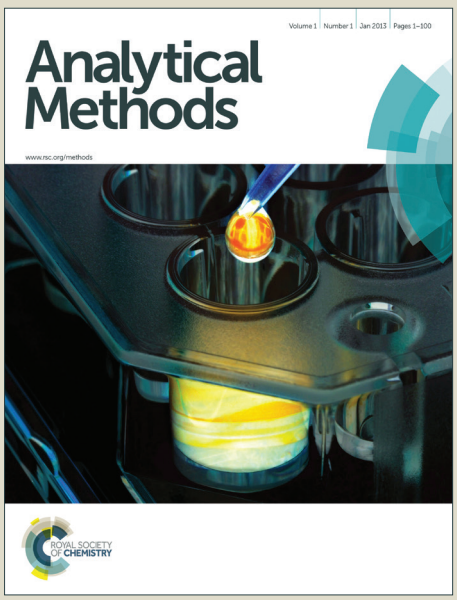

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ARTICLE

Synthesis of a novel cross-linker doubles as functional monomer for preparing water compatible molecularly imprinted polymer

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New bifunctional monomer acting as both crosslinker and functional monomer was synthesized and applied in preparing water-compatible naproxen sodium imprinted polymers. The bifunctional feature was endowed by including a quaternary ammonium as cationic functionalized group in the middle for reaction with anionic molecules, together with two reactive vinyl groups on both ends for polymerization. The monomer owned superb water solubility, which was particularly conducive to prepare MIP in aqueous solution. Taking advantage of this double functionalized monomer, naproxen sodium imprinted polymers were manufactured in aqueous media. A small quantity of the new monomer embedded in the polymers demonstrated a significant influence on the binding performance of the MIPs. Results of rebinding experiments revealed that in water, the bifunctional monomer based MIPs exhibited much higher adsorption capacity (34.4 mg g^{-1}) than acrylamide and 2-vinyl pyridine based MIPs (8.6 mg g^{-1} and 8.9 mg g^{-1}, respectively). The maximum imprinting efficiency of the MIP reached 9.1. Besides, recoveries of template spiked in distilled water, drinking water and waste river water were 85%, 84% and 70%, respectively. We believe that the new bifunctional monomer can be extended to prepare more water compatible MIPs.

Introduction

Molecular imprinting is a versatile and straightforward method to prepare artificial receptors for a given target molecule.[1-5] Due to the high selectivity, low cost of preparation, good physical and chemical stability, molecularly imprinted polymers (MIPs) have been applied widely in many fields such as solid-phase extractions,[6] chromatographic separations,[7] catalysis, drug delivery systems[8] and biosensors.[9]

Generally, MIPs were synthesized by copolymerization of functional monomer with large quantity of cross-linker in the presence of template molecule. The role of functional monomer was to provide functional groups and form a complex with template by covalent or non-covalent interactions. Crosslinker served to fix functional monomer/template complex, forming highly cross-linked rigid polymer. After removal of the template, cavities with memory of the shape and functional groups of template possessed highly selective recognition toward the template molecule. Usually the best MIP formulation is a very time-consuming process to achieve and complicated by optimization of variables such as the amounts of functional monomers, crosslinkers and templates. Moreover, a large amount of cross-linking agent (around 80–90%) had to be used to preserve the memory of template in MIPs. As a result, only a small portion of the imprinted sites remained available leading to the undesired low adsorption capacities.[10-12]

Recently, a new type of MIP was prepared by simply using one monomer acted as both crosslinker and functional monomer.[13-16] By this way, optimizing processes in traditional MIP including the amount of functional monomer and cross-linker, the ratio of functional monomer/crosslinker, and the ratio of functional monomer/template were all eliminated. More important thing lies in that this type of crosslinker can act as functional monomer simultaneously. Therefore, MIPs formulated with the crosslinking monomer possessed much more imprinting sites and exhibited enhanced adsorption capacities over traditional MIPs correspondingly.[14] Unfortunately, these MIPs were synthesized in aprotic organic solvent, and exhibited their best performance only in non-aqueous environment. This is because hydrogen bonding interactions were utilized in manufacturing these MIPs and the presence of polar solvent, especially water, would strongly disturb this interaction.[17]

Actually, many target molecules of interest are only present in water and analyses need to be carried out in aqueous environment, such as small molecular organic pollutants in wastewater or proteins in bodily fluids. So far, most of the MIPs were synthesized by non-covalent approach based on hydrogen bonding, which were not suitable for use in water as discussed above. On the other hand, in aqueous media target molecules can bind in an aspecific manner to the MIPs because of the hydrophobic effect,[18] which severely hampers applications of MIPs in aqueous condition. Therefore, it is important to develop water compatible MIPs, which can bind target molecules in a specific and selective manner in pure aqueous environment. Meanwhile, recognition performance in

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aqueous media is also need to be addressed and it is possible to be solved by developing a new type of water-soluble crosslinker double as functional monomer.

In this study, we propose to synthesize a water-soluble cross-linking functional monomer (WSCFM) aiming at preparing high performance water compatible MIP. First of all, being a hydrophilic quaternary ammonium salt together with two terminal vinyl groups on both sides, this new crosslinking monomer possesses superb water solubility. Additionally, the bifunctional monomers bearing a positive charge could form electrostatic interaction with negatively charged templates in water. All of these characteristics enabled the bifunctional monomer capability for preparing water compatible MIPs. To validate this, naproxen sodium (NS), an emerging drug pollutant in waste water, was employed as the model template. NS imprinted polymers were prepared in water with the new bifunctional monomer by precipitation polymerization and adsorption behaviours were evaluated in aqueous medium.

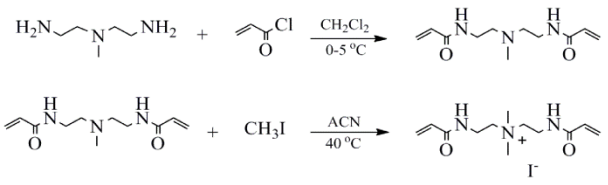
Experimental

Materials

N-methyl-2,2'-diaminodiethylamine, acryloyl chloride, methyl iodide, Amberlite IRA-400 (Cl^-) resin, acrylamide, 2-vinyl pyridine, naproxen sodium, sodium benzoate, and ibuprofen sodium were purchased from Beijing J&K Co., Ltd. (Beijing, China). N,N'-methylenebisacrylamide (MBA) was obtained from Sigma-Aldrich (St. Louis, MO, USA). Potassium persulfate, dichloromethane, acetonitrile was purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). All other reagents were of analytical grade and were used without further purification.

Synthesis of water-soluble cross-linking functional monomer (WSCFM)

The synthesis route of the WSCFM is shown in Scheme 1. N-methyl-2,2'-diaminodiethylamine (0.5 mmol) was dissolved in a round bottom flask containing 20 mL dichloromethane and 7.5 mL aqueous NaOH solution (6 M). Acryloyl chloride (0.7 mmol) dissolved in 20 mL of dichloromethane was added dropwise into the flask at 0-5 °C within 30 min. The mixture was then stirred for 3 h, and the organic phase was subsequently washed twice with saturated sodium carbonate aqueous solution. The dichloromethane was evaporated, and a pale yellow solid was observed. Then the above solid was dissolved in 2 mL acetonitrile, followed by the addition of 1 mL methyl iodide. The mixture was stirred for 12 h at 40 °C. Then, the acetonitrile and excess methyl iodide were removed with rotary evaporation apparatus, and a final yellowish, oily product was obtained. To prohibit iodide ions be oxidized into solid iodine by the initiator during the preparation of MIPs, we exchanged iodide ions into chloride ion by anion exchange resin before usage.



Scheme 1. Synthetic route of WSCFM.

Preparation of naproxen sodium imprinted polymers

MIPs and non-imprinted polymers (NIPs) were synthesized using precipitation polymerization method. The compositions of MIPs were described in Table 1. NIPs were synthesized exactly the same way with the void of a template molecule. Briefly, Naproxen sodium and WSCFM were dissolved in 1 mL water and the mixture was incubated for 30 min. Then N,N'-methylenebisacrylamide (MBA) dissolved in 5 mL of Na_2HPO_4 aqueous solution (0.5 M) was added. The solution was sonicated and degassed using N_2 for 5 min. Free radical initiator potassium persulfate was added and the flask was sealed. Polymerization proceeded in a water bath at 70 °C for 6 h. The resultant particles were collected by centrifugation at 10, 000 rpm for 15 min. The template molecule was extracted by washing repeatedly with mixture of methanol/ammonia (9:1, v/v) for 12 h. Then the particles were sonicated with methanol to remove residual ammonia and were dried in vacuum.

Table 1 Compositions of the monomer mixtures used for MIPs synthesis

Formulation	Template	Functional monomer		Cross-linker		Content of WSCFM (%)
	NS (mmol)	AM (mmol)	2-VP (mmol)	WSCFM (mmol)	MBA (mmol)	
MIP_1	0.2	0	0	0.0	1.20	0
MIP_2	0.2	0	0	0.06	1.14	5
MIP_3	0.2	0	0	0.12	1.08	10
MIP_4	0.2	0	0	0.18	1.02	15
MIP_5	0.2	0	0	0.24	0.96	20
MIP_6	0.2	0	0	0.30	0.90	25
MIP_7	0.2	0.24	0	0	1.20	0
MIP_8	0.2	0	0.24	0	1.20	0

Chemical characterization

^1H NMR and ^{13}C NMR spectra (300 and 75 MHz for ^1H and ^{13}C, respectively) were recorded at room temperature in D_2O on BRUKER DPX (Karlsruhe, Germany). FT-IR spectra were recorded on a Nicolet NEXUS-470 Spectrometer (Madison, USA) from KBr pellets at room temperature. Samples (2 mg) were thoroughly ground with KBr and pellets were prepared using a hydraulic press under a pressure of 600 kg cm^{-2}. All spectra were recorded with an accumulation number of 32 scans and a resolution of 8 cm^{-1}.

Scanning electron microscope (SEM) analysis

Surface morphologies were examined by SEM using a JEOL JSM 5400 scanning microscope from JEOL Ltd. Co. (Tokyo, Japan) at an

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accelerating voltage of 15 kV. Samples were mounted on metal stubs and coated with gold–palladium by Denton Vacuum Desc II.

Particle size and porosity measurements

The particle size and size distribution of the particles were measured by PCS (Malvern ZetasizerZS, Malvern, UK). Particles were suspended in acetonitrile and measured at a fixed scattering angle of 90 °. The surface areas and porosities of the MIPs and NIPs were measured by nitrogen adsorption porosimetry using a TriStar surface area and porosity analyzer (Micrometrics Instruments, Norcross, GA, USA). Prior to measurement, 200 mg samples of the polymers were heated at 80 °C for 5 h in vacuum. The specific surface areas were calculated using the BET method, and the specific pore volumes and average pore diameters were calculated by the BJH method.

Binding experiments

MIPs or NIPs (5 mg) were added into 5 mL naproxen sodium aqueous solutions with different concentrations ranging from 0 to 0.20 mg mL^{-1}. The mixtures were agitated on a rocking table at ambient temperature for 1 h followed by filtration. The amount of naproxen sodium in the supernatant was detected using a Shimadzu 160-A UV-vis spectrophotometer (Shanghai, China) at a wavelength of 332 nm. Meanwhile, the adsorption dynamics of the MIPs was performed by measured the free naproxen sodium (0.05 mg mL^{-1}) in the supernatants at certain time intervals (10-120 min). The selectivity of the MIPs was investigated using ibuprofen sodium (IS) and sodium benzoate (SB) as the competitive compounds. The concentration of each analyte was 0.10 mg mL^{-1}.

The adsorption capacity (Q) was calculated by subtracting of the free fraction from the initial concentrations using the following formula:

$$Q = (C_i - C_f) \times V / W$$

Where C_i (mg mL^{-1}) is the initial concentration of the analytes, C_f (mg mL^{-1}) is the final concentration of the analytes, V (mL) is the volume of the adsorption mixture, and W (g) is the mass of polymer in each rebinding mixture.

For the recovery experiments, distilled water was purified by Milli-Q system (Millipore, Bedford, USA), drinking water (Wahaha) was purchased from local shop, and waste water was obtained from local polluted river (Xiao Jiahe, Beijing). Water samples were filtered through 0.45 μm filters and stored at 4 °C in glass bottles before usage. Recovery study was carried out on the samples (5 mL) spiked with 60 μg/mL NS. 100 mg MIPs were added to the mixtures and incubated for 1 h followed by filtration. After that, the adsorbed NS was eluted from the MIP particles with 10 mL methanol/ammonia (9:1, v/v) and the concentration of the NS was detected using a Shimadzu 160-A UV-vis spectrophotometer (Shanghai, China) at a wavelength of 332 nm. The recovery (R) was calculated by the equation $R(\%)=C_f/C_i \times 100$, where C_i is the concentration of NS initially added, and C_f is the concentration of NS detected by MIPs.

All the experiments were performed in triplicate and error bars used to indicate the derived standard deviations.

Results and discussion

Synthesis and properties of WSCFM

The WSCFM was synthesized by a simple two-step method. Firstly, N-methyl-2,2'-diaminodiethylamine was reacted with acryloyl chloride, two double bonds were formed at both ends of the monomer during this process which was transformed into a cross-linker. Then, methyl iodide was used to react with the cross-linker to convert the tertiary amine group into a quaternary ammonium salt. In this way, the obtained product was given double functions: a cross-linker as well as a functional monomer. ^1H NMR and ^{13}C NMR spectra of WSCFM were shown in Fig. S1 and Fig. S2, respectively. As far as we know, this is the first time that bifunctional monomer was synthesized for preparing water compatible MIPs.

Unlike commonly used cross-linkers such as ethylene glycol dimethacrylate (EGDMA), which are insoluble in water, the WSCFM possessed extremely high solubility in water. As shown in Fig. 1, WSCFM (50 mg) was completely dissolved in 1 mL water at 20 °C. The highly solubility of WSCFM is attributed to the dissociation of quaternary ammonium salt monomer. In contrast, an oil layer was formed after adding the same amount of EGDMA into 1 mL of water indicating they were basically insoluble in water. N,N-methylenebisacrylamide (MBA), commonly the only option of water soluble cross-linker for MIPs synthesis in aqueous system, its solubility was not desirable and saturated state was reached merely at 50 mg/mL. Thus, instead of using aprotic and low polar organic solvents such as toluene, acetonitrile and chloroform, MIP was ready to be made in pure aqueous solution using the WSCFM.

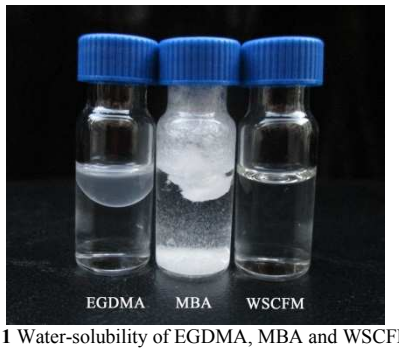

Fig. 1 Water-solubility of EGDMA, MBA and WSCFM.

Overall, the featured structure with two double bonds and quaternary ammonium salt endowed this new monomer with double functions. More importantly, this bifunctional monomer could be used to manufacture water-compatible MIP which was highly demanded for water-soluble targets.

Characterization of MIP particles

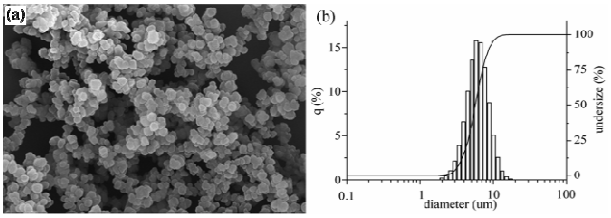

Fig. 2. (a) Scanning electron micrographs of MIPs and (b) particle size distribution.

Fig. 2a shows the SEM image of WSCFM based MIPs and it was found that the prepared material is consisted of conglutinated particles. Specific surface areas and pore volume of the imprinted polymers (48.931 $m^2 g^{-1}$ and 0.107 $cm^3 g^{-1}$) was considerably higher than those of the non-imprinted polymers (19.679 $m^2 g^{-1}$ and 0.067 $cm^3 g^{-1}$). These data demonstrated that the MIPs have many imprinted cavities created by removal of the template molecules. These cavities remembered the shape of the template and could be used to recognize the target template.

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Fig. 3 shows FT-IR spectra of raw template and the synthesized polymers. The peak at 1712 cm^{-1} was for the C=O absorption of the bifunctional monomer and MBA. The stretching vibration absorption peaks of N-H in amide group appeared in the regions of 1455-1391 cm^{-1}. The peak 862 cm^{-1} appeared in the spectrum of naproxen sodium template was assigned to the bending vibrations of the C-O-C in the structure. The peak 549 cm^{-1} is another characteristic peak belonging to naproxen (Fig. 3a). These characteristic peaks also emerged in the spectrum of the MIP precursor (without template removal, Fig. 3b). The spectra of MIP (Fig. 3c) and NIP (Fig. 3d) were found to be almost identical, but the characteristic peaks of naproxen sodium disappeared. These results confirmed that the MIPs were synthesized successfully and template molecules were removed completely.

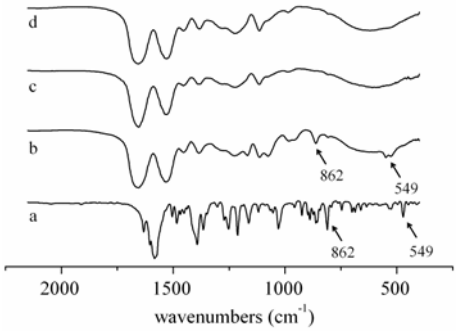

Fig. 3. FT-IR spectra of (a) naproxen (b) MIP without template removal (c) MIP and (d) NIP.

Evaluation of bi-functional effect of WSCFM on MIPs

Generally, MIPs were synthesized by the use of a high level of crosslinker (usually around 80-90%) to construct the memory to the template in the polymer network.[19] Therefore, only 10-20% of the imprinting cavities can reuptake the template, and the capacity of the network was drastically reduced.[20, 21] Unlike traditional crosslinkers, the newly synthesized WSCFM could act as a functional monomer at the same time. Therefore, the resulting MIPs owned more imprinting sites at the equal cross-linking degree. As shown in Fig. 4, the imprinting sites (illustrated as pores inside the balls above the columns) increased as the content of as-prepared WSCFM increased from 0%-20% (MIP1-MIP5). The amount of NS adsorbed by 0% WSCFM based MIPs (4 mg g^{-1}) was as low as corresponding NIPs. However, the capacity jumped to 17 mg g^{-1} when 5% WSCFM was used, and kept increasing as the molar ratios of WSCFM increased. When 20% WSCFM was added, the maximum adsorption capacity of the MIP reached 35 mg g^{-1}, while more WSCFM (25%, MIP6) resulted in difficult polymerization. This may be related to the electrostatic repulsion between the extra cationic quaternary ammonium salt groups. The first step product (WSC) before cationization as shown in Fig.1 was also employed to synthesize MIP with the same process. Experimental results (Fig.S3) showed that the adsorption capacities for NS were low and kept constant as the content of WSC increased from 0%-20%. Therefore, WSC only acted as a crosslinker, while WSCFM acted as both functional monomer and crosslinker.

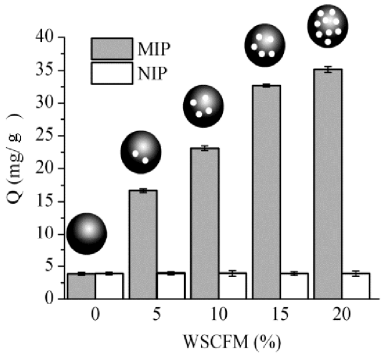

Fig. 4. Effect of WSCFM ratios on binding amounts of naproxen sodium on MIPs and NIPs (the concentration of template was 0.05 mg mL^{-1}).

To demonstrate the super water compatibility of the WSCFM based MIPs, acrylamide (AM) and vinyl pyridine (2-VP), which were used for synthesis of naproxen imprinted polymers in organic solvent such as chloroform and toluene,[22,23] were employed as the functional monomers in this experiment. The compositions of three MIPs (MIP5, MIP7, and MIP8) were listed in Table 1, and the whole experimental process was the same as described in experimental section. As shown in Fig. 5, the WSCFM based MIPs revealed considerably higher binding capacity for naproxen sodium in water than AM or 2-VP based MIPs. The capacity of AM based MIPs (8.6 mg g^{-1}) was as low as the corresponding NIPs (8.9 mg g^{-1}). Obviously, AM was not suitable for synthesis of water compatible MIPs. This is because the hydrogen bonding interaction between the AM and template was unfavourable for imprinting processes conducted in aqueous media.[24] When water was used as porogen during the synthesis process, hydrogen bonding interactions between AM and the template were disrupted leading to weak imprinting effect. The AM based NIP and MIP still had some adsorption capacity for template, since target molecule can bind in an aspecific manner to the matrix because of the hydrophobic effect which is well established in water.[25] 2-VP was a frequently used functional monomer based on π-π interactions with acidic target molecules for MIP preparation. In this experiment, the adsorption capacity of 2-VP based MIPs (8.9 mg g^{-1}) was almost doubled than that of 2-VP based NIPs (4.5 mg g^{-1}), whereas much lower than that of WSCFM based MIPs (34.4 mg g^{-1}). The imprinting efficiency (I_e) calculated by the equation $I_e=Q_{MIP}/Q_{NIP}$ was used to evaluate the special recognition ability of the MIPs. For WSCFM based MIPs, the Ie value was 9.1, which was much higher than that of 2-VP based MIPs (I_e 2.0). In addition, the capacity of bifunctional monomer based MIPs was higher than that of AM and 2-VP based MIPs prepared in organic solvent (Fig.S4). These results strongly demonstrated that WSCFM based MIPs had high specific adsorption capacity for target template compared to conventional functional monomers.

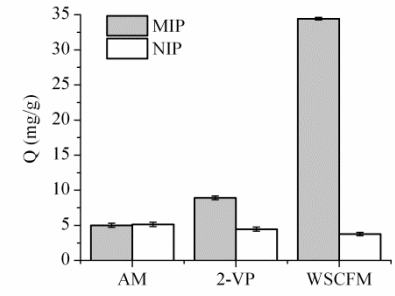

Fig. 5. Influence of functional monomer AM, 2-VP and WSCFM on naproxen sodium binding to MIP and NIP (the concentration of template was 0.05 mg mL^{-1}).

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Static and dynamic adsorptions of WSCFM based MIPs and NIPs

Fig. 6a shows the binding isotherms of MIP and NIP for naproxen sodium (20-200 μg mL^{-1}) in distilled water. The adsorption capacities of both the MIP and NIP increased as the initial concentrations increased. The adsorption capacity of the MIP was much higher than that of the NIP for different individual concentration of naproxen sodium. When the initial concentration was 150 μg mL^{-1}, the maximum adsorption capacities of the MIP and NIP were 51.0 and 10.0 mg g^{-1}, respectively. Small amounts of naproxen sodium were bound to the NIP because of the existence of cationic groups in the polymers.

In this study, the adsorption equilibrium was reached after 10 min for both MIP and NIP (Fig. 6b). This result revealed that the recognition time was much faster than that of typical imprinted materials.[26-28] The short equilibrium time was mainly ascribed to the strong electrostatic binding between cationic WSCFM and anionic naproxen sodium in water. Therefore, it is very efficient for this material to be applied in practice.

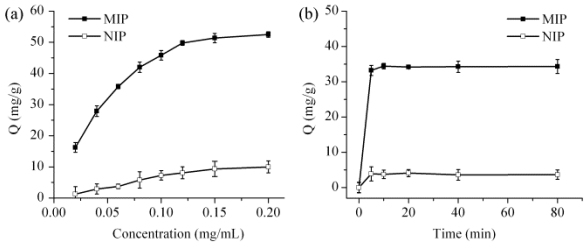

Fig. 6. (a) Static and (b) dynamic adsorption curves of the MIPs and NIPs for naproxen sodium.

Selectivity investigation of WSCFM based MIPs

Sodium benzoate (SB) and ibuprofen sodium (IS) were employed as the structural analogues of NS to evaluate the selectivity of WSCFM based MIPs in aqueous media. As shown in Fig. 7. The amount of template NS adsorbed by the MIPs (46 mg g^{-1}) was found to be significantly higher than that of sodium benzoate (16 mg g^{-1}) and ibuprofen sodium (27 mg g^{-1}). While NIPs showed unbiased enrichment towards benzoate sodium, ibuprofen sodium, and naproxen sodium. The I_e of NS, BS, and IS were 9.0, 4.2, and 4.3, respectively. These results indicated that the MIPs possessed a high level of selectivity for the template molecule naproxen sodium. In contrast, only chemical interaction retained on the NIPs, and the selectivity was therefore comparable for NS, BS, and IS. The selectivity was promoted not only by the binding sites created by the template molecule effectively leaving a memory of its size and shape, but also by the strong electrostatic interactions that occurred between the target molecules and the WSCFM.

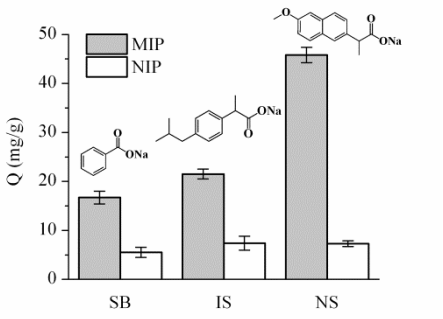

Fig. 7. Selectivity of the MIPs and NIPs to Sodium benzoate (SB), Ibuprofen Sodium (IS) and Naproxen Sodium (NS).

Regeneration of WSCFM based MIPs

One of the major advantages of MIPs compared to other adsorption materials is their good physical and chemical stability. In this work, the regeneration of the WSCFM based MIPs was tested by 8 consecutive loading, washing, and elution procedures. The recovery (RE) was calculated using the equation $RE=Q_n/Q_1*100$, where Q_1 is the amount of NS adsorbed by MIPs in the first use and Q_n is the amount adsorbed in each subsequent use. As shown in Fig. 8, RE was 98% after eight rebinding cycles. This demonstrates the good reusability of these MIPs for the detection of NS.

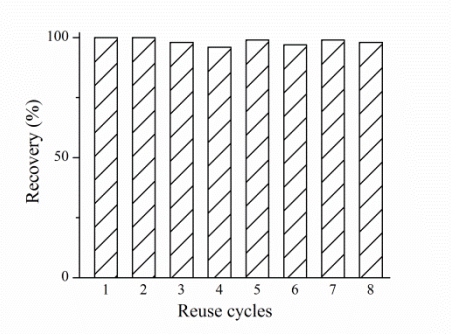

Fig. 8 Regeneration of the MIPs

Application to water sample analysis

To demonstrate the applicability of the MIP for real environmental application, recovery efficiency of NS spiked in different water sources were evaluated. Among them, river water samples were collected from local rivers (Xiao Jiahe, Beijing). These water samples were filtered through 0.45 μm filters and stored at 4 ℃ in glass bottles before usage. As no NS was detectable by the proposed method, a recovery study was carried out on the samples spiked with 60 μg/mL NS. As shown in Table 2, the recoveries of NS were 85% and 84% from distilled water and drinking water, respectively. Even in the polluted city river sample, the recovery reached 70%. This suggests that as-synthesized WSCFM based MIPs is applicable to detect NS in environmental water samples.

Table 2 Recoveries of NS spiked in various environmental samples

Samples	Added (μg/mL)	Found (μg/mL)	Recovery (%)
Distilled water	60	50.7	85±3.6
Drinking water	60	50.1	84±2.7
Waste water	60	42.1	70±4.0

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Conclusions

In this work, pure water compatible MIP was prepared in aqueous solution with a new synthesized water-soluble cross-linking functional monomer (WSCFM). The synthesis process was simple, mild and efficient. Due to the superb solubility of WSCFM, the synthetic media of MIP is totally organic-solvents free. The resulting WSCFM-MIPs showed higher adsorption capacity and imprinting efficiency in pure aqueous media than other common functional monomer based systems. Since the polymer bearing quaternary ammonium ions, the newly prepared MIP had a specific recognition towards its template in aqueous media. Finally, the MIPs were successfully applied in the collection of NS spiked in waste water samples. We believe that the new bifunctional monomer WSCFM could be further applied in synthesis of water compatible MIPs for more targets.

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Notes and references

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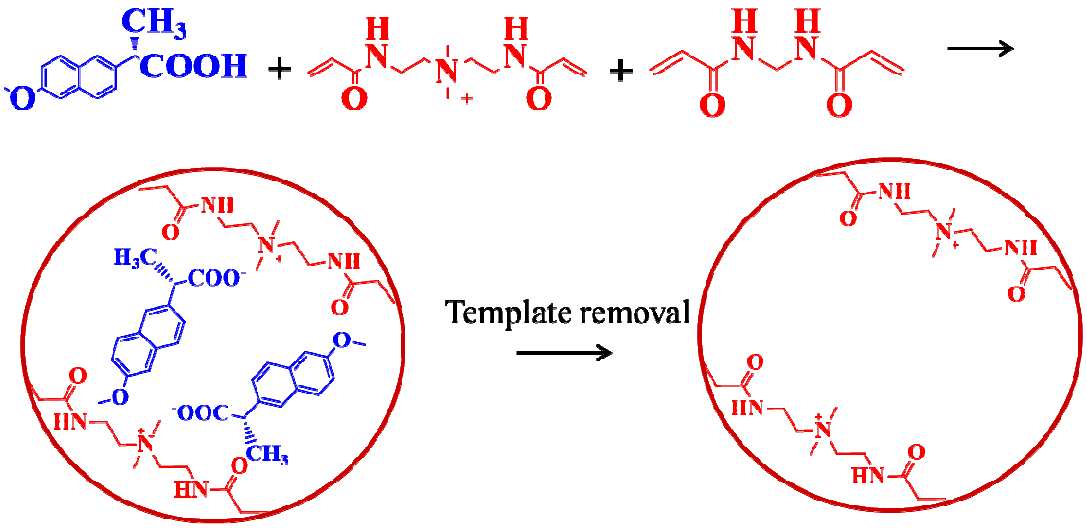

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