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Selective adsorption of norfloxacin in aqueous media by an imprinted polymer based on hydrophobic and electrostatic interactions

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Abstract

Based on hydrophobic and electrostatic interactions, a norfloxacin (NOF) imprinted polymer (P_1) was prepared by the combined use of bismethacryloyl-β-cyclodextrin (BMA-β-CD) and 2-(diethylamino)ethylmethacrylate (DEAEM) as functional monomers. Compared with the molecularly imprinted polymers (MIPs) using only BMA-β-CD or DEAEM as a functional monomer, P_2 and P_3, respectively, P_1 showed higher binding affinity and specificity for NOF in aqueous media. Scatchard plot analysis revealed that two classes of binding sites were formed in the imprinted polymer with dissociation constants of 0.32 μmol/ml and 1.19 μmol/ml, respectively. It demonstrated that the combination of hydrophobic effect and electrostatic interaction in molecular imprinting was essential for the improvement of the selective ability of the imprinted polymer. Factors that influenced rebinding of the imprinted polymer including pH, water content in the adsorbed solution were explored.

Keywords: Molecular imprinting; Norfloxacin; β-Cyclodextrin; Binding specificity; Hydrophobic effect

1. Introduction

Molecular imprinting technique is one of the most promising methodologies for synthesizing artificial receptors and has already demonstrated its potential for the separation and analytical application [1–6]. In non-covalent approaches to molecular imprinting, multiple interactions between templates and functional monomers are crucial not only for producing ligand-selective recognition sites in the imprinted polymers, but also for recognizing the templates. Non-covalent interactions such as hydrogen bonding, π–π bonding and electrostatic interaction, hydrophobic effect and metal ion-coordination, can be exploited to organize the functional monomers around the template. Hydrogen bonding is the most commonly exploited interaction for the non-covalent molecular imprinting. However, hydrogen bonding interactions between template and functional monomers are easily destroyed in aqueous media because aqueous solvents can compete with the template for the functional monomers. Previous studies have shown that an imprinted polymer prepared based on hydrogen bonding interactions lost its molecular recognition ability in an aqueous media or organic solvents with high polarity [7,8]. Since biological recognition mainly occurs in aqueous systems, and many biological important compounds are not very soluble in non-polar organic solvent, it is quite important to make MIPs capable of recognition in aqueous media.

For this purpose, different methods, such as metal ion-mediated imprinting [9], stoichiometric imprinting [10–12], have been investigated during the past few years. Combining the features of β-cyclodextrin (β-CD) and molecularly imprinting method, the molecularly imprinted poly(β-CD) was prepared and was successfully used to separate some biomolecules, such as steroids and cholesterols in aqueous solution [13–16]. The orientation of β-CD molecule residues in the imprinted poly(β-CD) was suitable for the cooperative binding of the templates.

Quinolones are antibiotics used widely to prevent and treat a large variety of infectious diseases in human and veterinary medicine. It is important to develop analytic methods for determining these drugs present in environment at low levels.

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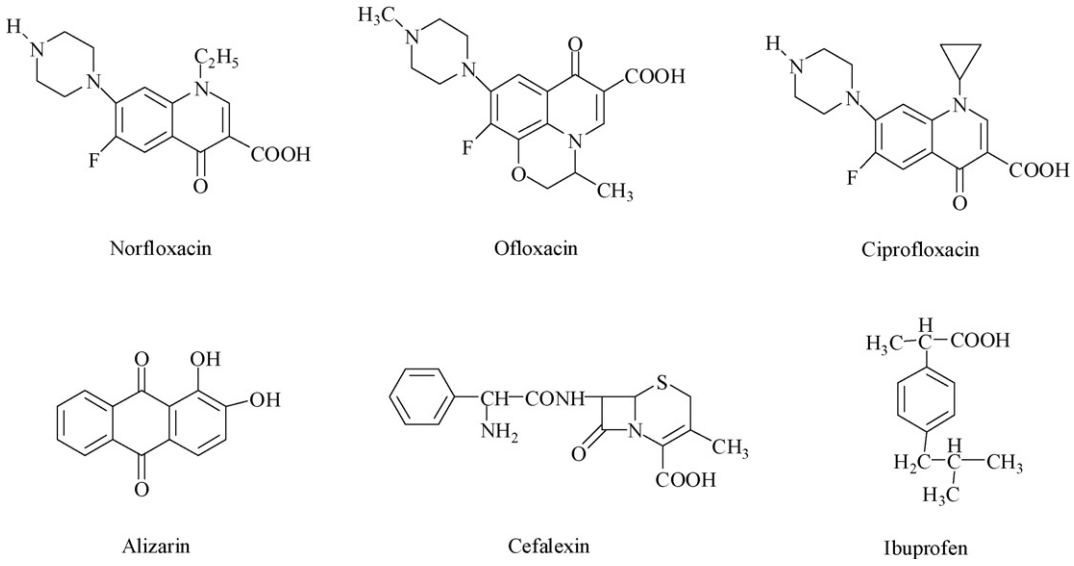

Fig. 1. Structures of NOF and related substrates used in this study.

Although an artificial receptor for enrofloxacin has been previously reported [17], it showed a high degree of cross-reactivity for other antibiotics. In this study, we attempted to synthesize MIPs with strong affinity and high specificity toward a fluorinated quinolone, norfloxacin (NOF, Fig. 1) in aqueous media. We adopted a similar strategy developed by Piletsky, who used the combination of an acrylate derivative of β-CD along with an acidic monomer for a small molecule receptor toward phenylalanine [18]. A MIP was prepared using NOF as the template, 2-(diethylamino)ethylmethacrylate (DEAEM) and bismethacryloyl-β-cyclodextrin (BMA-β-CD) as functional monomers. In order to gain more insight into the origin of the recognition properties of the imprinted polymers, two referenced MIPs using only BMA-β-CD or DEAEM as a functional monomer were also prepared. The recognition abilities of the synthesized polymers were studied. Some factors that influenced rebinding of the imprinted polymers including pH, water content in the adsorbed solutions were explored.

2. Experimental

2.1. Materials and instruments

β-CD was purchased from Shanghai Chemical Plant (Shanghai, China), it was recrystallized from water and dried under vacuum at 110.0 °C for 24 h. Ethylene dimethacrylate (EDMA) was obtained from Jiangsu Anli Chemical Plant (Suzhou, China), it was distilled under vacuum after being extracted with 10% sodium hydroxide and dried over anhydrous magnesium sulfate. 2,2′-Azobisisobutyronitrile (AIBN) and alizarin were obtained from Shanghai Chemical Plant and AIBN was recrystallized from methanol. NOF, cefalexin, ibuprofen, ciprofloxacin and ofloxacin were obtained from South Hospital (Guangzhou, China). DEAEM was purchased from Acros (NJ, USA) and was distilled under vacuum to remove the inhibitor. DMSO and pyridine were purchased from Guangzhou Chemical Plant (Guangzhou). Before use, they were dried by molecular sieve 3A and distilled under vacuum. All the other solvents were of analytical grade and used as received.

Methacryloyl chloride was synthesized by the reaction of methacrylic acid and dichlorosulfoxide, 74 % yield: bp 97–98.5 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.02 (s, 3H, CH_3); 5.03 (s, 1H, $-CH_a=C-$), 6.50 (s, 1H, $-CH_b=C-$).

^{1}H spectrum was measured on a Mercury-plus 300 MHz spectrometer (Varian, USA). FT-IR spectrum was recorded on an EQUINOX55 FT-IR spectrophotometer (Bruker, Germany). UV–vis was performed on a UV2100 spectrophotometer (Unico, China). The differencial scanning calorimetry (DSC) analysis was performed under nitrogen using a DSC-204 (Netzsch, Germany) at heating rate 10 °C/min. The thermal gravimetric analysis (TGA) was performed using a TGS-2 (Perkin-Elmer, USA) at heating rate 10 °C/min under air atmosphere. The elemental analysis was measured on a Vario EL CHNS Elemental Analyzer (Elementar, Germany). The morphology of the polymer particles was characterised by field emission scanning eletron microscope using a Jeol model JSM-6330F (JEOL Ltd., Japan).

2.2. Synthesis of bismethacryloyl-β-cyclodextrin (BMA-β-CD)

The synthesis procedure of BMA-β-CD was as below: β-CD (18.50 g, 16.30 mmol) was dissolved in 120 ml of pyridine, the solution was cooled to 0 °C. Then, an ice-chilled solution of methacryloyl chloride (3.91 g, 37.50 mmol) in ether (20 ml) was added dropwise to this solution with stirring magnetically under nitrogen. The reactive mixture was slowly warmed to room temperature and stirred for 24 h. After that, the solvent was evaporated in rotary evaporator. The residue was washed with ethanol for several times and gave a white product in 71% yield. The product was substitutional isomers with 2.0 methacryloyl substitutions per β-cyclodextrin determined from the elemental

analysis (Anal. Calcd. for BMA-β-CD: C 46.09, H 5.99%; found: C 46.31, H 5.67%). FT-IR (KBr) ν (cm^{-1}): 3600–3000, 2928, 1726, 1635, 1489, 1406, 1154, 1080, 1031, 756, 683, 579.

2.3. Synthesis of BMA-β-CD–NOF complex

The 1:1 BMA-β-CD-NOF inclusion complex (1.59 g containing 1.0 mmol β-CD unit) was prepared following the literature [19]. NOF (0.638 g, 2.0 mmol) was dissolved in 60 ml of distilled water at 60.0 °C. To this solution, a solution of BMA-β-CD (2.54 g, 2.0 mmol) in distilled water (120 ml) was added dropwise under stirring. After being stirred at 60.0 °C for 3 h, the mixture was slowly cooled to room temperature and further stirred for 12 h. Then, the mixture was placed in refrigerator for 2 days. The precipitate formed was collected by filtration and washed with water, methanol in turn to remove the residual of BMA-β-CD and NOF. After drying in vacuum, a yellowish powdered product of the complex was obtained. DSC is a powerful analytical tool for the physicochemical characterization of association complexes of drugs with cyclodextrins. In the present work, DSC was applied to analyze NOF, BMA-β-CD, NOF/BMA-β-CD physical mixture (1:1) and BMA-β-CD–NOF complex (Fig. 2).

As shown in Fig. 2, DSC thermograms revealed marked structural differences between the physical mixture and the complex. The thermal profile of the physical mixture (Fig. 2c) showed both the unchanged BMA-β-CD endothermic broad bands at 66 °C and 232 °C and a well-distinct melting peak of NOF, which appeared at 220 °C. This indicated that NOF and BMA-β-CD maintained their original crystalline structures in the mixture. A different pattern was observed in the thermogram of the complex (Fig. 2d). The melting peak of NOF and the peak of BMA-β-CD (at 232 °C) disappeared. A new peak at 228 °C appeared together with the broadening of BMA-β-CD broad band (at 66 °C). These results were indicative of the changes in the structure of the substrates and a tight interaction between NOF and BMA-β-CD.

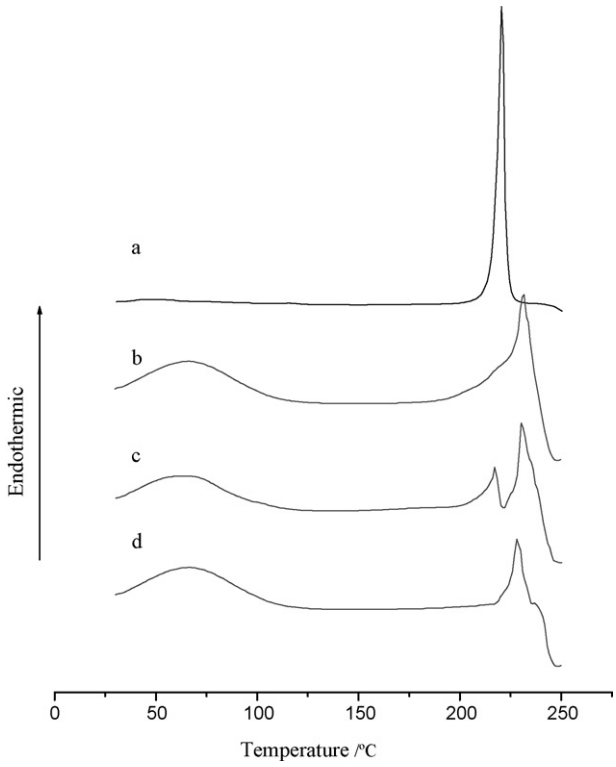

Fig. 2. DSC curves: NOF (a), BMA-β-CD (b), physical mixture (NOF/BMA-β-CD, 1:1) (c) and BMA-β-CD–NOF complex (d).

2.4. Polymer synthesis

The components of the reaction mixtures for making imprinted (P_1) and non-imprinted (NP_1) polymers are listed in Table 1. The synthesis procedure of the imprinted polymer P_1 is as follows (Fig. 3): BMA-β-CD–NOF complex and DEAEM were dissolved in DMSO in a 50 ml glass ampoule, EDMA and AIBN were added. After degassing and nitrogen purging, the ampoule was sealed under vacuum and the mixture was kept in a water bath at 60 °C for 24 h. The resultant rigid polymer was ground and passed through a 90 μm sieve. Fine particles were removed by repeated sedimentation in acetone. The obtained particles were Soxhlet extracted with a mixture of methanol–acetic acid (9:1, v/v) until NOF in the elution could no longer be detected at 276 nm by spectrophotometer. Then the particles were washed with methanol to remove residual acetic acid and dried under vacuum at 80 °C. The corresponding non-imprinted polymer (NP_1) was prepared similarly.

Two reference imprinted polymers (P_2, P_3) using only BMA-β-CD or DEAEM as a functional monomer and their corresponding non-imprinted polymers (NP_2, NP_3) were also prepared (Table 1).

2.5. Equilibrium binding experiments

Equilibrium binding experiments were carried out to evaluate the binding properties of the polymers. The polymer particles

Table 1
Composition of the polymerization mixtures for synthesizing polymers

Polymer	BMA-β-CD-NOF (mmol)	NOF (mmol)	BMA-β-CD (mmol)	DEAEM (mmol)	EDMA (mmol)	DMSO (ml)
P_1	0.63	–	–	0.63	6.0	10
NP_1	–	–	0.63	0.63	6.0	10
P_2	0.63	–	–	–	6.6	8
NP_2	–	–	0.63	–	6.6	8
P_3	–	0.63	–	0.63	10.1	8
NP_3	–	–	–	0.63	10.1	8

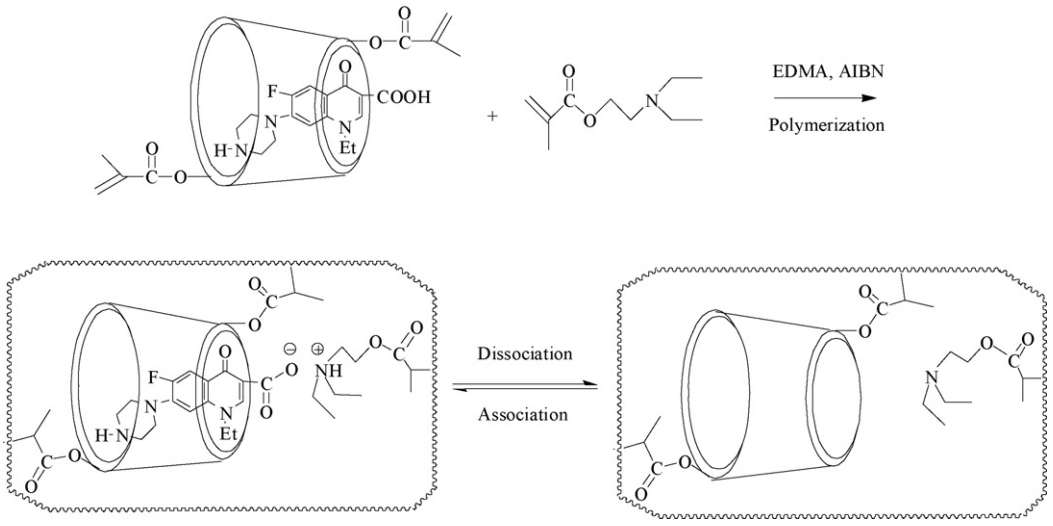

Fig. 3. Schematic illustration of the molecular imprinting procedure.

(20.0 mg) were placed in a 10 ml conical flask and mixed with 3.0 ml of a known concentration of solution of selected substrate. The conical flask was shaken for 6 h at 30 °C. Then, the mixture was filtrated through a 0.45 μm filter. After that, 1.0 ml of the filtrate was used and diluted to 10.0 ml with addition of solvent. The concentration of the diluted solution was determined by spectrophotometer. The amount of substrate bound to the polymer (Q) was calculated according to

$$Q\,(\mu\text{mol}) = V(C_\text{i} - C_\text{l})$$

where V, C_i and C_l represent the volume of the solution (ml), initial solution concentration and the solution concentration after adsorption (concentration at equilibrium) (μmol/ml), respectively. The average data of triplicate independent results were used for the following discussion.

3. Results and discussion

3.1. Method for preparation of MIPs

When hydrogen bonding interactions between template and functional monomers are destroyed by aqueous solvent, hydrophobic effect can be exploited and can play an important role in molecular imprinting. Hydrophobic effect is less specific because it is applicable to broad groups of compounds. A solution to this problem is to combine hydrophobic effect with other types of interactions (for instance, electrostatic interaction, metal ion-coordination, etc.) in the imprinting process [18].

A cyclodextrin (CD) molecule is a torus-shaped cyclic oligosaccharide consisting of 1,4-linked D-glucopyranose units with an internal hydrophobic cavity. This structure enables cyclodextrin to form inclusion compounds with guests in water through hydrophobic interactions. Chen et al. [19] prepared the 1:1 inclusion complex of NOF and hydroxypropyl-β-CD (HP-β-CD) and confirmed the structure of the complex. The lipophilic aromatic ring and the piperazine ring of NOF were entrapped inside the hydrophobic core of HP-β-CD, the more polar carboxyl group (–COOH) of NOF was left outside the cavity. This result inspired us that it may be able to produce effective imprint for NOF by the method of combination of hydrophobic effect and electrostatic interaction.

For the synthesis of the NOF-imprinted polymer P_1, the 1:1 BMA-β-CD-NOF inclusion complex was prepared at first. Then, it was mixed with DEAEM in DMSO, allowing the carboxyl group of NOF to form strong ionic interactions with the basic functional group of DEAEM. Using EDMA as the cross-linker, the mixture was polymerized and gave the imprinted polymer (P_1). To investigate the contribution of the used functional monomers, the other two reference imprinted polymers (P_2, P_3) and their corresponding non-imprinted polymers were also prepared. To ensure that the concentrations of the β-CD residues in P_2 and NP_2 and the DEAEM residues in P_3 and NP_3 are equal to that in the P_1 and NP_1, different amounts of cross-linkers were used (Table 1).

3.2. Properties of the polymers

The results of the elemental analysis of P_1 and NP_1 were as follows: P_1 found: C 55.20, H 6.47, N 0.40%; NP_1 found: C 54.70, H 6.45, N 0.43%. Anal. Calcd. for P_1 and NP_1 (calculated according to the chemical composition for making these polymers): C 55.76, H 5.96, N 0.419%. These indicated that most of the components for making the polymers had participated in the polymeric reactions. The stability of the polymers was investigated by the TGA analysis. The TGA curves indicated that both P_1 and NP_1 begin to decompose at around 220 °C (figures are not presented). The scanning electron microscope (SEM) was used to characterize the polymers morphologically (Fig. 4). We can see that both of the polymers (P_1 and NP_1) showed an irregular, rough surface and that the morphologies of P_1 and NP_1 were quite similar. This can be explained because porogen plays an important role in the final polymer morphology by influencing its surface morphology and the pore diameter. In this study, the same porogen was used for preparation of P_1 and NP_1.

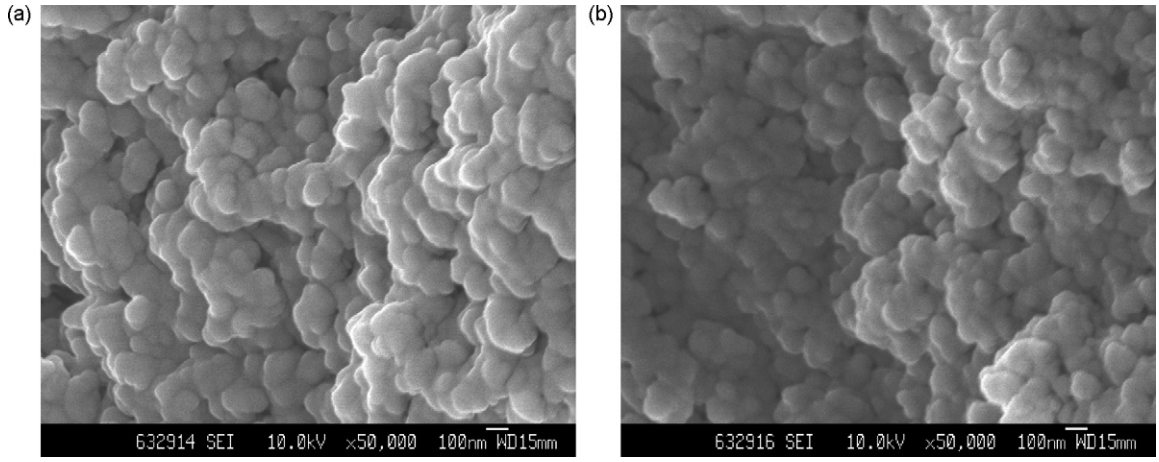

Fig. 4. SEM micrographs (50,000×) of polymers: (a) P_1 and (b) NP_1.

3.3. Binding characteristics of the polymers for NOF

The amount of NOF bound to the polymers was determined by equilibrium binding experiments. The specificity of the polymers was estimated by the distribution coefficients of NOF between polymer and solution. The distribution coefficient (K_d) is defined as [20]:

$$K_d\,(\mathrm{ml/g}) = \frac{C_p}{C_l}$$

where C_p is the amount of NOF bound per gram of support, it was calculated according to

$$C_p\,(\mu\mathrm{mol/g}) = \frac{Q\,(\mu\mathrm{mol})}{\text{mass of polymer in grams}}$$

The molecular imprinting factor (IF) was used to evaluate the imprinting effect. IF was calculated according to

$$\mathrm{IF} = \frac{K_d(\mathrm{MIP})}{K_d(\mathrm{NP})}$$

The obtained distribution coefficients and the IF values are listed in Table 2.

The polymer P_2, which was imprinted with NOF only using the BMA-β-CD as the functional monomer, showed almost no imprinting effect, due to the lack of the electrostatic interacting, i.e. the absence of complementary electrostatic interactions produced by functional monomer DEAEM. Table 2 shows that P_3 had low binding affinity for the template. P_3 was prepared in the absence of the BMA-β-CD monomer, there are only electrostatic interactions between the templates and the basic monomers (DEAEM), and the electrostatic interactions also induced some imprinting effect. In the case of P_1, containing both functional monomers, BMA-β-CD and DEAEM, and imprinted with NOF, demonstrated superior selectivity to the reference polymer (NP_1). Compared with P_2 and P_3, P_1 showed the highest IF value. The results of binding experiments indicated that the combination of hydrophobic and electrostatic interactions was essential for the efficient improvement in the affinity and specificity for the guest of the imprinted polymer.

Table 2
Recognition of NOF on the polymers prepared with different functional monomers

	P_1	NP_1	P_2	NP_2	P_3	NP_3
K_d	38.13	20.20	8.74	8.35	13.26	9.73
IF	1.89		1.05		1.36	

Initial concentration: 1.0 mmol/l; solvent:methanol/water (1:1, v/v); volume: 3 ml.

The binding isotherms of P_1 and NP_1 for NOF were determined in the 0–1.0 mmol/l range of initial concentration of NOF (the initial concentration of NOF which is larger than 1.0 mmol/l cannot be prepared due to the solubility of NOF). The results are shown in Fig. 5. It can be seen that the amounts of NOF bound to both P_1 and NP_1 at equilibrium C_p increased along with increasing the initial concentration of NOF, but the binding amount of NOF on P_1 was more than that on NP_1 in the whole concentration range. This result could be ascribed to the imprinting effect. In this range, the obtained binding data were further processed

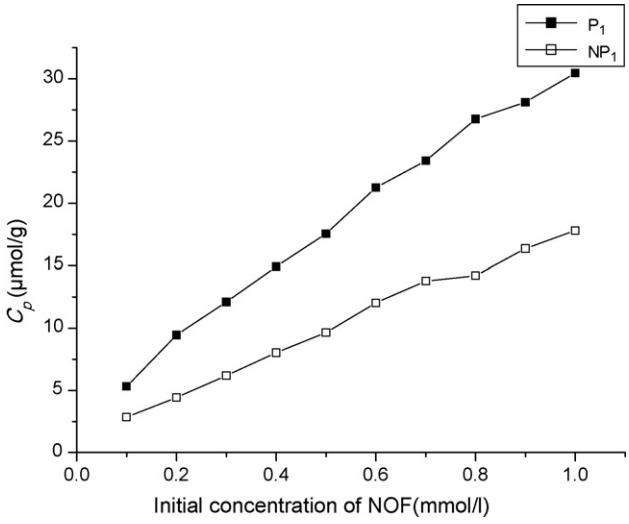

Fig. 5. Binding isotherm of P_1 and NP_1, solvent: methanol/water (1:1, v/v); adsorption time: 6 h; temperature: 30 °C.

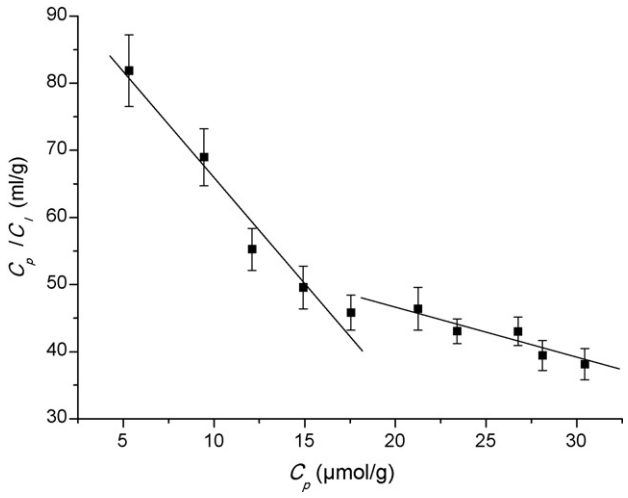

Fig. 6. Scatchard plot analysis of the binding of NOF to the polymer P_1. Values represent the means of three independent measurements. Error bars are indicated.

with Scatchard equation to estimate the binding properties of MIP [21]:

$$\frac{C_p}{C_l} = \frac{C_{p\,max} - C_p}{K}$$

Where $C_{p\,max}$ is the apparent maximum number of binding sites and K is the dissociation constant. As shown in Fig. 6, the Scatchard plot is not a single straight line, but consists of two linear parts with different slope. The linear regression equations for the two linear regions are $C_p/C_l = -3.08C_p + 96.83$ ($r = 0.98$) and $C_p/C_l = -0.84C_p + 63.83$ ($r = 0.94$), respectively. This suggests that the binding sites in the MIP are heterogeneous in respect to the affinity for NOF, and indicates that the binding sites could be classified into two groups with specific binding properties. The K and $C_{p\,max}$ of the higher affinity binding sites can be calculated to be 0.32 μmol/ml and 31.43 μmol/g, respectively, from the slope and the intercept of the Scatchard plot. Similarly, The K and $C_{p\,max}$ of the lower affinity binding sites were found to be 1.19 μmol/ml and 75.98 μmol/g, respectively.

3.4. Binding specificity of P_1 and NP_1

In order to verify that the imprinted polymer P_1 was selective for NOF, the selectivity tests of P_1 and NP_1 were performed using some structurally related substrates (Fig. 1). Their amounts bound to P_1 and NP_1 were also determined by equilibrium binding method. The obtained K_d values of the substrates are shown in Table 3.

P_1 obviously exhibited high binding specificity for NOF, and it showed the highest K_d for NOF compared to all other substrates tested. In this study, NOF can insert in the cavity of the modified β-CD and form 1:1 inclusion complex through hydrophobic effects. The carboxyl group of NOF can form strong ionic interactions with the basic functional group of DEAEM in aqueous media. Thus, hydrophobic effect and electrostatic interactions are combined in molecular imprinting. The results of selectivity experiments further demonstrated that this imprinting method can increase the specific binding sites in the cavities of the polymer and thus enhances its molecular recognition ability. Table 3 shows that besides the template NOF, ibuprofen also has some affinity for the imprinted polymer. This could be easily explained because there is some analogy between NOF and ibuprofen in structure, and thus, it would be reasonable to assume that ibuprofen was able to insert in the cavity of β-CD with the substitutional aromatic ring and its carboxyl group can form ionic interaction with the basic functional group remained by DEAEM. Fig. 1 shows that the structures of two other fluoroquinolones, ciprofloxacin and ofloxacin, are also similar to that of NOF. However, P_1 showed almost no affinity for them. This may be explained because the substituents on quinolone ring of ciprofloxacin and ofloxacin are bigger and more rigid than that of NOF and it is difficult for them to fit into the cavities created by imprinting. The data presented in Table 3 show that P_1 has little or no affinity for the other compounds.

3.5. Influence of H_2O content in methanol on adsorption

Different contents of H_2O in methanol (v/v) were used as solvents to evaluate the influence of H_2O on the binding of NOF on the polymers (Fig. 7). On account of the solubility of NOF, it cannot evaluate the polymers with a solvent containing more

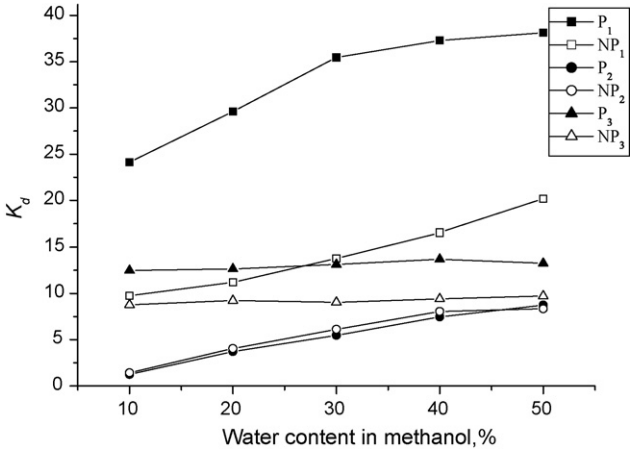

Fig. 7. The influence of H_2O content on adsorption.

Table 3
K_d values of the substrates on P_1 and NP_1 under equilibrium binding conditions

	Ofloxacin	Ciprofloxacin	Ibuprofen	Alizarin	Cefalexin	NOF
P_1	7.37	10.44	21.64	1.78	9.46	38.13
NP_1	7.06	9.35	16.78	1.80	7.85	20.20

Initial concentration: 1.0 mmol/l; solvent:methanol/water (1:1, v/v); volume: 3 ml.

than 50% of H_2O in methanol. It can be seen that the distribution coefficients of NOF on P_1, NP_1, P_2 and NP_2 increased with increasing the H_2O content in the range of 10–50% (v/v). All of these polymers contain β-CD residues. As we know, the cavity of β-CD is relatively hydrophobic compared to water. It should be noted that the main body of NOF molecule could be accommodated in the cavity of β-CD. When the content of H_2O increased in the solvent, the hydrophobic effect increased also, more template molecules have been driven into the cavities of the polymers. The binding of NOF to P_1 was caused by (1) insertion of NOF into cavities created during the imprinting process, which are complementary both in shape and functional group arrangement to the template molecule, (2) insertion of NOF into the cavities of β-CD residues, and (3) unspecific interactions (e.g. electrostatic interaction, hydrophobic effect) between NOF and polymers. The binding of NOF to NP_1 was caused by points (2) and (3) mentioned above. The difference in binding mechanism between P_1 and NP_1 gives rise to the observed difference in the values of K_d between P_1 and NP_1. The binding of NOF to P_2 and NP_2 originated from points (2) mentioned above. Fig. 7 shows that the change of contents of H_2O in methanol had little influence on the binding performance of P_3 and NP_3. Therefore, it could be further confirmed that the imprinting effect of P_3 was due to electrostatic interactions.

3.6. Effect of pH on NOF adsorption on P_1 and NP_1

Using KH_2PO_4–K_2HPO_4 (aq)/methanol (2/3, v/v) as an aqueous buffer solvent system, a correlation between binding and pH (in the range 4–8) of adsorbed solution is shown in Fig. 8. The pH values were altered by adjusting the balance of mono- and dibasic phosphate salts, while the total concentration of phosphate salts was held constant at 50 mmol/l. The binding of NOF on both polymers is strongly influenced by the pH in the solutions. Enhanced binding was obtained in the pH 6.5–7.5 range. When the pH is lower than 6.5, the nitrogen atoms of the NOF molecule can bind protons to form a positively charged species. It is more difficult for a positively charged NOF to insert into the hydrophobic cavity of β-CD due to the increase of the polarity of the guest. Meanwhile, the protonation of the nitrogen atom of DEAEM residue ceased the interaction between the carboxyl group of NOF and the basic group of DEAEM. These two factors lead to the decrease of binding capacities of the polymers. When the pH is higher than 7.5, the proton of carboxyl group of NOF can be lost to form a carboxylate ion. The carboxylate ion cannot interact with the basic group of DEAEM residue, and therefore the binding capacities of the polymers are decreasing.

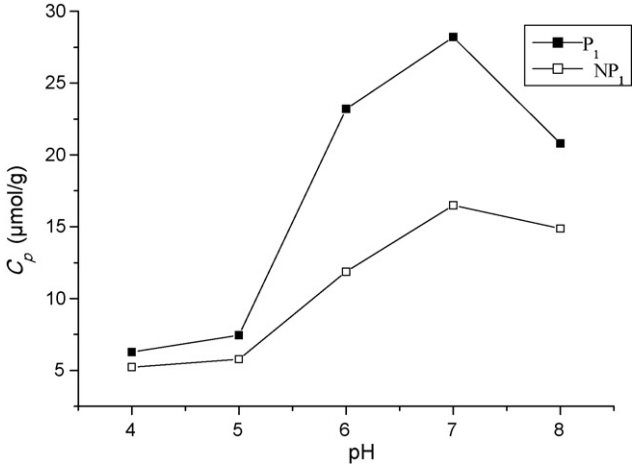

Fig. 8. Effect of pH on the binding of NOF on P_1 and NP_1 in buffer solvent system.

4. Conclusions

The novel molecular imprinting process presented in this work was an attempt to achieve molecular recognition in aqueous media exploiting hydrophobic and electrostatic interactions for preparing molecularly imprinted polymers. A norfloxacin-imprinted polymer (P_1) was prepared by using DEAEM and BMA-β-CD as bi-functional monomers. This polymer was capable of recognizing the template in aqueous solvent. Using BMA-β-CD or DEAEM as the functional monomers, two reference imprinted polymers (P_2, P_3) were also synthesized. The imprinted polymer P_1 demonstrated superior selectivity to the polymers synthesized with a single functional monomer (P_2, P_3).

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