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Preparation of surface molecularly imprinted polymer and its application for the selective extraction of teicoplanin from water†

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In this study, a new surface molecularly imprinted polymer (SMIP) of teicoplanin (TEC) was prepared in an aqueous solution using amino-modified silica gel as a carrier. The molar ratio of the template molecule, functional monomer and cross-linker in the optimized synthesis system was 1 : 15 : 40. The structure and morphology of SMIP were characterized by Fourier-transform infrared spectra and scanning electron microscopy, respectively. It was shown that the silica gel modified with different active groups; the type and structure of functional monomers have a great influence on the specificity of SMIP. The SMIPs synthesized from a series of methacrylic acid and its hydroxylalkyl esters as functional monomers have good specificity for TEC. The results of static adsorption experiments showed that the adsorption capacity of SMIP was 6.5 times that of non-molecularly imprinted polymer, which were 152.6 mg g^{-1} and 23.6 mg g^{-1}, respectively, indicating that SMIP had a larger affinity for TEC. Finally, the SMIP was successfully used as a dispersive solid-phase extraction adsorption material to selectively extract and enrich TEC from the water sample. The limit of detection of the proposed liquid chromatographic method for TEC was 5 μg L^{-1}.

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1. Introduction

Teicoplanin (TEC) is a natural glycopeptide antibiotic (GPA) produced by soil-dwelling filamentous actinomycetes.[1] It is mainly composed of five compounds with similar structures (A2-1, A2-2, A2-3, A2-4 and A2-5), A2-2 (Fig. 1). TEC has excellent antibacterial activity against Gram-positive bacteria. It interferes with the formation of the peptidoglycan skeleton by binding to D-Ala-D-Ala of the membrane-bound lipid II of peptidoglycan,[2,3] which is the main component of the cell wall of Gram-positive bacteria. Therefore, TEC is mainly used for treating various diseases caused by Gram-positive bacterial infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) and susceptible enterococcus. Especially for MRSA infections, TEC can be used as an alternative treatment for vancomycin (VCM, Fig. 1), which is the last-line defense against serious infections caused by staphylococci, enterococci and other Gram-positive bacteria.[4,5] For elderly people, newborns, patients with renal insufficiency and other people who cannot use VCM, TEC can be considered as the first choice for the treatment of multi-drug resistant *Staphylococcus aureus* and enterococcus infections. Taking into account the cross-resistance of antibiotics, GPAs including TEC and VCM have been banned in the veterinary field by the European Union (EU), China and some other countries.[6,7] The application of GPAs, and even abuse in food animals will eventually have a negative effect on the eco-environment, especially the environmental water, which might affect environmental safety and the health of humans and animals. Therefore, it is necessary and important to develop new methods for selective extraction, separation and enrichment of GPAs from environmental samples.

Molecular imprinting technology (MIT) is a late 20th-century emergence of highly selective separation technology. The idea of this technique was derived from the specific recognition of antigen–antibody. The molecularly imprinted polymer (MIP) prepared on the basis of MIT is characterized by its high selectivity to the target molecule, and has been widely applied in different fields such as sample pretreatment,[8] chiral resolution,[9] chemical/biological sensing,[10] catalytic degradation[11] and controlled release of drugs.[12] Tan *et al.*[13] selected the glycosyl moiety of TEC as the template, 4-vinylphenylboronic acid and methyl methacrylate (MMA) as the functional monomers for preparing MIP *via* precipitation polymerization, and applied it to the extraction of TEC in biological samples. The average recoveries of TEC in urine, milk and plasma samples ranged

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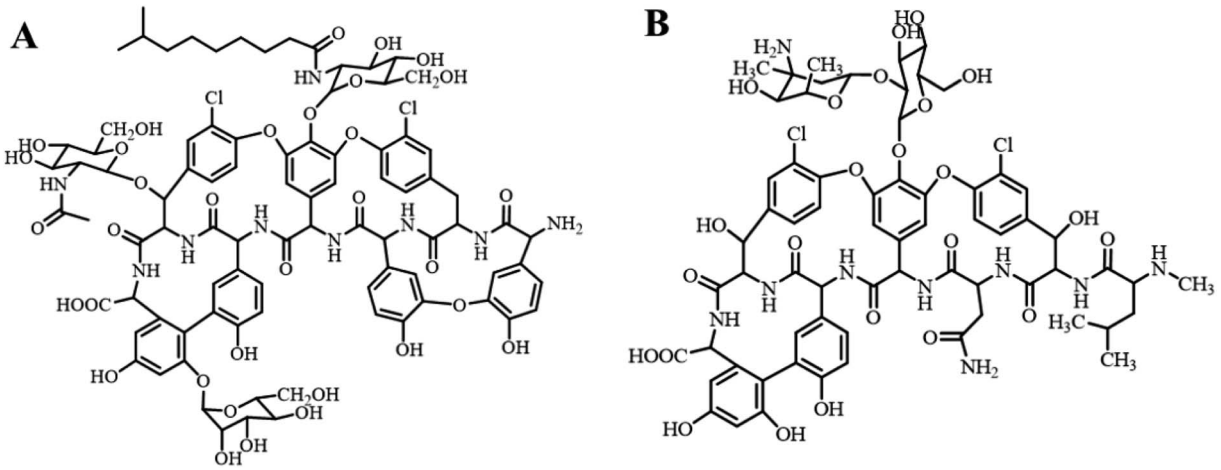

Fig. 1 Chemical structures of (A) the prevalent teicoplanin component A2-2 and (B) vancomycin.

from 75.2% to 92.4%. However, because some template molecules were embedded in the interior of the imprinted microspheres, for the MIP prepared using precipitation polymerization, there are some limitations such as difficulty in the elution of the template molecule, low adsorption capacity and slow mass transfer. The surface molecular imprinting technique can overcome these shortcomings. In this technique, the polymer is grafted onto the surface of a solid substrate to obtain the surface molecularly imprinted polymer (SMIP).

In the surface-imprinting technique, the carrier material plays a supporting role in grafting the polymer onto its surface. Many materials can be used as the carrier including magnetic Fe_3O_4 microspheres,[14] silica gel,[15,16] quantum dots (QD),[17] polystyrene,[18] carbon nanotube[19] and nano-TiO_2.[20] They usually have a large specific surface area, controllable morphology and particle size, low preparation cost and strong surface reaction ability. Silica gel particle is the most widely used among these materials due to its unique properties. The favorable stability and rich porous structure of silica gel can promote the diffusion of solvents and template, thus helping the removal of the template. In addition, most of the template molecules are situated at the surface of polymers, which will increase the molecular recognition ability between polymers and target compounds and improve the mass transfer kinetics of SMIP.[21] Therefore, this strategy can avoid the disadvantages of traditional MIP to some extent. The SMIP prepared with silica gel microspheres as the carrier had excellent properties and was used as an adsorbent for solid-phase extraction (SPE),[22] matrix solid-phase dispersion (MSPD)[23] and dispersive solid-phase extraction (dSPE)[24] for the selective separation, cleanup and enrichment of target compounds from animal-derived food and environmental samples. Cheng *et al.*[25] synthesized a melamine-SMIP on silica gel carrier by surface molecular imprinting technique and then used it to selectively extract melamine in milk as an SPE adsorbent. The results showed that the recovery of the spiked sample was between 75.6% and 96.8%, and the relative standard deviation (RSD) was less than 10%. Anene *et al.*[26] prepared SMIP for patulin in acetonitrile for the selective extraction of patulin from apple juice samples. In the range of 0.1–10 mg L^{-1}, the recovery of patulin was from 82% to 98%, and the RSD was less than 3.83%. The SMIP was also tested for its reusability and the results showed that the average recovery was more than 80% after 6 reuse cycles. Ren *et al.*[27] prepared SMIP for bisphenol A with a sol–gel process on the surface of silica nanoparticles, which could serve as an efficient selective material for the determination of bisphenol A in the water environment. Zhu *et al.*[28] synthesized a magnetic SMIP by microwave-assisted surface-imprinting technology, and SMIP could effectively adsorb and extract 4-nitrophenol from water. In addition, the imprinted polymer was also widely used in the removal of metal ions such as Cd(II)[29] and Pb(II)[30] from wastewater. There are few reports on the separation and purification of GPA with surface-imprinting technique. Therefore, the establishment of a highly selective pretreatment method based on SMIP has great significance for rapid and reliable monitoring of TEC residues in complex matrices.

Herein, this work represents the first attempt to prepare surface-imprinted polymer for TEC based on modified silica gel. The synthesis conditions of SMIP, including the type of porogenic solvent, molar ratios of the monomer and cross-linker were optimized. The morphology and structure of the prepared SMIP were studied, and the selectivity of SMIP related to the characteristics of monomers and cross-linkers were inferred. The adsorption experiments showed that the obtained SMIP had good selective recognition ability to TEC. Finally, the prepared SMIP was used as a dSPE adsorbent and successfully applied to enrich TEC from real water samples.

2. Materials and methods

2.1. Reagents and materials

MMA, methacrylic acid (MAA), acrylic acid (AA), hydroxyethyl methacrylate (HEMA), 2-hydroxypropyl methacrylate (HPMA), hydroxyethyl acrylate (HEA), hydroxybutyl acrylate (HBA), ethyl methacrylate (EMA), *n*-propyl methacrylate (PMA), butyl methacrylate (BMA), ethylene glycol diglycidyl ether (EGDE), trimethylolpropane triacrylate (TMPTA), glycidyl methacrylate (GMA) and *N*,*N*-methylenebisacrylamide (MBA) were purchased from J&K scientific. 4-Vinyl pyridine (4-VP), 2-vinyl pyridine (2-VP), acrylamide (AM), trimethylolpropane trimethacrylate (TMPTMA), ethylene

glycol dimethacrylate (EGDMA), 2,2-azobisisobutyronitrile (AIBN), γ-methacryloxypropyltrimethoxysilane (γ-MPS) and 3-aminopropyltriethoxysilane (APTES) were purchased from Sigma Aldrich. HPLC grade acetonitrile (ACN), formic acid (FA) acetic acid (AA) and methanol (MeOH) were purchased from Fisher Scientific (Fairlawn, NJ, USA). Other analytical-grade solvents including *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were brought from Guangzhou Chemical Reagent Factory (Guangzhou, China). Ultrapure water was produced using the Milli-Q water system (Molsheim, France). High purity silica gel (SPS100-5), carboxyl-modified (COOH SPS100-5) and sulfo-modified silica gel (SO_3H SPS100-5) were provided by FUJI Corporation (Japan).

TEC and VCM hydrochloride were purchased from Shanghai Haoyun Chemical Technology Co., Ltd. (Shanghai, China). Bacitracin (BAT) and colistin (CS) were purchased from Dr Ehrenstrofer (Germany). Spiramycin (SPM) and timicox (TIM) were provided by Sigma Aldrich (USA). Sulfamethazine (SM2), enrofloxacin (EN) and virginiamycin M1 (VGM) were all purchased from J&K scientific (China).

2.2. Apparatus and analytical conditions

High-performance liquid chromatography (HPLC) separations were performed on Agilent 1260 HPLC system equipped with a quaternary pump, an autosampler and an ultraviolet detector. The analytes were separated using an Agilent Extend-C_{18} column (250 mm × 4.6 mm i.d., 5.0 μm). The mobile phase consisted of (A) MeOH and (B) water containing 0.1% FA and 5 mmol L^{-1} of ammonium acetate. The gradient elution procedure was as follows: 0–1 min 40% A, 1–4 min 70% A, 4–8 min 70% A, 8–8.1 min 40% A and 8.1–10 min 40% A. The flow rate was 1.0 mL min^{-1}, the injection volume was 10 μL and the UV monitoring was at 254 nm.

2.3. Preparation of SMIP

Anhydrous toluene (100 mL), silica gel (5 g, 5 μm) and modifier (APTES, 5 mL) were added to a 150 mL round bottom flask, then triethylamine (1 mL) was added as a catalyst, and the reaction was stirred at 120 °C for 12 h under the argon atmosphere. The product was washed with MeOH and water and dried in a vacuum at 60 °C to obtain amino-modified silica gel particles. Under the same conditions, γ-MPS was used as the modifier to prepare vinyl-modified silica gel.

The SMIP was prepared based on surface-modified silica gel. TEC (0.235 g) was dissolved in 30 mL of water. The functional monomer (HPMA, 0.263 mL) and carrier (amino-modified silica gel, 0.5 g) were added in the above solution. The mixture was vortexed and sonicated for 10 minutes and pre-polymerized at 4 °C for 6 hours. Subsequently, the cross-linker (TMPTMA, 1.6 mL) and initiator (AIBN, 10 mg) were added. The solvent was vortexed and sonicated to obtain a homogeneous solution and then argon was purged for 10 minutes to remove oxygen. The polymerization was carried out in an oil bath at 60 °C for 24 hours. After polymerization, the template was extracted with AA/MeOH solvent (5 : 5, v/v) using the Soxhlet extractor until TEC could not be detected by HPLC. As a control, non-imprinted polymer (NIP) was also prepared without TEC in the same way.

2.4. Morphological characterization of the polymer

The morphology of SMIP and NIP was studied using scanning electron microscopy (ZEISS EVO18). The polymer microspheres were dried and sprayed with gold before the observation. The average particle size was analyzed using a laser particle size analyzer (Coulter LS230, Coulter Co., USA). The infrared spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} using a Fourier transform infrared spectrometer (Nicolet 6700) with potassium bromide as a blank background. The thermostability of SMIP and NIP was measured using a thermogravimetric analyzer (NETZSCH TG 209 F1 Libra) in the range of 100 °C to 900 °C.

2.5. Adsorption and selectivity experiments

The adsorption experiments were carried out using a constant temperature oscillator (SHA-C, China). The influence of different factors on the adsorption capacity of SMIP and NIP were evaluated, such as solvent, pH, adsorption time and concentration of the substrate. 20 mg of polymers were dispersed in 5 mL of different proportions of MeOH–water (0, 10%, 20%, 40%, 50%, 60%, 80% and 100%) solutions with the initial concentration of 1 mg mL^{-1}. The series of mixtures were shaken for 24 h at room temperature. After centrifugation, the equilibrium concentrations of the TEC were measured using HPLC. The adsorption capacity (Q, mg g^{-1}) was calculated from the following equation:

$$Q = (C_0 - C_e) \times \frac{V}{W}$$

where C_0 (mg L^{-1}) and C_e (mg L^{-1}) are the initial and equilibrium concentrations of TEC, respectively; V (L) is the volume of the solution, and W (g) is the weight of the polymer. The imprinting factor (IF) was calculated using the following equation:

$$IF = Q_{SMIP}/Q_{NIP}$$

where Q_{SMIP} (mg g^{-1}) and Q_{NIP} (mg g^{-1}) are the adsorption capacity of SMIP and NIP, respectively.

The influence of pH on the adsorption of polymer to TEC was studied in phosphate buffers with different pH values. Under the optimum conditions of solvent and pH, the static adsorption isotherm was performed at the initial concentrations ranging from 0.05 to 1.0 mg mL^{-1}. Similarly, for the kinetic experiments, 20 mg of the polymer was dispersed in 5 mL of 50% MeOH–H_2O with the TEC concentration of 1.0 mg mL^{-1} and then the mixtures were continuously shaken at certain intervals (1, 3, 5, 15, 30, 45, 60 and 90 min). Selective experiments were performed using structural analogs (such as VCM, CS, BAT, VGM) and other commonly used antimicrobials including EN, SPM, TIM and SM2. 20 mg of the polymer was added to 5 mL of each drug solution (200 μg mL^{-1}). After incubation for 30 minutes at room temperature, the adsorption capacity and imprint factor were calculated.

2.6. Sample preparation

Lake, spring and Pearl River water were collected from the surrounding areas of Guangzhou. After sedimentation, they were filtered with a 0.25 μm microporous membrane to remove

fine particles. The real water samples were stored in brown glass bottles at 4 °C. 100 mg of the polymer was dispersed in 250 mL of environmental water samples and shook for 20 minutes at room temperature. The samples were filtered and the polymer particles were collected, then the polymer was washed twice with 3 mL water and eluted with 5 mL of 10% ammonia in methanol. The eluate was evaporated to dryness under a gentle stream of nitrogen and the residue was reconstituted with 0.5 mL mobile phase solution before HPLC analysis.

3. Results and discussion

3.1. Optimization of surface molecularly imprinted polymer

Due to the absence of specific purification approaches, most available methods for the analysis of GPAs had low selectivity and poor sensitivity. The purpose of this study was to synthesize highly selective imprinted polymer, which can selectively bind TEC and its structural analogues. Therefore, the effects of polymerization factors including carrier, monomer, cross-linker and porogen on the performance of surface-imprinted polymer were evaluated.

3.1.1. Modification of silica gel. In the process of surface imprinting, the polymer easily forms secondary particles itself, so it is difficult to form an imprinted layer on the surface of silica gel. In order to ensure successful grafting of SMIP on the surface of the carrier material, silica gel microspheres must be modified to increase the affinity and form the corresponding imprinting layer. Generally, silica gel can be modified by introducing different functional groups such as amino,[15,16] carboxyl,[31,32] aldehyde[33] and vinyl.[34,35] These functional groups have strong reactivity and can effectively induce and participate in the polymerization reaction. In this study, four different modified silica gels were used as the carrier to synthesize SMIP. As shown in Fig. 2A, the polymers prepared with the carboxyl-

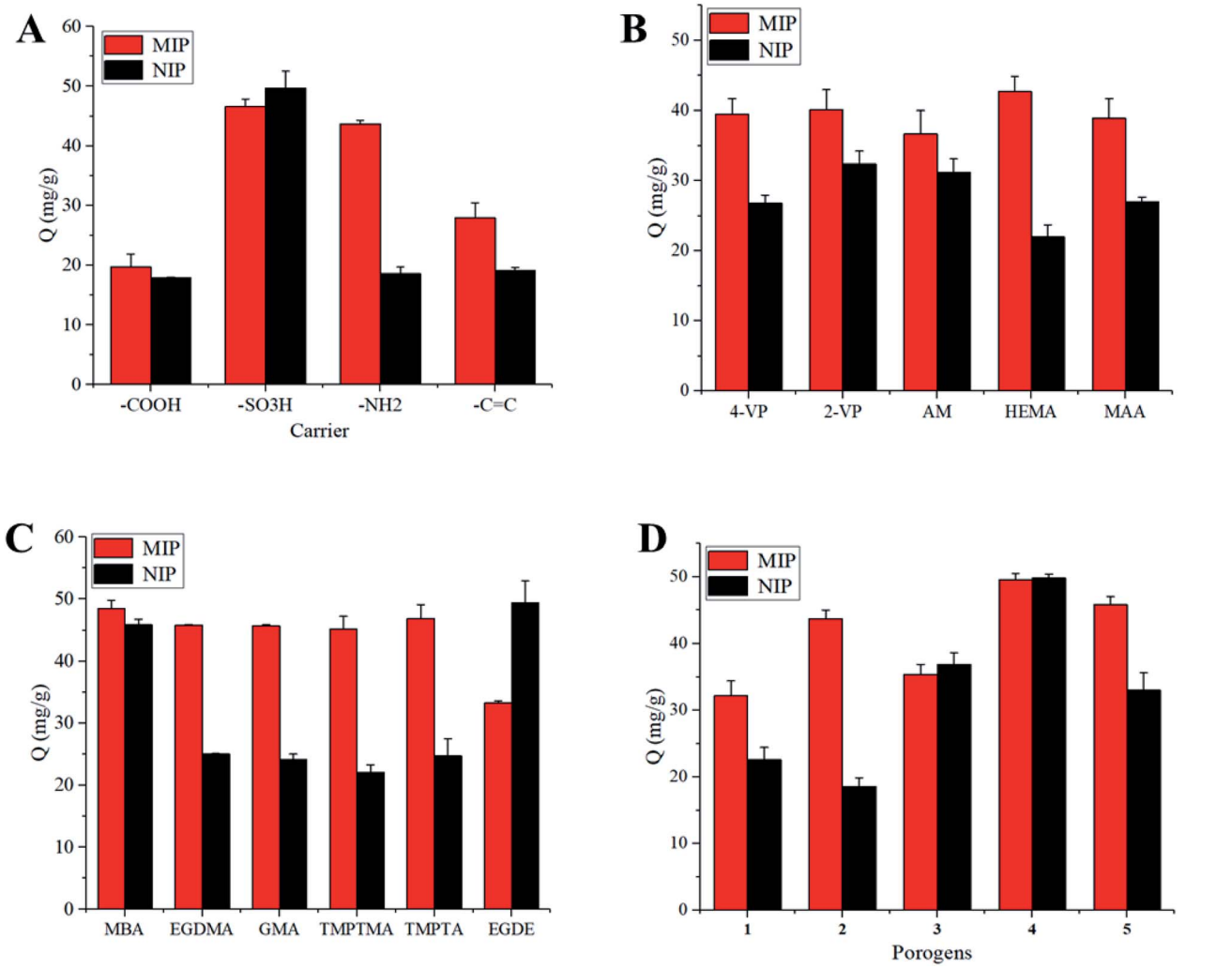

Fig. 2 The influence of synthesizing factors of the polymer on the adsorption capability to teicoplanin (A) different modified silica gel, (B) different functional monomers, (C) different cross-linkers, (D) different porogens: (1) DMSO (2) H_2O (3) DMSO/H_2O (v/v, 1 : 1) (4) DMSO/methanol (v/v, 1 : 1) (5) H_2O/methanol/toluene (v/v/v, 1 : 1 : 1). 4-VP, 4-vinyl pyridine; 2-VP, 2-vinyl pyridine; AM, acrylamide; HEMA, hydroxyethyl methacrylate; MAA methacrylic acid; MBA, *N*,*N*-methylenebisacrylamide; EGDMA, ethylene glycol dimethacrylate; GMA, glycidyl methacrylate; TMPTMA, trimethylolpropane trimethacrylate; TMPTA, trimethylolpropane triacrylate; EGDE, ethylene glycol diglycidyl ether.

modified silica gel (weak acid modifier) had poor adsorption capacity and specificity. Although the sulfo-modified silica gel (strong acid modifier) could significantly improve the adsorption capacity, the specificity of SMIP was quite poor (IF < 1.5). It hinted that the adsorption capability might be related to the grafted groups on the surface of silica gel, and silica modified with the acid group was not suitable for a carrier.

Compared with the acid-modified silica gel, polymers with higher specificity were obtained using both amino- and vinyl-modified silica gel (synthesized in our laboratory) as carriers. Generally, vinyl groups on the surface of the silica gel could participate in the free radical reaction of the imprinted polymer. However, the adsorption capacity and specificity of the polymer prepared with vinyl-modified silica gel were far lower than those prepared with amino-modified silica gel. It could be explained by the fact that there are a large number of alcohol hydroxyl and phenolic hydroxyl groups in the TEC molecule, which could form abundant hydrogen bonds with amino groups on the surface of the carrier. The SMIP with many specific imprinting sites that are complementary in size and shape to the template was produced. The aminopropyls on the surface of silica gel particles would initiate polycondensation during surface imprinting process. In addition, it could also act as an assistant group to drive template molecules into the formed imprinting polymer during the imprinting polymerization.[36] The reactive amino groups on the surface of silica gel continuously capture the newly formed oligomers in the solution through the hydrogen bond interaction with TEC and the monomer, and finally, the imprinted polymer was embedded on the surface of silica gel.

3.1.2. Functional monomer. Despite the rapid development of MIT, related research still lags behind other technologies such as nanomaterial synthesis and a fluorescent probe. One reason is the limited number of functional monomers available in molecular imprinting, which is unfavorable for the selectivity and further application of SMIP to a certain extent.[37] The role of the functional monomer during the polymerization is to bind particular groups of the template *via* covalent or non-covalent means, which allow the polymerization to be predictable and controllable. Generally, the functional monomer is composed of two parts: one is the recognition unit and the other is the polymerizable unit. The commonly used monomers include MAA, 4-VP, 2-VP, AM and HEMA. Among these monomers, MAA has been used as the "universal" functional monomers due to its characteristics of hydrogen-bonding donor and acceptor. Unlike small molecules, polypeptide drugs such as TEC and VCM present a large number of potential recognition sites. Different regions of polypeptides exhibit distinct physicochemical properties, so the recognition and cross-reactivity may be problematic. Therefore, it is imperative to select a suitable functional monomer that can form strong interactions with the polypeptide (template). Therefore, five common monomers including MAA, HEMA, 4-VP, 2-VP and AM were tested in this study. As shown in Fig. 2B, the results showed that the specificity and adsorption capacity of the SMIP prepared from neutral monomer AM were lowest, and basic monomer 2-VP (maybe due to steric hindrance) came second. Theoretically, the electrostatic interaction produced by the introduction of charged monomers can lead to more specific and stronger template–imprint interactions.[38] Both MAA (acidic monomer) and 4-VP (basic monomer) could provide electrostatic interaction, SMIPs prepared with them indeed produce relatively higher specificity and adsorption capacity. However, the selectivity of SMIP prepared with HEMA as a monomer (hydroxyethylated MAA) was the highest among all the tested five monomers. Therefore, different functionalized MAA esters were further compared.

As shown in Table 1, when HPMA (hydroxypropylated MAA) was used as a monomer, the adsorption capacity and selectivity (IF > 2.0) of SMIP were slightly higher than those of HEMA. It was supposed that hydrogen bonds between the template and monomer are the most important for the specificity of SMIP. To prove this view, the derivatives obtained by esterifying MAA with an alkyl side chain (methyl-, ethyl-, propyl- and butyl-) were tested as monomers (Fig. S1†), the adsorptive amounts of all SMIPs increased (possibly due to the increase of hydrophobicity), while the selectivity decreased (IF < 1.4). It was further indicated that the side chain hydroxyl group providing hydrogen bond acceptor (donor) in the series of esterified MAAs had a great influence on the selectivity. Interestingly, the adsorption capacity and selectivity of SMIPs synthesized with AA and its hydroxyalkyl esters as monomers were significantly lower than those of MAA esters, indicating that the existence of α-methyl (steric hindrances) in esterified MAA monomers was very important. Finally, HPMA was selected as the functional monomer in this experiment.

3.1.3. Cross-linker. In the process of polymerization, the cross-linker is used to fix the functional monomers and make their functional groups around the template molecule to form a highly cross-linked rigid polymer.[37] The type and amount of cross-linker have a profound effect on the performance of the polymer. Six alternative cross-linkers (Fig. S2†) were selected for comparing the adsorption capacity and specificity of the polymer. The results showed that the polymer synthesized by the

Table 1 Adsorption capacity of polymers prepared with different monomers ($n = 3$)[a]

		Q (mg g^{-1})		
No.	Monomers	SMIP	NIP	IF
1	Methacrylic acid	38.9	27.0	1.44
2	Hydroxyethyl methacrylate	42.7	22.0	1.94
3	2-Hydroxypropyl methacrylate	44.8	21.9	2.05
4	Methyl methacrylate	48.0	45.9	1.04
5	Ethyl methacrylate	48.1	36.4	1.32
6	*n*-Propyl methacrylate	48.6	43.9	1.11
7	Butyl methacrylate	47.8	34.9	1.37
8	Acrylic acid	42.7	31.4	1.36
9	Hydroxyethyl acrylate	18.0	18.8	0.96
10	Hydroxybutyl acrylate	20.2	19.8	1.02

[a] SMIP, surface molecularly imprinted polymer; NIP, non-imprinted polymer; IF, imprinting factor.

binary cross-linkers (EGDMA and GMA) and the ternary cross-linkers (TMPTMA and TMPTA) had high adsorption capacity and specificity (Fig. 2C). Moreover, the presence of α-methyl in the cross-linker seemed to improve the specific adsorption capacity of the polymer, especially in TMPTMA. The common use of cross-linkers in the aqueous phase, MBA and EGDE did not show significant improvement on the adsorption or specificity of polymer. The amount of cross-linker had a significant influence on the binding ability and configuration of the imprinted polymer. Theoretically, a low concentration of cross-linker will lead to unstable mechanical properties of the polymer, while an excessive amount of cross-linker can mask the recognition sites on the surface of SMIP. An appropriate cross-linker will form effective pores and imprinted binding sites and increase the adsorption capacity of the polymer. In addition, the ratio of template to monomer will affect the growth of cross-linked polymer on the surface of amino-modified silica gel particles.[36] Optimizing the reaction system could effectively avoid secondary nucleation. In this study, the ratio of template, monomer and cross-linker was optimized using the orthogonal test to ensure that SMIP had the highest adsorption capacity and specificity, which minimized secondary nucleation. The results showed that the optimal molar ratio of template, monomer (HPMA) and cross-linker (TMPTMA) was 1 : 15 : 40, respectively.

3.1.4. Porogen. The porogen can provide a porous structure for the imprinted polymer and promote the bonding speed of the guest molecule. Besides, an appropriate porogen may disperse the heat released during polymerization to avoid the occurrence of some undesired side reactions caused by excessive local temperature. Most molecular imprinting is carried out in apolar organic solvents to maximize hydrogen bond interactions, which many SMIPs rely on for recognition. However, most polypeptides and proteins have poor stability and solubility in apolar solvents. The apolar conditions used in the polymerization process may denature polypeptide molecules or force them into conformations or aggregates that are unsuitable for imprinting, which may affect selectivity. We initially selected polar solvents such as water and MeOH as porogens and tried to improve the specificity of SMIP by adding apolar solvents such as toluene and dichloromethane. However, the performance of the prepared SMIP was relatively poor, and it might be that the template molecules were not completely dissolved. Considering the solubility of the polypeptide, finally, pure water was used as the porogen to obtain SMIP with higher adsorption capacity and specificity (shown in Fig. 2D).

3.2. Characterization

3.2.1. SEM analysis. The surface morphology of the modified silica gel and imprinted silica gel was observed using scanning electron microscopy with different magnifications. As shown in Fig. 3, there were obvious differences in the surface of silica gel before and after imprinting. The surface of SMIP

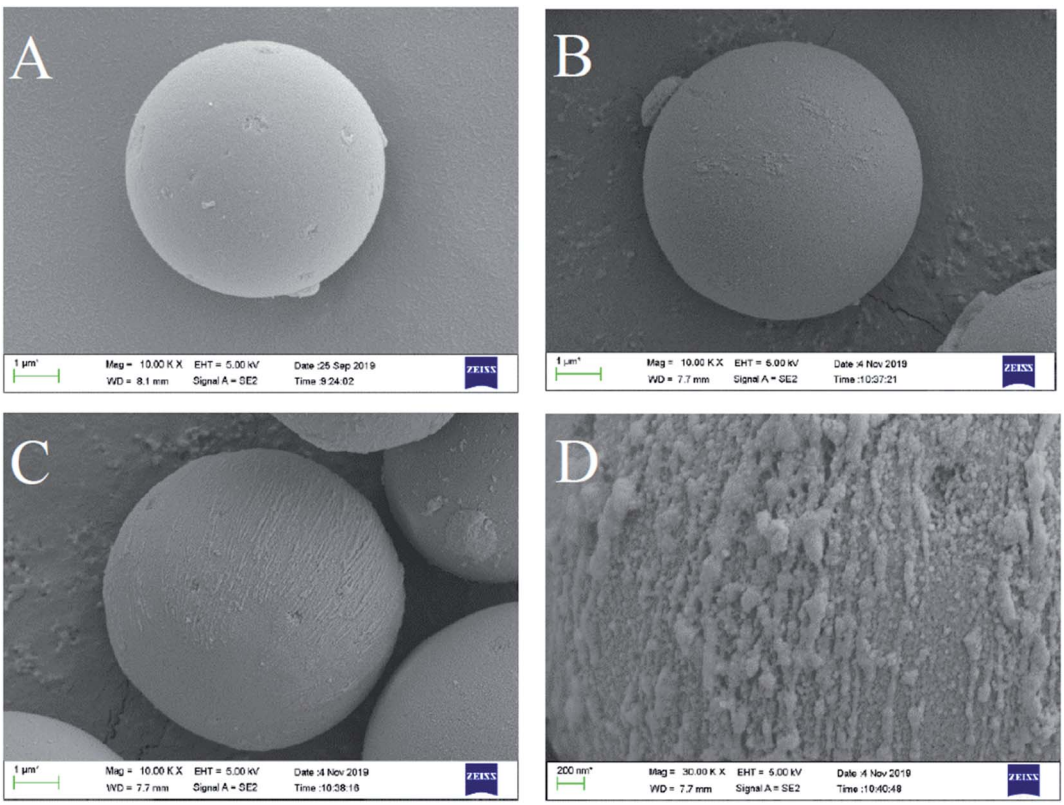

Fig. 3 Scanning electron micrographs of (A) modified silica gel, (B) NIP, (C) SMIP at 10 K magnification and (D) SMIP at 30 K magnification SMIP, surface molecularly imprinted polymer; NIP, non-imprinted polymer.

became rougher after the polymer was grafted onto the surface of modified silica gel. There were more cavities on the surface of SMIP than those on NIP, which indicated that the thicker polymer film with three-dimensional cavities was present on the SMIP. Obviously, the amino-modified silica gel was involved in the polymerization, and the imprinted polymer showed extensible growth on the surface of silica gel and wrapped the silica gel microsphere. Due to the lack of template molecules during the NIP preparation process, the amino-modified silica gel had a weak effect on the oligomers formed in the solution, resulting in a thinner imprint film.

3.2.2. FT-IR analysis. The FT-IR spectra of the modified silica particles and prepared SMIP are displayed in Fig. S3.† The main absorption bands ranged in 3600–3400 cm^{-1}, 1639 cm^{-1} and 1084 cm^{-1} were mainly assigned to the stretching vibrations of Si–O–H of silica gel and the band around 810 cm^{-1} was attributed to Si–O vibrations. For SMIP particles, the absorption bands ranged in 1723 cm^{-1} and 2957 cm^{-1} due to the C=O stretching vibration and aliphatic C–H stretching, respectively, which confirmed that HPMA and TMPTMA were successfully grafted on the surface of amino-modified silica gel.

3.2.3. Thermogravimetric analysis. The thermostability of the imprinted microspheres is shown through the data in Fig. S4.† NIP and modified silica gel have similar thermogravimetric curves. All samples were stable between 100 and 300 °C with very little change in mass. SMIP began to change rapidly at 300 °C and reached a peak at 470 °C. The mass loss of SMIP was 23.4% at 900 °C. In the thermogravimetric analysis, the mass change of SMIP was more obvious than that of NIP due to the thicker imprinting layer and the larger number of imprinting sites of SMIP.

3.3. Adsorption and selectivity characteristics

3.3.1. Effect of solvent and pH on adsorption capability. The influence of different solvents on the adsorption efficiency was evaluated. As shown in Fig. 4A, the IF value of imprinted polymer increased significantly with the increase in the water proportion and reached the highest in the 50% MeOH aqueous solution. The effect of different pH conditions (5 to 9) on the adsorption amount was investigated and the results are shown in Fig. 4B. The obtained data indicated that the pH of the buffer affected the adsorption capacity of SMIP. The SMIP exhibited relatively strong adsorption capacity under both neutral and weak acid conditions. The adsorption capacity of SMIP was significantly higher than that of NIP under the same conditions. Different pH values would affect the protonation state of the template and monomer in SMIP, thus affecting the binding affinity between the TEC and the polymer. The maximum adsorption capacity was obtained at pH 7.0, so it was selected in subsequent experiments.

3.3.2. Adsorption isotherm. In general, nonlinear models including Langmuir and Freundlich isotherm models were used to describe the adsorption process of the molecularly imprinted polymer. As shown in Fig. 5A, the adsorption of SMIP gradually increased with the increase in initial concentration, fitting for a line model (r^2 = 0.9978). De Smet *et al.*[39] also reported a similar situation, which may be caused by the template. The adsorption capacity of NIP was significantly lower than that of SMIP in the tested concentration range. The adsorption capacities of SMIP and NIP for TEC at the concentration of 1 mg mL^{-1} were 152.6 mg g^{-1} and 23.6 mg g^{-1}, respectively. The results indicated that the recognition sites had been created during the process of molecular imprinting. Furthermore, the remarkable adsorption of SMIP might result from the "memory" function of imprinting cavities. Under the same experimental conditions, the higher capacity-imprinted cavities in the framework of SMIP made specific active positions for the TEC, so the adsorption affinity of SMIP was higher than that of NIP.

3.3.3. Adsorption kinetics. Kinetic adsorption is one of the important factor in evaluating the adsorption efficiency. The effects of the adsorption of SMIP and NIP for TEC were investigated by varying the time at the range from 1 to 90 min. As shown in Fig. 5B, the adsorption capacity of SMIP increased rapidly and reached equilibrium within 1 min. The fast adsorption capacity was mainly attributed to the thin imprinting coating layer that greatly reduces the transmission resistance, and the large specific surface area conferred by silica

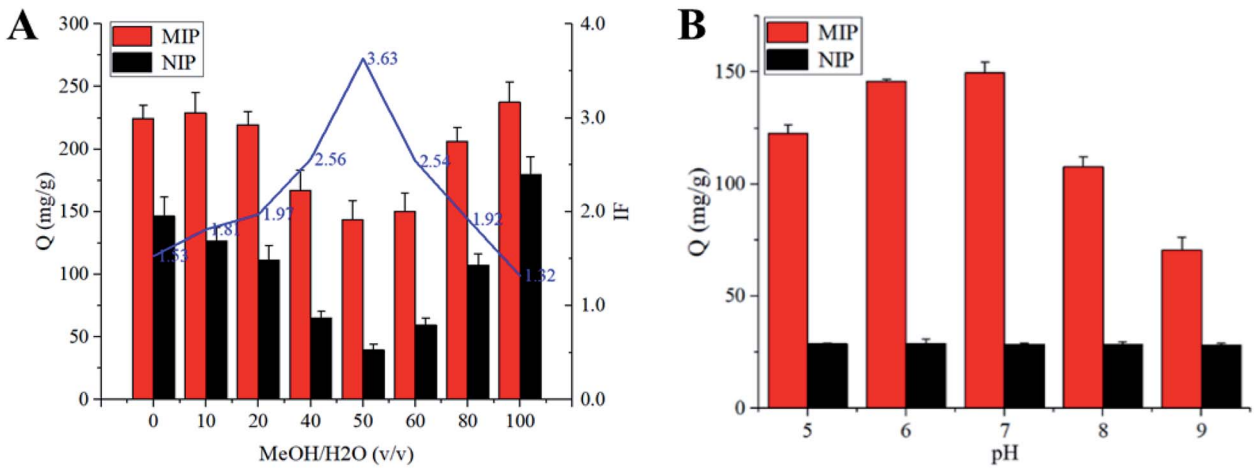

Fig. 4 Effects of different ratios of solvents (A) and pH (B) on adsorption capability of the imprinted polymers for teicoplanin.

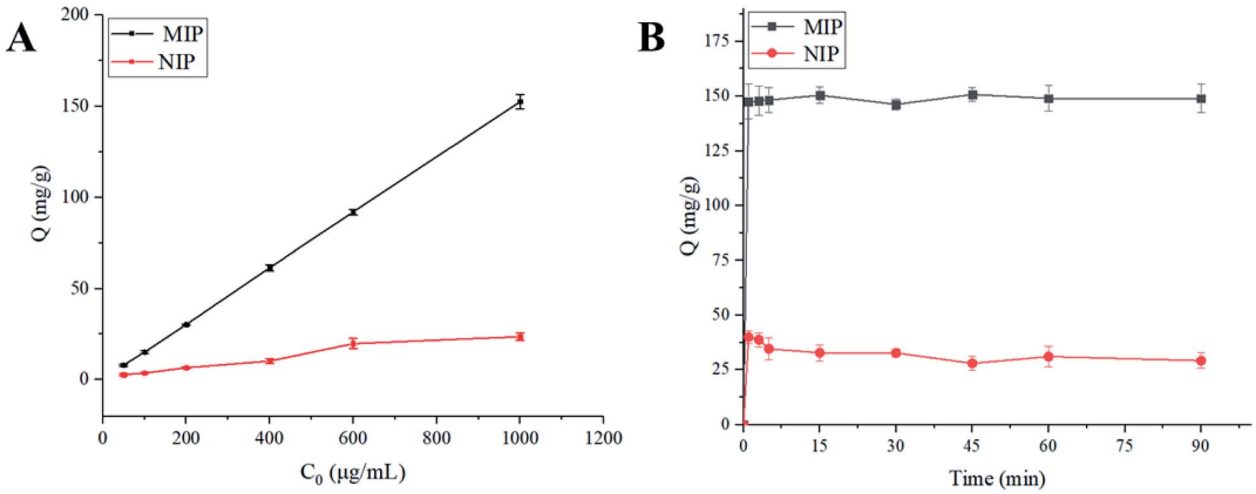

Fig. 5 Adsorption isotherm (A) and adsorption kinetics (B) of the imprinted polymers for teicoplanin.

gel allows the imprinting material to have more opportunities to contact the template molecule in the solution. Because of the rapid adsorption process, it is difficult to obtain data before equilibrium for fitting kinetic curves using existing instruments and equipment. Although both SMIP and NIP have similar dynamic adsorption curves, the adsorption capacity of SMIP is always much higher than that of NIP.

3.3.4. Selectivity. It is known that MIP only specifically recognizes the template and its analogues. The results showed that the SMIP hardly adsorbed peptide antibiotics including VGM, BAT, CS and macrolide antibiotics (SPM and TIM). The SMIP also showed a low affinity to SM2 and EN (small molecules). Surprisingly, the prepared SMIP had poor adsorption capability to VCM (analogue of TEC) in pure aqueous solution, while it showed better adsorption in MeOH solution. Under the concentration of 200 μg mL^{-1}, the adsorption capacities of SMIP and NIP for VCM were 22.9 mg g^{-1} and 13.5 mg g^{-1}, respectively. The SMIP had relatively low recognition for other drugs, suggesting that the prepared polymer had selective recognition ability to recognize template molecules from complex mixtures.

3.4. Determination of TEC in real water samples

The feasibility of SMIP was investigated by enriching TEC from real water. The TEC was extracted and enriched from real water samples by dispersive solid-phase extraction and TEC was not detected in all blank water samples. The typical chromatograms obtained before and after the selective extraction are shown in Fig. S5.† It could be seen that there was no peak of TEC in the blank real water sample, and there was an obvious peak after spiking it with 10 μg L^{-1} of TEC. The peak of TEC was weak after selective extraction by SMIP, which meant that the templates had been selectively captured. For the proposed HPLC method based on SMIP-dSPE, the average recoveries of TEC in real water samples ranged from 81.4% to 94.6% and the RSD was less than 10.4%. The recoveries were determined based on real water samples spiked at three concentration levels (10, 20 and 50 μg L^{-1}), and the linear range was from 5 μg L^{-1} to 100 μg L^{-1}. The limit of detection for the TEC was 5 μg L^{-1}, and the enrichment factor was more than 500. The results showed that SMIP could be used for selective extraction, enrichment and detection of TECs in real water samples.

4. Conclusions

In this study, a selective surface SMIP was synthesized with TEC as a template and amino-modified silica gel as supporting material. Under the optimized conditions, the SMIP showed good adsorption performance for TEC. The SMIP as a dSPE material could selectively adsorb TEC from environmental water, and recovery and precision met the requirements for trace analysis. This study can provide a reference for the application of surface imprinting technique to glycopeptide antibiotics, also it will help in further development and application of SMIP.

Conflicts of interest

The other co-authors declare that they have no conflict of interest.

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References

1 E. Binda, P. Cappelletti, F. Marinelli and G. L. Marcone, *Antibiotics*, 2018, 7(2), 36.
2 D. J. Newman, *ACS Med. Chem. Lett.*, 2018, **9**, 66–67.

3 P. Sarkar and J. Haldar, *Glycopeptide Antibiotics Mechanism of Action and Recent Developments*, 2020.
4 Y. Peng, X. Ye, Y. Li, T. Bu, X. Chen, J. Bi, J. Zhou and Z. Yao, *PLoS One*, 2013, **8**(11), e79782.
5 S. Svetitsky, L. Leibovici and M. Paul, *Antimicrob. Agents Chemother.*, 2009, **53**, 4069–4079.
6 S. Schwarz, C. Kehrenberg and T. R. Walsh, *Int. J. Antimicrob. Agents*, 2001, **17**, 431–437.
7 Ministry of Agriculture and Rural Affairs No. 250 Bulletin of the People's Republic of China, 2020, http://www.moa.gov.cn/gk/tzgg_1/gg/202001/t20200106_6334375.htm.
8 X. Song, T. Zhou, J. Zhang, Y. Su, H. Zhou and L. He, *Polymers*, 2019, **11**(7), 1109.
9 Y. Liu, Z. Li and L. Jia, *J. Chromatogr. A*, 2020, **1622**, 461147.
10 B. Babamiri, A. Salimi and R. Hallaj, *Biosens. Bioelectron.*, 2018, **117**, 332–339.
11 C. C. de Escobar, Y. P. Moreno Ruiz, J. H. Z. dos Santos and L. Ye, *Colloids Surf., A*, 2018, **538**, 729–738.
12 K. Ji, X. Luo, L. He, S. Liao, L. Hu, J. Han, C. Chen, Y. Liu and N. Tan, *J. Pharm. Biomed. Anal.*, 2020, **180**, 113036.
13 L. Tan, Y. Li, X. Pan, M. L. Marina and Z. Jiang, *J. Chromatogr. A*, 2020, **1615**, 460776.
14 R. Gao, S. Zhao, Y. Hao, L. Zhang, X. Cui, D. Liu and Y. Tang, *RSC Adv.*, 2015, **5**, 88436–88444.
15 K. Bashir, P. Guo, G. Chen, Y. Li, Y. Ge, H. Shu and Q. Fu, *Arabian J. Chem.*, 2020, **13**, 4082–4091.
16 X. Kong, F. Li, Y. Li, X. He, L. Chen and Y. Zhang, *J. Sep. Sci.*, 2020, **43**, 808–817.
17 X. Wang, H. Ding, X. Yu, X. Shi, A. Sun, D. Li and J. Zhao, *Talanta*, 2019, **197**, 98–104.
18 J. Li, X. Hu, P. Guan, X. Zhang, L. Qian, R. Song, C. Du and C. Wang, *RSC Adv.*, 2015, **5**, 62697–62705.
19 M. Amatatongchai, W. Sroysee, P. Sodkrathok, N. Kesangam, S. Chairam and P. Jarujamrus, *Anal. Chim. Acta*, 2019, **1076**, 64–72.
20 L. Sun, J. Guan, Q. Xu, X. Yang, J. Wang and X. Hu, *Polymers*, 2018, **10**(11), 1248.
21 N. Casado, S. Morante-Zarcero, D. Perez-Quintanilla, J. S. Camara and I. Sierra, *Trends Food Sci. Technol.*, 2020, **98**, 167–180.
22 X. Hou, W. Huang, F. Zhu, F. Geng and M. Tian, *Anal. Methods*, 2019, **11**, 317–326.
23 S. Shi, D. Fan, H. Xiang and H. Li, *Food Chem.*, 2017, **237**, 198–204.
24 D. Fan, H. Li, S. Shi and X. Chen, *J. Chromatogr. A*, 2016, **1470**, 27–32.
25 W. Cheng, Z. Liu and Y. Wang, *Talanta*, 2013, **116**, 396–402.
26 A. Anene, K. Hosni, Y. Chevalier, R. Kalfat and S. Hbaieb, *Food Control*, 2016, **70**, 90–95.
27 Y. Ren, W. Ma, J. Ma, Q. Wen, J. Wang and F. Zhao, *J. Colloid Interface Sci.*, 2012, **367**, 355–361.
28 W. Liang, Y. Lu, N. Li, H. Li and F. Zhu, *Microchem. J.*, 2020, **159**, 105316.
29 F. Zhu, L. Li and J. Xing, *J. Hazard. Mater.*, 2017, **321**, 103–110.
30 F. Zhu, Y. Lu and L. Li, *RSC Adv.*, 2016, **6**, 111120–111128.
31 Z. Zhang, L. Chen, F. Yang and J. Li, *RSC Adv.*, 2014, **4**, 31507–31514.
32 G. Guan, R. Liu, Q. Mei and Z. Zhang, *Chem.–Eur. J.*, 2012, **18**, 4692–4698.
33 Z. Zhang, J. Li, J. Fu and L. Chen, *RSC Adv.*, 2014, **4**, 20677.
34 X. Li, X. Ma, R. Huang, X. Xie, L. Guo and M. Zhang, *J. Sep. Sci.*, 2018, **41**, 2837–2845.
35 W. Huang, P. Xu, W. Yang and W. Xu, *RSC Adv.*, 2016, **6**, 74734–74741.
36 L. Tan, W. Li, H. Li and Y. Tang, *J. Chromatogr. A*, 2014, **1336**, 59–66.
37 L. Chen, X. Wang, W. Lu, X. Wu and J. Li, *Chem. Soc. Rev.*, 2016, **45**, 2137–2211.
38 E. Verheyen, J. P. Schillemans, M. van Wijk, M.-A. Demeniex, W. E. Hennink and C. F. van Nostrum, *Biomaterials*, 2011, **32**, 3008–3020.
39 D. De Smet, V. Kodeck, P. Dubruel, C. Van Peteghem, E. Schacht and S. De Saeger, *J. Chromatogr. A*, 2011, **1218**, 1122–1130.