

Preparation of Molecularly Imprinted Polymer for Selective Solid-Phase Extraction and Simultaneous Determination of Five Sulfonylurea Herbicides in Cereals

(Penyediaan Polimer Teraan Molekul untuk Pengekstrakan Fasa-Pepejal Terpilih dan Penentuan Serentak Lima Herbisid Sulfonylurea dalam Bijirin)

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ABSTRACT

Molecular imprinting polymer (MIP) has been increasingly employed for sulfonylurea herbicides (SUHs) detection in different matrices. A novel MIP that was effective as a highly class-selective sorbent in molecularly imprinted solid-phase extraction (MISPE) was successfully prepared for isolation and purification of SUHs, namely, metsulfuron-methyl, chlorsulfuron, chlorimuron-ethyl, prosulfuron, and pyrazosulfuron-ethyl, in rice, corn and soybean samples. The MIP was synthesized by precipitation polymerization using metsulfuron-methyl as the template, 4-vinylpyridine as the functional monomer, ethylene glycol dimethacrylate as the crosslinker, and MeCN as the porogen. The polymerization system of the MIP was optimized, and its adsorption performances were evaluated by comparing its adsorption isotherms and adsorption kinetics with those of a non-imprinted polymer (NIP). Following MISPE for extracting and enriching SUHs from rice, corn and soybean samples, high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) was performed. Acceptable recoveries were observed at SUHs contaminant concentrations of 10, 20 and 40 µg/L: from 77.56 to 99.81%, with relative standard deviations of <13.8% (n = 5) for all samples. The limits of detection for the five SUHs were 0.21-0.26 µg/L. The results demonstrated that the proposed MISPE-HPLC-MS/MS method is an effective approach for the simultaneous and sensitive determination of the five SUHs in rice, corn and soybean samples.

Keywords: Cereals; HPLC-MS/MS; molecularly imprinted polymers; solid-phase extraction; sulfonylurea herbicides

ABSTRAK

Polimer teraan molekul (MIP) semakin banyak digunakan untuk pengesanan herbisid sulfonylurea (SUH) dalam matriks yang berbeza. MIP novel yang berkesan sebagai penjerap selektif kelas tinggi dalam pengekstrakan fasa pepejal teraan molekul (MISPE) telah berjaya disediakan untuk pengasingan dan penulenan SUH, iaitu, metsulfuron-metil, klorosulfuron, klorimuron-etil, prosulfuron, dan pirazosulfuron-etil, dalam sampel beras, jagung dan kacang soya. MIP telah disintesis melalui pemolimeran pemendakan menggunakan metsulfuron-metil sebagai templat, 4-vinilpiridin sebagai monomer berfungsi, etilena glikol dimetakrilat sebagai penghubung silang dan MeCN sebagai porogen. Sistem pemolimeran MIP telah dioptimumkan dan prestasi penjerapannya dinilai dengan membandingkan isoterma penjerapan dan kinetik penjerapan dengan polimer tidak dicetak (NIP). Melalui penggunaan MISPE untuk mengekstrak dan memperkayakan SUH daripada sampel beras, jagung dan kacang soya, spektrometri jisim tandem kromatografi cecair berprestasi tinggi (HPLC-MS/MS) telah dilakukan. Pemulihan yang boleh diterima telah diperhatikan pada kepekatan pencemar SUH sebanyak 10, 20 dan 40 µg/L: dari 77.56 hingga 99.81%, dengan sisihan piawai relatif <13.8% (n = 5) untuk semua sampel. Had pengesanan untuk lima SUH ialah 0.21-0.26 µg/L. Keputusan menunjukkan bahawa kaedah MISPE-HPLC-MS/MS yang dicadangkan merupakan pendekatan yang berkesan untuk penentuan serentak dan sensitif lima SUH dalam sampel beras, jagung dan kacang soya.

Kata kunci: Bijirin; HPLC-MS/MS; pengekstrakan fasa pepejal; polimer teraan molekul; racun herba sulfonylurea

INTRODUCTION

SUHs are a class of highly selective and active herbicides with a common structure where the R1 moiety can be an aromatic, an aliphatic, or a heterocyclic group connected by the sulfonylurea bridge to the R2 moiety of a pyrimidine system or substituted triazine (Sarmah & Sabadie 2002). The known mode of action of these herbicides is to inhibit the synthesis of acetolactate synthase (ALS), an essential enzyme in the biosynthetic pathway of branched-chain amino acids (Walter et al. 2014). On account of their excellent herbicidal activity at low application rates (10-40 g/ha) and their low mammalian toxicity (Tranel & Wright 2002), SUHs have been widely used in rice, wheat, barley, corn, soybean and other crop fields since their launch in 1980s (Bouri et al. 2012; Ghobadi et al. 2015). However, despite the above significant advantages, the extensive and improper use of these pesticides has raised concerns about not only their adverse environmental impacts (Coyner et al. 2001; Heine et al. 2016; Michael 2003) but also their potential threats to human health (Dasgupta et al. 2007; Ding et al. 2010). Therefore, the maximum residue limits (MRLs) of several SUHs in agricultural products have been established in China (M.M.O.A. (PRC) 2019), the USA (United States Department of Agriculture 2008) and the European Union (European Commission 2016). In view of the regulatory requirements and food safety concerns, a simple, sensitive, and reliable method is urgently required to monitor SUH residues in agricultural products, especially cereal grains.

In recent years, a variety of chromatographic methods have been established to analyze SUH residues in environmental matrices such as soil (Mehdizadeh et al. 2017; Sofu et al. 2012; Yan et al. 2016) and surface water (Ghobadi et al. 2015; He et al. 2012; Pei et al. 2018). The common methods are liquid chromatography (LC) (You & Chen 2016), gas chromatography (GC) (Klaffenbach & Holland 1993), gas chromatography-mass spectrometry (GC/MS) (Springer & Lista 2010) and high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) (Rejczak & Tuzimski 2015). However, few studies have focused on the analysis of SUH residues in cereals and other plant samples. The most probable explanation for this is that the complex nature of these biological matrices might adversely affect the sensitivity and reproducibility of the analytical methods. Further, the most common pretreatment method employed prior to analysis in order to remove other compounds co-extracted with the SUHs has been solid-phase extraction (SPE) with C₁₈ cartridges, which is not completely effective. Hence,

a novel alternative pretreatment method is imperative for the efficient extraction and enrichment of trace-level SUHs in complex matrices.

MIPs are one of the powerful tools for the preparation of polymeric materials capable of specifically binding a chemical species (Augusto et al. 2013). Because of their selective recognition and stability, MIPs have a wide range of applications, including in SPE (Alizadeh et al. 2012; Zhao et al. 2014), biomimetic sensors (Asghar et al. 2019; Lee et al. 2020), chromatographic separation (Núñez et al. 2010; Sellergren 2001) and the isolation of active ingredients from plants (He et al. 2016). In particular, MIPs are being extensively employed as sorbents in SPE for the selective extraction and enrichment of analytes in numerous complex biological matrices (Qin et al. 2020; Rico-Yuste et al. 2018; Svoboda et al. 2017). Molecularly imprinted solid-phase extraction (MISPE) has been increasingly employed for SUH detection in different matrices (She et al. 2010; Tang et al. 2014, 2008). MIPs, which are critical sorbents in this process, have been mainly synthesized by two approaches: Bulk polymerization and precipitation polymerization. Bastide et al. (2005) reported the synthesis of MIPs by bulk polymerization, but despite the high affinity for the templates and their analogs, various problems were encountered: Tedious processes, low yield and irregular size after grinding and sieving. In contrast, the recently developed precipitation polymerization enables the one-step preparation of homogeneous MIP microspheres that are suitable for SPE separation because of the optimal surface contact with the target molecules. For example, She et al. (2010) and Tang et al. (2008) prepared MIPs by precipitation polymerization using chlorsulfuron (CS) and bensulfuron-methyl (BSM) as the templates, respectively. In these two studies, MISPE with the MIPs as adsorbents enabled the successful specific extraction of CS, monosulfuron (MNS), thifensulfuron-methyl (TFM), BSM, metsulfuron-methyl (MSM), nicosulfuron (NS) and tribenuron-methyl (TBM) from maize and soybean samples, respectively.

To date, however, there has been no report about the application of MIPs in SPE for the simultaneously determination of trace SUHs in various agricultural crops with complex chemical components. In this study, a novel MIP was prepared by precipitation polymerization using MSM as the template. Further, MISPE with the prepared MIP as the selective sorbent was employed in combination with HPLC-MS/MS, for the extraction and quantification of trace amounts of MSM, CS, CME, PRS and PSE in rice, corn and soybean samples.

EXPERIMENTAL DETAILS

CHEMICALS AND REAGENTS

MSM, CS, chlorimuron-ethyl (CME), prosulfuron (PRS), pyrazosulfuron-ethyl (PSE), foramsulfuron (FS), triasulfuron (TRS) and mesosulfuron-methyl (MM) were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany). The chemical structures of these SUHs are shown in Figure 1. Methacrylic acid (MAA) from Alfa Aesar (Massachusetts, USA) was distilled under reduced pressure for removing the inhibitor, and stored at 4 °C. 4-vinylpyridine (4-VP), trimethylolpropane

trimethacrylate (TRIM) and ethylene glycol dimethacrylate (EGDMA) were obtained from Beijing Bailingwei Technology Co., Ltd. (Bjing, China). The free radical initiator 2,2-azobisisobutyronitrile (AIBN, purity > 98%) was obtained from Shanghai No.4 Reagent & H. V. Chemical Co., Ltd. (Shanghai, China). Chromatographic-grade methanol and MeCN were supplied by Sigma-Aldrich (St. Louis, MO, United States). All the remaining chemical reagents were of analytical grade and obtained from the Chemical Reagent Company (Beijing, China). Ultrapure water obtained using the Milli-Q Plus water purification system (Millipore, Bedford, MA, USA) was used throughout the experiments.

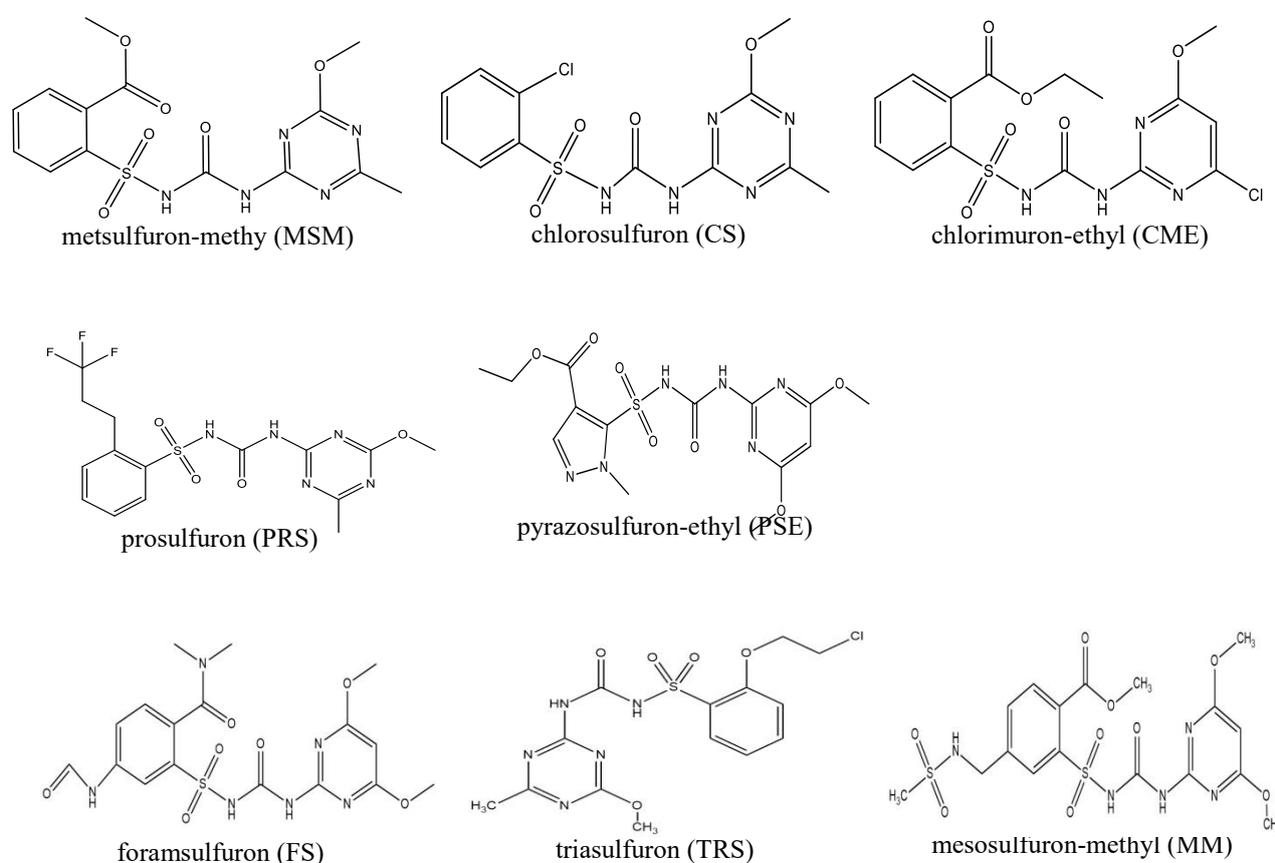


FIGURE 1. Chemical structures of the studied sulfonylurea

PREPARATION OF MOLECULARLY IMPRINTED
POLYMERS

The MIPs were synthesized by precipitation polymerization. The molar ratios of the template molecule MSM to the functional monomers MAA or 4-VP were determined in advance by ultra-violet absorption

spectrometry. Polymers prepared with the different functional monomers, crosslinkers (EGDMA and TRIM) and porogens (dichloromethane and MeCN) in different proportions were evaluated to identify the optimal MIP ideal for application in MISPE.

For producing the MIPs, MSM (0.2 mmol) and the functional monomer (0.8 mmol) were dissolved in MeCN (25 mL) in a 100 mL round-bottomed flask with a rubber cap. After shaking for 30 min for pre-polymerization, the crosslinker (4 mmol) and AIBN (50 mg) were added. Then, the solution was placed in an ultrasonic water bath for 5 min, followed by sparging with a weak nitrogen stream for 10 min. Thermo-polymerization proceeded at 60 °C in a water bath for 24 h. The polymeric particles were collected by centrifugation at 3000 rpm for 15 min. In order to remove the template, the resulting polymer was then purified by Soxhlet extraction with methanol–acetic acid (80:20, v/v) until MSM could not be detected by HPLC. Finally, the polymer was washed repeatedly with methanol, dried in a vacuum dryer overnight and stored at ambient temperature.

Further, NIP particles were prepared and processed under the same conditions but without the template MSM.

BINDING OF MIPs TO MSM

The adsorption performances of MIPs and NIPs were investigated by performing both dynamic and static adsorption experiments. The polymer particles (10 mg) were accurately weighed and placed in a 2.5 mL centrifugal tube, and mixed with 1 mL of 15 µg/mL MSM in MeCN. The solution was shaken for different periods (0.5, 1, 1.5, 2, 4 and 6 h) at room temperature to determine the saturation adsorption time. To realize the maximum binding of MSM to the polymers, the same amounts of the polymers were added into 1 mL of MSM solutions with different concentrations (1, 10, 20, 30, and 50 µg/mL). The mixtures were incubated on shakers for 4 h (saturation adsorption time) and rapidly centrifuged. Then, the supernatants were filtered through 0.45 µm membranes and the free MSM in the filtrate was analyzed by HPLC. Class-selective adsorption was also evaluated as follows: 10 mg of the polymer particles was dispersed in 1 mL of a mixed standard solution containing the eight SUHs (MSM, CS, CME, PRS, PSE, FS, TRS, MM) in MeCN at a concentration of 5 µg/mL. The rest of the steps were the same as above.

The equilibrium adsorption amounts of MSM were calculated according to the following equation (1):

$$Q = (C_0 - C_e) V / m \quad (1)$$

where Q (µg/g) is the MSM adsorption capacity; C_0 (µg/mL) and C_e (µg/mL) represent the initial and equilibrium MSM concentrations, respectively; V (mL)

represents the total volume of the MSM solution; and m (µg) is the mass of MIP or NIP particles.

The selective binding characteristics of the MIPs were subjected to Scatchard analysis. The binding isotherms obtained through the equilibrium experiments were transformed to linear equations by use of the Scatchard equation (2):

$$Q / C_e = (Q_{\max} - Q) / K_d \quad (2)$$

where Q_{\max} is the apparent maximum number of binding sites; and K_d is the equilibrium dissociation constant of the binding sites.

MISPE COLUMN PREPARATION AND OPTIMIZATION OF PROCEDURE

MIP particles (40 mg) were packed into a cartridge that was attached to two sieve plates (20 µm pore diameter), one each at its bottom and top ends. Previously conditioned with MeCN (3 mL) and water (2 mL) without pressure, a 1 mL aliquot of 20 µg/mL MSM MeCN solution was loaded onto the cartridge. For optimizing the MISPE procedure, the composition of the washing solution and eluting solvent were evaluated as follows. The cartridge was rinsed with 1 mL of MeCN, methanol, *n*-hexane, water, and MeCN–water (80/20, v/v, pH = 3) sequentially. Finally, the analyte retained on the sorbent particles was eluted with 6 mL of methanol, 6 mL of acetone, or 3, 4, or 6 mL of acetic acid/methanol (20/80, v/v) at a flow rate of 1.0 mL/min. All of the fractions from the washing and elution steps were collected and dried under a stream of nitrogen gas. The residues were redissolved in 1 mL of the mobile phase for further analysis by HPLC-MS/MS.

INSTRUMENTATION

The adsorption capacities and selectivity of the MSM–MIPs were analyzed by HPLC. HPLC analysis was carried out with a Waters 2695 Alliance HPLC system (Waters Corporation, Milford, MA, USA) equipped with a diode array detector. Chromatographic separation was performed using a Waters X Bridge C_{18} column (250 × 4.6 mm i.d., particle size, 5 µm). For HPLC, the injection volume was 10 µL, and the column temperature was 30 °C. Further, the detection wavelength was 227 nm, and a gradient elution program was used with a flow rate of 0.95 mL min⁻¹, by combining solvent A, i.e. water–acetic acid (99.5:0.5, v/v) and solvent B, i.e., methyl alcohol as follows (time, solvent B v/v): 0–2 min, 10–35%; 2–4 min, 35–60%; 4–5 min, 60%; 5–8 min, 60–80%; 8–9 min,

80%; 9–12 min, 80–90%; 12–15 min, 90%; 15–15.5 min, 90–50%; 15.5–16 min, 50–10%; 16–22 min, 10%.

HPLC-MS/MS was employed for the detection of SUHs in rice, corn and soybean samples by using an Agilent Series 1200 liquid chromatograph (Agilent Technologies, Palo Alto, CA, USA) coupled with an API 5000 triple quadrupole mass spectrometer (Applied Biosystem/MDS SCIEX, Foster City, CA, USA). Chromatography was carried out using an Agilent ZORBAX SB-C₁₈ column (2.1 × 100 mm i.d.; particle size: 3.5 μm). The column temperature was kept at 25 °C, and the injection volume was 5 μL. The HPLC mobile phase consisted of a mixture of (A) 0.1% formic acid–water (v/v) and (B) 0.1% formic acid–MeCN (v/v), and the

flow rate was 300 μL/min; further, the gradient elution procedure was as follows (time, solvent B v/v): 0–2 min, 10–40%; 2–6 min, 40–60%; 6–12 min, 60–90%; 12–15 min, 90%; 15–15.1 min, 90–10%; 15.1–21 min, 10%.

Mass spectrometry was performed in the multiple reaction monitoring mode with positive electrospray ionization (ESI+) as follows: ion spray voltage (IS+) = 5500 V; ion source temperature (TEM) = 450 °C; air curtain gas pressure (CUR) = 15 psi; nebulizer gas pressure (GS1) = 14 psi; auxiliary gas pressure (GS2) = 20 psi; entrance potential (EP) = 10 V; and collision cell exit potential (CXP) = 25 V. The m/z values, representing the potential and collision energy of both parent and product ions, are shown in Table 1.

TABLE 1. MS/MS parameters for determination of eight sulfonylurea herbicides

Analyte	Parent ions (m/z)	Product ions(m/z)	Declustering potential (V)	Collision energy(V)
MSM	382.3	167.2*,199.0	73	22,30
CS	358.2	141.3*,167.4	80	29,24
CME	415.4	119.2*,186.1	73	27,24
PRS	420.3	141.1*,167.2	92	28,29
PSE	415.2	182.4*,119.3	64	24,28
FS	453.3	182.7*,255.2	95	28,29
TRS	402.1	167.3*,141.2	92	23,29
MM	504.3	182.5*,306.6	81	31,32

Note: *Quantitative ion

PREPARATION AND ANALYSIS OF RICE, CORN, AND SOYBEAN MARKET SAMPLES

10 g of rice samples were accurately weighted and transferred into a 50 mL centrifugal tube in which 5 mL of ultrapure water was added. After vortexing for 30 s, 10 mL MeCN, 1 g NaCl and 4 g anhydrous magnesium sulfate were added sequentially. The mixture was then agitated on a reciprocating shaker for 20 min, followed by centrifugation at 5000 rpm for 5 min. Finally, the supernatant was completely pipetted out and evaporated on a rotary evaporator; the resultant precipitate was dissolved in 1 mL of MeCN and then extracted via the optimized MISPE procedure.

Corn and soybean samples were also prepared in the same way but with additional degreasing and decolorization steps. To remove the fat from the sample, the extract obtained was mixed with saturated *n*-hexane–MeCN (1:1, v: v) solution. By vortexing for 2 min, the mixture was separated into two layers, and the lower solution layer was retained. Then, the decolorization treatment was performed as follows: the solution was mixed with graphitized carbon (GCB) in a 1:10 (v/w) proportion. This was followed by vortexing, centrifugation at 5000 rpm for 5 min and MISPE.

In order to evaluate the effectiveness of the MISPE column in practical application, it was employed for the extraction and enrichment of SUHs from rice, corn and soybean samples purchased from local farmers' markets. For this, 1 mL of the above extracted sample solution was used in the optimized MISPE procedure. The column was activated with MeCN (3 mL) and water (2 mL) without pressure. Next, the cartridge was rinsed with 3 mL of MeCN–water (80:20, v/v, pH = 3) and eluted with 6 mL of acetic acid-methanol (2: 8, v/v). Finally, the eluent was dried under nitrogen and redissolved in 1 mL of the mobile phase for further analysis by HPLC–MS/MS.

RESULTS AND DISCUSSION

OPTIMIZATION AND IDENTIFICATION OF POLYMERIZATION SYSTEM

The ratio of the amount of template monomer to that of the functional monomer was one of the most important

factors impacting the target molecule adsorption capacity (Zhao et al. 2017). To obtain polymers with a high affinity and selectivity toward SUHs in complex matrices, the interactions between MSM and MAA or 4-VP in various ratios (1:2, 1:4, 1:6) were investigated by UV spectrophotometry. As shown in Figure 2, the two functional monomers both caused redshifts in the spectra compared with pure MSM dissolved in MeCN. Moreover, in both cases, the maximum redshifts occurred when the molar ratios of MSM to MAA or to 4-VP was 1:4.

The amount of crosslinker (Xu et al. 2015) and porogen (Castro et al. 2012) can directly affect the morphology, particle size and adsorption capacity of the polymer, so different ratios of the crosslinker (EGDMA or TRIM) and porogen (dichloromethane or MeCN) amounts in the polymerization system were also investigated. The optimum polymerization system was then identified by comparing the adsorption properties of the resultant polymers. Based on the results listed in

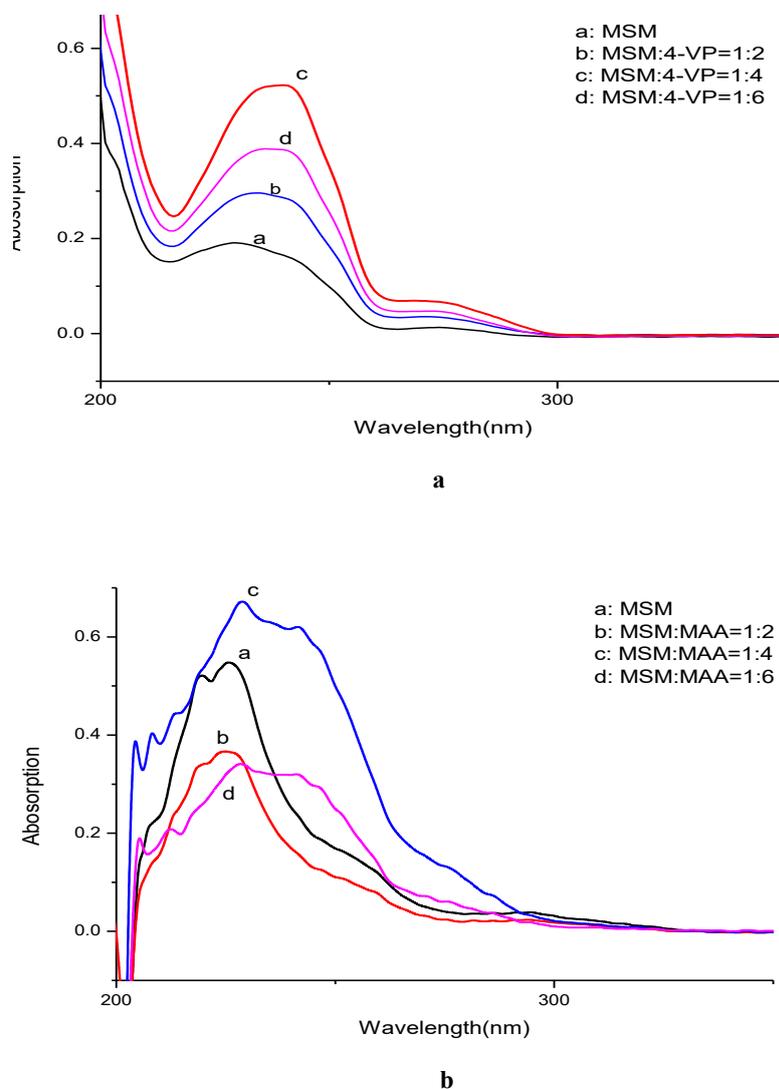


FIGURE 2. The UV spectra of MSM with different ratios of 4-VP (a) or MAA (b) in pre-polymerization

Table 2, the optimum polymerization system contains MSM as the template, 4-VP as the functional monomer, EGDMA as the crosslinker, and MeCN as the porogen. Further, when the molar ratios of MSM/4-VP/EGDMA was 1:4:20, the best molecular recognition ability was realized, so this ratio was employed in the subsequent experiments. The highly selective molecular recognition ability might be mainly attributable to two binding forces: the hydrogen bonds between the pyrimidine ring of 4-VP and protons in the sulfonylurea bridge and π - π interactions between aromatic groups of 4-VP and MSM

(Bastide et al. 2005). Both of EGDMA and TRIM are common crosslinkers. Because there are three double bonds in TRIM, it is easier to cross link, whose usage is less. While EGDMA has two unsaturated C=C double bonds, so the polymers formed with it are less rigid and have bigger volume. Isarankura-Na-Ayudhya et al. (2008) found that when MIPs are used for chromatographic analysis, they need to be larger crosslinking degree to obtain sufficient mechanical stability and good separation ability. In this study, the proportion of crosslinker and functional monomer was controlled at 1:5, which was helpful to synthesize the polymer with better properties.

TABLE 2. Composition of the polymerization mixtures used for the preparation of the MIPs and their adsorption capacities

Polymer number	Template	Functional monomer	Cross-linker	Composing proportion	Porogen	Adsorption capacities ($\mu\text{g/g}$)
1				1: 4: 10		679
2	MSM	MAA	EGDMA	1: 4: 15	MeCN	756
3				1: 4: 20		878
4				1: 4: 6		135
5	MSM	MAA	TRIM	1: 4: 8	MeCN	675
6				1: 4: 10		890
7				1: 4: 10		233
8	MSM	4-VP	EGDMA	1: 4: 15	MeCN	326
9				1: 4: 20		1098
10				1: 4: 6		799
11	MSM	4-VP	TRIM	1: 4: 8	MeCN	878
12				1: 4: 10		357
13				1: 4: 10		655
14	MSM	MAA	EGDMA	1: 4: 15	dichloromethane	970
15				1: 4: 20		754
16				1: 4: 6		311
17	MSM	MAA	TRIM	1: 4: 8	dichloromethane	568
18				1: 4: 10		987
19				1: 4: 10		235
20	MSM	4-VP	EGDMA	1: 4: 15	dichloromethane	126
21				1: 4: 20		335
22				1: 4: 6		376
23	MSM	4-VP	TRIM	1: 4: 8	dichloromethane	866
24				1: 4: 10		642

MORPHOLOGY AND STRUCTURE CHARACTERIZATION OF MIP

Scanning electron microscopy (SEM) was utilized to characterize the morphologies of the synthesized polymers. As shown in Figure 3, spherical MIPs with a uniform diameter of about 1 μm were prepared with precipitation polymerization (Figure 3(a)); these had rougher surface folds than did the NIPs (Figure 3(b)). Effects of types and amounts of crosslinker and porogen on the shape and structure were also further investigated by SEM. When EGDMA was used as the crosslinker, consistent-size microspheres with a regular shape were obtained (Supplementary Figure S1(a)), while irregular-shaped particles with nonuniform diameters and distribution were formed when TRIM was used as the crosslinker (Supplementary Figure S1(b)). In a certain range, with the increase of EGDMA concentration, the sphericity of polymer microspheres is more regular, leading to a better adsorption effect. However, TRIM is just the opposite. The explanation for this result was that the proportion of crosslinker and functional monomer for TRIM was too high to obtain good molecular imprinting structure and effect. Furthermore, when the MSM/4-VP/EGDMA molar ratio was 1:4:20, three-dimensional holes were evenly distributed in the microspheres (Supplementary Figure

S2). The polymer particles presented poor uniformity in size and exhibited more compact and overlapping structure when dichloromethane, rather than when MeCN, was used as the porogen (Supplementary Figure S3). Because affinity between porogen and polymer is one of the key factors for forming regular and uniform microspheres, excessive affinity may result in the inability to form monodisperse microspheres, thereby causing the adhesion among microspheres. Consequently, the poor uniformity in size obtained for dichloromethane may be due to its higher absorbability to polymer. As seen in Supplementary Figure S4, when the dosage of MeCN was reduced from 30 to 20 mL, the polymer particles became irregular and enlarged owing to the increase in the crosslinking degree, but their actual adsorption capacity decreased.

In order to further clarify the structures of the microspheres, Fourier transform infrared spectroscopy analysis was performed. As shown in Figure 4, in contrast to the NIPs, the MSM-MIP had three characteristic absorption peaks, which were assigned as follows: the bands around 1590.6 and 1567.3 cm^{-1} resulted from the N-H bending vibration, and the peak at 1390.1 cm^{-1} corresponded to the C-H bending vibration. After elution with acetic acid-methanol (20:80, v/v), these peaks disappeared. This indicates that the templates and monomers had been polymerized successfully.

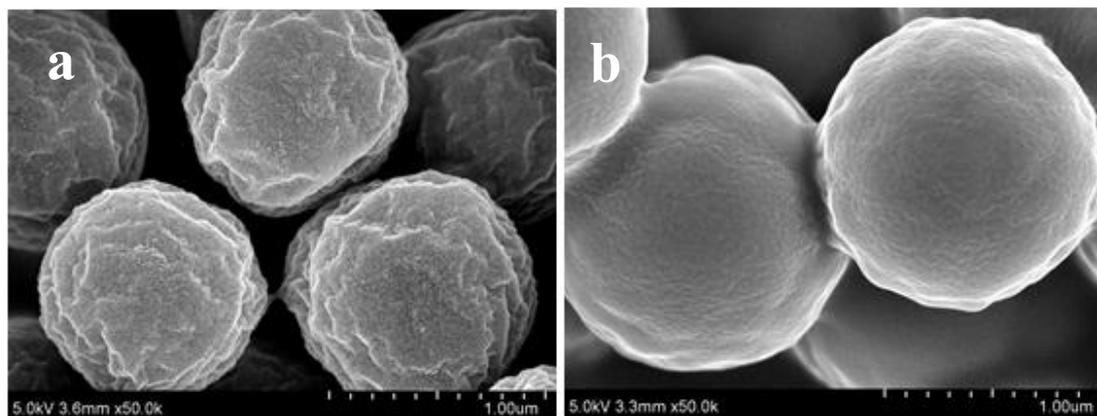


FIGURE 3. SEM micrographs of MIPs (a) and NIPs (b)

MIP BINDING SPECIFICITY

The selectivity's of the MIPs for adsorbing MSM and its analogs were verified in this experiment. As shown in Figure 5, the adsorbed amount gradually increased with the adsorption time and reached a maximum of 912.64 $\mu\text{g/g}$ at 4 h. Further, the discrepancy between the nonspecific adsorption by the NIP and specific adsorption by the MIP became evident after 1 h, and the desorption by the NIP occurred earlier at 2 h. Further, as illustrated in Figure 6, the amount of MSM bound to

the MIP and NIP at equilibrium increased with the initial MSM concentration. However, the adsorbed amount on the MIP was larger than that on the NIP at concentrations above 10 $\mu\text{g mL}^{-1}$ and reached the value of 1183.36 at 50 $\mu\text{g/mL}$. These results showed that adsorption mainly occurred via non-specific hydrogen bonding at low concentrations. In contrast, class-specific imprinted sites began to play a major role at high concentrations. The conclusion obtained was consistent with that reported in a previous paper (Zhu et al. 2002).

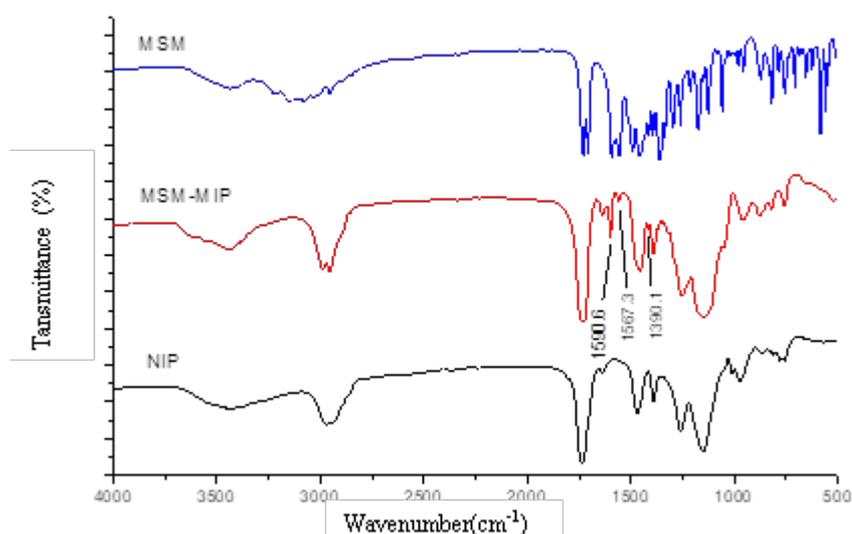


FIGURE 4. FTIR spectra of MSM, MSM-MIP, and NIP

The results of the static adsorption experiment were subjected to the Scatchard analysis (Figure 7) to estimate the adsorption properties of the MIPs. The different slopes for the MIPs indicate two types of binding sites because of hydrogen bonding, π - π conjugation effects and other interactions. The Scatchard equations were: $Q/C_e = -2.1265Q + 1731$ ($R^2 = 0.0607$) and $Q/C_e = -0.3566Q + 464.67$ ($R^2 = 0.9522$). Further, two typical binding parameters were calculated from the equations. The values for K_d were 0.47 and 2.8 $\mu\text{g}/\text{mL}$, and the corresponding Q_{max} values were 814.01 and 1302.29 $\mu\text{g}/\text{g}$, respectively. The MIP obviously showed a high binding affinity for MSM, CS, CME, PRS and PSE (Figure

8), which was similar to the binding specificity of the polymers prepared by Bastide et al. (2005) and Zhu et al. (2002); on the other hand, it displayed less affinity toward the other SUHs: FS, TRS and MM (Figure 8). This difference can be attributed to the similarity of the chemical structures and functional groups between the template MSM and other SUHs (Bastide et al. 2005; She et al. 2010). However, the MIP synthesized in this work had a lower binding affinity for FS and MM in spite of the minimal difference in the structures between MSM and FS and MM. Therefore, the detailed mechanisms of the SUH molecular recognition by MIP should be further explored.

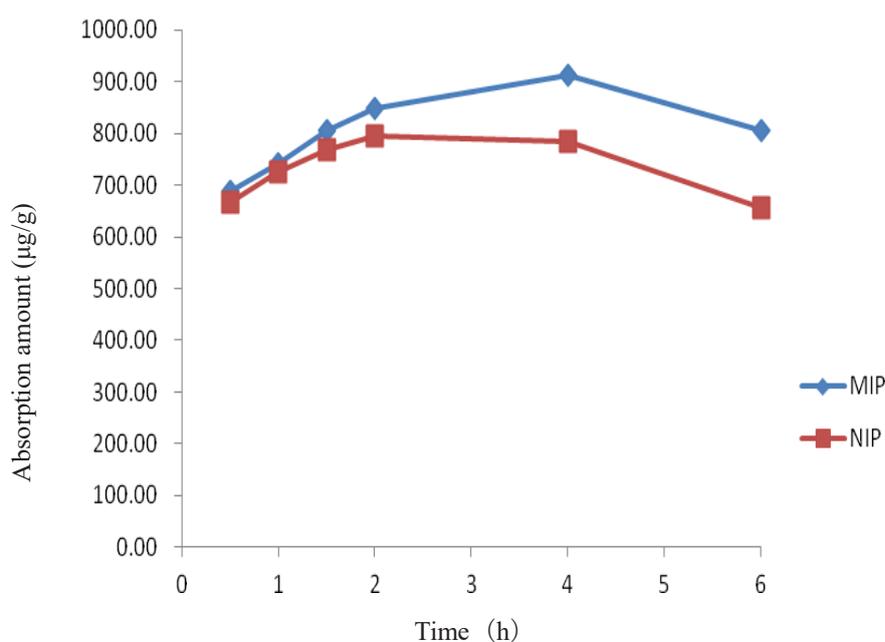


FIGURE 5. The binding isotherm of MIP and NIP for MSM with different adsorption time

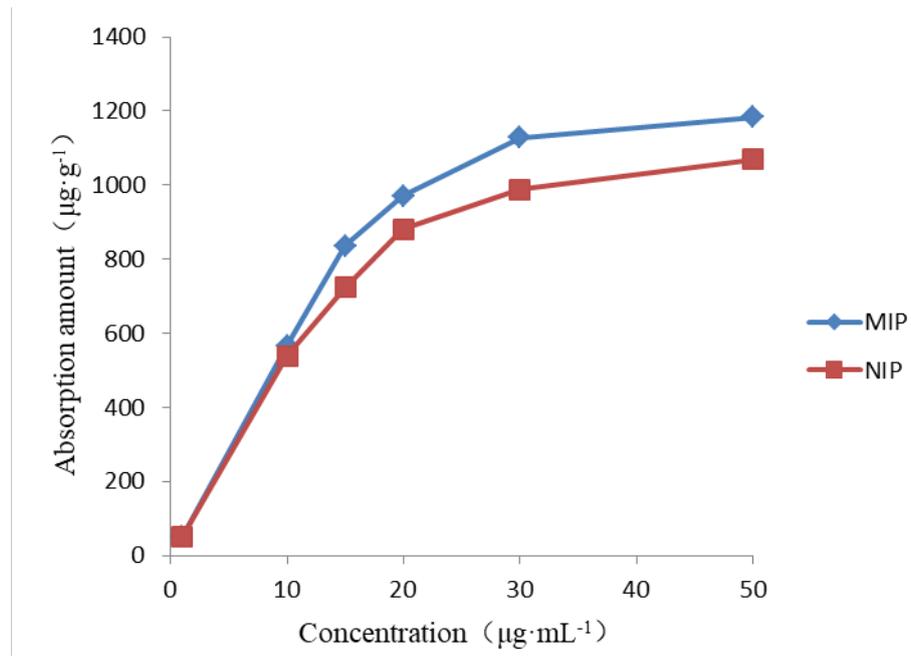


FIGURE 6. The binding isotherm of MIP and NIP for MSM with different MSM concentrations

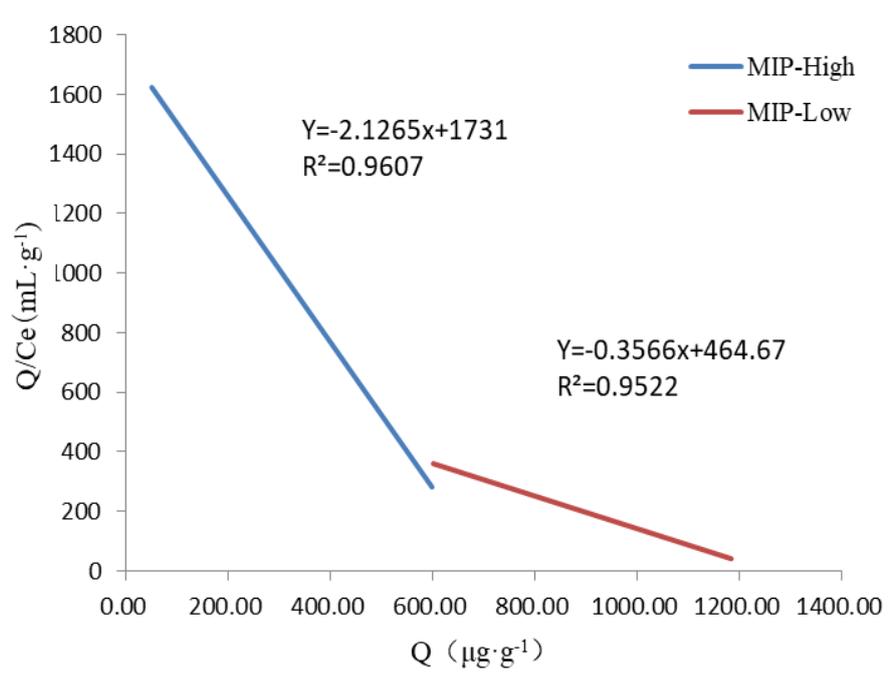


FIGURE 7. Scatchard plot analysis of MIP for MSM

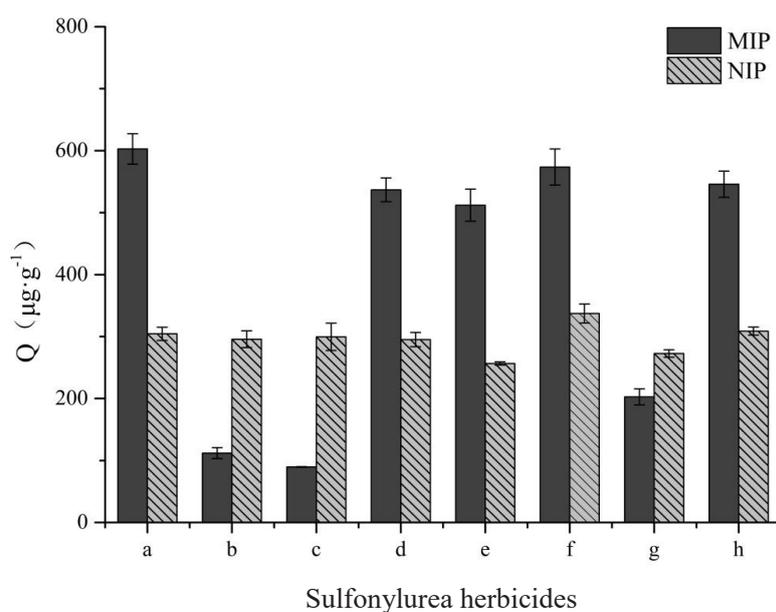


FIGURE 8. The adsorption capacity of MIP and NIP for eight sulfonylurea herbicides

OPTIMIZATION OF MISPE

To achieve efficient sample purification and concentration using MISPE for sample pretreatment, the washing solution and elution steps of the MISPE cartridges were investigated and optimized. The aim of the washing step is to maximize specific interactions of the MIP with the target analyte and to remove the other interfering compounds. As presented in Figure 9, MSM recovery from MeCN–water (80:20, v/v, pH = 3) was higher than that from each of the other washing solutions. Further, the quantitative retention of MSM on the NISPE cartridge was

lower than that on the MISPE cartridge. This confirms that the MIP was more effective than the NIP in recognizing the template.

The elution solvent is also a critical factor in the desorption of target analytes (Hong & Chen 2013). Therefore, a variety of elution solvents were investigated, and the results are shown in Figure 10. These results indicate that 6 mL of acetic acid–methanol (20:80, v/v) had the best elution ability, which provided the satisfactory recoveries. Consequently, 6 mL of acetic acid–methanol (20:80, v/v) was employed as the eluting solvent in the subsequent experiment.

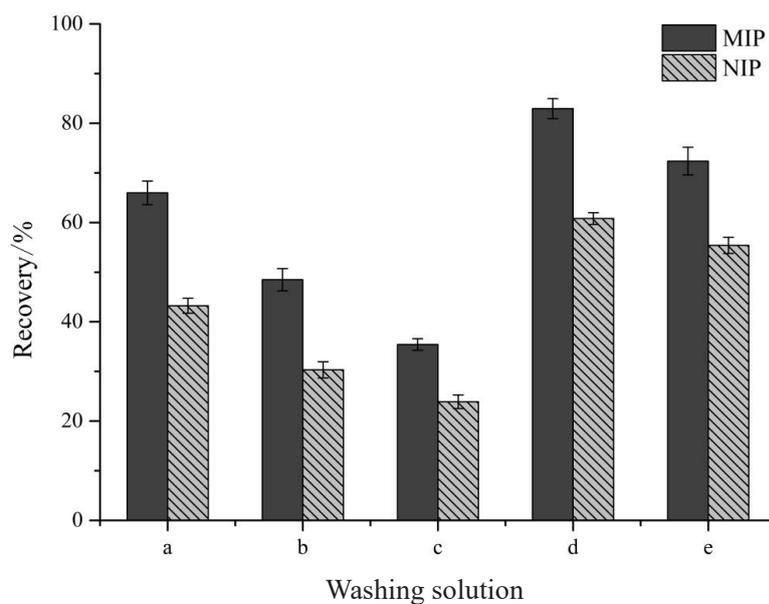


FIGURE 9. Comparison of different washing solutions on analyte recoveries

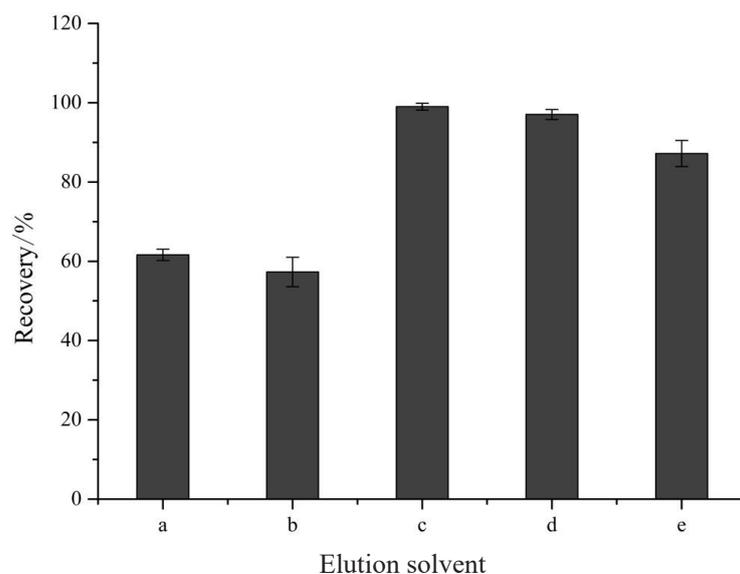


FIGURE 10. Comparison of different elution solvents on analyte recoveries

VALIDATION OF MISPE-HPLC-MS/MS METHOD BY USING CEREAL SAMPLES

To evaluate the feasibility of the MISPE procedure in the clean-up of the rice, corn and soybean samples for the determination of the five SUHs by HPLC-MS/MS, the linearity, sensitivity and precision of the proposed method were determined.

Matrix-matched calibration curves were applied to the quantification of the SUHs in spiked rice, corn and soybean blank samples. To test the linearity of the calibration curves, standard solutions of the eight mixed SUHs (MSM, CS, CME, PRS, PSE, FS, TRS, and MM), at concentrations of 0.1, 0.5, 1, 5, 10, 20, 50, and 100 $\mu\text{g}/\text{kg}$, were added to blank rice, corn and soybean sample matrices. An example chromatogram of the SUHs in a rice sample is shown in Supplementary Figure S5. The linear regression equations for the five SUHs (MSM, CS, CME, PRS, PSE) (Supplementary Table S1) showed good linearity over the concentrations ranging from 0.1 to 100 $\mu\text{g}/\text{kg}$, with high correlation coefficients (r^2) above 0.99. Compared with the linearity range (0.40-20.0 $\mu\text{g}/\text{kg}$) reported by Tang et al. (2014), the result in this work was much wider, which indicates the suitability for practical measurement.

To evaluate the precision of the proposed method, the recoveries were calculated after spiking the above

blank samples with the five SUHs at three concentration levels (10, 20 and 40 $\mu\text{g}/\text{kg}$). Five replicated analyses were carried out for each concentration. The recoveries of five compounds from the spiked samples are summarized in Tables 3, 4, and 5, respectively. Average recoveries of the five SUHs, namely, MSM, CS, CME, PRS and PSE from the spiked rice samples were 87.31, 88.02, 89.54, 89.06, and 88.55%, respectively. Further, the corresponding recoveries for corn samples were 87.98, 83.50, 86.48, 86.75, and 85.52%, respectively, while those for soybean samples were 88.47, 87.73, 84.70, 88.24, and 88.79%, respectively. The relative standard deviations were <13.8% ($n = 5$) for all analytes.

The LODs and LOQs, defined as the levels of the five SUHs in the three matrices that produced signal-to-noise ratios of 3 and 10, respectively, are also listed in Tables 3-5, respectively. Although the LODs (0.21-0.26 $\mu\text{g}/\text{kg}$) and LOQs (0.70-0.87 $\mu\text{g}/\text{kg}$) of the five compounds were higher than the values reported in water and soil (Liu et al. 2007; Pei & Huang 2018), the results were similar or better than the previously reported results for complex matrices (She et al. 2010; Tang et al. 2014). Further, the values were well below the MRLs set by China (M.M.O.A. (PRC) 2019), indicating that the proposed method is appropriate for regulation of SUHs in cereal grains.

TABLE 3. Recoveries, relative standard deviations, limit of detection and limit of quantification of five sulfonylurea herbicides in rice samples (n=5)

Analytes	Spiked level in rice samples						LOD ($\mu\text{g}/\text{kg}$)	LOQ ($\mu\text{g}/\text{kg}$)
	10 $\mu\text{g}/\text{kg}$		20 $\mu\text{g}/\text{kg}$		40 $\mu\text{g}/\text{kg}$			
	Recovery(%)	RSD (%)	Recovery(%)	RSD (%)	Recovery(%)	RSD (%)		
MSM	78.21	11.6	87.5	9.8	96.22	8.3	0.25	0.83
CS	82.64	10.2	88.9	9.8	92.53	7.5	0.24	0.8
PRS	77.56	13.7	93.73	9.3	97.33	8.7	0.26	0.87
CME	85.38	10.9	86.59	9.1	95.21	8.7	0.23	0.77
PSE	80.87	13.1	88.9	8.6	95.88	7.6	0.22	0.74

TABLE 4. Recoveries, relative standard deviations, limit of detection and limit of quantification of five sulfonylurea herbicides in corn samples (n=5)

Analytes	Spiked level in corn samples						LOD ($\mu\text{g}/\text{kg}$)	LOQ ($\mu\text{g}/\text{kg}$)
	10 $\mu\text{g}/\text{kg}$		20 $\mu\text{g}/\text{kg}$		40 $\mu\text{g}/\text{kg}$			
	Recovery(%)	RSD (%)	Recovery(%)	RSD (%)	Recovery(%)	RSD (%)		
MSM	80.32	12.2	84.76	8.8	98.87	10.2	0.24	0.8
CS	77.96	10.1	82.75	8.7	89.79	10.7	0.24	0.79
PRS	79.8	11.1	88.54	10.7	91.11	10.3	0.22	0.74
CME	80.49	9.7	86.23	8.8	93.54	10.8	0.21	0.71
PSE	78.76	12.8	81.23	13.3	96.56	9.9	0.21	0.70

TABLE 5. Recoveries, relative standard deviations, limit of detection and limit of quantification of five sulfonylurea herbicides in soybean samples (n=5)

Analytes	Spiked level in soybean samples						LOD ($\mu\text{g}/\text{kg}$)	LOQ ($\mu\text{g}/\text{kg}$)
	10 $\mu\text{g}/\text{kg}$		20 $\mu\text{g}/\text{kg}$		40 $\mu\text{g}/\text{kg}$			
	Recovery(%)	RSD (%)	Recovery(%)	RSD (%)	Recovery(%)	RSD (%)		
MSM	82.33	9.6	90.75	6.7	92.33	10.8	0.24	0.81
CS	81.05	11.3	88.87	9.8	93.27	6.5	0.24	0.79
PRS	74.05	13.8	89.91	9.8	89.68	8.7	0.22	0.72
CME	83.02	9.8	84.84	6.7	96.85	9.4	0.22	0.73
PSE	81.74	10.2	86.66	11.2	97.97	10.7	0.26	0.87

ANALYSIS OF REAL SAMPLES

The established method of MISPE coupled with HPLC-MS/MS was used to determine the residues of SUHs in 30 rice, corn and soybean samples purchased from local farmers' markets. MSM ($2.3 \pm 0.89 \mu\text{g}/\text{kg}$) was detected in four rice samples, CME ($1.2 \pm 0.46 \mu\text{g}/\text{kg}$) was found in three soybean samples, and no SHUs were found in corn samples, which manifested that the present situation of SUHs residues in cereal grains, at least to some degree.

CONCLUSIONS

In this work, a highly class-selective molecularly imprinted polymer for the detection of SUHs was prepared by precipitation polymerization using MSM as the template molecule, 4-VP as the functional monomer, EGDMA as the crosslinker and MeCN as the porogen. The composition of the polymerization system was rigorously optimized, and the obtained MSM-MIPs were evaluated by performing morphology and structure characterization, and a series of adsorption experiments. The results showed that the MIPs had uniform sizes, and exhibited good recognition of and selectivity toward MSM and its analogs, suggesting that it could be suitable as a sorbent for SPE. An optimized procedure that includes a washing solution and elution steps for the clean-up of samples using the MIP particles as new adsorbents in SPE was successfully investigated. The developed MISPE showed specific selectivity for MSM, CS, CME, PRS, and PSE, and its capability in detection of SHUs in real cereal samples from markets was verified. Subsequently, a simple and highly selective pre-treatment method based on the MISPE procedure was developed for the analysis of the five SUHs in rice, corn and soybean samples before HPLC-MS/MS. The results showed that the MISPE was significantly better than regular SPE in terms of recovery, repetitive usage rate, and reagent consumption. The MISPE-HPLC-MS/MS method enabled the simultaneous detection of the five SUHs in the three matrices: rice, corn and soybean.

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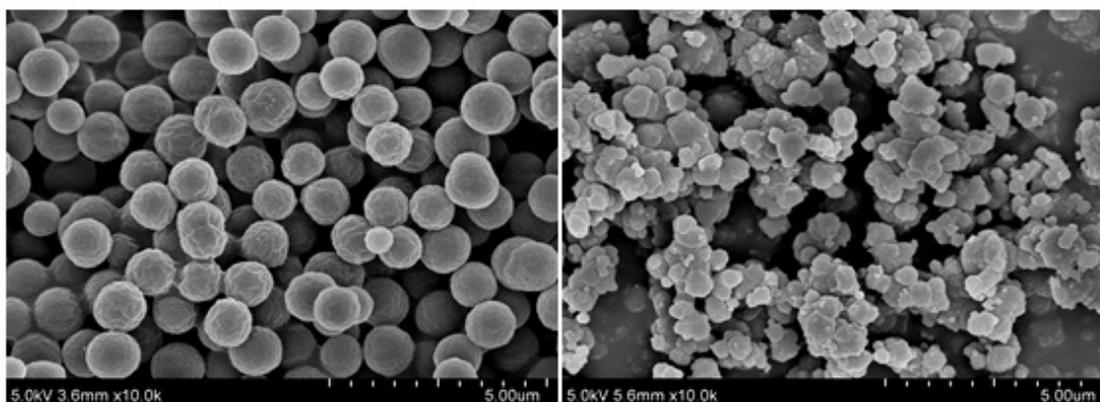


FIGURE S1. SEM micrographs of MIPs with EGDMA or TRIM as crosslinker



FIGURE S2. SEM micrographs of different polymers

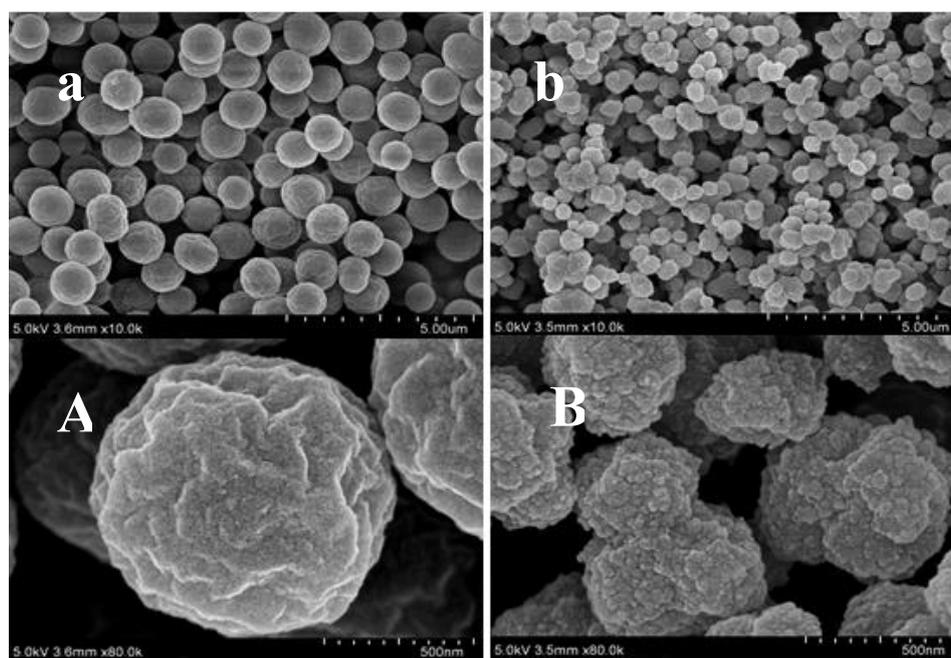


FIGURE S3. SEM micrographs of MIPs with MeCN (a: 10000 \times magnification, A: 80000 \times magnification) or dichloromethane (b: 10000 \times magnification, B: 80000 \times magnification) as porogen

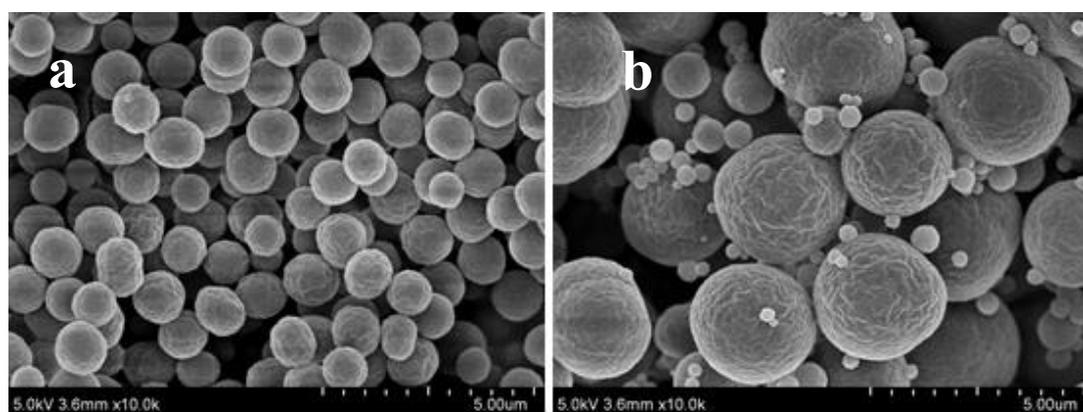


FIGURE S4. SEM micrographs of MIPs with different volumes of MeCN as porogen

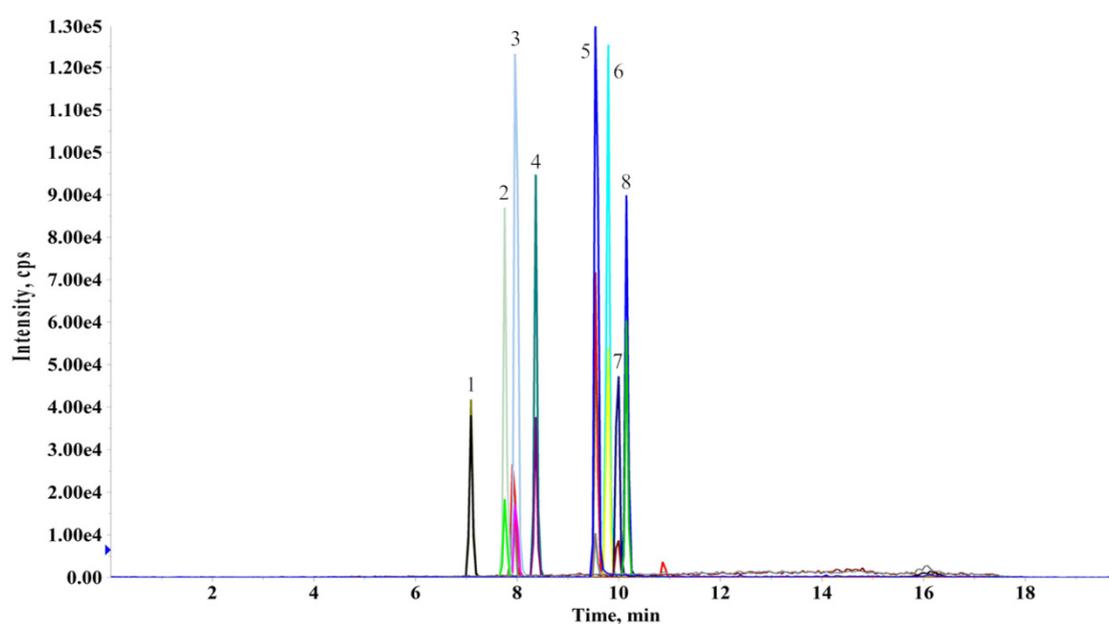


FIGURE S5. Chromatogram of the spiked rice samples

TABLE S1. Standard linear equations and correlation coefficients (r^2) of five sulfonylurea herbicides

Matrix	Analyte	Lineare quation	r^2
Rice	MSM	$Y=1.18e+005x-3.23e+004$	0.9970
	CS	$Y=1.05e+005x+1.78e+004$	0.9933
	PRS	$Y=1.36e+004x+5.97e+004$	0.9958
	CME	$Y=4.83e+005x-3.88e+004$	0.9981
	PSE	$Y=2.21e+004x-6.28e+004$	0.9975
Corn	MSM	$Y=3.36e+005x+2.67e+004$	0.9994
	CS	$Y=1.09e+004x+5.83e+004$	0.9968
	PRS	$Y=2.65e+005x+5.28e+004$	0.9943
	CME	$Y=5.32e+005x-1.03e+004$	0.9922
	PSE	$Y=2.25e+005x-5.08e+004$	0.9935
Soybean	MSM	$Y=4.08e+004x-1.13e+004$	0.9987
	CS	$Y=3.85e+005x+6.78e+004$	0.9957
	PRS	$Y=1.38e+005x-1.73e+004$	0.9930
	CME	$Y=2.55e+005x+4.48e+004$	0.9951
	PSE	$Y=1.28e+005x-3.76e+004$	0.9913

Y: peak area; x: mass concentration, $\mu\text{g/L}$