



Dummy molecularly imprinted polymers based on a green synthesis strategy for magnetic solid-phase extraction of acrylamide in food samples

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ABSTRACT

In this work, novel dummy molecularly imprinted polymers (DMIP) with propanamide as a dummy template molecule were prepared based on a green synthesis strategy of less consumption of hazardous/organic reagents and at mild conditions for magnetic solid-phase extraction (MSPE) of acrylamide in biscuit samples, followed by high performance liquid chromatography (HPLC) determination. The resultant DMIP was well characterized by FT-IR, SEM, TEM and VSM, exhibiting uniform nanoscale coreshell structure and good magnetic property in favor of simple rapid separation. Several main variables influencing MSPE efficiency were investigated, including DMIP dosage, sample solution pH, extraction time and desorption solvent; central composite design (CCD) and response surface methodology (RSM) were employed to assist in the MSPE condition optimization with rapidity and reliability. Under optimized conditions, excellent linearity for acrylamide was obtained in the range of 5.0–5000.0 $\mu\text{g kg}^{-1}$, and low detection and quantification limits were 1.3 $\mu\text{g kg}^{-1}$ and 4.4 $\mu\text{g kg}^{-1}$, respectively. The method recoveries at five spiked concentrations were found within 86.0–98.3% with relative standard deviations (RSDs) of 1.2–4.1%. Furthermore, endogenous acrylamide was detected in five different biscuit samples and the RSDs values were lower than 3.3%. The present study suggested promising perspectives of water-compatible eco-friendly DMIP based MSPE-HPLC method for highly effective sample pretreatment and targeted analytes determination in complicated matrices.

1. Introduction

Acrylamide also named 2-propenamide, as a small unsaturated hydrophilic amide, has been widely used in water treatment, food packaging, plastic products, paper, cosmetics, and cement production [1]. In 1994, International Agency for Research on Cancer (IARC) identified acrylamide as neurotoxic compound and “probably carcinogenic to humans” (Group 2A) which could be readily absorbed through the skin (IARC, 1994). A few years later in 2002, Stockholm University and Swedish National Food Administration reported that heat treated processed foods viz. French fries, breakfast cereals and coffee contained large amounts of acrylamide [2]. Acrylamide can be easily formed by Maillard reaction during frying baking and grilling carbohydrate-rich

food such as potato chips, crispy layer rice (Iranian traditional food) and biscuit, when they are exposed to high temperature exceeding 120 °C under low moisture conditions [3,4]. According to the World Health Organization (WHO) guideline, the threshold limit for acrylamide in drinking water is 0.5 $\mu\text{g L}^{-1}$ [5]. It should be pointed out that an exposure to low amount of acrylamide (0.5–0.98 $\mu\text{g kg}^{-1}$ b.w./day for adults > 15 years and 1.25–2.54 $\mu\text{g kg}^{-1}$ b.w./day for 3–14 years) by consuming of foodstuffs increases the risk of cancer [6]. Therefore, accurate determination of acrylamide in food stuffs is a vital issue for food safety and human health.

Recently, chromatographic techniques coupled with sensitive detectors (hyphenated techniques) such as gas chromatography-mass spectrometry (GC-MS) [7], GC-electron capture spectrometry [8],

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liquid chromatography-MS (LC-MS) [9] and LC-MS/MS [10] have been employed as powerful tools for monitoring and quantitative analysis of acrylamide in different complex food. Nevertheless, direct injection of raw extracts easily leads to poor separation and pollutants separator/detector due to the complexity of sample's matrices and the low concentration of target analytes [11]. Hence, for accurate quantification of trace acrylamide in complicated food matrices, efficacious sample preparation and instrumental analysis are equally important. Among various sample preparation techniques, great attention has been paid to magnetic solid-phase extraction (MSPE) owing to unique superiorities viz. least consumption of organic solvent, no need to conditioning the sorbent and also column packing elimination, and high contact surface enhancing efficiency and repeatability, and on the other part, magnetic sorbents are gathered easily by magnetic field, omitting filtration, centrifugation and precipitation procedures [12,13]. Despite foresaid advantages, MSPE often suffers from poor selectivity which could be overcome by combination with selective adsorbents.

Molecularly imprinted polymers (MIPs), based on creation of specific recognition sites in strict polymer network that have complementary shape, size and functional groups toward the imprinted molecule, have attracted increasing interest as selective adsorbents for isolation and enrichment of small organic molecules, metal ions, biomacromolecules, etc [14]. Meanwhile, MIPs face to some major drawbacks [14], for example, especially while acrylamide used as template during traditional MIPs preparation and subsequently the synthesized MIPs applied as sorbent during extraction process. Firstly, acrylamide is high toxicity and strong linking through double bond (C=C) with cross-linker (in radical polymerization) and could act as a functional monomer which cause failure to be removed after exhaustively eluting [15]. Moreover, template molecules are embedded too deep in three-dimensional polymer structure and easily cause inadequate removal of template, so available sites are dramatically reduced. On the other hand, undesirable mass-transfer and binding capacity have serious impact on the accuracy of quantitative analysis [16,17]. To address this obstacle, we purposed to employ dummy imprinting strategy for acrylamide recognition, by selecting propanamide as dummy template owing to its similarity of shape, size, and functional groups without interference in analytical determination of acrylamide. By using dummy imprinting strategy not only the leaching of residual template can be avoided easily that would enhance accuracy of analytical method, but also it would lead to increasing the number of specific binding sites and adsorption capacity.

On the other hand, it has been largely proved that, MIPs often fail to show high selectivity and rebinding ability toward small organic molecules in aqueous media. The shrinking/swelling of the MIPs, namely specific cavities are easily resized in aqueous media, significantly decreases their practical applications in such areas as environmental and food analysis [18,19]. Meanwhile, in majority of MIPs synthesis routes such as precipitation [20], sol-gel [21], and emulsion [22], amounts of organic porogens and/or toxic reagents are usually used, which is not economic or user-friendly and is in contrast with principles of green chemistry. To overcome the two challenges, aqueous-phase synthesis is highly desirable.

Therefore, in this work, a novel green synthesis strategy was proposed for preparation of dummy MIP (DMIP) in aqueous media without consuming organic solvents, which were subsequently used as sorbents of MSPE for recognition and extraction of acrylamide in biscuit samples, followed by HPLC determination. Chitosan as versatile natural hydrophilic polymer in presence of dummy template was employed to construct three-dimensional imprinted network in aqueous media. The particular synthesis route is presented by following steps in sequence: (I) preparation of Fe_3O_4 nanoparticles as an appropriate support for the surface imprinting due to its magnetic property, high surface area, suitable functionality for further modification, and biocompatibility, non-toxicity and eco-friendliness. (II) encapsulation of Fe_3O_4 nanoparticles by anchoring hydrophilic polyethylene glycol chain by facile

and one step process with no consumption of organic solvent; and (III) polymerization and imprinting of chitosan on the surface of modified Fe_3O_4 nanoparticles to produce specific molecular binding sites. The as-prepared water-soluble DMIP was used as MSPE sorbent for efficient clean-up and preconcentration of acrylamide, and the MSPE conditions were optimized with the aid of experimental design of central composite design (CCD) and response surface methodology (RSM) with minimum effort, expense, and higher accuracy. The DMIP based MSPE method was well validated and successfully applied to biscuit sample analysis, demonstrating high sensitivity, repeatability, simplicity, rapidity, good practical feasibility, and environmental benignity.

2. Experimental

2.1. Materials and instruments

Iron (III) chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$), iron (II) chloride tetrahydrate ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$), poly(ethylene glycol) (PEG) with average W% of 6000 g mol^{-1} , acrylamide, propanamide, sodium hydroxide (NaOH), methanol, ethanol, acetonitrile (HPLC grade), acetic acid, and ammonium hydroxide (NH_4OH) were purchased from Merck (Darmstadt, Germany). Chitosan powder (low molecular weight), with $\geq 75.0\%$ degree of deacetylation and 20–30 cps of viscosity, was supplied from Sigma-Aldrich (St. Louis, MO, USA). Ultrapure water was obtained from a Milli-Q water purification system (Millipore, Bedford, MA, USA).

Scanning electron microscope (SEM) images were recorded on a Hitachi S4160 microscope and transmission electron microscopy (TEM) images on a Hitachi S-570 microscope, from Hitachi (Tokyo, Japan). Magnetic properties of materials were studied using a vibrating sample magnetometer (VSM, LDJ 9600-1, USA). For identification of functional groups Fourier transform-infrared spectroscopy (FT-IR-8300, Shimadzu) using KBr pellet was employed. Tecno-GAZ SPA Ultra Sonic System at 40 kHz coupled to a temperature controller was used for adsorption/desorption processes.

Acrylamide determination was performed by an Agilent 1100 liquid chromatography (Wilmington, DE, USA) equipped with a micro vacuum degasser (model G1379A), a quaternary pump (model G1311A), a multiple wavelength detector (model G13658), a sample injection valve with a 20 μL sample loop, and an Agilent C_{18} column (4.6 mm i.d. 250 mm, 5 μm). Mobile phase consisted of a water-methanol (95:5, v/v) which was filtered through a 0.45 μm filter, degassed under vacuum and passed with the flow rate of 1.0 mL min^{-1} . Separation process was carried out at ambient temperature and detector wavelength was set at 210 nm.

2.2. Preparation of DMIP

First, Fe_3O_4 nanoparticles were synthesized using chemical co-precipitation according to our previous work [23]. Briefly, 15 mmol of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and 10 mmol of $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ were added to 80 mL of deionized water in a 250 mL tri-neck flask under nitrogen atmosphere. 50 mL ammonium solution was added dropwise into the flask under vigorous stirring of nitrogen stream to get a black mixture. Subsequently, the black mixture was strongly stirred and heated at 80°C for 30 min. Then, the black precipitate was separated by Nd-Fe-B permanent magnet and repeatedly rinsed with deionized water until achieving a neutral pH for the washed solution and dried under vacuum at 60°C .

Surface modification of Fe_3O_4 nanoparticles was performed by one-pot, green, and very quick method with PEG as surface modifier. Briefly, 10 g of PEG was dissolved in 30 mL of deionized water and 2.0 g Fe_3O_4 nanoparticles were whisked into solution. After sonicating for 30 min, PEG- Fe_3O_4 particles were separated by external magnetic field, washed with deionized water, and dried at 60°C for 12 h.

The basic preparation procedure for DMIP is schematically shown in Fig. 1. 0.5 mL acetic acid was added into 50 mL of deionized water

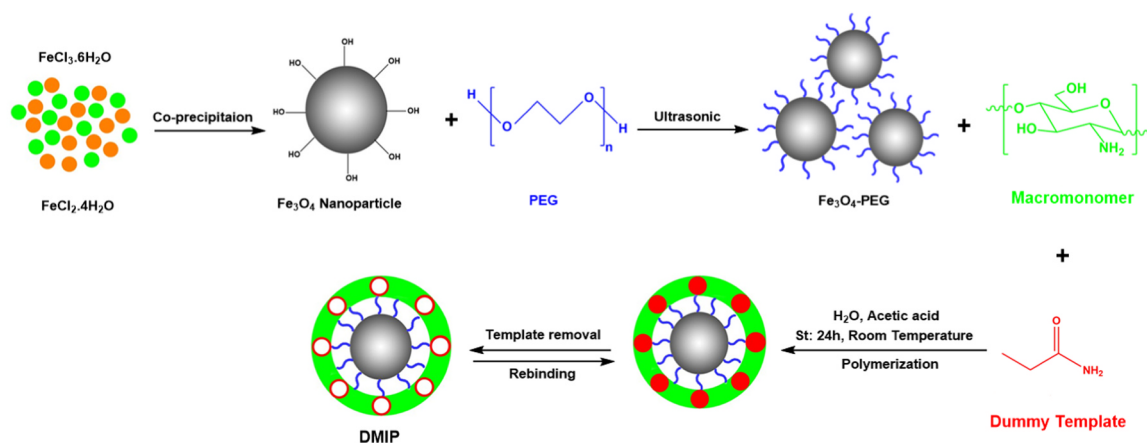


Fig. 1. The basic preparation procedure of DMIP.

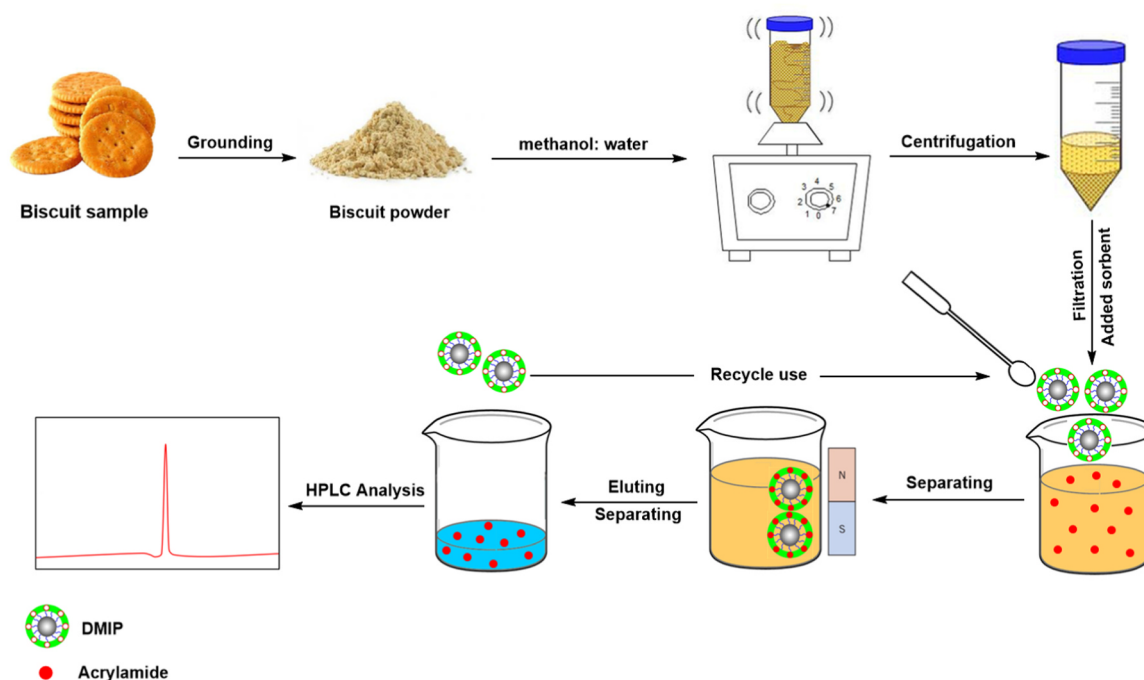


Fig. 2. The DMIP based MSPE procedure for acrylamide extraction.

under stirring, followed by dissolving 2 mmol of propanamide (dummy template). Then, 0.52 g chitosan was added to the mixture, kept stirring to appearance clear solution and allowing forming functional monomer-dummy template preassembly for 12 h. Next, 0.25 g PEG- Fe_3O_4 was added to above solution followed by stirring vigorously and polymerization was allowed to proceed for 24 h at ambient temperature. Afterward, 50 mL of 1 mol L^{-1} NaOH solution was transferred swiftly into the resultant solution and kept stirring for 3 h. Then, the prepared material was collected by external magnetic field followed by washing with deionized water repeatedly until reaching natural pH and was re-dispersed in 0.5 mol L^{-1} H_2SO_4 for 5 min under ultrasonic irradiation. Finally, the polymer material was washed repeatedly with dispersion in the eluent of methanol-deionized water (50:50, v/v), due to the high solubility of dummy template in the eluent, and then was easily rapidly isolated with external magnetic field, until the imprinted molecule propanamide could not be detected anymore by HPLC-UV in concentrated eluent. Consequently, DMIP was obtained. The non-imprinted polymers (NIP) were synthesized using the same procedure but without the addition of dummy template.

2.3. Adsorption test

To investigate the binding capacity of acrylamide by the prepared sorbents, 30 mg of DMIP or NIP was suspended into 15 mL of aqueous solution of acrylamide (pH adjusted to 5.0) at varied initial concentrations ($50.0\text{--}600.0 \text{ mg L}^{-1}$). The mixture was mechanically stirred at 25°C for 20 min, and then the sorbents were collected by an external magnetic field, and residual (non-sorbed) concentrations of acrylamide were determined by HPLC. The amount of acrylamide adsorbed by the DMIP/NIP was calculated according to the following equation:

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

where Q (mg g^{-1}) is the sorption amount of acrylamide; C_0 (mg mL^{-1}) is the initial concentration of acrylamide, C_t (mg mL^{-1}) is the supernatant concentration of acrylamide after adsorption; V (mL) is the total volume of sample solution and m is the mass of the sorbent used.

As well as, the binding kinetics of DMIP and NIP were analyzed at different time period ranging from 1 to 28 min following addition of 40 mg of DMIP/NIP to 15 mL aqueous solution of acrylamide

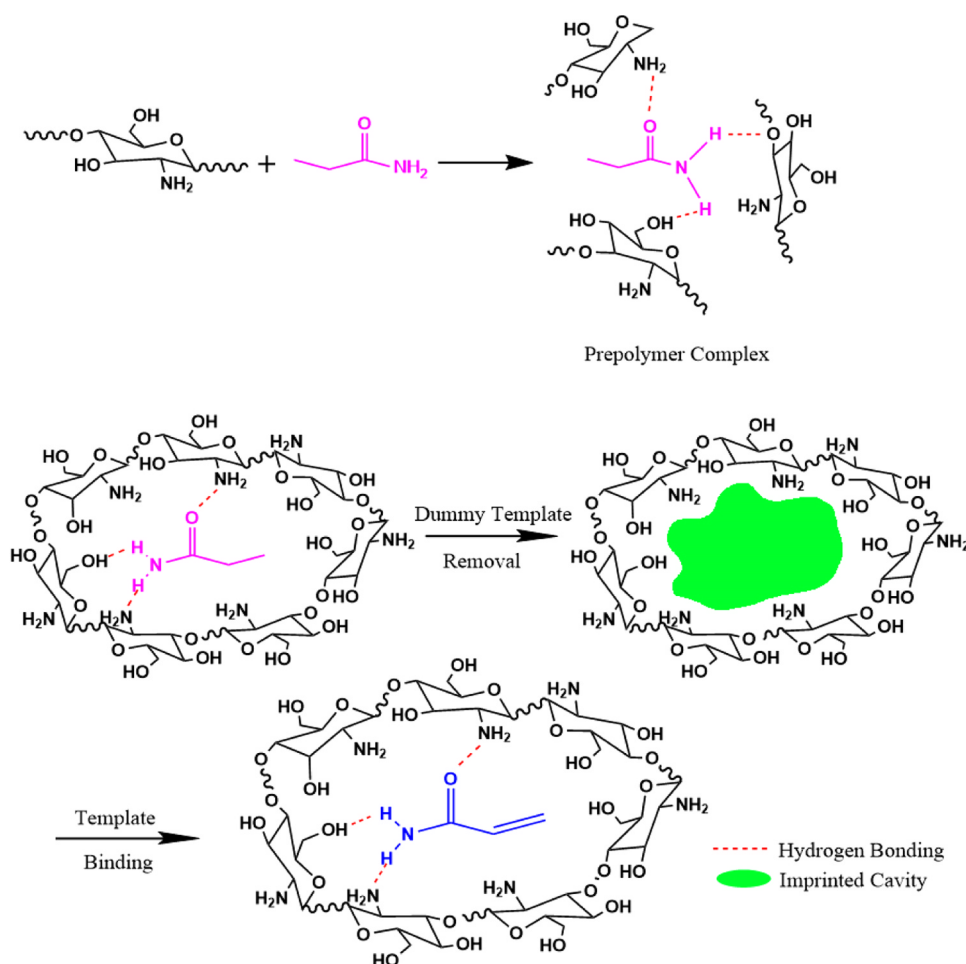


Fig. 3. Schematic for possible hydrogen bonding formation.

(450.0 mg L⁻¹). Then, the sorbents were isolated and the residual acrylamide in supernatant solution were determined by HPLC.

2.4. Preparation of calibration standard and MSPE procedure of acrylamide from biscuit samples

A standard stock solution of acrylamide was prepared in deionized water at 1.0 mg mL⁻¹ and kept in 4 °C. Subsequently, the working solutions were obtained by the appropriate level of dilution with deionized water. Five different brands of biscuit samples were purchased from local supermarket in Yasouj and stored at 4 °C in dark before use. Fig. 2 displays the DMIP based MSPE procedure. Biscuit samples were grounded and blended into the homogenous powder by a mortar and pestle. Then, 2.0 g biscuit powder mixed with 15 mL methanol:water (50:50 v/v) was extracted by vigorous shaking for 30 min. Three different solvents including methanol, deionized water, and methanol/deionized water (50:50, v/v), were investigated for extraction of acrylamide. Experimental results suggested methanol/deionized water (50:50, v/v) provided the maximum extraction efficiency due to polarity and miscibility of acrylamide in the mixed polar solvents. Afterwards, the extract was held in an ice bath for 30 min to create two phases followed by centrifugation and filtration to obtain clear extract solution. At the next, 40 mg of DMIP was added into the extract solution with pH adjusted at 5.0 followed by ultrasonication for 20 min at ambient temperature. The DMIP was separated by a magnet from the solution, and subsequently acrylamide was eluted by re-dispersion of DMIP in 2 mL of methanol/ammonium hydroxide (90:10, v/v) by sonication. The eluent was evaporated to dryness under nitrogen stream in water bath (35 °C) and the residue was subsequently reconstituted in

50 µL mobile phase (deionized water/methanol (95:5, v/v)) and ready for HPLC-UV analysis.

2.5. Building of calibration curves in standard aqueous solution and biscuit samples

Calibration curves were built in standard aqueous solution and biscuit samples, respectively. In this regard, blank aqueous solutions and biscuit samples were spiked with different concentrations of acrylamide, and the acrylamide was extracted under the optimized conditions and analyzed according to the method described in Section 2.4.

3. Results and discussion

3.1. Preparation of DMIP

Fig. 1 illustrates the schematic preparation procedure of DMIP. First, Fe₃O₄ nanoparticles were synthesized by coprecipitation method. The criterion for selection of coprecipitation method is based on less consumption of hazardous chemicals and organic solvents, although magnetic nanoparticles synthesized by a solvothermal method have higher magnetic response [24]. Furthermore, Fe₃O₄ nanoparticles are highly compatible with aqueous phase and can be decorated with hydroxyl groups which offer excellent sites for further interfacial bond and interaction between the Fe₃O₄ and PEG. Prior to polymerization, Fe₃O₄ was functionalized with PEG chain in very short time and at ambient temperature. In order to improve the stability of Fe₃O₄, various surface modifiers have been applied for encapsulation of Fe₃O₄ viz. SiO₂, carbon, oleic acid, chitosan, and PEG. The period of encapsulation

was dramatically shortened by treating with PEG which was 12 times lower than mentioned other surface modifiers. Therefore, we adopted PEG for surface modification which have several merits including: 1) PEG is hydrophilic, cheap, bio-compatible and environmentally friendly [25], 2) surface modification was quickly performed in one pot in aqueous media at ambient temperature, 3) Fe_3O_4 with slight acidic properties in aqueous media [26] is protonated easily that can electrostatically interact with the hydroxyl groups of PEG [27]. Moreover, hydrogen bonds between hydroxyl groups of Fe_3O_4 and hydroxyl groups of PEG can form that leads to impressive capsulation [28]. Next, a layer of chitosan network was anchored onto Fe_3O_4 @PEG via one-pot facile surface imprinting in the presence of propanamide as dummy template. Chitosan could significantly interact with PEG chain with strong electrostatic interactions in acidic media whereas chitosan was protonated and PEG induced negative charge. Chitosan was selected as natural functional monomer that could supply four supreme benefits: 1) chitosan is non-toxic, cheap, readily available, biocompatible, biodegradable and easy to polymerize in mild condition; 2) because of multifunctional groups (-OH, $-\text{NH}_2$, -O-) in its structure, it could significantly interact with propanamide in aqueous media with at least by-effects of water to form sustainable hydrogen bonding and pre-assembled complex, as shown in Fig. 3, herein, chitosan was used as monomer, which effectively resolved radical polymerization problems owing to using traditional monomers etc; 3) due to the similarity between the hydrophilicity of chitosan and acrylamide, it is a good idea to convert chitosan to specific imprinted network; 4) it could simplify cross-linking by sulfuric acid with ionic reaction very quickly in mild conditions [29] that would minimize swelling of chitosan avoiding re-sizing/deformation of specific cavities and improving the mechanical stability. Although, enhancing MIP performance is a vital task, observing the principles of green chemistry is equally important. Therefore, the combination of molecular imprinting technology with green synthesis approach is promising for separation of small organic molecules.

The synthesis procedure was compared with that reported in terms of precursors and synthesis conditions [15,30–34]. As can be seen from Table S1, in all the reported synthesis routes, chemical precursors and organic solvents are used which are hazardous and expensive. In addition, temperature controlling is another disadvantage. Interestingly, our proposed synthesis procedure benefits from remarkable superiorities viz. eco-friendliness, cost-effectiveness, simplicity, rapidity and high-efficiency.

3.2. Characterization of DMIP

The prepared DMIP was characterized by FT-IR, SEM/TEM and VSM. Fig. 4 shows the FT-IR spectra of Fe_3O_4 (a), Fe_3O_4 @PEG (b), propanamide-contained DMIP (c) and propanamide-removed DMIP (d). The strong band at 570 cm^{-1} in all samples was clearly observed that was attributed Fe–O groups. Peak intensity of Fe–O in DMIP was lower than Fe_3O_4 @PEG and Fe_3O_4 which confirmed Fe_3O_4 was decorated with PEG and MIP layer. The broad absorption peak around 3445 cm^{-1} corresponded to stretching vibrations of O–H groups of PEG (Fig. 4b). The C–O symmetric stretching observed at 1107 cm^{-1} demonstrated that the PEG was successfully covered onto the surfaces of Fe_3O_4 nanoparticles. The characteristic peaks of DMIP at 1630 cm^{-1} and 1154 cm^{-1} could be attributed to the bending vibration of NH_2 and C–N stretching vibration, respectively, which proved that chitosan layer was anchored onto the Fe_3O_4 @PEG. Moreover, the disappearance of C=O band at 1700 cm^{-1} (Fig. 4d) proved that dummy template has been removed from the DMIP.

Surface morphology and particle size of DMIP were investigated by SEM and TEM. SEM image indicated that DMIP had regular spherical shape, and relatively identical size distribution with no significant aggregation (Fig. S1). As seen, DMIP had velvety surface which might be related to the removal of dummy template and solvent molecules that were trapped in polymer network. It should be noticed that DMIP had nanoscale diameter (below 100 nm), which would provide supreme structure to facilitate mass transfer of propanamide, and after dummy template removal, would cause high adsorption capacity, accessible specific cavities and fast sorption kinetics. Meanwhile, as can be seen from TEM image (Fig. S2), there were dark regions suggesting that Fe_3O_4 nanoparticles were embedded into PEG and chitosan substrate. Although the FT-IR spectra demonstrated successful synthesis of imprinted chitosan on the Fe_3O_4 @PEG, PEG and chitosan network couldn't be seen clearly in TEM image; possibly, the density of PEG and chitosan was not much to be seen like Fe_3O_4 nanoparticles [35]. Bare Fe_3O_4 nanoparticles were aggregated owing to magnetic feature of Fe_3O_4 nanoparticles [36]. After polymerization of chitosan on the surface of Fe_3O_4 nanoparticles, the DMIP had good dispersibility due to the enhancement of repulsive force among the nanoparticles [37]. In addition, thickness of imprinted shell layer could ameliorate the mass transfer rate for swift adsorption/desorption of analyte. These results implied that DMIP nanospheres were successfully synthesized.

As for hysteresis loops of Fe_3O_4 and DMIP from the magnetization curve by VSM test, as shown Fig. S3, both samples hysteresis showed a

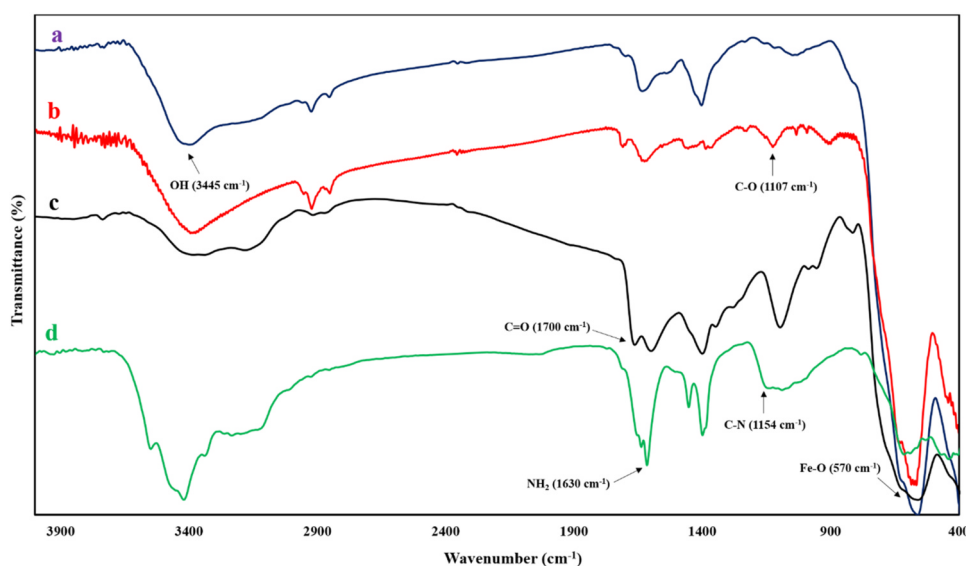


Fig. 4. FT-IR spectra of (a) Fe_3O_4 , (b) Fe_3O_4 @PEG, (c) propanamide-contained DMIP and (d) propanamide-removed DMIP.

similar shape and non-hysteresis which confirmed they had super paramagnetic behavior. The magnetic saturation of bare Fe₃O₄ (66.5 emu g⁻¹) was higher than that of DMIP (61.0 emu g⁻¹), which was related to contribution of PEG and MIP layer that coated Fe₃O₄ effectively. It should be noted that magnetic saturation of DMIP was approximately 88 times higher than reported acrylic-based MIP [38], as well as synthesis route was attractive according to green chemistry. In addition, the high magnetic responsivity and hydrophilicity of DMIP facilitated the magnetic isolation of sorbent from sample solution within 5 s when exposed to external magnetic field; whereas, DMIP was dispersed rapidly with a slight shake when magnetic field didn't exist. As a result, strong magnetism of DMIP caused fast accumulation of sorbent and subsequently shortened sample preparation time significantly.

3.3. Binding study of the DMIP for acrylamide

Binding study of the DMIP for acrylamide was performed including adsorption kinetics, static adsorption (binding isotherm) and corresponding models. The adsorption kinetics of acrylamide onto the DMIP and NIP at different time intervals were firstly studied. Fig. S4a reveals that both DMIP and NIP exhibited fast adsorption rate which could be attributed to the thin imprinted-layer leading to substantial accessibility to the specific binding cavities and subsequently fast mass-transfer of acrylamide into them. As seen from the binding saturation plot (Fig. S4a), the adsorption capacity increased rapidly in the first 10 min, and then the increment slowed down until the process approximately reached equilibrium after 20 min which is almost 7.5 times shorter than reported acrylic-based surface imprinting MIPs [39]. At the beginning of the adsorption process, acrylamide could enter many empty specific binding sites easily and rapidly and mass-transfer resistance was significantly small. With time prolonging, it became difficult to find an imprinted site for acrylamide. So, the adsorption rate decelerated up to reaching equilibrium. The Pseudo-first order and Pseudo-second order kinetic models were used to investigate the adsorption kinetics. These kinetic models and their corresponding parameters were listed in Table S2. The results indicated that Pseudo-second order kinetic model was more suitable for fitting the kinetic data due to its higher R² value than Pseudo-first order kinetic model. Then, based on the assumptions of the Pseudo-second order kinetic model, it was assumed that chemical interactions were possibly involved in the adsorption process, which may involve valency forces through sharing or exchange of electrons between acrylamide and DMIP/NIP.

The binding isotherm of analyte onto DMIP and NIP is a notable factor to appraise the recognition capability of imprinting memory and specific binding. Accordingly, static adsorption capacities of DMIP and NIP for acrylamide were examined in different concentrations of acrylamide from 50 to 600 mg L⁻¹. Fig. S4b indicates that the amount of acrylamide adsorbed by both DMIP and NIP increased by raising the initial concentration up to 450 mg L⁻¹, and subsequently binding sites reached saturation. Various isotherm models such as Freundlich, Langmuir, Tempkin and Dubinin-Radushkevich were applied for analyzing binding properties of DMIP and NIP. As shown in Table S3, Freundlich equation with R² > 0.99 was a better model to reflect the adsorption behaviors, which supposed that the adsorption referred to heterogeneous surfaces. Therefore, Freundlich isotherm was selected for fitting the isotherm data to estimate binding mechanisms by the below equation [40]:

$$\text{Log } Q = m \text{ Log } C + \text{Log } \alpha \quad (2)$$

where Q (mg g⁻¹) is the binding capacity of the polymers at the equilibrium concentration, C (mg L⁻¹) is equilibrium acrylamide concentration in sample solution, α corresponds to Freundlich constant demonstrating average affinity and measure of capacity while m is heterogeneity index which can take values from 1 to 0. The excessive m value of 1 reveals that the system is homogeneous and 0 value refers to heterogeneous systems.

Fig. S4c displays the adsorption isotherm for acrylamide on the polymers that were fitted to Freundlich isotherm with linear correlation coefficients 0.993 and 0.955 for DMIP and NIP respectively, which indicated both polymers contained heterogeneous binding sites that was in good agreement with most non-covalently imprinted polymers [41]. The m value for DMIP (0.3805) lower than that for NIP (0.8527) suggested that DMIP had more heterogeneous binding sites than NIP due to a substantial role of template molecule during polymerization. The maximum adsorption capacities achieved for acrylamide were 24.1 mg g⁻¹ by DMIP, much higher than that by NIP (6.9 mg g⁻¹), proving that propanamide was qualified molecule as dummy template and specific cavities were successfully formed in the DMIP structure.

Moreover, to evaluate the affinity of DMIP toward acrylamide, Scatchard analysis was used which can be defined as follows:

$$Q/C_e = (Q_{\max} - Q)K_d \quad (3)$$

where Q is the amount of acrylamide bound to the DMIP at equilibrium, C_e is the equilibrium concentration of acrylamide in solution, Q_{\max} is the apparent maximum binding amount and K_d is the dissociation constant of the binding sites. As shown in Fig. S4d, two different straight lines were obtained for the DMIP Scatchard plot, indicating there were two distinct binding sites: the high-affinity (specific) (left side) and the low-affinity (non-specific) (right side) sites. According to the slopes of these two straight lines, the corresponding dissociation constants (K_d) values were calculated to be 43.85 and 250 mg L⁻¹ for the high and low affinity binding sites with correlation coefficients (R²) of 0.9640 and 0.9277, respectively. That means corresponding affinity constants were 0.023 and 0.004, respectively.

3.4. Selectivity examination of DMIP

Selectivity of MIPs is the chief and prominent advantage of MIPs. In this regard, the selectivity of DMIP was appraised by comparing adsorption capacity, imprinting factors (IF) and selectivity factors (SF) for acrylamide and other similar compounds including propanamide, L-asparagine, 6-aminocaproic acid and N-tert-Butylacrylamide. As seen in Fig. 5 the adsorption capacity for propanamide is the highest that is owing to remarkable matching among imprinted cavities and propanamide structure in terms of size, stereochemistry and functionality. It should be pointed out that the adsorption capacity for acrylamide is slightly lower than propanamide which can affirm that propanamide is highly qualified molecule as a dummy template for acrylamide. In other word, high symmetry of acrylamide with propanamide caused acrylamide to easily enter to imprinted cavities and no barrier existed for mass-transfer of analyte. However, for other three analogue compounds, significant distinctions in volume, shape and functional-group position decreased the affinity of DMIP toward them. In addition, as shown in Fig. 5, the IF values of DMIP for acrylamide, propanamide, L-asparagine, 6-aminocaproic acid and N-tert-Butylacrylamide were 3.49, 3.54, 2.14, 1.73 and 1.5, respectively, while the SF values were the four analogues were 0.90, 1.67, 2.13 and 2.48, respectively. These results indicated that the propanamide dummy DMIP had highly selective recognition capability toward acrylamide.

3.5. Variable optimization for DMIP based MSPE

In order to achieve maximum extraction recovery of acrylamide in biscuit samples, the preliminary effects of main variables including sample solution pH, DMIP dosage, extraction time, kind and volume of desorption solvent were investigated, at the spiked concentration level of 200.0 µg L⁻¹.

Acrylamide is an extremely hydrophilic compound that could exist in biscuit samples at the presence of matrix interferences especially long chain fatty acids which could seriously pollute/block HPLC column or give interferent peaks overlapping with peak of acrylamide. To dominate the obstacles, a number of researchers have used large volumes of

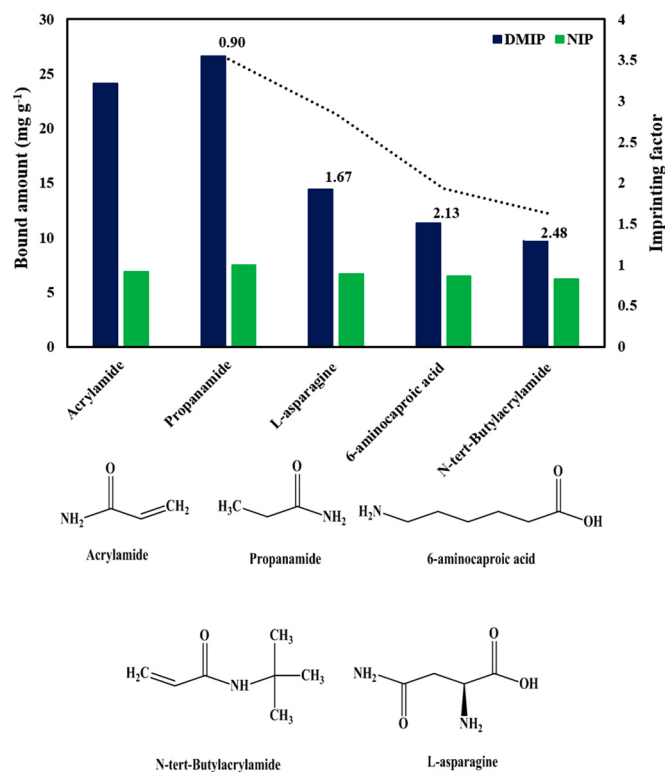


Fig. 5. (Upper) Selectivity of the DMIP and NIP for acrylamide over four analogues including propanamide, L-asparagine, 6-aminocaproic acid and N-tert-Butylacrylamide; (below) chemical structures of the tested five compounds. Experimental conditions: 30 mg of DMIP or NIP, concentration of acrylamide and four analogues at 400 mg L⁻¹ individually.

toxic organic solvent (hexane) as rinsing solvent to remove hydrophobic impurities due to non-solubility of acrylamide in hexane or used commercial SPE cartridges for clean-up, which usually include several steps and are time/labor consuming [42,43]. To eliminate the utilization of organic solvent and waste prevention, herein, we used ice bath for solidification of oil layer which could easily be removed for defating sample solution. Thus, using ice bath could be a superior alternative instead of organic solvent in washing step, which could facilely avoid interferences.

For selecting appropriate polarity of desorption solvent, solubility of the target analyte and its compatibility with chromatographic system should be considered. Due to the good polarity and miscibility of acrylamide, different types of polar solvents with potent rinsing strength were examined, including acetonitrile, methanol, deionized water, methanol/acetonitrile (50:50, v/v), acetonitrile/ammonium hydroxide (90:10, v/v), methanol/ammonium hydroxide (90:10, v/v), and deionized water/ammonium hydroxide (90:10, v/v). Among the tested desorption solvents, methanol/ammonium hydroxide (90:10, v/v) provided maximum desorption efficiency, in which most amounts of acrylamide could be desorbed from the DMIP. This may be due to the similarity between the polarity of acrylamide and methanol and high solubility of acrylamide in methanol which could break hydrogen bonds between trapped analyte and sorbent easily. In addition, the effect of volume of the selected desorption solvent was tested in the range of 1.0–5.0 mL and results demonstrated the adequacy of 2.0 mL of the solvent to desorb acrylamide completely.

3.6. Variable effects evaluation by CCD and RSM

Conventional optimization approaches namely one-variable-at-a-time have been widely used, which often suffer from deficiency viz. necessity too much extents of experimental run, labor effort, high

amounts of chemical waste production, time consuming, high cost and most importantly incapable to distinguish the significance of each variable, and ignoring the effects of interaction between variables and subsequently unable to attain the true optimum level. To overcome the mentioned drawbacks, multivariate optimization is a proper and applicable statistical approach that could eliminate the limitations of conventional optimization [44]. Central composite design (CCD) based response surface methodology (RSM) provides contribution of individual variables and their interactions on target response empirically polynomial function at least of expense and time [45,46]. Therefore, valuable information for a predestinated process was attained via experimental design methodologies. Hence, in this study the influence of DMIP dosage (A), sonication time (B) and sample solution pH (C) as three effective main parameters on MSPE of acrylamide from biscuit samples were evaluated via CCD based on RSM as an effective statistical and mathematical approach for assessment and optimization of parameters and their interactions. The total number of design points in CCD was 15 including 4 fractional factorial points, 6 axial points and 5 central points, as listed in Table S4. Among different statistic models including linear, 2FI, quadratic and cubic, quadratic model based analysis of variance (ANOVA) has been widely applied to investigate the statistical significance of factors. The significance and adequacy of model, parameters, their interactions and quadratic effects on extraction process were investigated through ANOVA (Table S5) based on Fisher's tests (acceptance or rejection of the null hypothesis). At certain confidence level ($\alpha = 0.05$), the terms with higher values of *F* or *p*-values less than 0.05 strongly support their significant contribution on extraction process. The reliability and robustness of fitted quadratic model were checked via lack-of-fit test and multiple correlation coefficients. In this proposed model, the lack-of-fit value higher than 0.05 and the correlation coefficient higher than 0.98 have confirmed the high accuracy and reliability of suggested models. The obtained results from CCD for each parameter were fitted to a polynomial equation with quadratic multiple regressions, which expressed the relationship between response and variables. Extraction recovery (ER) was used as the indicator of MSPE. Accordingly, the second order polynomial equation of acrylamide was generated as below:

$$ER\% = +87.44 + 8.93A + 10.00B - 6.59C + 5.52AB + 14.48AC + 4.27BC - 2.91A^2 - 3.86B^2 - 4.90C^2 \quad (4)$$

Response surface 3D plots provided valuable information about influential interactions of main parameters, as shown in Fig. S5. By considering the chemical structures of the acrylamide (ionic or natural form) and DMIP, the pH of the sample solution had significant effect on the dominant sorption mechanism (electrostatic and hydrogen bonding interactions) between the analyte and the sorbent, and therefore impressive influences on extraction efficiency. Fig. S5a depicts semi-curvature plot between sample pH and DMIP dosage that indicated interactive effects. As seen, by increasing initial sample pH up to 5 the extraction efficiency was increased, then in pH 6 the efficiency decreased slightly. After pH 6 the extraction efficiency diminished remarkably. As a matter of fact, acrylamide is a solely weak base, and at pH lower than 3.0 the protonated form starts to emanate and induces a positive charge to its structure. At any other pH above 3 acrylamide is in its molecular (natural) form, so no pH dependency can be found. However, the recorded pH dependency of the binding efficiency was most probably given by the dissociation process of the chitosan NH₃ groups (pK_a value ~6.5). Amide group of acrylamide and amine group of chitosan (pK_a value ~6.5) were easily protonated concurrently at pH below 3.0, which established major repulsion leading to deteriorative extraction efficiency. At any other pH above 3.0, acrylamide would be deprotonated and also would be in molecular form. On the other hand, at acidic pH (below ~6.5) chitosan gained dominant positive charge (due to NH₂ group). As a result, carbonyl group of acrylamide had impressive affinity to link with NH₃⁺ group of chitosan by ionic interaction. Furthermore, NH₂ group of acrylamide could interact with

other functional groups of chitosan viz. –O– and –OH by hydrogen bonding and thereby provide additional driving forces; this would accompany with memory effects built in DMIP structure and thereby would enhance extraction efficiency remarkably. On the other hand, in basic media both acrylamide and chitosan are in molecular dominant species form leading to deteriorative interactions and subsequently poor extraction recovery. As seen in Fig. S5, maximum efficiency was attained at pH 5.0 which was completely in agreement with above claim.

Ultrasound irradiations could provide influential mixing by cavitation phenomenon that would impel excellent dispersion of sorbent in sample solution, resulting in that the mass transfer of analyte to sorbent occurs gradually effectively. Fig. S5c shows the extraction efficiency decreased obviously using low amounts of sorbent and short sonication time, which could be ascribed to the probable formation of DMIP aggregate due to the slight opportunity for analyte to penetrate into binding sites. By simultaneous increment of sorbent dosage and sonication time, the preconcentration of acrylamide was raised gradually, that could be attributed to the increased available specific active sites and surface areas which are qualified for trapping acrylamide molecule along with great dispersion compelled by cavitation phenomenon which universally led to significant betterment of mass transfer. As depicted in Eq. (4), the coefficients of parameter AC were the highest that demonstrated it had the most impact on the extraction efficiency while the positive or negative coefficients of the parameter represented the direction of the effect on the response.

As a result, the maximum extraction recoveries were achieved at acidic pH of 5.0, 30 mg of DMIP and sonication time of 20 min with desirability 0.90 (the value of 1.0 corresponds to highest extraction percentage and extremely desirable condition; score 0.0 illustrates minimum extraction recovery), which was repeated for three times to investigate applicability of this optimum level. The desirability value for individual parameters was displayed in Fig. S6. According to Fig. S7, the adequate compatibility between experimental and predicted results and desirability certification were proved with high sufficiency of the purposed model.

3.7. Method validation and real sample analysis

In order to validate the developed DMIP-MSPE-HPLC/UV method for the determination of acrylamide, further experiments with regard to calibration linearity range, limit of detection (LOD), limit of quantification (LOQ), robustness and accuracy were conducted under the optimized experimental conditions. The calibration curves were built by plotting peak area versus acrylamide concentration in the wide range of 2.0–5000.0 $\mu\text{g kg}^{-1}$ and 5.0–5000.0 $\mu\text{g kg}^{-1}$ with the correlation coefficients of 0.9991 and 0.9985 for standard aqueous solution and biscuit samples, respectively, demonstrating excellent linearity. The LOD and LOQ defined as three times and ten times ratio of signal to noise for chromatograms obtained from the blank [47], respectively, were 0.57 $\mu\text{g kg}^{-1}$ and 1.90 $\mu\text{g kg}^{-1}$ for standard aqueous solution. For biscuit samples, the LOD and LOQ were 1.3 and 4.4 $\mu\text{g kg}^{-1}$, respectively, which proved worthy operational condition and competency of the present method. Owing to the more complex matrices in biscuit samples compared with standard aqueous solutions, the LOD and LOQ values in biscuit samples were slightly higher. Despite the existence of some published papers using calibration curves in standard aqueous solutions, it is more reasonable and scientific for the method validation in real samples, owing to fully considering the matrix effects and presenting more accurate results. So, we adopted the calibration curves in biscuit samples. The repeatability and reproducibility (intra-day and inter-day precisions) were assessed by determination of acrylamide spiked standard in biscuit samples at five different concentration level (5.0, 50.0, 200.0, 500.0 and 5000.0 $\mu\text{g kg}^{-1}$). As seen in Table 1, the extraction recoveries and relative standard deviations (RSDs) of intra-day precision were found to be 86.0–98.3% and 1.2–3.0%, respectively,

Table 1

Intra-day and inter-day precision and recovery of the DMIP-MSPE-HPLC/UV method for acrylamide determination in spiked biscuit samples ($n = 4$).

Add ($\mu\text{g kg}^{-1}$)	Found ($\mu\text{g kg}^{-1}$) \pm SD	RSD (%)	Recovery (%)
Intra-day			
5.0	4.3 \pm 0.13	3.0	86.0
50.0	47.5 \pm 1.30	2.7	95.0
200.0	187.5 \pm 3.32	1.8	93.8
500.0	456.0 \pm 12.54	2.8	91.2
5000.0	4915.0 \pm 59.72	1.2	98.3
Inter-day			
5.0	4.4 \pm 0.18	4.1	88.0
50.0	43.5 \pm 1.30	3.0	87.0
200.0	182.0 \pm 2.82	1.6	91.0
500.0	488.0 \pm 12.75	2.6	97.6
5000.0	4870.0 \pm 87.18	1.8	97.4

while that of inter-day recoveries and precisions were 87.0–97.6% and 1.6–4.1%, respectively, which indicated excellent reproducibility of the developed method. Meanwhile, the accuracy and applicability of the DMIP-MSPE-HPLC/UV method were validated for extraction and preconcentration of acrylamide in biscuit samples.

Fig. 6 shows the chromatograms of biscuit samples. As shown in Fig. 6a, the chromatogram of direct injection of biscuit without applying DMIP-MSPE was very complex, and due to the overlapping of interference peaks with the peak of acrylamide, acrylamide couldn't be found. Even though the y-scale of chromatogram changed to 0–15 mAu, the acrylamide's peak wasn't seen yet (inset of Fig. 6a). After spiking the standard solution of acrylamide, the direct injection of biscuit sample without pretreatment step revealed that matrix impurities seriously overlapped with acrylamide's peak (Fig. 6b), so quantitative analysis of acrylamide was still impossible. Interestingly, after DMIP-MSPE, most of impurity signals of the biscuit samples were greatly reduced (Fig. 6c and d), owing to high clean-up potential of the DMIP-MSPE. More excitingly, for the spiked biscuit sample, the interference-free acrylamide's peak emerged significantly (Fig. 6d), proving high potential of the DMIP-MSPE method for clean extraction of acrylamide from complicated biscuit samples. Consequently, the DMIP-MSPE method was practically applicable.

Furthermore, five kinds of different biscuit samples were analyzed. As listed in Table 2, the acrylamide was detected in all biscuit samples within 65.8–2962.4 $\mu\text{g kg}^{-1}$ and the RSDs values were lower than 3.3% for three replicated extractions, indicating the high accuracy of the developed method. These results proved that the established DMIP-MSPE method was capable for influential clean-up and preconcentration of acrylamide from the complicated food samples with high precision and accuracy.

3.8. Reusability of the DMIP

Reusability of a sorbent is the major profit in terms of practical applications and economic cost. Consequently, several adsorption-desorption cycles of DMIP were performed and results showed that five sequential recoveries were attained of 96.6%, 94.1%, 91.9%, 88.5%, and 86.2%, respectively. As can be seen from Fig. S8, after at least five times, the extraction recovery didn't decrease significantly. Thus, the DMIP-MSPE based method benefited from the advantages of cost-effectiveness, durability, rapidity and simplicity, and could highly sensitive and accurately quantify acrylamide in complicated aqueous samples.

3.9. Method performance comparison

The analytical characteristics of the developed DMIP-MSPE-HPLC/UV method was compared with previously reported literatures for the determination of acrylamide in various sample matrices, as listed in Table S6 [15,31,32,43,48–56]. As can be seen, our achieved LOD and

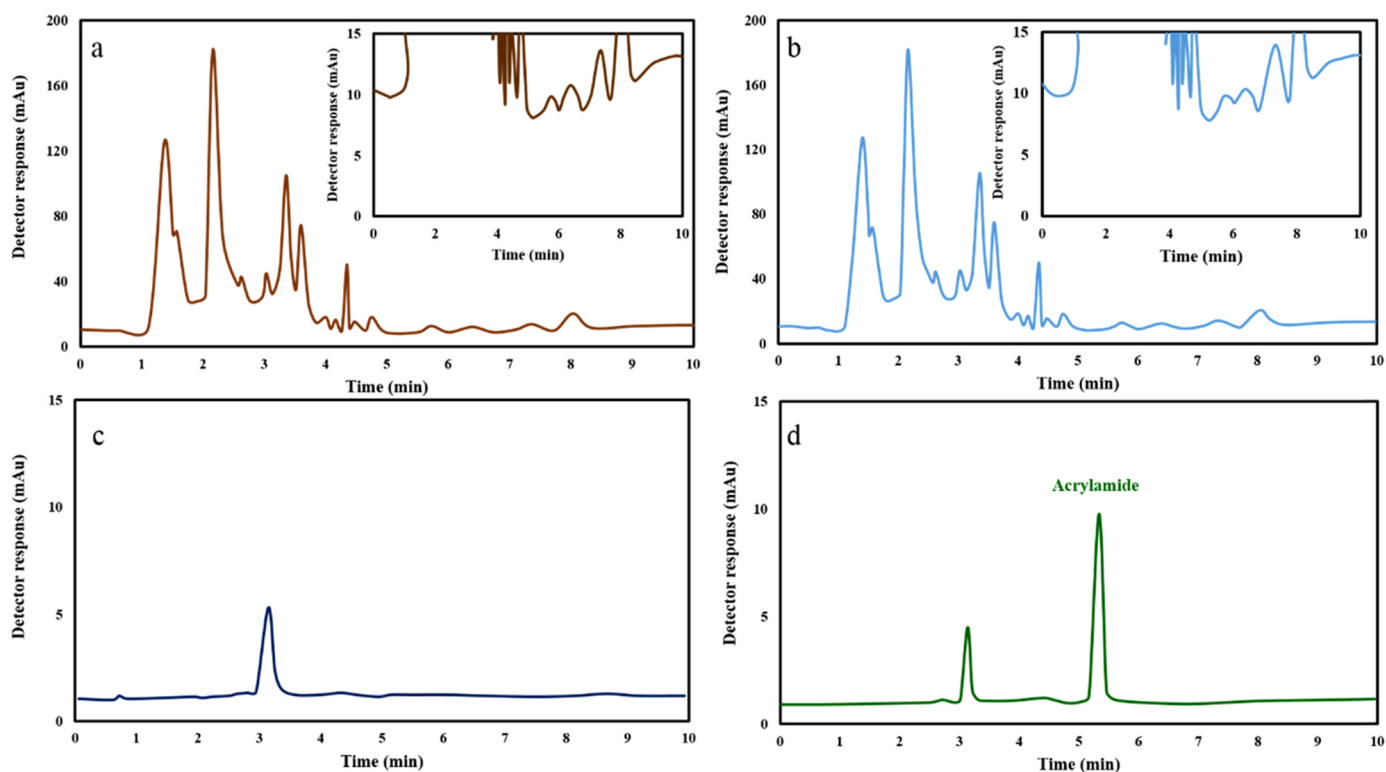


Fig. 6. Typical chromatograms of (a) direct injection of crude biscuit sample (different scale inset), (b) direct injection of spiked crude biscuit sample, (c) blank biscuit sample after DMIP-MSPE procedure and (d) spiked biscuit sample after DMIP-MSPE procedure. Spiked concentration: $10 \mu\text{g kg}^{-1}$.

Table 2

Endogenous contents of acrylamide in five different biscuit samples determined by DMIP-MSPE-HPLC/UV method ($n = 3$).

Sample	Found ($\mu\text{g kg}^{-1}$) \pm SD	RSD (%)
Biscuit 1	270.1 ± 7.1	2.6
Biscuit 2	2962.4 ± 41.0	1.4
Biscuit 3	955.1 ± 14.8	1.5
Biscuit 4	524.7 ± 11.6	2.2
Biscuit 5	65.8 ± 2.2	3.3

linear range is similar to other researches [49,54]. More excitingly, the LOD is also quite low in comparison with some fluorimetry and MS-based detection methods [43,50–53], which is very likely owing to the highly selective preconcentration ability of the DMIP-MSPE. Emphasis should be put on in the current work for the first time both synthesis and extraction procedure were in the line of sustainable and green chemistry with at least consumption of organic solvents and reagents in mild condition which is unique in terms of feasibility, natural origin, full biodegradability, and eco-friendliness for determination of acrylamide.

4. Conclusions

In summary, a novel water-compatible DMIP with super-paramagnetic behavior was rationally fabricated according to clean and low-cost strategy at least of time by combining dummy and surface imprinting technology with natural monomer. The DMIP was employed as versatile sorbent at the service of MSPE for clean-up and preconcentration of acrylamide from biscuit samples. During MSPE, washing step was intelligently omitted while long chain fatty acids impurities were removed by using ice bath which was an excellent alternative to toxic organic solvent (e.g., hexane). Both synthesis route and extraction procedure benefited from the impressive advantages, like time saving, waste eliminating, environmentally benign substances

and minimum chemical pollutions, minimum amount of glassware and working at mild condition. By immobilizing thin layer imprinted chitosan network onto Fe_3O_4 @PEG core, the DMIP provided fast equilibrium kinetics and high adsorption capacity, which decreased analysis time and increased aqueous applicability. The versatile DMIP not only denoted high magnetization that could be quickly separated from the suspension by magnetic field without requirement to SPE column packing, filtration, or centrifugation, but also the interference of the leaching residual template was completely circumvented by dummy imprinting strategy. Furthermore, by using multivariable optimization based on experimental design methodology, impacts of individual parameters and their interactions on the extraction efficiency were studied and subsequently the true optimum level was found with the minimum of expense, time, labor effort and chemicals. Consequently, we believe these appropriate features could contribute to enhancing the performances of MIPs in line of clean chemistry especially biopolymer usage, and thereby promote the rapid development and wide applications of molecular imprinting.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.talanta.2018.11.065](https://doi.org/10.1016/j.talanta.2018.11.065).

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