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Applying molecular modelling and experimental studies to develop molecularly imprinted polymer for domoic acid enrichment from both seawater and shellfish

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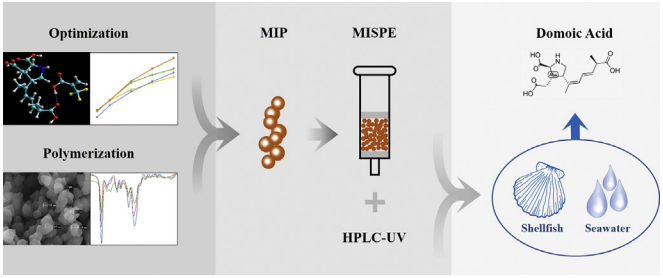
HIGHLIGHTS

- New molecularly imprinted polymer (MIP) was developed for domoic acid enrichment.
- Molecular modelling was firstly applied to screening for functional monomer.
- The obtained MIP showed high affinity and selectivity for domoic acid.
- MISPE column is more stable and precise than C18, SAX, and HLB columns.
- The developed MISPE-HPLC method successfully applied in both seawater and shellfish.

GRAPHICAL ABSTRACT



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ABSTRACT

A highly selective sample cleanup method using molecularly imprinted polymers (MIP) was developed for the enrichment of domoic acid (DA, an amnesic shellfish toxin) from both seawater and shellfish samples. Molecular modelling was firstly applied to screening a suitable functional monomer and optimize the polymer preparation. Theoretical results were in a good agreement with those of the experimental studies. MIP was prepared by precipitation polymerization using 1, 3, 5-pentanetricarboxylic acid and 2-(Trifluoromethyl)acrylic acid as the template molecule and functional monomer, respectively. The morphology and molecular structure of MIP were revealed by scanning electron microscope (SEM) and fourier transform infrared spectroscopy (FTIR), respectively. The obtained MIP showed high affinity and selectivity for DA with binding site numbers of 0.875 mg g^{-1} and an average association constant of 0.219 L mg^{-1} evaluated by adsorption experiments. The developed molecularly imprinted solid-phase extraction (MISPE) column achieved satisfied adsorption rate (99.2%) and recovery (71.2%) with relative standard deviation (RSD) less than 1.0%, which is more stable and precise than the C_{18}, SAX, and HLB columns. Finally, the determination method for DA in both seawater and shellfish samples was then successfully established and validated using MISPE coupled with high-performance liquid chromatography-ultraviolet detection (HPLC-UV). The method limit of detection was 20 μg L^{-1} and 50 μg kg^{-1} for seawater and shellfish, respectively. This study demonstrates that

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molecular modelling is a useful tool to screening functional monomer and optimize polymer preparation. It provides an innovative polymer for trace DA monitoring in both seawater and shellfish.

1. Introduction

Domoic acid (DA) is a natural amino acid originally isolated from the macroscopic red alga called *Chondria armata* in Japan (Daigo, 1959). It is more globally produced by several species of the diatom genus Pseudo-nitzschia, which are the main sources of poisoning in both humans and a variety of marine species. DA can contaminate the edible tissue of shellfish such as clams, mussels, and oysters and cause amnesic shellfish poisoning (ASP) (Zhou et al., 2011). The first outbreak of ASP caused by eating contaminated mussels occurred on the eastern coast of Prince Edward Island, Canada in 1987, resulted in 150 reported cases, 19 hospitalisations, and 4 deaths (Perl et al., 1990). The public began to pay attention to the DA poisoning because of the subsequent reports by USA (Schnetzer et al., 2007) and Canada, such as the large outbreak in California sea lions in 1998 (Bargu et al., 2010). Following the 1987 outbreak, the Canadian authorities imposed an action limit of 20 μg DA/g in shellfish tissue (Jeffery et al., 2004).

DA is stable and minimally degradable in alkaline solution (Johannessen, 2000). It can be readily accumulated in a wide variety of shellfish species, birds and mammals and introduced via the food web. DA is tagged as an excitatory and neurotoxic biotoxin, which can induce many serious symptoms such as nausea, temporary amnesia, persistent memory loss, coma, and even death (Humpage et al., 1993; Tryphonas et al., 1990a, 1990b). Unfortunately, to date, there is no specific antidote for DA poisoning.

Thus, the widespread occurrence of DA in a variety of marine species has led to the classification of this compound as a dangerous marine toxin, requiring constant monitoring and regulatory control (Piletska et al., 2008). In recent years, DA has been identified in samples such as seawater and aquatic organisms by different analytical methods, such as enzyme-linked immunosorbent assay (ELISA) (Smith and Kitts, 1994; Kawatsu et al., 2000; Yu et al., 2004), capillary electrophoresis (CE) (Martins et al., 2002; Kvasnička et al., 2006), biosensor (Stevens et al., 2007), liquid chromatography-mass spectrometry (LC-MS) (Furey et al., 2001; Tor et al., 2003), and high-performance liquid chromatography (HPLC) (Lawrence et al., 1994; Duxbury, 2000; He et al., 2017). HPLC is the first method developed to detect DA (Lawrence et al., 1989), and has become one of the most powerful methods for the detection of DA owing to its merits of sensitivity and selectivity (Lin et al., 2016). For example, Lopez-Rivera et al. (2005) developed a HPLC-ultraviolet detection (HPLC-UV) method to determine DA in shellfish and the method reached satisfactory limit of detection (LOD) of 0.2 $\mu g\, g^{-1}$. Although some other techniques (e.g. ELISA, LC-MS) display the advantages on sensitivity and selectivity, LC-UV is often the routine analytical tool available in many research institutes and regulatory agencies responsible for monitoring the occurrence of marine toxins, because of the less expensive and labor-saving (Mafra et al., 2009).

Nevertheless, trace level concentrations of DA and the complexity of the environmental and biological matrix pose a significant challenge to the development of an efficient pretreatment method before HPLC analysis. Solid-phase extraction (SPE) is usually selected as the extraction tool for DA from various samples because of the simple handle, less consumption of solvent, and high extraction efficiency (Li et al., 2015; Poole, 2003). However, the classical SPE sorbents (C_8, C_{18}, etc.) are usually based on general adsorption, which lacking molecular selectivity and resulting in low recoveries (Sorouraddin and Mogaddam, 2016). Although some sorbents such as the anion-exchange cartridge (SAX) and HLB can be applied for the purification of DA, the removal of matrix interferences and a quick single-step sample preparation are still problems that need to be further solved (Piletska et al., 2008; Tor et al., 2003). Therefore, the development of new efficient and selective SPE sorbents is necessary and urgent for the enrichment of trace level DA.

Molecular imprinting technique (MIT) is one of the most attractive methods for obtaining selective recognition abilities (Wulff et al., 1973). The template molecule, functional monomer, initiator, and cross-linking agent are simultaneously polymerized to generate a high selective molecularly imprinted polymer (MIP). MIP is able to rebind selectively with the template and other analogous chemical structures (Song et al., 2014), shows excellent thermal and chemical stability (Roland and Bhawani, 2016). MIP has been exploited in several applications, such as SPE, bionic sensor, and capillary electrochromatography (Caro et al., 2006). Molecularly imprinted-solid phase extraction (MISPE) combine SPE with MIT, which display superior specificity, selectivity, and sensitivity compared to conventional SPE columns (Zhou et al., 2011; Puoci et al., 2008). MISPE has been applied to the pretreatment of drugs, food, environmental and biological samples. For example, de Oliveira et al. (2016) successfully employed MISPE in the extraction of human urine to determine the concentrations of four kinds of fluoroquinolones. Similarly, high recoveries (88%) were obtained of a MISPE-HPLC method developed by Mei et al. (2016) when they enriching gonyautoxin in seawater. Unfortunately, only few studies attempted to apply MIP for the enrichment of DA, especially in seawater and shellfish samples simultaneously. For example, Zhou et al. (2011) applied 1,3,5-pentanetricarboxylic acid as the template molecule to develop a MIP based SPE column for DA extraction by bulk polymerization method. However, the proposed method was not applicable for seawater samples (Zhou et al., 2011). More recently, five carboxylicacid compounds were tested as the dummy templates by He et al. (2017), respectively, to develop MIPs for DA enrichment from seawater. It was found that the most efficient MIP was obtained when applying citric acid as template molecule. However, the interactions between template molecule and functional monomer were ignored in the report (He et al., 2017). Thus, the tedious workload on screening template molecule was inevitable.

As a matter of fact, the nature of the functional monomer plays an important role on the quality and performance of the final polymer product. Unfortunately, the broad range of functional monomers makes it difficult to develop a selective MIP for the analyte. Computer simulation is a useful method to screening functional monomer for preparing selective MIP. And its potential had been recognized in previous reports elsewhere (Dong et al., 2005). For example, molecular modelling approach was used to determine the optimal design of functional monomers by Farrington et al. (2006) to develop selective MIP for caffeine.

The aim of this study was to obtain a highly selective MIP, which is applicable for DA enrichment from both seawater and shellfish samples, by computational predicting and experimental studies.