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Switchable zipper-like thermoresponsive molecularly imprinted polymers for selective recognition and extraction of estradiol

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ABSTRACT

Zipper-like thermoresponsive molecularly imprinted polymers (MIPs) were prepared based on interpolymer complexation via the synergy of dual functional monomers of acrylamide (AAm) and 2-acrylamide-2-methyl propanesulfonic acid (AMPS) for selective recognition and extraction of estradiol (E2) by temperature regulation. The resulting E2-MIPs attained controlled adsorption and release of E2 in response to temperature change, with higher adsorption capacity (8.78 mg/g) and stronger selectivity (imprinting factor was 3.18) at 30 °C compared with that at 20 and 40 °C; the zipper-like interpolymer interaction between poly(AAm) and poly(AMPS) enabled switchable molecular recognition. The adsorption processes obeyed Langmuir isotherm and pseudo-second-order kinetic models. High recognition selectivity of the MIPs toward E2 was achieved over its structural analogues, and good reusability was displayed over 86% recovery after six adsorption-desorption cycles. Accordingly, the E2-MIPs were empolyed as new adsorbents for selective dispersive solid-phase extraction of E2, and offered low limits of detection and quantification of 4.81 and 16.03 μg/L, respectively. Recoveries from goat milk samples ranged from 76.2% to 89.7% with the precisions (relative standard deviations, n = 3, %) of 2.8–3.7% at 30 °C. The intelligent E2-MIPs combining good adsorption, special recognition and temperature sensitivity proved to be a promising alternative to the selective identification and controlled extraction/removal of E2 in complicated samples by simple temperature-responsive regulation.

1. Introduction

Environmental estrogens problems have become another international environmental issue, following the well-known global warming and the ozone destruction issues, through simulating or disrupting the physiological/biochemical effects of natural hormones. Estradiol (E2), considered as the most representative of phenolic environmental estrogens, can promote the growth and development of female reproductive organs in the appropriate concentration range [1]. E2 is intensively used in the livestock and poultry industry because of its acceleration effects in animal growth and milk production [2]. However, its release into the surrounding environment has much correlation with the occurrence and development of health-related problems [3–5]. Widespread proofs have shown that E2 is sufficient to affect the normal function of the reproductive and endocrine systems, and it can significantly increase the likelihood of breast and ovarian cancers in female, weaken the reproductive capacity of human and wildlife even at a very low concentration [6]. Moreover, E2 can be continuously enriched through the interrelated food chains in the ecological system, and eventually accumulate in the body adipose tissue through the consumption of meat and milk and any other food to form long-term toxicity.

Currently, the methods for the determination of E2 levels include immunoassay [7], high performance liquid chromatography (HPLC) [8], gas chromatography-mass spectrometry (GC-MS) [9], liquid chromatography-mass spectrometry (LC-MS) [10] and molecular luminescence analysis [11], etc. Among these, immunoassay based on an antigen–antibody reaction has high selectivity and sensitivity for targeted analytes, but it frequently suffers from instability of natural antibodies, time-consuming process and hight cost [12]. Molecular luminescence analysis can be accomplished very quickly; however, the luminescence is susceptible to molecular structure and environmental

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factors [11]. As far as we know, chromatography and chromatography-mass spectrometry assays are mature, fast and accurate with low limits of detection; still, the extraction or derivatization or other pretreatment procedure is often necessary prior to detection [13,14]. In view of the fact that low concentration analytes often occur in complicated matrices, clean-up and enrichment processes are usually required in order to minimize interferences of sample matrices and improve accuracy and sensitivity of analysis.

The common sample pretreatment technologies include solid-phase extraction (SPE), solid phase microextraction (SPME), liquid-liquid extraction (LLE), accelerated solvent extraction (ASE), etc. Amongst them, dispersive SPE (DSPE) based on SPE, in which the sorbents are directly added into the sample solution without conditioning, can avoid the tedious treatment of the conventional adsorbents, the easy blockage of the adsorption column, the poor repeatability and the excessive solvent consumption [15,16]. Meanwhile, DSPE often shows poor selectivity due to the generally non-specific interaction between the sorbents and analytes, which can lead to coextraction of interfering substances and negatively affect quantitation of analytes. So, selective sorbents are highly desirable. Fortunately, molecularly imprinted polymers (MIPs) with tailor-made recognition sites for a specific target molecule can be used as selective sorbents to effectively separate, purify and enrich trace targets in complicated matrices [17–20]. MIPs are also called “plastic antibody”, owing to their desired selectivity, physical robustness, thermal stability, as well as low cost and easy preparation. The introduction of MIPs as selective adsorbents for extracting and removing E2 has aroused widespread attention [21–25].

In the meantime, stimuli-responsive MIPs (SR-MIPs), also known as environmental responsive MIPs or intelligent MIPs, have also received great concerns owing to that the molecular recognition specificity can be regulated by specific external stimuli [26]. They can respond to various stimuli signals such as temperature [27,28], pH [29], magnetism [30,31], and lights [32], along with considerable changes in their physicochemical properties, including molecular chain structure, solubility, surface structure, swelling or dissociation behavior, etc. For examples, Li et al. described a temperature SR-MIP nanoreactor to realize temperature-controlled release and absorption for S-naproxen [33]. Chen and his coworkers prepared magnetic [34,35] and photonic-magnetic [36] SR-MIPs for E2, as well as temperature [37] and temperature-magnetic [38] SR-MIPs for bisphenol A. The smart and versatile functional materials, SR-MIPs, can provide convenient, cost-effective and environment friendly ways for contamination monitoring and remediation, drug dilivery and other aspects, which will take acitve roles in many fields.

Inspired by these studies, we purpose to prepare a novel zipper-like thermoresponsive SR-MIPs material based on interpolymer complexation via the synergy of dual functional monomers for selective recognition and extraction of E2. Acrylamide (AAm) as functional monomer and 2-acrylamide-2-methyl propanesulfonic acid (AMPS) as thermosensitive functional co-monomer formed the interpolymer complex of poly(AAm-*co*-AMPS) (PAAm-PAMPS) in this process. The morphologies, structures, and thermostability of the as-prepared E2-MIPs were well characterized by SEM, FT-IR, BET, and TGA. The responsivity of E2-MIPs to external stimuli was investigated, which achieved switchable zipper-like adsorption/release for E2 by swelling/shrinking of the polymer networks according to the temperature changes. The adsorption statics/dynamics, selectivity and reusability of E2-MIPs were systematically evaluated. And then the applications as adsorbents to DSPE of E2 from goat milk samples were also investigated.

2. Experimental

2.1. Reagents and instruments

Estradiol (E2) and bisphenol A (BPA) were purchased from Aladdin (Shanghai, China). Diethylstilbestrol (DES), dienestrol (DIES), 2-acrylamide-2-methyl propanesulfonic acid (AMPS) and ethylene glycol dimethacrylate (EGDMA) were provided by Sigma-Aldrich (Shanghai, China). Acrylamide (AAm) was purchased from Tianjin Kermel Chemical Reagent Co., Ltd. (Tianjin, China). And AMPS, AAm and EGDMA were purified in order to remove stabilizers. 2,2-Azobisisobutyronitrile (AIBN) was obtained from Shanghai Chemical Reagents Company (Shanghai, China) and recrystallized in 50 °C ethanol prior to use. Other affiliated reagents such as dimethylsulfoxide (DMSO), acetic acid, ethanol and methanol were all obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). High performance liquid chromatography (HPLC) grade acetonitrile was purchased from Merck (Darmstadt, Germany). Doubly purified deionized water used throughout the study was produced by a Milli-Q Ultrapure water system with the water outlet operating at 18.2 MΩ cm (Millipore, Bedford, MA, USA). All reagents were of at least analytical grade and used directly without further purification unless otherwise specified.

The morphological evaluation was examined by a scanning electron microscope (SEM, Hitachi S-4800FE-SEM, 3 kV; samples dispersed in ethanol and adding a drop on an silicon sheet followed by sputter-coated with gold for 85 s under high vacuum). The characteristic functional groups were characterized by a Fourier transform infrared (FT-IR) spectrometer (Thermo Nicolet Corporation, USA). Thermal gravimetric analysis (TGA), also known as thermogravimetry (TG), was carried out from 25 to 800 °C with a heating rate of 10 °C/min under nitrogen environment by thermal gravimetric analyzer (Mettler 5 MP), presenting TG and derivative thermogravimetry (DTG) data. N_2 adsorption-desorption isotherms were examined with Beishide Instruments (3H-2000PS4, Beijing) for Brunauer–Emmett–Teller (BET) analysis to determine the specific surface area and pore size. Dynamic light scattering (DLS) measurements were performed under different temperatures on a Malvern Zetasizer Nano-ZS90 (ZEN3590, UK). Chromatographic analysis was conducted on a high-performance liquid chromatorgraphy (HPLC) instrument (Waters, American) under the following conditions: injection volume, 20 μL; mobile phase, acetonitrile/ultrapure water (7:3, v/v); flow rate, 1.0 mL/min; detection wavelength, 280 nm for E2, 278 nm for BPA, 238 nm for DES and 228 nm for DIES; C18 column, Arcus Ep-C18 (5 μm, 4.6 mm × 250 mm column); temperature, room temperature.

2.2. Synthesis of E2-MIPs

MIPs were prepared according to that reported [39] with necessary modifications. Briefly, E2 (0.8 mmol), AAm (1.48 mmol) and AMPS (1.24 mmol) were completely dissolve in 7 mL of DMSO. EGDMA (12 mmol) and AIBN (0.6 mmol) were then added into the above solution followed by deoxygenating with sonication and nitrogen for 10 min, and the mixture was irradiated under the ultraviolet light for 2 h. Until the obtained polymers cooled to room temperature, they were crushed and washed with DMSO to remove excess substances. Then, the polymers were eluted with methanol/acetic acid solution (9:1, v/v) until no template was detected. Finally, the polymers namely E2-MIPs were dried to constant weight under vacuum at 40 °C. Fig. 1A schematically shows the preparation process. As a control, the corresponding non-imprinted polymers (NIPs), namely E2-NIPs, were prepared using the same processes without addition of the template E2.

2.3. Thermoresponsive property of E2-MIPs

The temperature sensitivity evaluation of E2-MIPs was performed using 10 mg of E2-MIPs with 2 mL acetonitrile solutions containing various concentrations of E2 within 0–250 mg/L. After 24 h of shaking at different temperature (20, 30, and 40 °C), the samples were centrifuged and filtered with a 0.45 μm microfiltration membrane before HPLC-UV analysis. The adsorption experiments of each tem-