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Photoresponsive hollow molecularly imprinted polymer for trace triamterene in biological samples

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ABSTRACT

This paper reports a photoresponsive hollow molecularly imprinted polymer for the determination of trace triamterene in biological sample. The photoresponsive hollow molecularly imprinted polymer was prepared on sacrificial silica microspheres via surface imprinting technique through atom transfer radical polymerization using a novel water-soluble azobenzene derivative, 4-[(4-methacryloyloxy)phenylazo]-3,5-dimethyl benzenesulfonic acid, as the functional monomer, and the sacrificial silica core was subsequently removed using HF etching method with 1.25 vol.% HF ethanolic solution. The morphologies and properties of the photoresponsive hollow molecularly imprinted polymer were further characterized and compared systematically with the corresponding photoresponsive surface molecularly imprinted polymer. Compared with surface imprinted polymer, the hollow material displayed higher binding capacity, better recognition ability, faster mass-transfer rate, and larger isomerization rate constants toward triamterene. The static binding properties of the imprinted materials were investigated under three irradiation conditions. The photoresponsive hollow molecularly imprinted polymer showed better specificity toward triamterene than its structural analogues (folic acid and caffeine) as examined by UV–vis and HPLC. The photoresponsive hollow molecularly imprinted polymer was utilized for the determination of trace triamterene in biological samples (human urine and serum) with advantages of simple sample pre-treatment, good recovery and good sensitivity.

1. Introduction

Triamterene (Scheme 1) is a mild and potassium-saving diuretic drug. It is widely used in conjunction with some potent diuretics (e.g., a thiazide or anthranilic acid derivative) in clinical practice for the treatment of hypertension and different kinds of edema [1,2]. However, the use of diuretics has been prohibited by the Medical Commission of the International Olympic Committee and World Anti-Doping Agency because diuretics are misused in sports to rapidly decrease the body weight or mask the ingestion of some doping agents by reducing their concentration in urine; the triamterene concentration in urine should be less than or equal to 0.2 μg mL^{-1} (0.2 ppm) [3–5].

Many methods, including spectrophotometry [6], spectrofluorimetry [7], capillary electrophoresis [8,9], liquid chromatography [10–12], and gas chromatography/mass spectrometry [13], have been reported for the determination of triamterene in pharmaceuticals and biological samples. Although these methods are sensitive and highly specific, most of them are either time consuming or require complicated and expensive instruments [14]. Therefore, a simple, selective, sensitive, and low-cost detection method should be developed for the separation and determination of trace triamterene in biological samples. Molecular imprinting technique creates cavities in molecularly imprinted polymers (MIPs), which are complementary in size, shape, and chemical functionality to that of templates. MIPs possess excellent recognition ability toward template molecules and many promising characteristics, such as physical robustness, thermal stability, low cost, and easy preparation [15]. MIPs also have potential application in purification and separation [16], chiral recognition [17], chemo/biosensing [18], and catalysis [19,20]. Furthermore, MIPs are fabricated for the recognition, determination, and extraction of triamterene from various samples [14,21–23]. Zhao [21] prepared a molecularly imprinted monolithic column for a selective recognition of triamterene in human serum and urine. Wang [23] prepared a MIP for a selective extraction of triamterene and its structural analogs. In their methods, the triamterene concentration in actual samples is quantitatively analyzed by high-performance liquid chromatography. Nezhadali [14] also reported an electrochemical method based on a MIP for the

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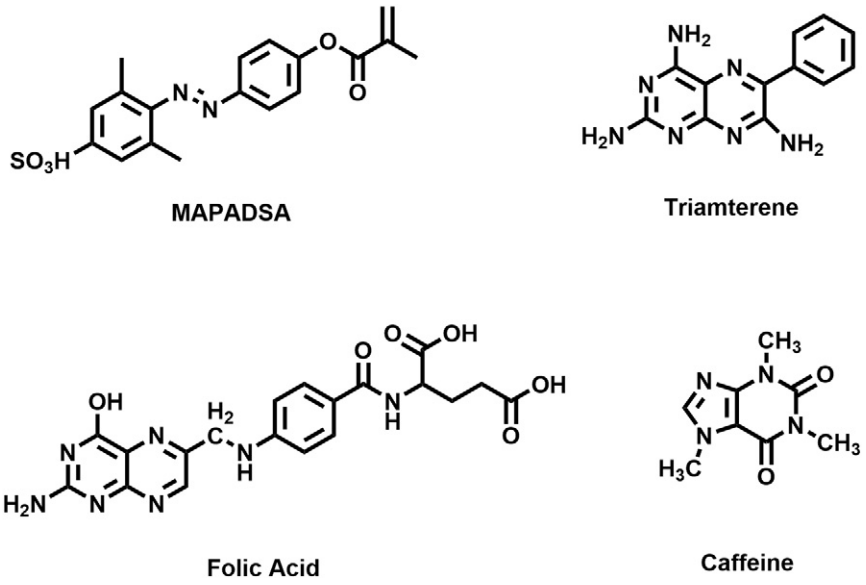

Scheme 1. Chemical structures of MAPADSA, triamterene, caffeine, and folic acid.

determination of triamterene. To the best of our knowledge, there are few reports on photoresponsive hollow molecularly imprinted polymer (PHMIP) for trace triamterene in biological samples.

In this paper, we report a simple, selective, sensitive, and low-cost detection method for detecting trace triamterene in biological samples using a PHMIP [24–28]. Using water-soluble functional monomer for polymerization is an effective method to realize MIP application in biological samples [24–28]. Therefore, a novel water-soluble azobenzene derivative, 4-[(4-methacryloyloxy)phenylazo]-3,5-dimethyl benzenesulfonic acid (MAPADSA), was designed and synthesized. Using MAPADSA as the functional monomer, a novel PSMIP was firstly fabricated on the surface of sacrificial silica microspheres through living radical polymerization [29–31]. After the removal of sacrificial silica core, PHMIP was obtained. The PHMIP displayed high-capacity, fast mass transfer rate, good sensitivity and selectivity toward triamterene in methanol and 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES; 4:1, *v*/*v*) solutions, as well as in biological samples. Using a novel photoresponsive water-soluble functional monomer and a clean control stimulus (light), the PHMIP enables the recognition and release of triamterene in biological samples clean and remotely. The PHMIP was used for the determination of trace triamterene in human urine and serum, and a limit of detection of 0.1 ppm and simple sample pretreatment were used.

2. Experimental procedure

2.1. Instruments and reagents

^{1}H NMR and ^{13}C NMR were recorded on a Bruker AV-600 NMR instrument at an ambient temperature using tetramethylsilane as an internal standard. Ultraviolet–visible (UV–Vis) spectra were obtained using an UV-4802 spectrophotometer (UNICO (Shanghai) Instruments Co. Ltd., China). A CEL S-500 Xe light was used as a light source (Beijing Zhong Jiao Jin Yuan Ke Ji Co. Ltd., China), and wavelengths of 365 and 440 nm were respectively selected using 365 and 440 nm filters. Moreover, the morphologies of silica microspheres, PSMIP, and PHMIP were identified by scanning electron microscopy (SEM; S-4800, Hitachi, Tokyo, Japan) and transmission electron microscopy (TEM; Philips CM200 FEG, Dutch). Fourier transform infrared spectroscopy (FT-IR) was recorded on a Perkin-Elmer Model GX spectrometer using a KBr pellet method. Fluorescence spectra were also recorded on a F380 system (Tianjin Gangdong Technology Co. Ltd., Tianjin, China). In addition, thermal gravimetric analysis (TGA) was conducted on a SDT Q600 thermal analyzer (USA) at a heating rate of 10 °C min^{-1} up to 700 °C under flowing nitrogen (100 mL min^{-1}). Nitrogen adsorption–desorption analysis was conducted at 77 K on an Autosorb-1 apparatus (Quantachrome, USA). Specific surface areas and pore diameters were calculated using the Brunauer-Emmett-Teller (BET) and Barrett-Joyner-Halenda (BJH) models, respectively. The mixtures of triamterene and analogues amounts was analyzed by the high-performance liquid chromatography (HPLC) system (Agilent, USA), which consisted of a QuatPump, and a G1315B dual-wavelength absorbance detector. The mobile phase used for HPLC experiments was a mixture of methanol and water (65:35, v:v), and all separations were carried out on a Luna 5u C18 column (5 μm, 250 mm × 4.6 mm, Phenomenex) with a flow rate of 0.4 mL min^{-1}. The detecting wavelength of the UV detector was set at 360 nm and 273 nm for the mixtures of triamterene and analogues.

2,6-Dimethylaniline (99%), copper (I) bromide (99%), N,N,N′,N″,N″-pentamethyldiethylenetriamine (PMDETA, 99%), ethyl α-bromoisobutyrate (98%), ethylene glycol dimethacrylate (EGDMA, AR), HEPES (99%), methanol (MeOH, AR), 3-methacryloxypropyltrimethoxysilane (MPS), tetraethyl orthosilicate (TEOS, AR), triamterene, folic acid, and caffeine were purchased from Aladdin Co., Shanghai, China. All the solvents used were of analytical reagent grade. HEPES (0.01 mol L^{-1}, pH 7.20) buffer was used throughout the experiment.

2.2. Synthesis of MAPADSA

Scheme 2 illustrates the synthetic route for MAPADSA. 3,5-Dimethyl sulfanilic acid (DMSA) was synthesized according to a method reported by Sun [32,33], with some modification. Typically, 2,6-dimethylaniline (1.00 g, 8.25 mmol) was sulfonated with concentrated sulfuric acid (1.7 mL, 32.0 mmol) at 180–190 °C for 2 h, followed by neutralization with NaOH to obtain the sodium salts. After filtration, the filtrate was washed with concentrated hydrochloric acid to pH 1–2, thereby generating a white solid. The solid was filtrated, washed with deionized water, and dried over a freeze drier. Approximately 1.20 g of white powder DMSA was subsequently obtained. The yield was 75.0%, and other parameters were observed as follows: ^{1}H NMR (600 MHz, d_6-DMSO) δ (ppm): 7.3 (s, 2H), 2.3 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 161.4, 151.1, 147.3, 146.0, 129.6, 126.6, 124.8, 116.3, 18.8; and MS (ESI): (MeOH, negative mode) *m*/*z*: 200.0 (mass = 201.1 g mol^{-1}).