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Hybrid molecularly imprinted polymers synthesized with 3-aminopropyltriethoxysilane-methacrylic acid monomer for miniaturized solid-phase extraction: A new and economical sample preparation strategy for determination of acyclovir in urine

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ABSTRACT

The miniaturized molecularly imprinted solid-phase extraction (mini-MISPE) coupled with high-performance liquid chromatography was proposed for the determination of acyclovir in urine. 1.5-mL tapered plastic centrifuge tube filled with hybrid molecularly imprinted polymers (HMIPs) was used as the cartridge of mini-MISPE, and the HMIPs synthesized with 3-aminopropyltriethoxy silane-methacrylic acid as monomer exhibited good recognition and selectivity for acyclovir. Under the optimized condition, good linear calibration was obtained in a range of 0.5–15 $\mu g\,mL^{-1}$ with the correlation coefficient of 0.9994, and the recoveries at three spiked levels were 91.6–103.3% in urine with the relative standard deviation (RSD) of $\leq$3.5%. Excellent intra-day and inter-day repeatability were achieved with RSD of $\leq$2.6% and 4.0% in three different concentrations. This method combined the advantages of HMIPs and mini-MISPE, and it could become an alternative tool for analyzing the residues of acyclovir in complex urine matrices.

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1. Introduction

Acyclovir is a synthetic acyclic purine nucleoside analog derived from guanine that lacks a 3′-hydroxyl on its side chain. It is one of the most effective antiviral drugs against herpes simplex virus types 1 and 2, varicella-zoster virus, epstein-barr virus, cytomegalovirus and human herpesvirus 6 [1,2]. However, acyclovir must be taken in an oral dose of 200 mg five times daily for ten days or 400 mg three times for five days because of its poor bioavailability, low water-solubility and short half-life (about 2.5 h), which may easily cause the abuse of drug to patients. Furthermore, many adverse reactions would occur if acyclovir were abused – neurotoxicity, urticaria, phlebophlogosis, diarrhea, cephalalgia, emesia, and swoon. In some cases, renal failure patients can aggravate their condition [3–6]. The situation of irrational drug use still exist as well as the urgency of pharmacokinetics study, so it is necessary to monitor the concentration of acyclovir in plasma and urine after oral administration.

Series of analytical methods have been proposed for the measurement of acyclovir including radioimmunoassay (RIA) [7,8], spectrophotometric methods [9–12], thin layer chromatography (TLC) [13], high-performance capillary electrophoresis (HPCE) [14], micellar electrokinetic chromatography [15], high performance liquid chromatography (HPLC) with different detections [16–25], flow injection-chemiluminescence [26], and electroanalytical method [27]. Due to the complexity of sample matrices and extremely low level of analytes, some sample preparation steps are necessary with the goal of enrichment and purification. As a result, some articles using various technologies such as liquid–liquid extraction (LLE) [28], matrix solid-phase dispersion (MSPD) [22], and solid-phase extraction (SPE) [29] have been reported in recent years. However, these technologies could also cause some problems, such as high cost, inability of reutilization, time consuming procedures, large volumes of hazardous or expensive organic solvents, and low recoveries resulted from complicated operation. Therefore, the preparation methods which have advantages of

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simple, efficient, economical, renewable, and rapid should be developed and improved for acyclovir monitoring.

Miniaturized chemical analysis systems have a tremendous potential for sample preparation, and it is a way to enhance capabilities, lower cost, and accelerate analysis speed [30]. Thus, important efforts have been made recently, and miniaturized solid-phase extraction (mini-SPE) is an obvious example of miniaturized chemical analysis systems applied to sample preparation [31]. It is foreseeable that mini-SPE would facilitate development of new diagnostic methods and revolutionize medicine [32,33], and it has extensive application in environmental monitoring [34], food analysis and industry [35].

To achieve the goal of efficient extraction, sorbents play a vital role in SPE procedure. Conventional organic sorbents show stability within entire range of pH and exhibit excellent compatibility when dealing with biological samples, including molecularly imprinted polymers. However, they suffer from shrinking or swelling under the effect of temperature and/or organic solvents, and the various degrees of shrinking or swelling may considerably change morphology of polymer network and relative positions of functional groups those are essential for recognition [36]. Hybrid molecularly imprinted polymers (HMIPs) are porous materials which can be prepared with independent control of silica skeletons, and they offer high permeability, excellent mechanical strength, and good organic solvent tolerance. HMIPs are fabricated by incorporation of template molecules into rigid inorganic or inorganic organic networks. After the removal of templates, molecular cavities with distinct pore size, shape, or chemical functionality remain in the cross-linked host [37]. Due to the attractive properties of HMIPs, they have been widely applied in environmental monitoring and food analysis. To ensure a firm cohesion of hybrid skeleton, there is an obvious covalent bond (silicate ester bond combining monomer and silicon substrate) which is designed to strengthen coalescent between organic and inorganic parts, replacing the adhesion of thermal initiated bulk polymerization procedure.

In this work, HMIPs sorbents which were synthesized with new hybrid monomer (3-aminopropyltriethoxysilane-methacrylic acid, APTES-MAA) were filled in tapered plastic centrifuge tubes for rapid and selective screening of acyclovir in urine. The present method had obviously improved the selectivity and purification effect, and it eliminated the effect of template leakage on acyclovir quantitation, because theophylline was dummy template. Additionally, inexpensive device of the mini-SPE consumes small amount of solvents and sorbents without other special auxiliary device for extraction. The method is easy to handle, it indicates the convenience for daily operation; therefore, it is promising to be applied to prepare complex samples.

2. Experimental

2.1. Chemicals and reagents

Acyclovir (≥98%), theophylline (grade BP), and caffeine (≥98%) were obtained from Jingchun Reagent Co. (Shanghai, China). Acetone, chloroform, acetic acid (HAc), and trifluoroacetic acid (TFA) were obtained from Guangfu Chemical Co., Ltd. (Tianjin, China). Dichloromethane (DCM), isopropanol (IPA), and ethyl acetate (EtOAc) were purchased from Huadong Chemical Reagent Co., Ltd. (Tianjin, China). 2,2-azobisisobutyronitrile (AIBN), methacrylic acid (MAA), methanol (MeOH), acetonitrile (MeCN), ethanol (EtOH), and ammonia water ($NH_3 \cdot H_2O$) were purchased from Kermel Chemical Co., Ltd. (Tianjin, China). Ethylene glycoldimethacrylate (EGDMA), tetraethoxysilane (TEOS), trimethylolpropane trimethacrylate (TRIM), and 3-aminopropyltriethoxysilane (APTES) were purchased from Sigma–Aldrich (St. Louis, MO). 1.5-mL tapered plastic centrifuge tubes and degrease cotton were obtained from Huaxin Chemical Reagent Co., Ltd. (Baoding, China). All water was double-deionized and filtered with 0.45-μm filter membrane before use.

2.2. Instrumentation and conditions

A FTIR-8400S Fourier transform infrared (FTIR) spectrometer (Shimadzu, Kyoto, Japan) was employed to examine the infrared spectra of HMIPs with a pressed KBr tablet in a range of 400–4000 cm^{-1}. The morphological evaluation was carried out by KYKY-2800B scanning electron microscopy (SEM, FBI Co., Hillsboro, USA). HPLC analysis was performed using a Shimadzu HPLC system equipped with two LC-20AT Solvent Delivery Units, a SUS-20A gradient controller, and a SPD-20A UV-VIS Detector (Shimadzu, Kyoto, Japan). An LC solution workstation (Shimadzu, Kyoto, Japan) was used to control the system and also for data processing. The analytical column was purchased from RStech. Co., Korea (250 mm × 4.6 mm I.D., C_{18}, 5.0 μm). The mobile phase was methanol–water (1:9, v/v, containing 0.4‰ TFA) and its flow rate was set at 1.0 mL min^{-1}. The detection wavelength of the detector was set at 252 nm and the injection volume was 10 μL.

2.3. Synthesis of the HMIPs

The scheme of HMIPs' preparation was illustrated in Fig. 1. First of all, APTES (6.4 mmol) and MAA (8.1 mmol) were heated together at 60 °C for 24 h to synthesis the monomer APTES-MAA. After that, the template (theophylline, 1 mmol) and APTES-MAA (3.3 mmol) were added to chloroform (12 mL), and the emulsion was sonicated for 10 min to make them fully dissolved and then stored at 4 °C in the dark for 1 h. TEOS (1.0 mL, 4.48 mmol) after alcoholysis, EGDMA (25 mmol), and AIBN (0.3 mmol) were then added into the solution. After deoxygenating the solution with bubbling nitrogen for 10 min, the mixture was polymerized at 60 °C for 24 h. After polymerization, obtained bulk polymers were ground and sieved with a 0.054 mm aperture sieve and the smallest particles of polymers were removed by sedimentation in acetone. In order to remove the template, polymers were washed in a soxhlet apparatus with MeOH–HAc (9:1, v/v) and MeOH successively during 24 h, and then dried under reduced pressure. The efficiency of this procedure was checked by HPLC. Non-imprinted polymers (HNIPs synthesized in the absence of template) were prepared and treated in an identical manner.

2.4. Adsorption capacity of the HMIPs

To evaluate the adsorption capacity of the HMIPs, 30 mg of HMIPs or HNIPs were weighed and suspended in 1.0 mL of water solution with various concentrations of acyclovir from 2 to 250 μg mL^{-1}. The mixtures were mechanically shaken for 12 h at room temperature with a horizontal shaker and separated by centrifugation at 4000 rpm for 15 min, and then the concentration of analyte in the supernatant was detected by HPLC. In addition, the adsorption kinetics of HMIPs was also investigated, and 30 mg of HMIPs or HNIPs were weighed and suspended in 1.0 mL acyclovir solution of 50 μg mL^{-1}. The mixtures were mechanically shaken for 1, 2, 4, 6, 7, 9, 10 h respectively at room temperature and separated by centrifugation at 4000 rpm for 15 min, then the concentration of analyte in the supernatant was detected by HPLC.

2.5. Procedure of mini-MISPE

A 1.5-mL tapered plastic centrifuge tube packed with 30 mg of HMIPs was prepared as the mini-MISPE column. The schematic

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