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Dendrimer-functionalized mesoporous silica as a reversed-phase/anion-exchange mixed-mode sorbent for solid phase extraction of acid drugs in human urine

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ABSTRACT

A new dendrimer-functionalized mesoporous silica material based on large-pore 3D cubic Korea Advanced Institute of Science and Technology-6 (KIT-6) was synthesized by the growing of dendritic branches inside the mesopores of aminopropyl functionalized KIT-6. Detailed physical characterizations using transmission electron microscopy, nitrogen adsorption–desorption measurements, Fourier transform infrared (FTIR) spectroscopy, and elemental analysis reveal that the multifunctional dendrimers have been grown successfully within the confined spaces of mesopores. Although the 3D ordered mesoporous architecture of KIT-6 was well preserved, there was a significant and continuous decrease in pore size, specific surface area (S_{BET}) and pore volume when increasing dendrimer generation up to six. In order to get a compromise between the S_{BET}, pore size and density of functionalities, the dendrimer-functionalized KIT-6 (DF-KIT-6) for generation 2 (S_{BET}, 314.2 $m^2 g^{-1}$; pore size, 7.9 nm; carbon and nitrogen contents, 19.80% and 1.92%) was selected for solid phase extraction (SPE) applications. The DF-KIT-6 was then evaluated as a reversed-phase/anion-exchange mixed-mode sorbent for extraction of the selected acidic drugs (ketoprofen, KEP; naproxen, NAP; and ibuprofen, IBU), since the dendrimers contained both hydrocarbonaceous and amine functionalities. The effective parameters on extraction efficiency such as sample pH and volume, type and volume of eluent and wash solvents were optimized. Under the optimized experimental conditions, the DF-KIT-6 based SPE coupled with HPLC-UV method demonstrated good sensitivity (0.4–4.6 ng mL^{-1} detection of limits) and linearity ($R^2 > 0.990$ for 10–2000 ng mL^{-1} of KEP and IBU, and 1–200 ng mL^{-1} of NAP). The potential use of DF-KIT-6 sorbent for preconcentration and cleanup of acid drugs in human urine samples was also demonstrated. Satisfactory recoveries at two spiking levels (30 and 300 ng mL^{-1} for KEP and IBU, 3 and 30 ng mL^{-1} for NAP) were obtained in the range of 85.7–113.9% with RSD values below 9.3% ($n = 3$).

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1. Introduction

In drug discovery and development, drug quantification in biological samples is essential for understanding the mechanisms underlying their efficacy and toxicity [1,2]. Biological matrices such as blood, serum and urine are very complex and contain high levels of interferences. In addition, the analytes of interest can often exist at low concentrations (pg mL^{-1}–μg mL^{-1}). Despite the development of highly efficient analytical instrumentation, most instrumental methods cannot handle the complex matrix directly. Hence, sample preparation is crucial in drug analysis which includes both analyte preconcentration and cleanup [3–5]. Solid phase extraction (SPE) has become the most popular sample preparation technique of biological samples due to its high recovery, low solvent consumption and easy operation [6–8], and there has been an increasing trend in recent years towards greater selectivity or greater specificity.

Most drugs have either acidic (e.g., carboxylic acids) or basic (e.g., amines) properties [4,9]. For example, most non-steroidal anti-inflammatory drugs (NSAIDs) are acidic with pK_a values of 4.0–4.8, while most β-blockers and anti-depressants are basic with pK_a values in the range 7.4–9.9. Classical C18 SPE showed limited recovery of polar and ionic drugs because the retention was merely based on hydrophobic interaction [10,11]. To solve this problem, mixed-mode ion-exchange sorbents are specifically designed to interact with ionic species by combining an effective

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reversed-phase chemistry (e.g., C18 and divinyl benzene) with ion-exchange groups (e.g., amines for anion exchange and carboxylic acid for cation exchange) [12–16]. The benefit of ion-exchange capability is that high selectivity towards acid or basic compounds can be achieved by using a suitable pH combination in each SPE step [17,18]. Many manufacturers have introduced mixed-mode SPE cartridges that utilize polymer (such as Oasis MAX and Oasis MCX) and silica substrates (such as SampliQ Si SAX, Bond Elut Certify and Bakerbond Narc). These types of SPE sorbents have been proved to be highly effective for both reducing matrix impurities and preconcentrating the acid or basic drugs in wastewater, urine and plasma samples [19–23].

Silica-based SPE sorbents are still the most popular because they are rigid, easy to modify, and immune to shrinking and swelling in most organic solvents. However, traditional silica-based mixed-mode SPE sorbents often suffer from relatively low binding capacities [7]. Recently, there is increased interest in the development of new SPE sorbents based on mesoporous silica, such as Santa Barbara Amorphous-15 (SBA-15), Mobil Composite of Matter-41 (MCM-41) and Korea Advanced Institute of Science and Technology-6 (KIT-6) [24], owing to its special characteristics of uniform pore structure, high pore volume, and high surface area. The use of supramolecular surfactant aggregates as structure directing agents leads to mesoscopically ordered surfactant-silica composites during condensation, and mesoporosity can be induced by subsequent removal of the surfactant by extraction or calcinations [25]. A variety of functionalized mesoporous silica SPE sorbents have been explored for determination of heavy metal ions, steroid hormones, herbicides and organotin compounds [26–32]. In general, a common theme of these functionalization strategies was attachment of the organic moiety containing a single functional group. For hybrid materials to achieve their full potential, the ability to synthesize complex/multifunctional organic moieties on mesoporous silica would be highly desirable.

Dendrimers are a unique class of macromolecules having highly branched, three-dimensional architecture with high functionality. They have exhibited high capacities for encapsulating pollutants (e.g., heavy metals, polycyclic aromatic hydrocarbons and dyes) and drugs [33–35]. High loading of ibuprofen has been achieved with SBA-15 supported poly(propyleneimine) dendrimers with high-density amine functionalities [36]. Therefore, dendrimer functionalized mesoporous silica provides an effective route to producing highly efficient SPE sorbents by combing the advantages of dendrimers with the ease of separation of solid supports [37]. Moreover, a mesoporous silica support with larger pores is necessary to perform such functionalization to eliminate the possibility of pore blocking resulting from the development of dendrimers [38,39].

In a previous work [40], we developed a new dendrimer-modified silica multi-mode stationary phase that exhibited a reversed-phase/anion-exchange (RP/AEX) mixed mode retention mechanism for acid drugs. In the current paper, the same dendrimer derived from multistep organic syntheses has been prepared using ordered mesoporous silica as a solid-phase support. KIT-6 was chosen for this application due to its larger pore sizes and highly interconnected 3D cubic mesoporous structure as compared to other types of mesoporous silica. The dendrimer-functionalized KIT-6 (DF-KIT-6) sorbent was then evaluated under RP/AEX conditions for SPE of acid drugs. The three most often prescribed NSAIDs (ketoprofen, naproxen and ibuprofen) are selected as the model drugs, since they predominate in environmental and biological analyses [41–44]. Fig. S1 shows the molecular structures, pK_a and $\log K_{ow}$ values of all the analytes. The promising application of DF-KIT-6 to preconcentrate and clean up the three acid NSAIDs in human urine was also demonstrated.

2. Experimental

2.1. Chemicals and materials

The reagents for preparing the DF-KIT-6 sorbent were mainly as follows: tetraethoxysilane (TEOS, 98%), (3-aminopropyl)triethoxysilane (APTES, 98%), 1,4-butanedioldiglycidyl ether (BDDE, 98%) and aniline (99.5%) from J&K Scientific (Beijing, China), hydrochloric acid, 1-butanol and toluene from Beijing Chemical Works (Beijing, China), and Pluronic P123 [poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol), Mn ~5, 800] from Sigma–Aldrich (Milwaukee, WI, USA). The three NSAIDs tested involved ketoprofen (KEP, >98%) from Sigma–Aldrich, naproxen (NAP, >98%) from J&K Scientific, and ibuprofen (IBU, >98%) from Tokyo Chemical Industry Co. (Tokyo, Japan). HPLC-grade hexane (95% *n*-hexane) was obtained from J.T. Baker (Philipsburg, NJ, USA). HPLC-grade methanol and ethyl acetate (EtOAc) was supplied by Fisher Scientific (Fair Lawn, NJ, USA). The reagents used to prepare the buffers were all of analytical grade and obtained from Tianjin Kermel Chemical Reagent Co. (Tianjin, China), including disodium hydrogen phosphate, sodium dihydrogen phosphate, phosphoric acid (H_3PO_4, 85%) and sodium acetate, glacial acetic acid (HAc). The water used in all experiments was deionized (DI) water from a Milli-Q purification system (Billerica, MA, USA). All solutions used for HPLC were passed through a 0.22 μm nylon filter before use.

The empty polypropylene SPE tubes (3 mL) with polyethylene frits (20 μm porosity) were from Dalian Sipore (Dalian, China). Cleanert C18 (a hydrophobic silica-based sorbent, 500 mg/6 ml) SPE cartridge was provided by Agela Technologies (Tianjin, China).

2.2. Instrumentation

The pH of the buffer solutions and samples was adjusted with a Mettler Toledo MPC 227 Dual Purpose Conductivity/pH/T Meter (Columbus, OH, USA). Manual SPE was carried out on a Supelco Visiprep SPE vacuum manifold (Bellefonte, PA, USA). The chromatographic system was an Agilent 1200 series LC system (Santa Clara, CA, USA) equipped with a quaternary pump, an on-line degasser, an autosampler and a diode array detector (DAD).

2.3. Preparation of the DF-KIT-6 sorbent

KIT-6 silica was first synthesized using the method reported by Kleitz et al. [25]. In detail, 4.0 g of Pluronic P123 was dissolved in 144 g of deionized water and 7.73 g of concentrated HCl (37%) by vigorous stirring. After complete dissolution, 4.0 g of *n*-butanol was added at 35 °C. After stirring for 1 h, 8.6 g of TEOS was added to the homogeneous solution. The mixture was left under stirring for 24 h at 35 °C. Then the mixture was transferred into a PTFE-lined stainless steel autoclave, and heated statically at 130 °C for 24 h. The solid product obtained was filtered and washed with DI water. After drying at 100 °C, it was finally calcined at 550 °C for 3 h, and the temperature ramp rate was estimated to be ~20 °C/min. Then, 2 g of vacuum dried KIT-6 was aminated by reaction with 4 mL of APTES in 100 mL of dry toluene for 12 h at 110 °C under nitrogen atmosphere. The solid was filtered, washed in series with toluene, methanol and acetone, and air-dried.

The DF-KIT-6 material was prepared using a multistep procedure similar to that reported previously [40]. Briefly, the obtained amine-KIT-6 was stirred with BDDE in water (100 mL, 0.2 M) at 80 °C for 3 h. The solid was then filtered and washed thoroughly with water. Subsequently, the epoxy-terminated KIT-6 was reacted with aniline in methanol/H_2O (100 mL, 0.2 M) at 80 °C for 3 h. After filtration, the solid (denoted as G1-DF-KIT-6) was washed thoroughly with methanol and dried under vacuum. Repeating the

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