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A novel one-pot strategy to prepare β-cyclodextrin functionalized capillary monoliths for enantioseparation of basic drugs

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ABSTRACT

With native β-cyclodextrin (β-CD) added into the polymerization mixture directly, a novel, convenient and low-cost one-pot strategy was developed to prepare the β-CD functionalized organic polymer monolithic capillary column. Diazabicyclo[5.4.0]undec-7-ene (DBU) as a basic catalyst for the ring opening reaction between β-CD and glycidyl methacrylate (GMA) was introduced into the polymerization system for the first time. Thereby, two consecutive reactions namely the in situ methacrylation of β-CD and copolymerization reaction can be achieved in one pot. The preparation conditions including the type and composition of porogens , the ratio of functional monomer to crosslinker and amount of 2-acrylamido-2-methyl propane sulfonic acid (AMPS) were optimized. The specific surface area and morphology of the prepared monolith were characterized using scanning electron microscopy (SEM) and nitrogen adsorption analysis, respectively. Raman spectroscopy and nuclear magnetic resonance (NMR) spectroscopy confirmed that β-CD was covalently bonded onto the monolith successfully. Then, the monolithic column was applied to enantioseparation of six basic drugs in capillary electrochromatography (CEC). Under the optimal conditions, tropicamide, homatropine, homatropine methylbromide, brompheniramine, chlorpheniramine and clorprenaline were all totally separated with the resolution (Rs) values of 2.84, 4.70, 4.61, 3.01, 2.57 and 2.33, respectively. Furthermore, the column demonstrated satisfactory stability and repeatability of retention time and enantioselectivity using homatropine as model analyte.

1. Introduction

In the past decades, monolithic materials as the ideal chromatographic stationary phases have attracted considerable attention in the separation fields. In comparison to traditionally packed columns, the main advantages of monolithic column are faster mass transfer, higher permeability and modifiable pore size [1]. Moreover, it eliminated most of the problems associated with in-situ frit formation and particle packing [2,3]. Meanwhile, the monolithic column show satisfactory selectivity and loading capacity superior to that of open tubular columns [4].

For enantiomeric separation, cyclodextrin (CD) and its derivatives as one of the most widely used chiral selectors [5,6] were introduced into the monolithic column by Koide et al. as early as 1998 [7]. Since then, great efforts have been devoted to developing more efficient, simple and stable preparation methods. Usually, CDs can be immobilized on the monoliths by chemical bonding or physical coating. The chemical bonding is the preferred methodology because the resulting monolith have higher stability and longer life time. So far, CDs were covalently bonded onto monoliths mainly via a triazole linkage, an amino linkage or an ether linkage [8].

In case of triazole linkages [9–12] and amino linkages [13–16], most of CDs functionalized monoliths were used for the enantioseparation of acidic and neutral analytes. For example, Guerrouache and coworkers grafted a 6-azido-6-deoxy-β-CD on the surface of the monolith through the click reaction [9]. The enantioselectivity of this monolithic column was evaluated using flavanon as the model analyte. A similar monolithic column prepared by one-step copolymerization strategy showed a partial separation toward 4-bromomandelic acid [11]. By using the amino linkage, a monolith grafted with a 4-dimethylamino-1,8-naphthalimde-β-CD derivative was prepared and baseline separations of racemic naproxen and ibuprofen were obtained on this monolithic column [13]. Additionally, Zhang et al. synthesized a poly(GMA-ethylenediamine-β-CD-*co*-EDMA) monolithic column by one-pot copolymerization strategy and the column was applied to the enantioseparation of chiral acidic compounds [16].

Also some papers reported the ether as linkage for immobilization of CDs onto the monolith [17–22]. Differently, these columns could also serve as good chiral stationary phase for resolving basic analytes. A representative example was reported by Gu and Shamsi [18]. In this

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method, a monolith was successfully synthesized by classic one-step copolymerization strategy in the presence of glycidyl methacrylate bonded β-CD as functional monomer and the resulting monolith showed moderate enantioresolution values for the tested analytes. Likewise, the post modification strategy was reported for the preparation of the β-CD functionalized monolith with the ether as linkage [20,22]. Commercial-available β-CD or hydroxypropyl-β-CD were immobilized onto the epoxy activated surface of the monoliths under harsh reaction conditions. The resulting monoliths showed enantioselectivity toward several amino acids.

Even though many methods were developed for anchoring CDs onto the monolith so far, the preparation of the CDs bonded monolith is still not an easy task. The post modification strategy is tedious and difficult to control [23]. Therefore, more studies were dedicated to the development of the direct polymerization strategy including classic one-step strategy and one-pot strategy. In particular, one-pot strategy has considerable prospects due to its merits of excellent column performance and simple preparation procedures [23]. Nevertheless, the applications of reported direct polymerization strategies are still limited, because compounds as functional monomer have to contain special anchoring groups like the vinyl group [15,25], methacrylate group [11,12,18,19] or amino group [16,23,24] in the polymerization system. It is known to us that β-CD derivatives which can be used as functional monomer are very expensive compared to native β-CD and most of them are not available in commercial market. Synthesis and characterization of the β-CD modified functional monomers are time-consuming and require a lot of experiences.

In this study, we introduced a catalyst into the polymerization system for the first time. The hydroxyl groups of β-CD were activated by the facile catalyst (Diazabicyclo[5.4.0]undec-7-ene), which made it possible to achieve fast methacrylation of native β-CD and the subsequent copolymerization in one pot. From easy-obtained and low-cost raw materials to the final monolithic column, the entire process needed less than 24 h only. The prepared monolith was successfully used for the enantioseparation of six basic drugs in capillary electrochromatography (CEC).

2. Experimental

2.1. Chemicals and reagents

β-cyclodextrin (β-CD), tris(hydroxymethyl)aminomethane (Tris) and ammonium acetate (NH_4OAc) were obtained from TianJin Bodi Chemical Holding (Tianjin, China). β-CD is dried under vacuum at 110 °C for 12 h to remove any moisture. Glycidyl methacrylate (GMA), ethylene dimethacrylate (EDMA), 2,2′-azobis(2-methylpropionitrile) (AIBN), γ-methacryloxy propyltrimethoxysilane (γ-MAPS), 2-acrylamido-2-methyl propane sulfonic acid (AMPS) and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) were obtained from Tokyo Chemical Industry (Tokyo, Japan). Sodium hydroxide, n-propanol (POH), 1,4-butylene glycol (BOH), hydrochloric acid, acetone of analytical grade and acetonitrile (ACN), glacial acetic acid of HPLC grade were purchased from Shandong Yuwang industrial Co., Ltd (Shandong, China). Anhydrous dimethyl sulfoxide (DMSO) were purchased from Aladdin Bio-Chem Technology Co., LTD (Shanghai, China). Water used throughout all experiments was doubly distilled and purified by a Milli-Q system (Millipore, Bedford, MA, USA). Tropicamide, homatropine Hydrobromide, chlorphenamine maleate and clorprenaline hydrochloride were obtained from National Institutes for Food and Drug Control. Brompheniramine maleate and homatropine methylbromide were purchased from Sigma-Aldrich (St. Louis, MO, USA). The structures of pharmaceutical racemates are shown in Fig. 1.

2.2. Apparatus

All CEC experiments were performed on a CE apparatus (CL1030, Beijing huayanglimin instrument Co., Ltd, Beijing, China). A syringe pump (SPLab04, Shenchen Precision Pump Co., Ltd, Baoding, China) was used to pump liquid through fused-silica capillaries. An HPLC pump (PU-1580, Jasco corporation, Japan) was used to flush monolithic columns with mobile phase for conditioning. The fused-silica capillaries (375 μm o.d. × 75 μm i.d.) were purchased from Ruifeng Chromatography Ltd. (Yongnian, Hebei, China). A microwave-ultrasound combined reactor (XH-300A, Beijing Xianghu Technology Co., Ltd.) provided continuous and homogeneous ultrasound and microwave irradiations. Morphological characterizations of monoliths were taken with a Hitachi S4800 scanning electron microscope (Hitachi, Ltd., Japan) after a gold coating of the samples. Microscopic pictures were taken with an Olympus microscope (BX60, Olympus, Germany). Raman spectra of monolithic materials (confined within capillary support) were obtained with a HORIBA labRAM HR Evolution raman spectrometer (Horiba Group, Japan) equipped with an Olympus objective LMPLAN FLN 50/0.5 and a double-frequency Nd: YAG laser (532 nm). The specific surface area was examined by nitrogen adsorption experiment on a Micromeritics TriStar II Plus apparatus (Micromeritics Instrument Ltd, USA). Nuclear magnetic resonance (NMR) spectroscopy was obtained with a Bruker Ultrashield Plus 600 MHz spectrometer (Bruker Corporation, Switherland).

2.3. Electrochromatographic conditions

The mobile phases were a mixture of water and acetonitrile containing 30 mM Tris and 5 mM NH_4OAc. The pH values of the mobile phases were adjusted by glacial acetic acid. UV detection wavelength was set at 214 nm for homatropine, clorprenaline and homatropine methylbromide, and 254 nm for clorpheniramine, brompheniramine and tropicamide, respectively. The analyte solutions were injected using a voltage of + 3 kV for 3 s. Mobile phases and the analyte solutions were filtered by 0.22 μm millipore filter before use.

2.4. Preparation of poly(GMA-β-CD-co-EDMA) monolithic columns

As illustrated in Fig. 2, the one-pot copolymerization approach was employed for the preparation of the β-CD functionalized organic polymer monolith. Prior to the polymerization, the inner wall of the 50-cm-long capillary was vinylized with γ-MAPS as reported in the literature [19]. The polymerization solution was prepared using the following procedures: (1) GMA (22 mg), DBU (6 mg), β-CD (60 mg) and DMSO (0.15 g) were accurately weighted into a 3-ml vial (2) The vial was placed into a DMSO bath at 100 °C for 30 min with ultrasound (300 W, 25 kHz) and microwave irradiations (500 W); (3) EDMA (0.024 g), POH (0.15 g), BOH (0.1 g), AMPS (7.5 mg) and AIBN (2.5 mg) were added into the same vial; (4) The resulting mixture was sonicated at around 15 °C for 15 min and then bubbled with nitrogen for 5 min. Subsequently, the pretreated capillary was filled with the prepared polymerization solution to a length of 30 cm, sealed with rubber stoppers and then submerged into a pre-adjusted water bath at 60 °C for 20 h. After the polymerization was completed, the capillary was rinsed with acetonitrile by an external HPLC pump to remove porogens and unreacted chemicals. Finally, the detection window was created at a 10-cm distance from the outlet end.

3. Results and discussion

3.1. Optimization of preparation conditions

The major advantage of our strategy is its simplicity for straightforward preparation of the chiral monolithic column by using the native β-CD. The method described herein process the in situ methacrylation of native β-CD and the subsequent copolymerization in one pot. Fig. 2 illustrates two consecutive reactions: (1) the ring opening reaction between the hydroxyl groups of β-CD and the epoxy groups of GMA