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Periodic mesoporous organosilica materials as sorbents for solid-phase extraction of drugs prior to simultaneous enantiomeric separation by capillary electrophoresis

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ABSTRACT

Two novel periodic mesoporous organosilica materials were synthesized with a neutral phenylene-bridged ligand, 1,4-bis(trimethoxysilylethyl)benzene, one of them using tetraethyl orthosilicate as additional silica source (PMO-TMSEB-1 and PMO-TMSEB-2). A third material was also synthesized with 1,4-bis(triethoxysilyl)benzene ligand (PMO-TESB-1) which use has scarcely been reported. The three materials were evaluated as solid-phase extraction (SPE) sorbents for the off-line extraction of a mixture of seven drugs of different nature (duloxetine, terbutaline, econazole, propranolol, verapamil, metoprolol, and betaxolol) from water samples. Subsequent simultaneous enantiomeric analysis by CE, using sulfated-β-cyclodextrin (2% w/v) dissolved in a 25 mM phosphate buffer (pH 3.0) and a voltage of −20 kV (negative polarity) was carried out. Enantiomeric resolutions ranging from 2.4 to 8.5 were obtained in an analysis time of 16 min. After optimization of SPE parameters, it was shown that using just 100 mg of PMO-TESB-1 as sorbent, a preconcentration factor of 400 with 200 mL solution was achieved, allowing recoveries between 80.5 and 103.1% (except for terbutaline), with good repeatability (% RSD = 2–8 %, n = 5). Analytical characteristics of the method were evaluated in terms of precision, linearity and accuracy with method quantitation limits between 5.6 and 21.9 μg/L. The developed method was applied to the analysis of spiked wastewater samples collected in different treatment plants, with recoveries between 73.9 and 102.9% except for econazole with recovery values ranging between 58.5 and 72.4%.

1. Introduction

Nowadays, more than 60% of commonly used pharmaceuticals are chiral [1]. These chiral drugs tend to exhibit different therapeutic activity depending on the enantiomer in an order of 50- to 500-fold effect [2] but also different toxicities [3]. This fact together with their ubiquitous presence in waters and other environmental samples make necessary to develop adequate analytical methodologies to individually analyse the enantiomers of a chiral drug in these samples enabling the correct assessment of their toxicity. Moreover, selective sorption, microbial degradation, and biologically catalysed chiral inversion can originate an enantiomer enrichment [3]. Although legal limits are not established for pharmaceuticals in waters [4], uncertainties in risk assessment of chiral pharmaceuticals as emerging environmental pollutants should be minimized [3].

Among the different analytical techniques enabling chiral separations (HPLC, GC, SFC, CE), CE has widely been employed to carry out the enantiomeric separation of many drugs due to its inherent advantages such as versatility and low volume of reagents and samples needed. Among the different chiral selectors employed in CE (cyclodextrins (CDs), proteins, surfactants, antibiotics, polysaccharides, etc.), CDs are the most widely used [5,6]. Pharmaceuticals

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are found in waters at concentrations generally ranging from ng to μg per liter [3,7], so that it is usually necessary to use a preconcentration technique, such as solid-phase extraction (SPE), prior to their analysis. SPE involves the use of adsorbing targets onto a solid support and it has been widely used to clean samples and to extract different types of analytes [8,9].

A family of mesoporous materials called PMOs (periodic mesoporous organosilicas) was reported for the first time in 1999 [10]. These PMOs are organic-inorganic hybrid materials that combine the properties of the organic functionality and the chemical stability of the inorganic silica and some other desirable characteristics like great surface area and ordered and narrow pores distribution [11]. Generally, PMOs are synthesized by the sol–gel method, using bridged organosilane precursors of the type $(R'O)_3Si\text{-}R\text{-}Si(R'O)_3$, as Si source and at the same time as organic moiety in which R is the organic functional group, and a directing agent [12]. In contrast to other modified mesoporous silicas, PMOs incorporate the organic functionalities directly into the silica framework, as molecular bridging ligands. This aspect allows higher degrees of organic functionality and improves the chemical and thermal properties of the materials. Moreover, the problems of channel blockage or diffusion of analytes are reduced in comparison with other mesoporous materials functionalized with the post-synthesis method [13]. On the other hand, PMOs can be modified or tuned with different organic moieties (such as methylene, ethylene, ethenylene, phenylene) and other more complex functionalities like thiol, metal complexes, chiral groups, ionic entities or disulfide groups [14,15]. These organic functionalizations allow the modification and optimization of their hydrophobic/hydrophilic behavior [16] or the ability to form metal complexes, among others [15]. All these properties stated above confer to these materials a great variety of applications such as catalysis, drug delivery, sensing, preparation of stationary phases for chromatography, etc, [17,18]. Moreover, PMOs were employed for adsorption of different analytes (drugs, mercury, lead, cupper) [18–22], the extraction of peptides and proteins [23,24], and to be anchored into the fiber in SPME of PAHs [25].

In this article, a simple method of synthesis, with only one step, is described for the preparation of two new PMOs using 1,4-bis(trimethoxysilylethyl)benzene (TMSEB) bridges as silica source, one of them with tetraethylorthosilicate (TEOS) as an additional silica source. A third PMO material was also prepared with 1,4-bis(triethoxysilyl)benzene (TESB) as ligand (Fig. S1 in Supplementary material). All the materials have been thoroughly characterized and evaluated as SPE sorbents for the extraction of seven drugs with different pharmacological activity ((*R,S*)-duloxetine (antidepressant), (*R,S*)-terbutaline (bronchodilator), (*R,S*)-econazole (antifungal), (*R,S*)-propranolol (antihypertensive), (*R,S*)-verapamil (antihypertensive, angina pectoris, arrhythmia, headache, vasodilator), (*R,S*)-metoprolol tartrate (antihypertensive, acute myocardial infarction), and (*R,S*)-betaxolol (antihypertensive)) from water samples prior to their simultaneous enantiomeric separation by CE. The effect of the combination of two silica sources to obtain mesoporous materials and of the presence of an alkyl chain join to the benzene ring on the performance of the synthesized materials as SPE sorbents was also investigated.

2. Materials and methods

2.1. Reagents and samples

Poly(ethylene glycol) (EO20PO70EO20, Pluronic 123), cetyltrimethylammonium bromide (CTAB) 98% and TEOS 98%, were purchased from Sigma-Aldrich (St. Louis, MO, USA). TESB 95% and TMSEB 85% were obtained from Gelest (Morrisville, PA 19067, USA). Ortophosphoric acid 85%, sodium hydroxide (NaOH), sulfated-β-CD (S-β-CD, DS 7-11), succinyl-β-CD (Suc-β-CD, DS 3.5) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Hydrochloric acid (HCl) 37%, dimethyl sulfoxide (DMSO), acetonitrile (ACN), methanol (MeOH), ethanol (EtOH) 99.5% and ethyl acetate (EtOAc) were obtained from Scharlau Chemie (Barcelona, Spain). The employed water was Milli-Q quality (Millipore, Bedford, MA, USA). Hydroxypropyl-β-CD (HP-β-CD, degree of substitution (DS) 0.6), hydroxypropyl-γ-CD (HP-γ-CD, DS 3.2), acetyl-β-CD (Ac-β-CD, DS 7), sulfated-γ-CD (S-γ-CD, DS 14), hydroxypropyl-buten-β-CD (HP-B-β-CD, DS not reported) and succinyl-γ-CD (Suc-γ-CD, DS 3.5) were purchased in Cyclolab (Budapest, Hungary).

Standard compounds with high purity (>99%) were purchased: (*R,S*)-duloxetine HCl from IS Chemical Technology (Shanghai, China), (*R,S*)-terbutaline, (*R,S*)-econazole, (*R,S*)-propranolol, and (*R,S*)-verapamil from Sigma-Aldrich; (*R,S*)-metoprolol tartrate from Astra (Hässleholm, Sweden) and (*R,S*)-betaxolol from Sanofi (Paris, France).

Influent and effluent wastewater samples analyzed in this work were collected from wastewater treatment plants located in different regions of Spain. Standard sampling method was employed. Wastewater samples were taken after primary (influent) and secondary (effluent) treatments. Pre-cleaned sampling glass vessels and automatic samplers (one sample per h) were used to collect 24 h composite, proportional to flow. Collected samples we transported to the laboratory on ice and in the dark. Wastewater sample 1 (influent, pH 7.3) and wastewater sample 2 (effluent, pH 7.6) were obtained in Sevilla. Wastewater sample 3 (effluent, pH 9.0) was collected in Guadalajara.

2.2. Preparation of stock and sample solutions

Stock standard solutions were prepared in MeOH, except for duloxetine that was prepared in DMSO, and then diluting with Milli-Q water until desired concentration, and were stored at 4 °C. All working solutions were filtered through a 0.45 μm pore size nylon filter membrane before analysis. In the drug mixture, terbutaline and econazole were analyzed at a racemic concentration of 20 mg/L, and the rest of drugs at 10 mg/L.

Wastewater samples were filtered firstly through a Whatman filter paper grade 44/50 followed by a 0.45 μm nylon filter and stored in glass bottles at 4 °C before being analyzed.

2.3. Synthesis of periodic mesoporous organosilicas

For the synthesis of the PMO materials, chemicals were added in a molar ratio as follows: 1 (ligand): 0.05 Pluronic 123: 0.15 CTAB: 7.14 HCl: 56.4 EtOH: 1471.4 H_2O: 5 TEOS (if required). For the synthesis of the organosilica with TESB as silica source (denoted PMO-TESB-1), 7 g of Pluronic 123 and 1.2 g of CTAB were dissolved in a solution formed by mixing 80 mL of 2 M HCl, 591 mL H_2O and 73 mL EtOH. After 1 h of stirring, 8.85 mL of the ligand TESB was added with a dropwise and stirring for 1 h. In the case of the synthesis of the PMOs employing TMSEB as organic ligand two materials were prepared, one of them using TMSEB as unique silica source (denoted PMO-TMSEB-1) and the other one with TMSEB and TEOS as silica sources (denoted PMO-TMSEB-2). To obtain the PMO-TMSEB-1 material, 5.9 g of Pluronic 123 and 1 g of CTAB were dissolved in a solution formed by mixing 67 mL of 2 M HCl, 500 mL H_2O and 62 mL EtOH and, after stirring for 1 h, 6.55 mL of the ligand TMSEB was added dropwise. To obtain the PMO-TMSEB-2 material, 2.1 g of Pluronic 123 and 0.4 g of CTAB were dissolved in a solution formed by mixing 25 mL of 2 M HCl, 182 mL H_2O and 23 mL EtOH. After stirring for 1 h, a mixture of 7.7 mL of TEOS and 2.8 mL of TMSEB (with a molar ratio 5:1) were added with droplet system.

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