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Research Paper

Co-assembly of exfoliated Mg/Al layered double hydroxides nanosheets with sulfobutyl ether-β-cyclodextrin for enantioseparation of racemic propranolol

Fawei Zhu, Lumin Wang, Sen Liao, Yuqiu Zhu, Wen Luo, Xueqian Huang, Feipeng Jiao*, Xiaoqing Chen*

School of Chemistry and Chemical Engineering, Central South University, Changsha 410083, People's Republic of China

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ABSTRACT

Co-assembly of exfoliated Mg/Al layered double hydroxide (Mg/Al-NO_3-LDH) nanosheets with sulfobutyl ether-β-cyclodextrin (SBE-β-CD) via swelling/restoration method was presented in this paper. SBE-β-CD located in the form of flat-lying intertwined bilayer arrangement in the interlayer region. The structural and characteristic features of the supramolecular products as prepared were studied by XRD, FT-IR, UV–vis DRS and TGA. The as-proposed SBE-β-CD-LDH materials were applied to recognize clinical medicine propranolol enantiomers (*R*,*S*-PPL). Series studies were carried out to address various experimental parameters including contact time, pH value and operational temperature, concentrations of *R*,*S*-PPL. The experimental results indicated that SBE-β-CD-LDH could tend to adsorb *R*-PPL and the *e.e.*% value of single separation was 17.4% under optimal experimental conditions. The special spatial structure of SBE-β-CD-LDH might play a key role to achieve the enantioseparation of racemic PPL. According to the kinetic studies, the separation of PPL enantiomers had been well described by pseudo-second-order kinetic model. The adsorption isotherms indicated that the adsorption data fitted the Freundlich isotherm equation well. The thermodynamic parameters indicated that the adsorption process was a spontaneous and endothermic chemisorption process.

1. Introduction

Chirality was one of the basic characteristics of biological systems. However, different chiral configurations of drugs frequently tended to exhibit their stereo-selectivity and differentiated pharmacological and toxicological properties in biological process, containing transport, metabolism and the combination with receptor targets (Liu et al. 2015; Nguyen et al. 2006). *R*,*S*-PPL (Fig. 1) was a kind of β-adrenergic blocker for clinical medicine which was widely used to treat arrhythmias, angina, and hypertension(Kagami et al. 2013; Pacanowski et al. 2008). Relevant researches showed that the diversity of pharmacological activity between the two PPL enantiomers was 98 times (Veloo and Koomen 1993). Therefore, it was of great economic benefits and pharmacological research values to obtain the single chiral configuration of *R*,*S*-PPL.

Recently, the adsorption separation technology had been paid more and more attention because of its advantages of economical operation, versatility and potential reproducibility (Anastassiades et al. 2003; Fan et al. 2016). For the adsorption separation technology, the properties of adsorbent materials play a decisive role, and these adsorbent materials tended to have a large specific surface area, good stability, modifiable structure and easy preparation (Baggiani et al. 2001; Carpinteiro et al. 2012; Chianella et al. 2003). Layered double hydroxides was a kind of two-dimensional layered anionic clay materials with the above mentioned advantages and widely used as adsorbents, drug sustained release and catalysts depended on its characteristic physical and chemical properties (Chakraborty et al. 2013; Siti Nurasikin et al. 2014; Yang et al. 2015). Basal layer of LDH possesses a large amount of positive charges. Besides, the various anions could be fixed between LDH layer board by means of anion-exchange adsorption, especially potentially functional organic anions, which broadened the application prospect of LDH. In addition, when the organic anionic molecules inserted into the basal layer of LDH could cause the changes of layer spacing which provided a good identification space for lots of potential interaction processes. In particular, these materials could be applied in the field of chiral separation when the organic anions with optical activity enter into the interlayer space which created a chiral environment in the interlayer space (Liu and Meng 2013; Liu et al. 2009).

In recent years, many of functionalized LDH which intercalated with the biological molecules and organic macromolecular organic macromolecular, such as cyclodextrins, carboxymethyl cellulose, myoglobin, bovine serum albumin, polyacrylamide, etc., were prepared by

* Corresponding authors.
E-mail addresses: jiaofp@163.com (F. Jiao), xqchen@csu.edu.cn (X. Chen).

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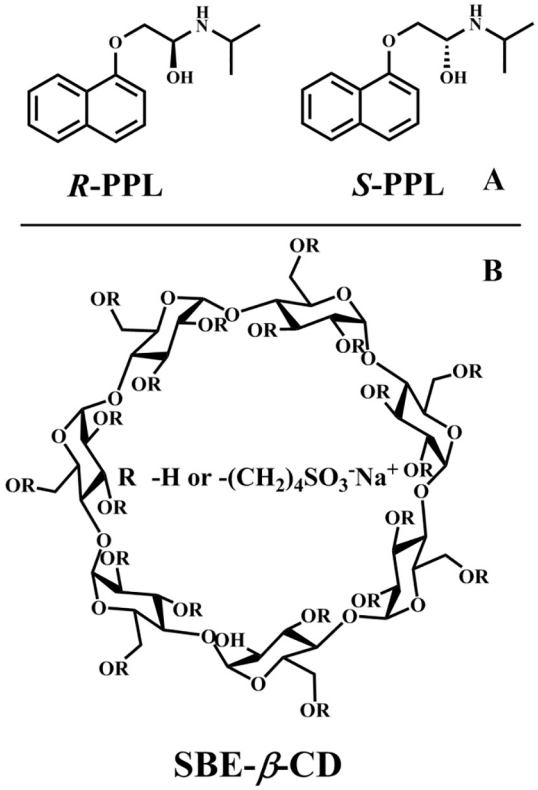

Fig. 1. The structures of *R,S*-PPL (A) and SBE-*β*-CD (B).

swelling/restoration method (Bellezza et al. 2012; Fu et al. 2010; Kang et al. 2009). This method could effectively eliminate the resistance when the object inserted into LDH layer, and the object molecule could entirely contact with the inner surface of the LDH layer which would improve the efficiency of the object molecules and increase the amount of object molecules in the interlayer of LDH(Liu and Meng 2013; Liu et al. 2007; Wu et al. 2013).

Cyclodextrins (CD) and their derivatives had been proven to have good chiral recognition properties for the chiral molecules possessed naphthalene rings, double or poly-substituted benzene rings. Among them, the chiral recognition ability of SBE-*β*-CD was stronger than that of other CD derivatives, because the presence of sulfur-butyl groups increased its hydrophobic cavity in the structure of SBE-*β*-CD (Wang et al. 2015b; Wang et al. 2016). Existing research often focused on as drug release carrier and used in the investigation of chiral separation were often limited to separate simple structure of molecules. The research of cyclodextrin and its derivatives intercalated LDH were rarely involved (Hu et al. 2016; Li et al. 2014).

In this paper, co-assembly of Mg/Al-NO_3-LDH nanosheets with SBE-*β*-CD was presented by swelling/restoration method. The investigation of the chiral adsorption ability of Mg/Al-SBE-*β*-CD-LDH for clinical *R,S*-PPL was carried out elaborately. The results showed that the chiral specific identification and separation process of PPL enantiomers could be achieved between the LDH layer with chiral space environment.

2. Experimental

2.1. Materials

Sulfobutyl ether-*β*-cyclodextrin (SBE-*β*-CD) (average degree of sulfobutyl ether substitution of 6.5) was purchased from Shandong Binzhou Zhiyuan Biological Technology Co., Ltd. (China). *R,S*-PPL was purchased from Alfa Aesar Co., Ltd. (Shanghai, China). Mg$(NO_3)_2{\cdot}6H_2O$, A1$(NO_3)_3{\cdot}9H_2O$, NaOH, NH_4COOH CH_3COOH with a purity > 99.0% were obtained from Bodi Chem. CO. LTD. (Tianjing, China). 2-propanol was supplied by Tianjin Hengxing Chemical Preparation Co., Ltd. (Tianjing, China). Organic solvent for chromatographic analysis was of HPLC grade. All other chemicals were of analytical-regent grade and water was deionized and bi-distilled.

2.2. Characterization of the composites

The phase identification and crystal structure of Mg/Al-NO_3-LDH and SBE-*β*-CD-LDH composites were measured by powder X-ray diffractometer (p-XRD, Bruker D8) using Cu/Kα radiation (λ = 1.5406 Å, 40 KV, 40 mA). The morphology and microscopy of the products were checked by scanning electron microscopy (SEM, TESCAN MIRA3 LMU) and transmission electron microscope (FEI-Tecnai G2 TF20 200 KV). The FT-IR spectra were recorded at room temperature on Nicolet iS10 spectrometer by the standard KBr disk method. The UV–vis diffused reflectance spectra (UV–vis DRS) of the sample powers were investigated by a UV–vis spectrophotometer (Shimadzu 2401 spectrophotometer). The thermogravimetric analysis (TGA) was recorded on the NETZSCH instrument STA449F3 in the temperature range of 30–700 °C with a heating rate of 10∘C/min in air atmosphere. The organic elemental analysis (EA) was recorded on the elementar instrument Vario EL III with operating mode: CHNS.

2.3. Analytical method

The concentration of *R,S*-PPL in the aqueous phase was recorded on Dionex UltiMate 3000 HPLC equipped with a DAD-3000 multiple wavelength detector (Thermo Fisher, MA USA) at the wavelength of 290 nm. The column was CHIRALPAK AGP, 5 μm particle size of the packing material, 100 mm × 4.6 mm I.D. (Daicel CHIRAL TECHNOLOGIES Co. Ltd., Japan). The pH of the mobile phase was maintained at 4.5 adjusted by NH_4COOH and CH_3COOH buffer solution. After equilibration, the mobile phase comprised water and methanol (98,2, *v*/v) containing NH_4COOH/CH_3COOH buffer solution (20 mmol/L) at a flow rate of 0.8 mL/min and the column temperature was 25 °C. The sample solution was filtered through a 0.45 μm membrane. All the experiments were performed under the same condition in triplicate and the data were obtained by averaged results of three experiment.

2.4. Synthesis of Mg/Al-NO_3-LDH

The precursor Mg/Al-NO_3-LDH was synthesized by a procedure similar to our previous work (Jiao et al. 2013). In brief, 50 mmol of Mg$(NO_3)_2$ and 25 mmol of Al$(NO_3)_3$ were put into a two-necked flask (1000 mL), dissolved in 500 mL of deionized water and equipped with a constant pressure funnel containing 2.0 mol/L NaOH solution. Then, NaOH solution was added into the mixed salt solution by dropwise under nitrogen protection until the pH value of mixed solution became 8. The obtained precipitate was stored under nitrogen protection at 80 °C in a thermostatic bath for 12 h. The product was centrifuged, washed thoroughly with deionized water until neutral pH and dried at 80 °C overnight, ultimately.

2.5. Synthesis of Mg/Al-NO_3-LDH nanosheets and SBE-β-CD-LDH

The SBE-*β*-CD-LDH was synthesized using the swelling/restoration method acccording to a previous literature (Li et al. 2014). Mg/Al-NO_3-LDH (1.0 g) was mixed with 400 mL of formamide and agitated vigorously in a mechanical shaker for 24 h, and then mixtures were supersonicated for 2 h. Eventually, the solution presented transparent colloidal suspension for the following experiments. The Tyndall light scattering indicates Mg/Al-NO_3-LDH nanosheets were successfully spun off (Fig. S1, Supporting information, SI). After that, 5 g SBE-*β*-CD was mixed in the prepared colloidal suspension of the LDH under nitrogen protection for 12 h with a slowly stirring. The white solid slurries were centrifuged and washed several times with ethanol and deionized