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Research paper

Intracrystalline structure and release pattern of ferulic acid intercalated into layered double hydroxide through various synthesis routes

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ABSTRACT

We intercalated ferulic acid (FA) molecules into a layered double hydroxides (LDHs) via three different synthesis routes—ion-exchange, exfoliation-reassembly, and reconstruction—to obtain FA-LDH nanohybrids. All the nanohybrids started from same MgAl-CO_3-LDH pristine, with a homogeneous particle size of 80 nm, in order to control particle size of final products. According to infrared spectroscopy, all the synthesis routes resulted in successful hybridization between anionic ferulate and positive LDH layers. X-ray diffraction, UV–Vis spectroscopy and thermal analyses showed that the FA molecules were arranged in a zig-zag manner to maximize π-π interactions among them. From scanning electron microscopy, it was revealed that reconstruction gave rise to structural re-organization of LDH layers resulting in a house-of-cards morphology in the nanohybrid, while other methods produced a hexagonal plate-like shape. It seems that FA moieties intercalated by a reconstruction method could be accommodated in the inter-particle cavity as well as the interlayer space in FA-LDH nanohybrids. We investigated time-dependent FA release profiles from each nanohybrid in deionized water and saline. The release patterns and kinetic model fitting results revealed that the release behavior was different each nanohybrid according to the synthesis method and followed Elovich and power function models.

1. Introduction

Layered double hydroxides (LDHs) have recently received a surge of interest as delivery nanocarriers due to their high biocompatibility, anionic drug capacity, and enhanced cellular permeation properties (Choy et al., 2004, 2007; Oh et al., 2006b; Choi et al., 2007, 2014; Kim et al., 2012). LDH is denoted as chemical formula $M(II)_xM(III)_{1-x}(OH)_2(A^{n-})_{x/n} \cdot mH_2O$ (M(II): divalent metal cation, M(III): trivalent metal cation, A^{n-}: anionic species, $0.2 < x < 0.4$) and consists of positively charged layers and exchangeable interlayer anions (Cavani et al., 1991; Rives, 2001). The ability for anion exchange allows LDHs to accommodate various biologically active anionic molecules, such as nucleotides, anticancer drugs, antibiotics, antioxidants, and vitamins (Choy et al., 1999; Yang et al., 2003; Choy and Son, 2004; Oh et al., 2006c; Aisawa et al., 2007; Trikeriotis and Ghanotakis, 2007; Kong et al., 2010a; Kim et al., 2012). LDH layers having biological inertness and positive charge have been reported to effectively stabilize vulnerable bioactive substances as well as deliver them into intracellular systems (Oh et al., 2006a,b), and thus LDHs hold great potential for drug delivery applications. Furthermore, LDHs, as delivery carriers, are capable of controlling release of payloads due to their ion exchange property and periodic molecular arrangement of incorporated moieties within two-dimensional interlayer space. The progress toward an LDH-based controlled release system for various bioactive molecules has been reviewed recently (Rives et al., 2014).

Among various anionic bioactive molecules, intercalation of phenolic acids such as cinnamic acid, ferulic acid, and caffeic acid, into LDH has attracted interest (Kong et al., 2010a; Biswick et al., 2011; Kim et al., 2013). Stabilization and controlled release of phenolic acids by LDH enable applications in cosmetics, drugs and functional food additives by utilizing ultraviolet absorption and antioxidant properties of phenolic acids. In particular, several reports have demonstrated intercalation of ferulic acids (FAs) into the interlayer space of LDH (Costantino et al., 2009) and investigated their possible interlayer orientation and release profiles (Rossi et al., 2005) with respect to temperature and pH (Schoubben et al., 2006).

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A number of LDH-based bioactive molecule loading routes have been developed, such as coprecipitation, ion-exchange, exfoliation-reassembly, and reconstruction (Rives, 2001; Oh et al., 2006c, 2012). In coprecipitation, a solution containing bioactive molecules and cationic precursors is titrated with base to simultaneously form drug intercalated LDH (Oh et al., 2012). For ion-exchange reaction, LDH containing easily exchangeable anions, such as nitrate, is first synthesized and target anions are then intercalated through a concentration gradient (Choy et al., 1999; Millange et al., 2000). In the exfoliation-reassembly reaction, LDH layers are delaminated into a single sheet or a few sheets by treatment in formamide, and the layers are restacked by reacting with appropriate anionic species (Wu et al., 2005). In the reconstruction reaction, LDH first undergoes a calcination process, yielding a MgAl-based metal oxide $Mg_{1-x}Al_xO_{1+0.5x}$. The calcined LDH spontaneously recovers the original structure of LDH in the presence of anionic molecules and water molecules (Pan et al., 2010).

Both host LDH and guest anionic species undergo characteristic environmental changes depending on loading methods, resulting in different interlayer orientations of guest molecules and crystallinity (Aisawa et al., 2007; Xing et al., 2007; Arco et al., 2010; Huang et al., 2012; Seftel et al., 2013). In some cases, the loading method determines the final morphology or hierarchical structure of LDH-based hybrids. For example, DNA incorporation into LDH via ion-exchange led to layer-by-layer structures (Choy et al., 1999), while exfoliation-reassembly resulted in a core–shell structure (Park et al., 2010). Thus, it is conceivable that different synthesis routes would result in different interlayer molecular arrangements, morphology, and release properties. It was reported that drug molecules stabilized in between LDH layers by either coprecipitation or ion-exchange were released through an initial burst followed by sustained release through intraparticle diffusion (Silion et al., 2012). Wang et al. (2009) reported that an amoxicillin-LDH nanohybrid obtained by reconstruction exhibited an initial bursting effect due to the surface-adsorbed moieties. Yang et al. (2007) compared drug release patterns of indole-3-acetic acid intercalated by coprecipitation and ion exchange, respectively, and reported that there was no significant difference in drug release according to the loading method. However, Zhenlan et al. (2009) reported that interlayer spacing and loading amount of bactericide in LDH were affected by loading method, and, consequently, the release amount and kinetic constant were influenced by the synthesis method. Similar results that synthesis method affected both interlayer spacing and release pattern were recently reported by Barahie et al. (2013). Despite that there have been a number of prior studies that examined loading method, structure and release profiles, to our knowledge, there has been no precedent works for comparative investigation for structure and release behavior of drug-LDH nanohybrids prepared via various routes in a systematic fashion.

In this study, we prepared FA-LDH (FL) nanohybrids through three different methods, such as ion-exchange, exfoliation-reassembly, and reconstruction. We investigated their controllable intracrystalline structure, morphology, and FA release. In order to prepare FL nanohybrids with similar particle sizes, we utilized MgAl-CO_3-LDH with a homogeneous size, ~80 nm, as a universal pristine because the dimension of LDH can be a determining factor in the release profile (Perioli et al., 2011; Zhang et al., 2014).

2. Experimental

2.1. Materials

Magnesium nitrate hexahydrate ($Mg(NO_3)_2 \cdot 6H_2O$), aluminum nitrate nonahydrate ($Al(NO_3)_3 \cdot 9H_2O$), sodium bicarbonate ($NaHCO_3$), sodium nitrate ($NaNO_3$), formamide ($HCONH_2$), nitric acid (HNO_3), and ferulic acid ($C_{10}H_{10}O_4$) were all purchased from Sigma-Aldrich Co. LLC(USA). Sodium hydroxide pellets (NaOH) were obtained from Daejung Chemicals & Metals Co., Ltd (Gyonggido, Korea). Sterilized saline, 0.9% NaCl solution, was purchased from Choongwae Pharmaceutical, Korea. Decarbonated water was used throughout the synthesis procedure. All reagents were used without further purification.

2.2. Preparation of FA-LDH (FL) nanohybrids

2.2.1. Preparation of pristine MgAl-CO_3-LDH

An aqueous solution containing 0.18 M $Mg(NO_3)_2 \cdot 6H_2O$ and 0.09 M $Al(NO_3)_3 \cdot 9H_2O$ was titrated with a NaOH/$NaHCO_3$ (2 M/0.18 M) solution to pH 9.5, and the reaction mixture was autoclaved for hydrothermal treatment at 100 °C for 12 h. The resulting precipitates were thoroughly washed with deionized water (DW) under centrifugation and lyophilized.

2.2.2. Synthesis of FA-LDH nanohybrid through ion-exchange (FL-I) method

Pristine LDH (MgAl-CO_3-LDH) was subject to a NO_3^- exchange reaction to obtain intermediate LDH (MgAl-NO_3-LDH), as previously reported (Li et al., 2005). Powdered pristine LDH was reacted with a 1 M $NaNO_3$ solution for 10 min under a N_2 atmosphere and then 1 M HNO_3 was added. The reaction mixture was kept for 24 h under a N_2 atmosphere and thoroughly washed with decarbonated water. The resulting slurry (MgAl-NO_3-LDH) was then placed into 0.1 M FA solution, which was previously titrated with NaOH solution to reach pH ~ 8.0. After 24 h of vigorous stirring at room temperature, the resulting precipitates were washed under centrifugation and lyophilized.

2.2.3. Synthesis of FA-LDH nanohybrid through exfoliation-reassembly (FL-E) method

The exfoliation-reassembly reaction was carried out by employing intermediate LDH (MgAl-NO_3-LDH) as previously described in the Section 2.2.2. In order to delaminate LDH layers, lyophilized MgAl-NO_3-LDH powder was soaked in formamide (1 mg/ml) and the dispersion was stirred for 24 h under a N_2 atmosphere. The delamination of the LDH layer was confirmed with the Tyndall effect, where a laser light that irradiated the dispersion showed its pathway due to scattering by well-dispersed nanolayers of LDH. The colloidal dispersion containing LDH layers was mixed with a 0.1 M of FA solution, titrated with NaOH to pH ~ 8.0, and then reacted for 24 h under a N_2 atmosphere. The resulting product was washed through centrifugation and lyophilized.

2.2.4. Synthesis of FA-LDH nanohybrid through reconstruction (FL-R) method

In order to obtain a FL-R nanohybrid, pristine MgAl-CO_3-LDH was calcined at 400 °C for 6 h. The resulting MgAl-mixed oxide powder was then directly dispersed in 0.1 M FA solution (pH adjusted to 8.0) for 24 h under an inert atmosphere. The resulting dispersion (pH ~ 9.28) was centrifuged, washed and dried as described above.

2.3. Characterization for intracrystalline structure of FL nanohybrids

The structure of each FL nanohybrid (FL-I, FL-E, and FL-R) was investigated by using a variety of characterization techniques. Fourier transform-infrared spectroscopy (FT-IR) was used to examine the hybridization of FA and LDH through electrostatic attraction. FT-IR spectra for lyophilized FL nanohybrids with Na-ferulate salt as a control were obtained by using a conventional KBr method (Fudala et al., 1999). Powder X-ray diffraction (PXRD) was used to probe the crystalline arrangement of LDH layers as well as the interlayer arrangement of FA molecules. PXRD using CuK_α radiation ($\lambda = 1.5418$ Å) was employed on the ground, lyophilized samples stacked on a glass substrate with a scanning range (2θ) from 3° to 80° and scanning steps of 0.02°. Samples subject to PXRD were FL nanohybrids as well as pristine LDH, intermediate LDH, calcined LDH, and FA alone as reference samples. In interpreting the full width half maximum (FWHM) of diffraction peaks, instrumental line broadening was calibrated with the XRD pattern of LaB_6. The one dimensional electron density map along the crystallographic c-axis was calculated according to the previous report (Zhang and Lerner, 1999)