



Dysprosium-containing layered double hydroxides nanoparticles intercalated with biologically active species as an approach for theranostic systems



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ARTICLE INFO

Article history:

Received 9 July 2015

Received in revised form

29 September 2015

Accepted 4 October 2015

Available online 23 October 2015

Keywords:

Hydroxides

MRI

Contrast agent

Carrier

Drug

ABSTRACT

A layered double hydroxide structure including dysprosium cations was prepared by co-precipitation. The nanoparticles showed a linear relationship with the reciprocal relaxation spin-lattice (T_1) time of water protons which is reflected as contrast in aqueous suspensions analyzed by magnetic resonance imaging. The interlayer space of dysprosium containing LDH was successfully intercalated with folate, ibuprofen and gallate ions, which are key molecules for recognition of some cancer cells and treatment of diseases. The paramagnetic property of the dysprosium-containing LDH detected in this work beside the ability to transport drugs open up the opportunity to design theranostic materials in a single crystal phase with nanometric dimensions.

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1. Introduction

In recent years the rising number of functional materials is boosted by the diversification of synthesis and processing methods, which allows producing materials with new compositions. Moreover, such techniques also control size and morphology of matter in nanometric scale, thus the discovery of new properties or their fine tuning is now possible.

Biomedicine is one area in which the advanced properties of new materials have been applied, for instance, there are reports related to the use of micellar and polymeric nanoparticles for tumor diagnostics and therapeutics since 1950s [1]. Theranostics is nowadays a developing science and technology area related to integration of different properties in one material capable to diagnose a disease and apply a therapy [2,3]. Significantly, the purpose is to diagnose and treat diseases at early stages, when they are more likely to be

cured or controlled. Therefore, in order to obtain theranostics materials, new markers or probes with diagnose applications based in nanotechnology have been coupled to drug delivery systems.

On the other hand, magnetic resonance imaging (MRI) is a technique for diagnosing and monitoring of diseases with a growing importance since it is not invasive nor ionizing.

MRI requires the use of contrast agents, which are compounds with ability to modify the longitudinal (T_1) and transversal (T_2) relaxation time of water protons [4]. T_1 and T_2 are the relaxation times required by spin of protons to recover the basal state after perturbation with a radiofrequency pulse applied to protons oriented under a magnetic field, and their magnitude is dependent on the media surrounding those water protons [5,6]. Some efficient contrast agents are organic complexes containing lanthanides. Trivalent gadolinium cation is the most common lanthanide used to modify relaxation times, however, its use as contrast agent requires a strong stabilization by non-toxic ligands like DPTA [7], otherwise the cation could produce toxicity [4]. An efficient strategy to retain Gd(III) is the insertion into nanohybrid or nanosilica materials [8].

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Despite the large number of scientific reports related to nano-materials with theranostic applications [2], their research is on early stage considering that ideal materials must comply with the following features: the ability of accumulation in a selected damaged tissue, capable to apply a selective and effective therapy, and degrade safely or be expelled from the body without producing toxic effects [9].

According to the bibliography, layered double hydroxide (LDH) materials have not been fully explored as a base to design theranostic nanomaterials. LDH are powders whose structure is composed by layers with di- and trivalent metallic cations with hydroxyl groups covering the surfaces. Residual positive charge into the layers raises due to the presence of trivalent cations and then, additional anions are retained between the layers along with water molecules. LDH are represented by the general formula: $[M^{2+}_{1-x}M^{3+}_x(OH)_2]^{x+} (A^{n-})_{x/n} mH_2O$, where M^{2+} and M^{3+} are metallic cations and A^{n-} corresponds to interlayer anions. The compositions most frequently reported are $M^{2+} = Ca^{2+}, Mg^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}$ and Mn^{2+} ; $M^{3+} = Al^{3+}, Cr^{3+}, Fe^{3+}, Co^{3+}, Ni^{3+}$ and Mn^{3+} ; and $A^{n-} = Cl^-, NO_3^-, ClO_4^-, CO_3^{2-}$ and SO_4^{2-} [10–13].

Regarding cations, the radii of M^{2+} and M^{3+} are important parameters controlling formation of layered structures. In principle, the synthesis of LDH is possible by combining M^{2+} and M^{3+} cations with radii between 0.67 and 0.93 Å [14,15]. Despite this restriction, Dy^{3+} cations with ionic radius of 1.05 Å have been used to prepare LDH [16]. The advantages of Dy^{3+} cations in LDH are their luminescent and paramagnetic properties that can be exploited for theranostics purposes as was demonstrated within oxides, hydroxides and hydroxyapatite particles [17,18]. Beside these physical features, the interlayer space of LDH can be occupied by organic anions to add new properties for biomedical applications; examples of those anions are anticancer, antibiotics, anti-inflammatory, anti-coagulant and antihypertensive drugs [11,12,19,20]. In addition, the inorganic moiety of LDH provides physicochemical stability, protects the organic anions and controls the release rate of drugs. Thus, it reduces the collateral effects of drugs.

That is why the possibility to combine organic compounds for cell recognition or treatment of diseases in one LDH particle with optical and magnetic properties deserves to be studied in order to provide knowledge to design theranostic materials.

In this work, we study the synthesis of LDH structures with Dy^{3+} cations aiming to demonstrate the significance of LDH as a basis to design theranostic materials with luminescent and magnetic properties beside the ability to retain organic species such as drugs or recognizers of tissues.

2. Methods

2.1. Synthesis of dysprosium-doped LDH

Analytical grade reagents and deionized water were used in all the experiments without additional purification.

The base composition of LDH was Zn^{2+} and Al^{3+} ions in a molar ratio $Zn/Al = 2.5:1$; to prepare it, a mixture with 6.72×10^{-3} mol of $Zn(NO_3)_2$, 2.69×10^{-3} mol of $Al(NO_3)_3$ and 60 mL of de-carbonated water was stirred, and then a 14% aqueous ammonia solution was added dropwise until pH 8.0 was reached. The white powder was recovered by decantation and washed with water. A second sample was prepared with an aqueous solution containing 6.72×10^{-3} mol of $Zn(NO_3)_2$, 2.55×10^{-3} mol of $Al(NO_3)_3$, and 1.34×10^{-4} mol of $Dy(NO_3)_3$, here the relationship of trivalent cations is 95 at% Al^{3+} and 5 at% Dy^{3+} . The solution of a third sample contained 6.72×10^{-3} mol of $Zn(NO_3)_2$ and 2.69×10^{-3} mol of $Dy(NO_3)_3$. These powders were labeled as Zn/Al, Zn/Al/Dy and Zn/Dy according to the metal cation included in each synthesis.

2.2. Intercalation derivatives

In order to intercalate ions derived from folic acid, gallic acid and ibuprofen, solutions with 15 mL of water and 0.32 g of folic acid or 0.15 g of ibuprofen were prepared and adjusted to pH 7 with 14% ammonia solution. In the case of gallic acid, 0.14 g of the reagent was dissolved in 15 mL of isopropanol to avoid degradation. Finally, 0.15 g of LDH (either Zn/Al or Zn/Al/Dy) was added to each solution and stirred for 24 h under nitrogen atmosphere at 25 °C. The powders were collected by decantation, washed three times with 50 mL of water (except the sample with gallic acid which was washed with isopropanol) and dried at 70 °C for 24 h.

2.3. Characterization

Samples for X-ray diffraction analysis were ground in agate mortar and deposited in the cavity of holder sample. The diffraction measurements were carried on a STOE diffractometer model SEIFERT Analytical X-Ray using Cu-K α radiation, a step of 0.03° and a dwell of 0.5 s per step; the potential and current were 30 kV and 20 mA respectively. The infrared (FTIR) analyses were performed in the reflectance mode using a Thermo Scientific spectrometer, model NICOLET iS5 iD5 ATR. Spectra were recorded in the range of 400–4000 cm^{-1} with resolution of 4 cm^{-1} and accumulation of 16 scans. UV–vis spectra were collected with an AVANTES AvaSpec-2048 UV–visible spectrometer equipped with an AvaLight-DHS light source and an optic fiber reflection probe. The X-ray photoelectron spectra (XPS) was obtained in a Riber XPS spectrometer with the Al anode, pass energy of 50 eV and 0.8 eV resolution. The C 1s binding energy was used to compensate surface charge effects. A Bruker Avance III 500 NMR spectrometer was used to measure the T1 relaxation time response; 0.55 mL of saturated solution of particles in 5% $H_2O/95\% D_2O$ mixture in standard 5 mm NMR sample tube was prepared and then T1 was measured using inversion-recovery sequence. Then the solution was diluted with 0.1 mL of 5% $H_2O/95\% D_2O$ mixture and T1 was measured again. The procedure was repeated 11 times until the sample tube was full. The magnetic resonance images (MRI) of LDH were acquired in suspension containing 0.2 and 0.4 $mg mL^{-1}$. The samples were introduced in a resonator General Electric Optima MR360 operating with an external field of 1.5 T. Images were acquired with field of view = 25.6, field of view phase = 1, thickness = 1 cm, repetition time = 8.3 ms, and time to echo = 3.1 ms. Scanning electron micrographs were acquired with a TESCAN microscope model MIRA 3 LMU with a field emission electron gun. Around 0.1 g of powder samples were dispersed in 3 mL of methanol and dispersed by ultrasound. One drop of the resulting suspension was dispersed on a carbon tape previously adhered to the microscope holder. The samples were not metallized with a gold layer in order to not hide fine characteristic. ImageJ software was used to extract statistical data from micrographs. The obtained nanoparticles were observed by transmission electron microscopy, using a JEOL JEM1010 microscope, at 100 kV.

3. Results and discussion

3.1. Structure of HDLs with dysprosium

The X-ray diffractograms of LDHs (see Fig. 1) were normalized for better visualization of reflections. All the patterns are characteristic of LDH [12,15]. The main difference observed is the increment of noise with the increment of dysprosium in the structure. The diffractogram from LDH with zinc and aluminum cations (Zn/Al) presented the sharpest reflections; the pattern from powder where 10% of aluminum cations were substituted by Dy^{3+} cations

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