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Professor P. N. Kumta
Editor-in-Chief of Materials Science and Engineering: B

Please find enclosed the revision of our paper formerly entitled "Layered double hydroxides nanoparticles: an approach for theranostic systems". According to revision 1 the title was changed to "**Dysprosium-containing layered double hydroxides nanoparticles intercalated with biologically active species as an approach for theranostic systems**".

Our original work describes the synthesis of LDH structures with dysprosium in cationic sites. This composition was first reported by our group and here we include the novel result demonstrating i) UV-vis and paramagnetic response along with ii) the capability to intercalate drugs. These both physical features are important to design materials for therapy and diagnostics (theranostics) in biomedicine.

Minor modifications are found in red within the manuscript and figure captions according to the suggestions of Reviewer 6.

The most remarkable result is the union of such properties in a single crystalline phase that allows miniaturizing and to the best of our knowledge such type of material is not yet reported. The manuscript is focused on synthesis and physicochemical properties of the LDH and we considered this content matches with the scope of MSE-B and we hope the revision complies the quality required by this journal.

We give you our assurance that this manuscript was not earlier submitted to this journal and is not under consideration elsewhere. We will not submit it to other journal until we have received your decision. All the authors are aware of the content and approve the submission. We also declare that no conflicts of interest exist.

We hope this will be favorable considered for publication in your esteemed journal after due peer reviewing. If so, the article will not be published elsewhere in the same form, in any language, without the written consent of the publisher.

In case that MSE-B makes part of the Elsevier Article Transfer Service we accept the transfer to another journal if the Editor decide it.

With best regards.

Gregorio G Carbajal Arízaga

Reviewer's Comments:

Changes can be found in red within the manuscript.

Reviewer #6: The revised manuscript by Quijada et al. addressing the most of the concerns rises by the reviewer and I suggest the publication of the manuscript in materials science and engineering B after some minor revisions as stated below.

1) In figure caption 3 "Uv-vis" should be corrected.

"Uv-vis" was changed by "UV-vis". The new caption is: "Figure 3. UV-vis spectra from layered double hydroxides (LDHs)."

2) In figure 4, X-axis label should change, the LDH should comes to the axis caption not in the unit. The caption should be Relative LDH concentration and unit should be mg/ml.

The changes were made and the new information is:

"Figure 4. Reciprocal response of spin-lattice relaxation time (T_1) versus relative LDH concentration (proportional to the content of Dy^{3+})."

3) Reference section should be checked very carefully. It is very hard to follow the references now. Reference 16 don't have any specified page number, reference 21 don't have journal name.

References were revised. Ref 16 doesn't have page number, instead of that, the ID number and number of pages were added, similar to that in ref25.

The journal name fo ref21 was added.

The other references and the final list was checked and handled with Mendeley using the "Elsevier with titles" style. Changes can be found in red in Refs 7, 10, 13, 16, 21, 24, and 25.

Additionally, we detected an error in the graphical abstract. There "Folate or drug carrie" was substituted by "Carrier of biologically active species"

Graphical abstract

Highlights

1- LDH structure including dysprosium was prepared by co-precipitation.

2- LDH was capable to produce contrast in the T1 mode of MRI.

3- LDH were intercalated with folate, ibuprofene and gallate ions.

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

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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 (T₁) 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, ibuprofene 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.

Keywords

Hydroxides, MRI, Contrast agent, Carrier, Drug

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 from 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 diagnose 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 (T1) and transversal (T2) relaxation time of water protons [4]. T1 and T2 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].

Despite the large number of scientific reports related to nanomaterials 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 hydroxides (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 represented by general formula: $[M^{2+}_{1-x} M^{3+}_x (OH)_2]^x (A^{n-})_{x/n} \cdot H_2O$, where M^{2+} and M^{3+} are metallic cations and A^{n-} corresponds to interlayer anion. The compositions most frequently reported are $M^{2+} = Ca^{2+}, Mg^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}$ y Mn^{2+} ; $M^{3+} = Al^{3+}, Cr^{3+}, Fe^{3+}, Co^{3+}, Ni^{3+}$ y Mn^{3+} ; y $A^{n-} = Cl^-, NO_3^-, ClO_4^-, CO_3^{2-}$ y 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 has 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, anticoagulant 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 matrix with optical and magnetic properties deserves to be studied in order to provide knowledge to design theranostics 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 were Zn^{2+} and Al^{3+} ions in a molar ratio $\text{Zn}/\text{Al} = 2.5:1$; to prepare it, a mixture with 6.72×10^{-3} mol of $\text{Zn}(\text{NO}_3)_2$, 2.69×10^{-3} mol of $\text{Al}(\text{NO}_3)_3$ 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 $\text{Zn}(\text{NO}_3)_2$, 2.55×10^{-3} mol of $\text{Al}(\text{NO}_3)_3$; and 1.34×10^{-4} mol of $\text{Dy}(\text{NO}_3)_3$, here the relationship of trivalent cations is 90% at Al^{3+} and 10% at Dy^{3+} . The solution of a third sample contained 6.72×10^{-3} mol of $\text{Zn}(\text{NO}_3)_2$ and 2.69×10^{-3} mol of $\text{Dy}(\text{NO}_3)_3$. These powders were labeled as Zn/Al, Zn/Al/Dy and Zn/Dy according to 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 were 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 hours.

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- $k\alpha$ radiation, a step of 0.03 degrees and a dwell of 0.5 seconds 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 to 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 C1s 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% H₂O 95% D₂O 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% H₂O 95% D₂O 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-rays diffractograms of LDHs (see **Figure 1**) were normalized for better visualization of reflections. All the patterns are characteristics 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 (Zn/Al/ Dy) has observable low level of noise level with reflections of acceptable intensity, whereas the compound prepared exclusively with dysprosium as trivalent cation (Zn/Dy) has the highest noise level or the lowest intensity reflections. It indicates that particles of the latter sample have a layered structure, but also a low crystalline quality, probably affected by the large volume of Dy^{3+} cations. In fact, dysprosium in layered hydroxides salts (structures exclusively composed by lanthanide cations) contain lanthanide sites with 9- and 8-fold coordination in contrasts with the 6-fold coordination in LDHs [21], i.e. the large volume of dysprosium could require a higher coordination number, however, the coprecipitation of dysprosium with aluminum and zinc cations probably produces Dy^{3+} sites where aluminum is substituted isomorphically since the XRD pattern of Zn/Al is similar to that of Zn/Al/Dy.

Another change induced by the addition of dysprosium is a small shift in the basal reflection (proportional to interlayer separation) from 8.9 to 8.6 Å that could be the result of a tilt in nitrate ions.

Figure 1.

Even though the ionic radius of Dy^{3+} is larger than that of Zn^{2+} (105 and 88 pm, respectively [22]), their presence into layers do not produce a detectable distortion in cationic sites since the 2p core-level spectrum in zinc analyzed by XPS appears with the same symmetry and FWHM in the three LDHs (**Figure 2**). Therefore zinc cations are in the same chemical environment, where, Zn (II) centers are completely coordinated by OH-groups.

Figure 2.

The presence of Dy^{3+} cations in the LDH structures is evidenced by UV-Vis spectra acquired in solid state. **Figure 3** shows that LDH without dysprosium (Zn/Al) produce a spectrum with only one absorption pick at 296 nm, related to absorption of nitrate ions [23]. Such absorption is not affected by addition of 10%at of Dy^{3+} in the Zn/Al/Dy sample; however, two absorption peaks appear at 810 and 915 nm; these signals are more likely associated with transitions into dysprosium centers since also these bands appear in the spectrum of Zn/Dy (the structure with the highest content of dysprosium). Such transitions have been observed in dysprosium hydroxide around 800 and 900 nm and they are associated to transition from the $^6\text{H}_{15/2}$ ground state towards $^6\text{F}_{5/2}$ y $^6\text{F}_{7/2}$ levels, respectively [24,25].

Figure 3.

3.2. Magnetic response

To evaluate the feasibility of using dysprosium-containing LDH particles as diagnose agent by MRI, it is necessary to determine its ability to affect the spin-lattice relaxation time (T_1) of water protons. The sample with the larger content of dysprosium (Zn/Dy) was used for the semi-quantitative evaluation. Since the dysprosium content in the LDH particles was calculated according to the nominal amount of dysprosium salt used during the synthesis, the value plotted in the X axis (**Figure 4**) corresponds to the relative content of Dy^{3+} which is proportional to the LDH mass in the analyzed suspensions. The significant result presented in the **Figure 4** is the linear relationship between the dysprosium relative concentration and $1/T_1$. Although this effect has been observed also in dysprosium hydroxide nanoparticles [17] due to a large magnetic moment ($10.6 \mu\text{B}$) [3,26], dysprosium-containing LDH could be used as fluorescent probes since visible light is emitted when these particles are excited with UV light [16]. Then, dysprosium combines two remarkable properties useful for magnetic and fluorescent imaging unlike other

common lanthanides exclusively used to prepare magnetic or fluorescent materials, such as gadolinium or europium, respectively [26]. Additionally, the ionic radius of Dy^{3+} produce stable LDH structures and this is the most remarkable feature since the intercalation capability is retained (as it is demonstrated in the next section) and the M^{3+} content regulate the electrostatic charge density, thus, controlling the amount of organic species that can be intercalated.

Figure 4.

3.2. Intercalation of key molecules for theranostics

After detecting a linear effect between the concentration of LDH (proportional to the content of Dy^{3+}) on $1/T_1$ relaxation time due to the presence of Dy^{3+} cations within the structure, the capability of intercalation must be verified in order to consider these structures as prospect multifunctional materials for theranostic applications. Specific recognition of tissues and capability to transport drugs are two important functionalities needed. In order to achieve them, the ideal strategy to modify the LDH structures is the intercalation of drug molecules in the interlayer space besides functionalization of the outer surface of crystallites with agents that help to recognize a tissue or to promote the accumulation of nanoparticles within. This idea is represented in **Figure 5**, where rigid inorganic layers formed by metal cations including dysprosium or any other lanthanide (red spheres in the color electronic version of this article) are covered by -OH groups, therefore Dy^{3+} ions would not be released to the *in vivo* system. The ionic species intercalated in the interlayer space provides the therapeutic activity, which is represented in the **Figure 5** by gallate ions, and finally, the functionalization of the crystallite surface with folate ions would improve the recognition of damaged tissues since numerous cancer cells express folate receptors at high levels [27]. The proposed material is then an idealized system joining theranostic properties in a single crystal phase with even nanometric size (as it will be demonstrated in the electron microscopy section) which is important to pass through tissues or even cell membranes [28].

Figure 5.

3.4. Intercalation of organic ions for theranostics into LDH

This section evidences the intercalation of dysprosium-containing LDH with low volume anions such as folate, ibuprofen and gallate. Folate was selected since this ion aids to recognize or promote accumulation in specific cancer cells [28–30]. Although the scheme in **Figure 5** contains folate functionalization exclusively on the surface of crystallites, the experiment in this section tends to evaluate whether the large volume of folate impedes intercalation or so does only external functionalization.

Ibuprofen and gallate ions were selected since these are drugs for treatment of some kinds of cancer and as anti-inflammatory, respectively [31,32].

Figure 6, at the left hand, shows the diffraction patterns of the LDH without dysprosium (Zn/Al) subjected to exchange reactions in folate, ibuprofen and gallate solutions. The diffractogram from folate derivate presents a basal reflection related to a distance of 16.0 Å, which is the reported value for LDH of Mg/Al intercalated with folate [33]. The basal distance for the ibuprofen derivate is 22.9 Å and it is very close to 21.7 Å reported for LDH Mg/Al [32]. The resultant product from the gallate solution presents a basal space of 8.8 Å, which is close to the value in the LDH without intercalation depicted in **Figure 1**, however this distance is reported in the literature for confirmed intercalation of gallate in LDH and hydroxide salts structures supported by spectroscopic techniques [31,34].

Figure 6.

Infrared spectroscopy confirms the presence of the above cited organic ions, specially the region between 1580 and 1250 cm⁻¹ contains bands of vibrations in the three ions (dashed area in **Figure 7**) related to vibrations in aromatic rings, methylene and N-H stretching in folate [33], ibuprofen and gallate [32,34].

Figure 7.

The capability of intercalation was tested in dysprosium-containing LDH (Zn/Al/Dy) and the resulting XRD patterns (**Figure 6** at the right hand) are in agreement with the profile of a layered compound with basal reflections related to distances of 15.2 and 11.4 Å in the samples treated with solutions of folate, ibuprofen and gallate ions, respectively. The infrared spectra confirms that such ions are responsible of the large basal distances since bands in the region between 1600 and 900 cm⁻¹ are present as in the case of the intercalation products in the LDH structure without dysprosium (dashed area in **Figure 7**).

These results demonstrate that it is possible to get hybrid dysprosium containing LDH. Consequently, this is a promising material for theranostic application considering that the lanthanide Dy³⁺ that generates the signal in the diagnosis remains in an inorganic insoluble LDH lattice; additionally, the layered structures are stable and tolerate drugs intercalation despite of the presence of the bulky lanthanide.

On the other hand, although the toxicity levels of the lanthanide-LDH must be evaluated, the low content of dysprosium in the Zn/Al/Dy samples (5%at with respect to aluminum) should likely have negligible toxicity and stability as several LDH compositions widely described in the literature [12,19,35,36].

3.5. Response of hybrid LDH in MRI analyses

The magnetic effect of LDH on the T1 relaxation time evidenced in the **Figure 8** becomes important when contrast is produced in MRI images collected in commercially available equipment. The images in **Figure 8** correspond to a deionized water sample as blank (identifies as W) and its comparison with aqueous suspensions of the Zn/Al/Dy sample intercalated with folate (F), ibuprofen (i) and gallate (G) ions. The observed contrast suggests that LDH with dysprosium could be used as contrast agents or even more, as a theranostic materials once the contrast is observed even when the layered structure is intercalated with organic compounds.

Figure 8.

3.6. Electron microscopy studies

Size and morphology of LHD particles play key role in theranostics hence they influence the ability to cross tissues, cell walls and even the syringe needles for administration in bioassays (*in vitro* or *in vivo*). Transmission electron microscopy is a fast and reliable technique to determine particle size in LDH. Although the samples were sonicated in ethanol before the analysis, those prepared with ibuprofene and gallate were not disaggregated, on the contrary, the folate derivative samples presented finely dispersed particles (Figure 9). While the particles modified with folate ions presented the typical plate-like morphology and mean sizes of 12.5 nm (SD = 3.4, n = 39), those with ibuprofene and gallate ions presented aggregates with individual with mean sizes of 691 nm (SD = 400, n = 7) and 202 nm (SD = 137, n = 14), respectively. The ibuprofene derivative sample presented the largest particle size in agreement with preliminary SEM results; the strong cohesion in this sample produces large aggregates and restricts some theranostic assays, then this sample require further studies to control aggregation as reported elsewhere [37]. Regarding the gallate sample, despite the observed aggregates, smaller particles with irregular morphology can be detected with mean size of 36 nm (SD = 11, n = 20). Then, sizes in folate and gallate LDHs particles are in principle suitable for theranostics applications and allow to administrate LDH suspensions through needles.

Figure 9.

4. Conclusions

Layered double hydroxides prepared with dysprosium showed low crystalline quality due to probable distortions induced by the large volume of the lanthanide, despite this, the zinc cationic sites did not change at least in the coordination number. The presence of dysprosium produces the absorption of light at 800 and 900 nm; additionally, dysprosium within the structure is capable to linearly reduce relaxation time of water protons and acts as contrast agent in MRI analyses. The interlayer space of dysprosium containing LDH was successfully intercalated with folate, ibuprofene and gallate ions, which are key molecules for recognition of some cancer cell and treatment of diseases. Therefore, this lanthanide

modified layered structures possess relevant features to serve as a basis for designing
theranostic materials.

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References

- [1] G. Pazzaglia, *Il grande libro delle terapie anticancro*, Sperling & Kupfer, 2012.
- [2] E. Peng, F. Wang, J.M. Xue, Nanostructured magnetic nanocomposites as MRI contrast agents, *J. Mater. Chem. B*. 3 (2015) 2241–2276.
- [3] Y. Zhang, G.K. Das, V. Vijayaragavan, Q.C. Xu, P. Padmanabhan, K.K. Bhakoo, et al., “Smart” theranostic lanthanide nanoprobe with simultaneous up-conversion fluorescence and tunable T1–T2 magnetic resonance imaging contrast and near-infrared activated photodynamic therapy, *Nanoscale*. 6 (2014) 12609–12617.
- [4] K. Hanaoka, Development of responsive lanthanide-based magnetic resonance imaging and luminescent probes for biological applications, *Chem. Pharm. Bull.* 58 (2010) 1283–1294.
- [5] V. Kuperman, *Magnetic resonance imaging: Physical principles and applications*, Academic Press, 2000.
- [6] P. V. Prasad, *Magnetic Resonance Imaging: Methods and Biologic Applications*, Springer, 2006.
- [7] Z.P. Xu, N.D. Kurniawan, P.F. Bartlett, G.Q. Lu, Enhancement of relaxivity rates of Gd–DTPA complexes by intercalation into layered double hydroxide nanoparticles, *Chem. Eur. J.* 13 (2007) 2824–2830.
- [8] S.L.C. Pinho, H. Faneca, C.F.G.C. Geraldes, M.-H. Delville, L.D. Carlos, J. Rocha, Lanthanide-DTPA grafted silica nanoparticles as bimodal-imaging contrast agents, *Biomaterials*. 33 (2012) 925–35.
- [9] Z. Fan, P.P. Fu, H. Yu, P.C. Ray, Theranostic nanomedicine for cancer detection and treatment, *J. Food Drug Anal.* 22 (2014) 3–17.

- [10] V. Rives, Layered double hydroxides: present and future, **First edition**, Nova Science Publishers, Inc., Netherlands, 2011.
- [11] V. Rives, M. del Arco, C. Martín, Intercalation of drugs in layered double hydroxides and their controlled release: A review, *Appl. Clay Sci.* 88-89 (2014) 239–269.
- [12] U. Costantino, V. Ambrogi, M. Nocchetti, L. Perioli, Hydrotalcite-like compounds: Versatile layered hosts of molecular anions with biological activity, *Microporous Mesoporous Mater.* 107 (2008) 149–160.
- [13] X. Duan, D.G. Evans, Layered Double Hydroxides, **First edition**, Springer-Verlag, Heidelberg, 2006.
- [14] M. Rajamathi, G.S. Thomas, P.V. Kamath, The many ways of making anionic clays, *Proc. Indian Acad. Sci.* 133 (2001) 617–680.
- [15] S. Carlino, The intercalation of carboxylic acids into layered double hydroxides: a critical evaluation and review of the different methods, *Solid State Ionics.* 98 (1997) 73–84.
- [16] D.R. Martínez Vargas, M.J. Oviedo, S. Lisboa, G.A. Hirata, G.G. Carbajal Arizaga, Phosphor dysprosium-doped layered double hydroxides exchanged with different organic functional groups, *J. Nanomater.* (2013) **730153 (8pp)**.
- [17] K. Kattel, J. Young, W. Xu, H. Gyeol, E. Jung, B. Alam, et al., Paramagnetic dysprosium oxide nanoparticles and dysprosium hydroxide nanorods as T2 MRI contrast agents, *Biomaterials.* 33 (2012) 3254–3261.
- [18] A.K. Sánchez Lafarga, F.P. Pacheco Moisés, A. Gurinov, G.G. Ortiz, G.G. Carbajal Arizaga, Dual responsive dysprosium-doped hydroxyapatite particles and toxicity reduction after functionalization with folic and glucuronic acids, *Mater. Sci. Eng. C.* 48 (2015) 541–547.
- [19] C. Del Hoyo, Layered double hydroxides and human health: An overview, *Appl. Clay Sci.* 36 (2007) 103–121.
- [20] R. Rojas, Y.G. Linck, S.L. Cuffini, G. a. Monti, C.E. Giacomelli, Structural and physicochemical aspects of drug release from layered double hydroxides and layered hydroxide salts, *Appl. Clay Sci.* 109-110 (2015) 119–126.
- [21] F. Geng, Y. Matsushita, R. Ma, H. Xin, General synthesis and structural evolution of a layered family of $\text{Ln}_8(\text{OH})_{20}\text{Cl}_4 \cdot n\text{H}_2\text{O}$ ($\text{Ln}=\text{Nd}, \text{Sm}, \text{Eu}, \text{Gd}, \text{Tb}, \text{Dy}, \text{Ho}, \text{Er}, \text{Tm}, \text{and Y}$), *J. Am. Chem. Soc.* 130 (2008) 16344–16350.

- [22] R.D. Shannon, Revised effective ionic radii and systematic studies of interatomic distances in halides and chalcogenides, *Acta Crystallogr. Sect. A.* A32 (1976) 751–767.
- [23] A.A.A. Ahmed, Z.A. Talib, M.Z. Bin Hussein, A. Zakaria, Zn-Al layered double hydroxide prepared at different molar ratios: Preparation, characterization, optical and dielectric properties, *J. Solid State Chem.* 191 (2012) 271–278.
- [24] J.-G. Kang, J.S. Gwang, Y. Sohn, Synthesis and characterization of Dy(OH)₃ and Dy₂O₃ nanorods and nanotubes, *Ceram. Int.* 41 (2015) 3999–4006.
- [25] B.D.O. Richards, T. Teddy-Fernandez, G. Jose, D. Binks, A. Jha, Mid-IR (3–4 μm) fluorescence and ASE studies in Dy³⁺ doped tellurite and germanate glasses and a fs laser inscribed waveguide, *Laser Phys. Lett.* 10 (2013) 085802 (6pp).
- [26] W. Xu, B.A. Bony, C.R. Kim, J.S. Baeck, Y. Chang, J.E. Bae, et al., Mixed lanthanide oxide nanoparticles as dual imaging agent in biomedicine., *Sci. Rep.* 3 (2013) 3210.
- [27] C. Chen, J. Ke, X.E. Zhou, W. Yi, J.S. Brunzelle, J. Li, et al., Structural basis for molecular recognition of folic acid by folate receptors., *Nature.* 500 (2013) 486–490.
- [28] G. Choi, O.-J. Kwon, Y. Oh, C.-O. Yun, J.-H. Choy, Inorganic nanovehicle targets tumor in an orthotopic breast cancer model, *Sci. Rep.* 4 (2014) 4430.
- [29] S. Setua, D. Menon, A. Asok, S. Nair, M. Koyakutty, Folate receptor targeted, rare-earth oxide nanocrystals for bi-modal fluorescence and magnetic imaging of cancer cells, *Biomaterials.* 31 (2010) 714–29.
- [30] A. Shakeri-Zadeh, G.A. Mansoori, A. Reza Hashemian, H. Eshghi, A. Sazgarnia, A. Reza Montazerabadi, Cancerous cells targeting and destruction using folate conjugated gold nanoparticles, *Dyn. Biochem. Process Biotechnol. Mol. Biol.* 4 (2010) 6–12.
- [31] M.Z. Bin Hussein, M.Y. Ghotbi, A.H. Yahaya, M.Z. Abd Rahman, Synthesis and characterization of (zinc-layered-gallate) nanohybrid using structural memory effect, *Mater. Chem. Phys.* 113 (2009) 491–496.
- [32] V. Ambrogi, G. Fardella, G. Grandolini, L. Perioli, Intercalation compounds of hydrotalcite-like anionic clays with antiinflammatory agents - I. Intercalation and in vitro release of ibuprofen, *Int. J. Pharm.* 220 (2001) 23–32.
- [33] L. Qin, S. Wang, R. Zhang, R. Zhu, X. Sun, S. Yao, Two different approaches to synthesizing Mg-Al-layered double hydroxides as folic acid carriers, *J. Phys. Chem. Solids.* 69 (2008) 2779–2784.

- 1
2
3 [34] M. Yeganeh Ghotbi, M.Z. bin Hussein, Gallate-Zn-Al-layered double hydroxide as
4 an intercalated compound with new controlled release formulation of
5 anticarcinogenic agent, J. Phys. Chem. Solids. 71 (2010) 1565–1570.
6
7
8 [35] S. Hwang, Y. Han, J. Choy, Intercalation of functional organic molecules with
9 pharmaceutical, cosmeceutical and nutraceutical functions into layered double
10 hydroxides and zinc basic salts, Bull. Korean Chem. Soc. 22 (2001) 1019–1022.
11
12
13 [36] V.R.R. Cunha, A.Ma. da C. Ferreira, V.R.L. Constantino, J. Tronto, J.B. Valim,
14 Hidróxidos duplos lamelares: nanopartículas inorgânicas para armazenamento e
15 liberação de espécies de interesse biológico e terapêutico, Quim. Nova. 33 (2010) 159–
16 171.
17
18
19 [37] T. Posati, F. Bellezza, L. Tarpani, S. Perni, L. Latterini, V. Marsili, et al., Selective
20 internalization of ZnAl-HTlc nanoparticles in normal and tumor cells. A study of
21 their potential use in cellular delivery, Appl. Clay Sci. 55 (2012) 62–69.
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Figures

Figure 1. X-ray diffraction patterns of layered double hydroxides (LDHs) Zn/Al, Zn/Al/Dy and Zn/Dy.

Figure 2. XPS spectrum of Zn 2p contained in the layered double hydroxides structures.

Figure 3. UV-vis spectra from layered double hydroxides (LDHs).

Figure 4. Reciprocal response of spin-lattice relaxation time (T_1) versus **relative** LDH concentration (proportional to the content of Dy^{3+}).

Figure 6. XRD diffractograms of **Zn/Al** and **Zn/Al/Dy** LDHs intercalated with folate, ibuprofen and gallate ions.

Figure 7. Infra-red spectrum of Zn/Al and Zn/Al/Dy LDHs intercalated with folate, ibuprofen and gallate ions.

Figure 8. T1 weighted images generated by MRI from a water sample (W) and aqueous suspensions of the Zn/Al/Dy pristine sample (LDH) and the intercalation products with folate (F), ibuprofene (i) and gallate (G) in concentrations of (a) 2.0 and (b) 4.0 mg L⁻¹.

JEOL 1010 Mag: 400 kx 25 nm

a

JEOL 1010 Mag: 15 kx 800 nm

b

JEOL 1010 Mag: 80 kx 150 nm

c

Figure 9. Size distribution of Zn/Al/Dy particles intercalated **with (a) folate, (b) ibuprofen and (c) gallate ions.**