J. Nanoanalysis., 5(4): 210-226 Autumn 2018

REVIEW ARTICLE

Biological Application of Layered Double Hydroxides in Drug Delivery Systems

Nahid Shahabadi * and Mahtab Razlansari

Chemistry Department, Institute of Nanotechnology, Razi University, Kermanshah, Iran

Received: 2018-06-02 Accepted: 2018-08-03 Published: 2018-10-01

ABSTRACT

This review focuses on the extensive study of different layered double hydroxides (LDHs) nanostructures and also their biological and physicochemical (in vitro) properties to encapsulate and deliver drugs with a recognized pharmacokinetic profile in a sustained/modified manner for better remedial efficacy contrasted to the corresponding conventional treatments using different drugs. LDHs known as hydrotalcite like compounds possess positive charges due to isomorphic substitutions, which are counterbalanced by hydrated exchangeable anions located in the interlayer region. Some of the active ingredient molecules can be intercalated into the inner region of the LDHs through ionic bonding, hydrogen bonding or van der Waals interaction to form nanohybrids, which are more potent for their protection and controlled-release. In addition, this composite material exhibits a selective release toward cancer cells and good biocompatibility with normal cells, which would guarantee its practical applications in cancer therapy.

Keywords: *Biological application; Drug delivery; Layered double hydroxides; Release study*

How to cite this article

Shahabadi N, Razlansari M. Biological Application of Layered Double Hydroxides in Drug Delivery Systems. J. Nanoanalysis., 2018; 5(4): 210-226. DOI: 10.22034/jna.2018.544273

INTRODUCTION

Direct delivery of drugs and bioactive molecules does not lead to appropriate therapeutic results and suffers from the main difficulties like poor bioavailability, enzymatic degradation, adverse drug reaction owing to great dosage and toxicity due to positional accumulation etc.[1]. Therefore, the search for efficient and safe transport vehicles-carriers were a challenging yet very exciting area of research in recent years and is going to be of interest for many years to come [2]. Among all nanocarriers which applied as drug delivery vectors, layered double hydroxides (LDHs) with exchangeable anions in the positive brucite-like interlayers have been attracting much attention in the field of cellular delivery of anionic drug and other bio-functional molecules, due to their low toxicity, biocompatibility, high stability, pH dependent solubility and enhanced cellular uptake behavior compared with the conventional drug carriers [3]. For instance, clay minerals can act as transport vehicles/carriers for the efficient delivery of therapeutic molecules (drugs and genes) by modifying the rate and/or time of release, increasing the stability of the drug or improving the dissolution profile of a drug [4]. The LDHs have been known for many decades as a catalyst and ceramic precursors, traps for anionic pollutants, catalysts and additives for polymers, but their successful synthesis on the nanometer scale a few years ago opened up a whole new field for their application in nanomedicine [5]. The LDHs are available as naturally occurring minerals and as synthetic materials. They were first prepared in the laboratory in 1942 when Feitknecht reacted dilute aqueous metal salt solutions with base, although

* Corresponding Author Email: *nahidshahabadi@yahoo.com*

the first detailed structural analyses of LDHs were not carried out until the late 1960s by Allmann and Taylor and their co-workers [6]. The LDHs have many applications in various fields such as drug delivery, catalysis [7], wastewater treatment [8], cosmetic, etc. Particularly, in the pharmaceutical section, they are employed as (i) drug delivery systems [9-11], (ii) host materials for poorly soluble active pharmaceutical ingredients (APIs) [12, 13] (iii) rheological agents for topical formulations [14, 15]. These layered nanostructures consist of interlayer region containing charge compensating anions and solvation molecules. The metal cations occupy the centers of edge sharing octahedral, whose vertexes contain hydroxide ions that connect to form infinite 2D sheets. The most widely studied LDHs contain both divalent and trivalent metal cations, a generic formula for these LDHs may be written as; $[M^{2+}_{1-x}M^{3+}_{x}(OH)_2][A^{n-}]_{x/n}\cdot zH_2O$, where M^{2+} may be common; Mg^{2+}, Zn^{2+}, or Ni^{2+} and M^{3+} may be common; Al^{3+}, Ga^{3+}, Fe^{3+}, or Mn^{3+}. A^{n-} is a non-framework charge compensating inorganic or organic anion, e.g. CO_3^{2-}, Cl^-, SO_4^{2-}, RCO_2^-, and x is normally between 0.2-0.4 [16-18]. Various methods have been developed to prepare LDHs with different sizes, including co-precipitation of inorganic salts in basic solution at either low or high super saturation, hydrothermal synthesis, reconstruction, and ion-exchange methods. There are two typical co-precipitation processes based on operation: (1) co-precipitation at high super-saturation, in which typically an M^{2+} and M^{3+} containing solution is added to a basic solution with the desired interlayer containing anions and the reaction is stopped when reaching a set pH value; (2) co-precipitation at low super saturation, in which two solutions, one containing construction metal cations and the other containing counter anions and a precipitation base are mixed together drop by drop [19]. In the last decades, passive diffusion was shown to be the main mechanism in drug transport across biological barriers, it is a key determinant in pharmacokinetics. Later studies showed carrier mediated process in drug transport across the biological membrane also played major roles, adding to the existing passive mechanism [20]. Common organic-based DDS include polymers (such as polysaccharides, chitosan, amphiphilic block copolymers block copolymer micelles, cellulose, hydrogels), lipid particles (micro emulsions), and a few natural particulates (pathogens and mammalian). Organic-based DDS have some disadvantages such as high toxicity, low loadings and easy leakage of drugs which reduce their drug-delivering efficiency [21]. Drug carriers based on inorganic nanomaterials, such as silica materials, show much better properties than organic carriers, including ease of controlled synthesis and environmental friendliness. The recently developed organic-inorganic nanohybrids based DDS such as LDH-chitosan hybrid or enteric polymer show good biocompatibility and avoid the drug leaching, but endure the difficulty of artificial synthesis, ordered structure, and industrial scale-up [22]. In this review, we collect the information published, roughly from 2001, on the intercalation of various drugs in different LDHs, as well as their controlled release. Furthermore, this review aims to report and examine the latest developments in LDH nanoparticles as efficient drug delivery systems

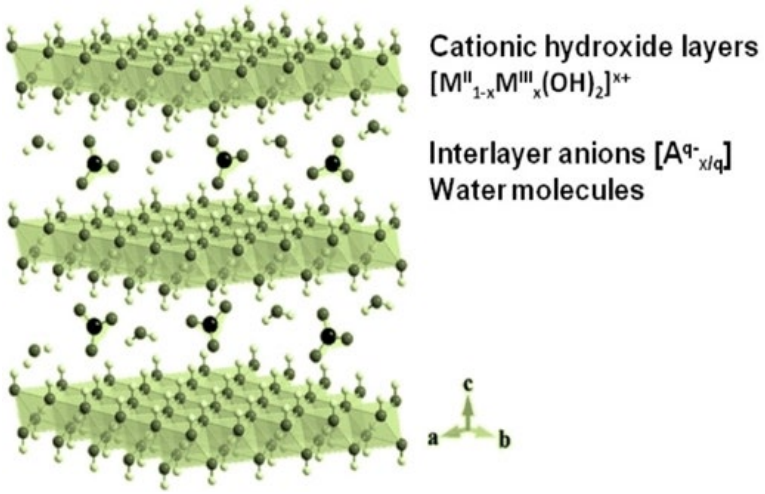

Fig. 1. Schematic structure of molecules in the LDH interlayer space.

(DDS) and to provide an outlook on possible future progress in this research area as well as some likely challenges that could be encountered.

Layered double hydroxides (LDH) Materials

The LDHs (Fig. 1) have a wide range of chemical compositions and their layer structure exhibits a variety of stacking faults to generate many different poly types. They exhibit various

particle sizes according to the synthetic route while the surface area values are generally lower than 100 m^2 g^{-1}. They also possess higher layer charge densities (2-5 meq g^{-1}), which results in strong electrostatic forces between the brucite-type sheets and the anions, thus swelling is more difficult than for clay minerals. LDHs particularly prefer multivalent anions within their interlayer space due to strong electrostatic interaction and therefore LDHs bearing monovalent anions like nitrate or chloride ions are good precursors for exchange reactions [23].

LDH family belongs to the 2-D layered materials displaying a low dimensional opened structure that favors intercalation and adsorption processes with a large variety of organic species ranging from molecules to macromolecules and bio macromolecules [24]. The LDH also referred as anionic clays are based on the stacking of brucite like layers, in which part of the divalent cations (M^{2+}) is replaced by the trivalent ones (M^{3+}). By virtue of their remarkable surface area to mass ratio, highly efficient drug loading can be achieved with atomically thin 2D structures [5].

The LDH nanoparticles have been explored widely owing to their biocompatibility, as well as biodegradability in the biomedical field for cancer treatment, termed nano oncology. These inorganic layered solids are stable and have the ability to encapsulate or immobilize various bio- and organic molecules in the interlayer space [25]. By the way, the core@LDH nanostructure is an effective carrier for drug delivery purposes.

Today, several methods have been developed for the synthesis of LDHs. These include co-precipitation, the sol-gel method, direct deposition and the urea method. Each method has its own unique advantages and disadvantages when compared to the other methods. LDH nanoparticles also applied as the shell of the structure of carriers with different cores. The core@LDH nanocomposites are equipped not only with the unique physicochemical properties (e.g. nanometer size and layered structure), but also with new and interesting functions

(e.g. Magnetism, porous structure, and high surface-to-volume ratio). We will summarize the synthesis strategy and morphology of the core@ LDH nanocomposites, and their applications in drug delivery.

These nanocomposites were prepared by different methods. The co-precipitation method is the simplest and, the most commonly used of all methods for the preparation of LDHs. This method involves the preparation of two solutions, the first containing the desired metal cations as salts (usually of chloride or nitrate) dissolved in solution in their desired stoichiometric ratio; and the second solution is a caustic solution at a pH of 9 or greater [26]. The caustic solution may also contain the desired interlayer anions depending on the co-precipitation method chosen. The LDH is then prepared by delivering the two solutions to each other dropwise from a burette, separating funnel or a peristaltic pump. The metal cations will co-precipitate, and then the solution reaches super saturation. Super saturation is achieved by the addition of the caustic solution which causes the solution pH to increase. When the solution pH exceeds the pH at which the most soluble hydroxide of the metals in solution is precipitated the LDH will precipitate [27]. The precise identity of the base is not particularly important, however, anions such as OH^- may be competitively intercalated into the interlayer of the LDH. Once the solutions are combined the hydrotalcite will form as a precipitate that can be collected by filtration. The precipitate must be dried to remove excess water and ground to a uniform consistency before it can be used. The co-precipitation method is often preferred as it is simple to carry out and does not require any volatile solvents or other harsh and expensive chemicals or apparatus. Unfortunately, LDHs prepared by co-precipitation often suffer from poor crystallinity and the presence of impurities. In contrast a method like the urea method (which is in many ways similar to co-precipitation) allows better control of particle size and higher crystallinity than other methods. However, the urea method is only suitable for preparation of LDHs with high charge density, meaning it cannot be used to prepare LDHs containing Cu^{2+} or Cr^{3+}[28].

Co-precipitation is a facile and commonly used method for synthesizing the LDH shell. The cores that have been widely studied include

silica nanospheres, metal oxide nanoparticles and nanowires, and the shells produced by co-precipitation are always LDH nanoparticles. In general, the core adsorbs two different metal cations that subsequently precipitate on the surface of the core, and the LDH crystal growth occurs with aging at a certain temperature or through hydrothermal treatment (Fig. 2A). Zhang *et al.* used the co-precipitation method to prepare an anti-inflammatory drug-loaded LDH shell on the magnesium ferrite core. In this work the magnesium ferrite particle core that first adsorbed Mg^{2+} and Al^{3+} cations was mixed with a solution containing sodium hydroxide and diclofenac or ibuprofen to precipitate [29] .The ultrasound-assisted co-precipitation method has also been applied to synthesis a variety of core@LDH nanocomposites, such as SiO_2@LDH, Fe_3O_4@LDH, and Y_2O_3:Er^{3+},Yb^{3+}@SiO_2@LDH [30].

Another common method which was applied more than other synthesis method in order to prepare LDH, is sol-gel. The first sol-gel method to fabricate LDH shells was reported by Wei and co-workers in 2010. In this method, the boehmite (AlOOH) primer sol prepared by hydrolyzing the precursor $Al(OPr)_3$ was deposited on the scaffold (i.e. paper, cloth or sponge) with several cycles of sol-gel deposition (Fig. 2C). The generated AlOOH coating as both substrate and source of aluminum resulted in LDH in situ growth on the scaffold (Fig. 2C). Using this method, Wang, J., *et al.* (2014) successfully synthesized SiO_2@LDH and Fe_3O_4@SiO_2@LDH core–shell composites with diameters of ~600 nm and ~900 nm, respectively. Based on the SiO_2@LDH core–shell structure and the sol-gel method, the same group also synthesized a SiO_2@LDH yolk–shell and hollow structure by adjusting the concentration of urea. Using the sol-gel method, Wang *et al.* coated a much smaller SiO_2 core (50 nm, compared with Wei *et al.*'s 340 nm) with LDH and generated SiO_2@LDH core-shell nanocomposites. The sol-gel method can also be applied to grow LDH on the carbon coated Fe_3O_4, but failed to produce well-dispersed, homogenous core-shell particles [31].

One of the new synthesis methods to prepare LDH is direct deposited. In the direct deposition approach, the core material and LDH nanoparticles or nanosheets are synthesized separately, and subsequent combination of these building blocks generates a core-shell structure of self-assembling, followed by some post-treatment (Fig. 2D) [32]. MgAl-NO_3 LDH was first delaminated in formamide to make a colloid solution with exfoliated LDH nanosheets. Polystyrene (PS) beads were dispersed in a formamide suspension containing LDH nanosheets, the suspension was then ultrasonically agitated to promote the adsorption of the LDH nanosheets onto the PS surface. The sample was recovered by centrifugation (6000 rpm, 30 min) washed with ultrapure water and then dispersed in an aqueous solution of PSS. Core-shell composites coated with multilayer shells of (PSS/LDH) were synthesized by repeating this procedure 20 times.

The so-called "urea hydrolysis method" is suitable for precipitation of various metal hydroxides.

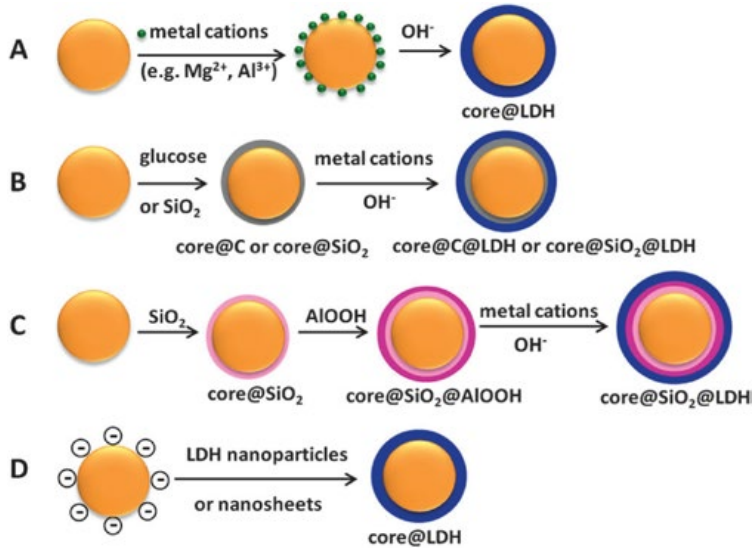

Fig. 2. Illustration of the fabrication of core@LDH nanocomposites by co-precipitation (A, B), sol-gel (C), and direct deposit (D).

Ammonium and carbonate are released during decomposition of urea, see equations 1-4 below. The hydrolysis of urea can easily be controlled by controlling the temperature. The rate constant increases by about 200 times when the temperature is increased from 60 to 100 °C [20]. Oxidation states of the metal cations can be controlled by addition of oxidizing agents such as, ammonium persulfate. Typically, the pH of the solution is controlled to be in the area of pH = 6-10, which is where precipitation of most LDHs will occur. The urea method favors growth of larger particles than the earlier mentioned co-precipitation method. The urea method, consequently yields products with much higher crystallinity [33]. A disadvantage is that the formation of LDHs with the urea method will nearly just give carbonate as the interplay anion because of its high affinity for carbonate. According to Inayat *et al*. the decomposition of urea in aqueous solution to carbonate and hydroxide takes place in the following reaction steps:

$$CO(NH_2)_{2\,(aq)} + H_2O_{\,(l)} \rightarrow CO_{2\,(aq)} + 2NH_{3\,(aq)} \quad (1)$$

$$NH_{3\,(aq)} + H_2O_{\,(l)} \rightleftarrows NH_4^{+} + OH^{-}_{\,(aq)} \quad (2)$$

$$CO_{2\,(aq)} + OH^{-}_{\,(aq)} \rightleftarrows HCO_3^{-}{}_{(aq)} \quad (3)$$

$$HCO_3^{-}{}_{(aq)} + OH^{-}_{\,(aq)} \rightleftarrows CO_3^{2-}{}_{(aq)} + H_2O_{\,(l)} \quad (4)$$

Recently, there has been reported a successful use of the urea method for direct synthesis of LDHs with nitrate as the interlayer anion. By carefully controlling the pH of the solution and by addition, excess nitrate, the intercalation of interlayer anion can be manipulated to other interlayer anions such as nitrate as well. The key parameter to control is the final pH of the synthesis mixture which are correlated to the initial nitrate/urea molar ratio and the synthesis time. By addition of ammonium nitrate to the reaction mixture, it is also possible to synthesize pure nitrate phase LHDs. Transition of pure phase of nitrate occurs at conditions pH < 7, via a mixed phase at pH = 7, to pure carbonate LDH at pH >7 [34].

Biological and pharmaceutical application of LDHs

The properties which make the LDHs useful in pharmaceutical applications are the high adsorption ability, high internal surface area, high cation-exchange capacity, interlayer reactions, chemical inertness, and low or null toxicity [35]. Nanostructured LDHs can serve as drug DDS, which exhibit the long-term stability and storage of the drug by isolating it from a hostile environment [36]. Depending on the field of applications, a large variety of LDH layer compositions have been studied ranging from MgAl, ZnAl, NiAl, MgFeAl to MgFe. Similarly, various intercalated anions have been tested, including inorganic anions (Cl^-, NO_3^-, CO_3^{2-}), organic surface modifiers (oleate, laurate, stearate, humic acid) but also functional organic species such as anticancer drugs, antibiotics and metal complexes [37].

Recently, considerable attention has been focused on the intercalation of biomolecules into LDHs. In addition to pharmaceuticals and enzymes which are discussed in more detail below, these include amino acids and peptides, vitamins, DNA and other nucleosides, ATP, and polysaccharides such as alginate, chitosan and carrageenan [38] .

Choy and co-workers (2002) have demonstrated that nanosized LDHs can be effective delivery carriers for drugs and genes by hybridization with DNA and antisense oligonucleotide

(As-myc). A strong suppression of cell growth (65%) was observed when HL-60 leukemia cells were incubated with 20 mM (As-myc)-LDH hybrid. The LDH itself was found to be non-cytotoxic against HL-60 cells. Consequently, LDHs can act as a new type of inorganic carrier that is completely different from existing non-viral vectors in terms of its chemical bonding and structure [39]. It is necessary to test cytotoxicity of LDHs themselves in the cells for use as antisense oligonucleotide delivery carrier. In fact, one critical element for the overall transfection efficacy of an oligonucleotide delivery system is cytotoxicity. Cell damage resulting from a cytotoxic delivery system is deleterious because following delivery, the cell must be capable of supporting translation and transcription. As shown in Fig. 3, LDHs themselves have no effect on the viability of HL-60 cells, the human promyelocytic leukemia cell, when administered at levels below 1000 μg mL^{-1} for up to 4 days. However, many cationic lipid complexes previously examined were bound to be toxic to cells at concentrations near their effective doses if exposure times were extended to several hours, suggesting that the molecules could not easily be metabolized [40].

Gene therapy is gaining attention for treatment of genetic deficiencies and life-threatening diseases. For the efficient introduction of foreign

DNA into cells, a carrier system is required. Both viral and non-viral vectors are presently under research. Generally, nonviral vectors, consisting of a targeting ligand and a DNA-binding moiety, have great potential for gene therapy due to their safety, simplicity, and capacity for packaging very large DNA molecules. The major limiting factor in the development and application of these vectors has been poor transfection efficiency due, primarily, to endosomal degradation [39].

Recent research showed nanobiohybrids as a novel gene and DDS. Leroux *et al.* (2005), reported the formation of Mg-Ga LDH-DNA nanohybrids using the co-precipitation method. This "self-assembly" approach enabled the incorporation of long DNA fragments. X-ray diffraction analyses indicated a parallel orientation of the DNA double helices in the interlamellar space with respect to the hydroxide sheets. The presence of adsorbed DNA macromolecules also inhibited the crystal growth: hydrodynamic diameter measurements revealed homogeneous populations of particles with a mean diameter ranging from 90 to 150 nm, compatible with cell penetration through endocytosis. Concerning the surface charges of this new DNA delivery system, zeta-potential measurements indicated negative values between −20 and 40 mV which suggest incomplete DNA intercalation. Nevertheless, this low negative surface charge might be suitable for protecting DNA from extra-cellular degradations without preventing cell penetration [41].

Application of LDHs in drug delivery systems

Drug release is an important phenomenon in the field of drug delivery and it refers to the process by which the drug solutes migrate from the initial position in the delivery system to the outer surface of the same and henceforward to the release medium [42]. The important factor in drug-delivery systems is their affinity to release the active agents (drugs/biomolecules/genes, etc.) in a constant manner at the target location. The tendency of LDHs to release the drug in a sustained manner in a particular pH makes them superior from other DDSs. The drug release from LDH can be in a two-phase manner, initially, fast followed by a slower release. In addition, LDHs are able to concentrate selectively and organize organic molecules [43].

Profiting from the biocompatibility and the anion-exchange properties of LDHs, they have been widely employed as support matrices of anionic drugs in DDS systems, among others. However, LDH is very sensitive to acid environments and the drug is often completely released in the stomach media (pH=1.2). Thus, the preparation of core-shell LDH-drug hybrids coated with a protective polymeric matrix, has been recently proposed to preserve the release properties through the gastrointestinal tract [44].

Khan, A. I., *et al.* (2001), reported that, a series of pharmaceutically active compounds including diclofenac, gemfibrozil, ibuprofen, naproxen, 2-propylpentanoic acid, 4-biphenylacetic acid and

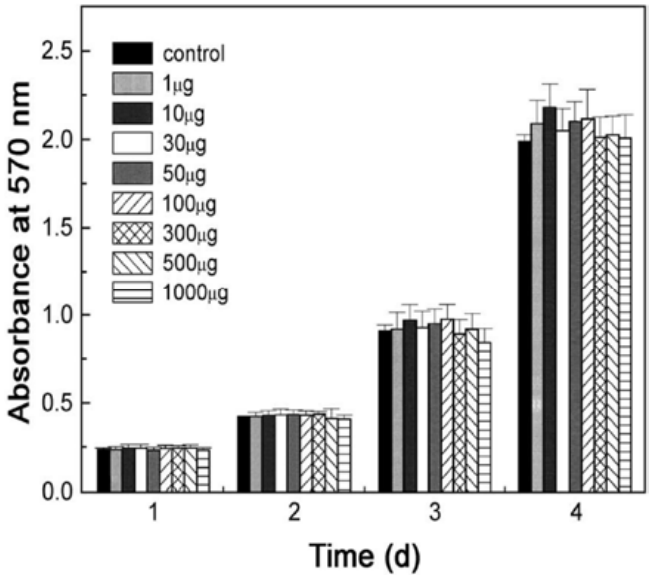

Fig. 3. Cytotoxicity test of pristine Mg_2Al-NO_3-LDH on the growth of HL-60. The final concentration of each material was 20 μM.

tolfenamic acid can be reversibly intercalated into a LDHs, initial studies suggest that these materials may have application as the basis of a novel tune able DDS.

Fig. 4, shows release profile plots for the deintercalation of diclofenac and of gemfibrozil on the addition of phosphate buffer at pH=4 and pH=7. At pH=4 the measured release of diclofenac and gemfibrozil is very fast with almost full deintercalation observed in less than 10 min. Surprisingly, the release curve for gemfibrozil at pH=7 is almost identical to the profile recorded at pH=4. At pH=7 the release of diclofenac is much slower and only after 28 min is 90% of the drug released into solution [45].

Li, B., *et al.* (2004) reported that the anti-inflammatory drug fenbufen has been intercalated into LDHs for the first time by co-precipitation under a nitrogen atmosphere. Drug release characteristics of the pillared LDH materials were investigated by a dissolution test in a simulated intestinal fluid (buffer at pH=7.8). The results show that the drug release of supramolecular LDH materials was a slow process, especially in the case of Mg/Al intercalated materials, suggesting that these drugs-inorganic hybrid materials can be used as an effective DDS [46].

Tamura *et al.* (2004) studied the intercalation of

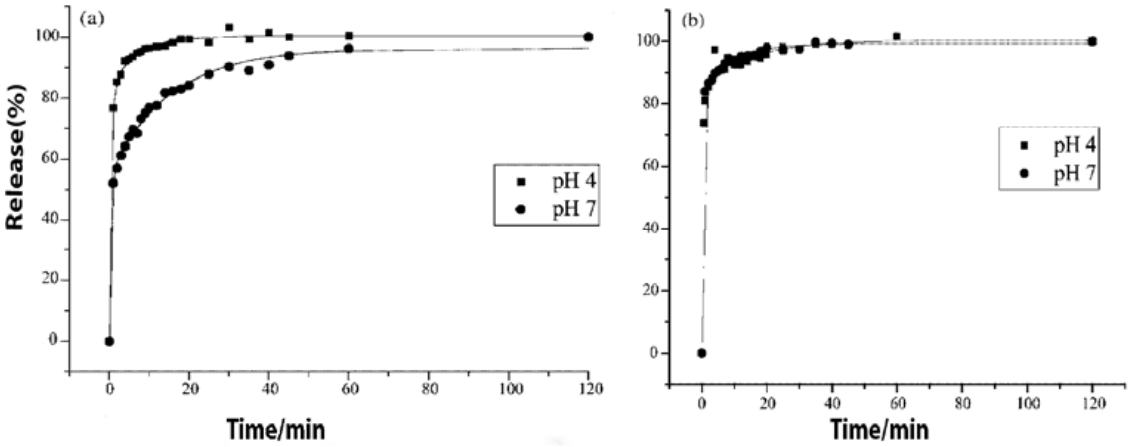

Fig. 4. Release profiles for (a) diclofenac at pH=4 and pH=7 and (b) gemfibrozil at pH=4 and pH=7.

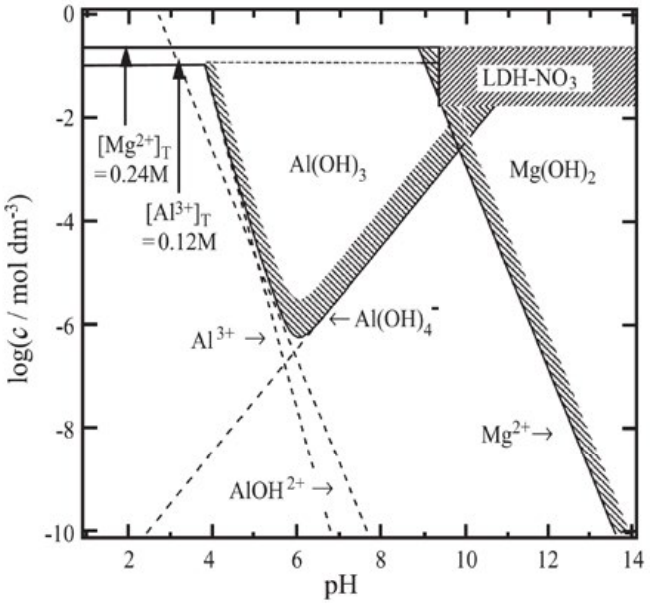

Fig. 5. Stability diagram of $Al(OH)_3$, $Mg(OH)_2$, and LDH-NO_3.

adenosine triphosphate (ATP) into MgAl LDH as a model for a DDS. Two intercalation methods were used: ion-exchange using nitrate as the interlayer anion and co-precipitation, adding Mg^{2+} and Al^{3+} ions into a sodium hydroxide solution. The stability diagram for aluminum hydroxide shows that it starts to form even at pH=4.0 (Fig. 5) and can contaminate the hydrotalcite that forms at higher pH (8.0 and 10). Pure hydrotalcite is not obtained with method B. From these results it was concluded that method A with a pH=10 and with an aging time of 24 h provides well crystallized pure hydrotalcite with a large ion-exchange capacity [47].

Three representative nonsteroidal anti-inflammatory drug molecules, Ibuprofen, Diclofenac, and Indomethacin, have been intercalated within the galleries of an anionic clay, Mg-Al LDHs (LDH) [48].

Gordijo *et al.* (2005) reported the immobilization of ibuprofen and copper-ibuprofen drugs on LDHs. Ibuprofen was intercalated in LDHs by: ion-exchange, reconstruction and co-precipitation. The drug and the copper-ibuprofen were also immobilized by adsorption on the external LDH surfaces. Pharmacological interests were compared considering the amounts of immobilized drugs and, most of all, their buffering properties. Samples obtained by exchange and co-precipitation exhibited poor buffering property, but contained high amounts of drug. Adsorption samples despite their buffering property contained low amounts of ibuprofen. The reconstructed hybrid systems combined significant amounts of immobilized drug with good buffering property. These organic–inorganic materials based on LDHs may be an interesting new formulation aiming to decrease gastric irritation, mainly due to their buffering property [49].

Controlled release formulation of an herbicide, 2,4-dichlorophenoxyacetate (24D) was developed by the virtue of the formation of organic-inorganic nanohybrid material and its ion-exchange property developed by bin Hussein, M. Z., *et al.* (2005). The inorganic Zn-Al LDHs (ZAL) was used as a matrix, hosting an active agent or a guest, 24D by self-assembly technique [50].

Concerning the interaction between antibiotics and LDH, there are some emphasized works. Mohanambe and Vasudevan (2005) have intercalated carboxymethyl beta-cyclodextrin cavities within the galleries of Mg-Al layered double hydroxide. The cyclodextrin functionalized LDH adsorbed neutral and nonpolar guest molecules [48].

Oh, J. M., *et al.* (2006), have been successful to intercalate anticancer drug, methotrexate (MTX), into LDHs, $Mg_2Al(OH)_6(NO_3)\cdot 0.1\ H_2O$, through conventional co-precipitation method. LDHs are endowed with great potential for delivery vector, since their cationic layers lead to safe reservation of bio functional molecules such as drug molecules or genes, and their ion-exchangeability and solubility in acidic media (pH<4) give rise to the controlled release of drug molecules. Moreover, it has been partly confirmed that LDH itself is non-toxic and facilitate the cellular permeation [51].

Nanostructural drug-inorganic clay composite involving a pharmaceutically active compound captopril (Cpl) intercalated Mg-Al-LDHs (Cpl-LDHs) with Mg/Al molar ratio of 2.06 has been assembled by co-precipitation method. Zhang, H., *et al.* (2006) considered that the dissolution mechanism is mainly responsible for the release behavior of Cpl-LDHs at pH=4.60, while the ion-exchange one is responsible for that at pH=7.45 [29].

Magnesium-aluminum-chloride-LDHs (MgAl-Cl-LDHs) intercalated with low molecular weight heparin (LMWH) were prepared for the first time by the co-precipitation method by Gu, Z, *et al.* (2008). In vitro release tests of LMWH-LDH in pH=7.4 PBS at 37℃ show a biphasic and sustained profile of LMWH anion release with ~20% in the first 12 h and another ~20% in the following 108 h. [52].

The morphology of individual nanohybrid particles is further examined using TEM (Fig. 6). As a consequence of LMWH intercalation the LDH nanoparticle shape changes from regular hexagon to ellipse (images a and b in Fig. 6). At higher magnification (images c and d in Fig. 6), the layered structure of both Cl-LDH and LMWH20-LDH is clearly observed. The dark and bright stripes represent the mixed hydroxide layers and the interlayers with exchangeable organic ($LMWHn^-$) and inorganic (Cl^-, CO_3^{2-}) anions, respectively. The average (003) spacing was calculated by measuring 10 repeated layer-interlayer units in 5 visual fields (images c and d in Fig. 6).

As shown in Fig. 6c, the pristine Cl-LDH has an average (003) spacing of ~0.65 nm, in line with the spacing determined using XRD (0.77 nm). The layered structure of LDH is still preserved

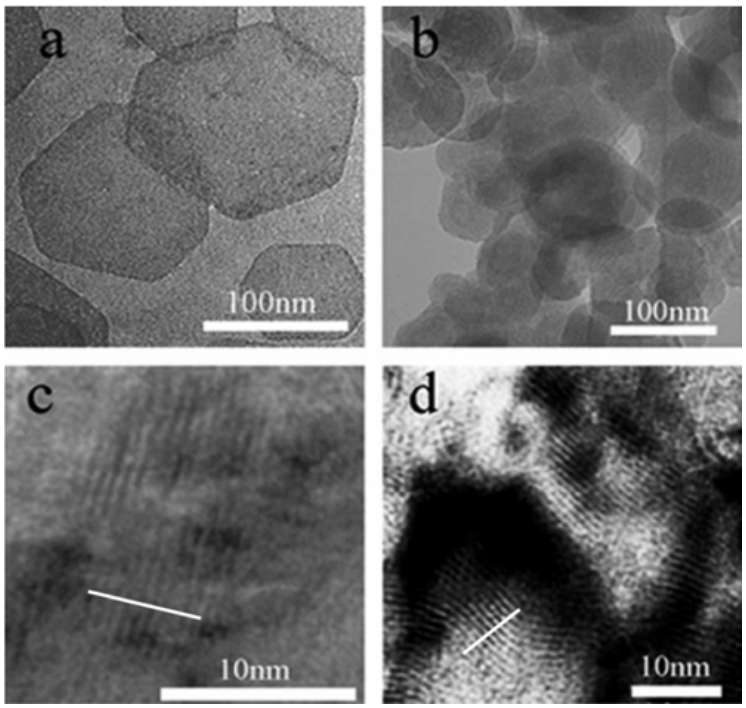

Fig. 6. TEM images of (a, c) Cl-LDH, (b) LMWH100-LDH, (d) LMWH20-LDH. A and b (low-magnification images) show the lateral dimension of particles; c and d (high-magnification images) show the layered structure of particles, in which the white line indicates the 10 layers-interlayer units in 5 visual fields.

after the incorporation of LMWH anions to form LMWH20-LDH (Fig. 6d). The average (003) spacing of LMWH20-LDH is ~1.00 nm, between 0.77 nm (Cl-LDH) and 1.40 nm (LMWH100-LDH) calculated from XRD data, and thus corresponding to partial intercalation [52].

The Enalaprilate (Enal), an active pharmaceutical component, was intercalated into LDHs (MgAl-LDH) by an ion-exchange reaction and it was carried out by Ribeiro, C., *et al.* (2009). The resulting hybrid system containing HDL-Enal-XG(3) slowly released the Enal. In an 8 h of test, the system protected 40% (w/v) of the drug [53].

In the other research which was performed by Li, F., *et al.* (2009), some nonsteroidal anti-inflammatory drugs (Indomethacin) were chosen as models of poorly water-soluble drugs. They were intercalated in MgAl-LDH and solubility measurements in acidic medium were performed. In acid pH hydrotalcite quickly dissolves and releasing the drug in molecular form [54].

Ibuprofen (IBU) has been chosen as a model drug, being intercalated in a Mg-Al LDH matrix by Aranda, P., *et al.* (2010). The combination of alginate and zein biopolymers gives rise to new matrices for DDS that can be used for direct encapsulation of a drug (e.g. IBU) and also to develop bio nanocomposite materials with drug-intercalated LDH systems. [44].

Qin, L., *et al.* (2010) intercalated anti-tumor drug Podophyllotoxin (PPT) into LDHs and investigated the in vitro cytotoxicity to tumor cells, the cellular uptake and in vivo anti-tumor inhibition of PPT-LDH [55].

Hydrophobic anticancer drug 5-fluorouracil (5-FU) has been included in the carboxymethyl modified β-cyclodextrin (CMCD), and the inclusion complex (5-FU/CMCD) was further intercalated into galleries of zinc aluminum LDHs (ZnAl-LDH) by the ion-exchange method by Jin, L., *et al.* (2010). It was found that 5-FU was released faster in pH=7.2 than in the acidic mediums (pH=4.8), and the released amount was higher [56].

The purpose of this study was to investigate the use of nanoparticulates composed of LDHs clays to bind various antibiotics (tetracycline, doxorubicin (DOX), 5-fluorouracil, vancomycin (VAN), sodium fusidate (SF)) and release them in a controlled manner (Chakraborti, M., *et al.* (2012)). MgAl (carbonate) LDHs clays may be useful for controlling release applications at sites requiring long-term antibiotic exposure as they maintain the

drug in a non-degraded state and release effective amounts of drug over long time periods [57].

In the other study, which was carried out by Saifullah, B., *et al.* (2013) para-amino salicylic acid (PASA) was intercalated into zinc/aluminum-LDHs (ZLDHs) by two methods, direct and indirect, to form nanocomposites: PASA nanocomposite prepared by a direct method (PASA-D) and PASA nanocomposite prepared by an indirect method (PASA-I). The in vitro release properties of the drug were investigated in physiological simulated phosphate-buffered saline solution of pH=7.4 and 4.8 [58].

Magnesium-aluminum LDHs intercalated with antitumor drug etoposide (VP16) were prepared for the first time using a two-step procedure, developed by Qin, L., *et al.* (2013). The mechanism of VP16-LDH release in the phosphate buffered saline solution at pH=7.4 is likely controlled by the diffusion of VP16 anions from inside to the surface of LDH particles [59].

In this research Li, L., *et al.* (2014), employed LDHs to simultaneously deliver an anticancer drug 5-fluorouracil (5-FU) and all stars cell death siRNA (CD-siRNA) for effective cancer treatment. The strategy takes advantage of the LDH anion-exchange capacity to intercalate 5-FU into its interlayer spacing and load siRNA on the surface of LDH nanoparticles. The combination of CD-siRNA and anticancer drug 5-FU with the same LDH particles significantly enhanced cytotoxicity to three cancer cell lines, e.g. MCF-7, U2OS and HCT-116, compared to the single treatment with either CD-siRNA or 5-FU. This enhancement is probably a result of coordinate mitochondrial damage process. Thus, the strategy to co-deliver siRNA and an anticancer drug by LDHs has great potential to overcome the drug resistance and enhance cancer treatment [60].

As an alternative to degradable organic coatings the possibility of using LDHs to generate implant coatings for controlled drug delivery was evaluated in vivo and in vitro. Coatings prepared from LDH suspensions dissolved slowly and appeared compatible with cultured cells. LDH coatings loaded with an antibiotic resulted in antibacterial effects in vitro. The LDH coating prolonged the drug release period and improved the proliferation of adherent cells in comparison to pure drug coatings. However, during incubation in physiological solutions the LDH coatings became brittle and pieces occasionally detached from the surface. For stress protection porous titanium implants were investigated as a substrate for the coatings. The pores prevented premature detachment of the coatings.

The other work that was reported by Barkhordari, S., *et al.* (2014), deals with the preparation of new DDSs based on the combination of LDHs and a pH-sensitive polymer, carboxymethyl cellulose (CMC). Ibuprofen (IBU) has been chosen as a model drug, being intercalated between LDH layers in order to prepare LDH-IBU nanohybrids (Fig. 7). The LDH-IBU nanohybrids and CMC/LDH-IBU nanocomposite beads were tested for controlling release of ibuprofen under conditions simulating the gastrointestinal tract, pH=1.2 (stomach) and 7.4 (intestinal tract). Studies of ibuprofen release from LDH-IBU nanohybrids and CMC/LDH-IBU nanocomposite beads show a better protection against drug release for a CMC/LDH-IBU nanocomposite at the stomach pH and a controlled release in the intestinal tract conditions [61].

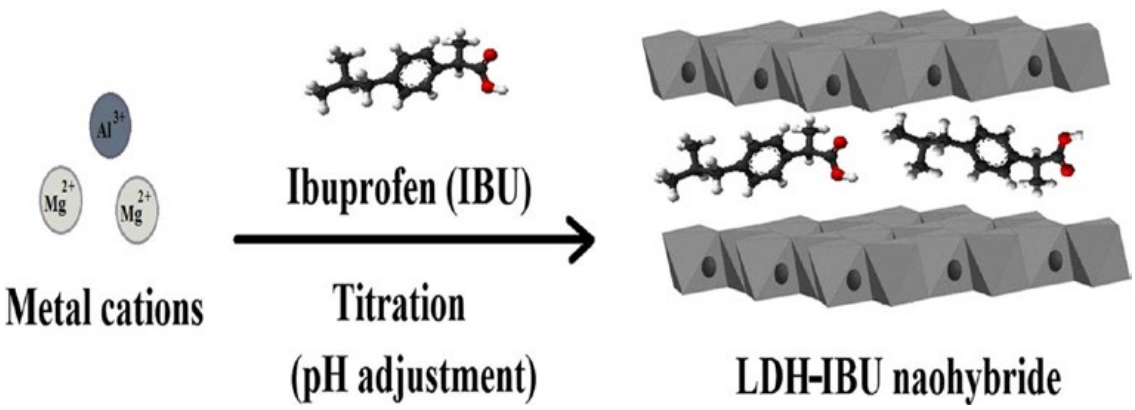

Fig. 7. Schematic representation of formation of LDH-IBU nanohybride via co-precipitation method

In this work, (Rojas, R., *et al.* (2015)) these aspects are studied using LDHs intercalated with ibuprofen (Ibu), naproxen (Nap) or ketoprofen (Ket) to understand the behavior of intercalation compounds as drug carriers.

The particle size and shape of LDH-D was assessed by SEM images. The SEM images showed the morphology of LDH particles. LDH particles were formed by agglomeration of smaller units or platelets of around 300 nm (Fig. 8). These platelets presented high diameter to thickness ratio and irregular shape [62].

In the other study, which was done by Mondal, S., *et al.* (2016), the efficacy of $Mg_{1-x}Al_x(NO_3)_x.(OH)_2$ LDH nanoparticles as a carrier and for controlled release of one of the non-Steroidal anti-inflammatory drugs (NSAID), sodium salicylate. The cumulative release kinetic of salicylate from MgAl-LDH-SA hybrids in phosphate buffer saline (PBS) at pH=7.4 showed a sustained release of salicylate up to 72 h that closely resembled first order release kinetics through a combination of drug diffusion and dissolution of LDH under physiological conditions (Fig. 9) [63].

Hydrophobic anticancer drug, raloxifene hydrochloride (RH) is intercalated into a series of magnesium aluminum LDHs with various charge density anions through ion-exchange technique for controlled drug delivery by Senapati, S., *et al.* (2016). The particle nature of the LDH in presence of drug is determined through electron microscopy and surface morphology. The release of drug from the RH intercalated LDHs was made very fast or sustained by altering the exchangeable anions followed by the modified Freundlich and parabolic diffusion models. The drug release rate is explained from the interactions between the drug and LDHs along with order–disorder structure of drug intercalated LDHs. Nitrate bound LDH exhibits greater interaction with drug and sustained drug delivery against the loosely interacted phosphate bound LDH-drug, which shows fast release. Cell viability through MTT assay suggests drug intercalated LDHs as better drug delivery vehicle for cancer cell line against the poor bioavailability of the pure drug (Fig. 10) [64].

A novel MgAl-LDH nanoparticle/thermogel composite DDS for sustained release of Brimonidine (Bri) has been designed, prepared, and characterized by Sun, J., *et al.* (2017), for treatment of severe glaucoma. The in vitro drug release of Bri@LDH/Thermogel shows a sustainable release for up to 144 h, a significant delay of drug release compared to that from Bri@LDH nanoparticles. [65].

This study, which was reported by (Wu, J., *et al.* (2017)) focuses on the synthesis and in vitro evaluation of magnetic nanocomposites (Fe_3O_4@

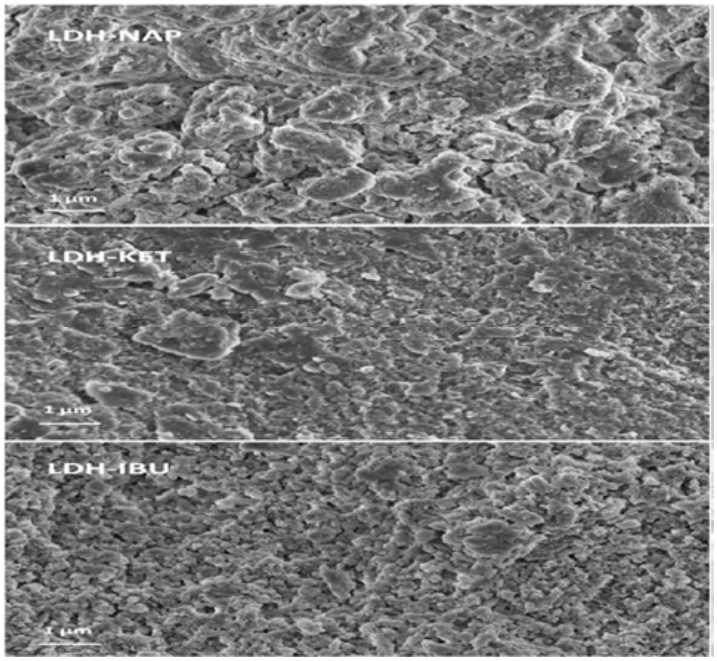

Fig. 8. SEM images of LDH-D with ibuprofen, naproxen and ketoprofen.

LDH) as methotrexate (MTX) delivery system for targeted anticancer therapy and 84.94% MTX was released within 48 h, at pH=3.5 via the co-effect of dissolution of LDH layer and ion-exchange [66].

The 2D mono LDHs (MLDH) nanosheets were employed by Mei, X., *et al.* (2018) to localize doxorubicin (DOX), an anticancer drug, with a loading capacity of as high as 3.6 mg mg^{-1} (w/w). With the assistance of the targeting agent folic acid (FA), DOX-FA/MLDHs demonstrate targeted cellular uptake and superior anticancer behavior based on in vitro tests performed with cancer cells [5].

The pH-responsive smart capsules were developed by Katagiri, K., *et al.* (2018), the layer-by-layer assembly with a colloid templating technique. Acid-soluble inorganic nanosheets were prepared from MgAl-LDH by an exfoliation technique [67].

The intercalation of Kynurenic acid (KYNA) molecules into biocompatible MgAl-LDH lamellae were investigated by Deák, Á., *et al.* (2018). LDH layers were almost completely dissolved at gastric pH during the in vitro study and the anti-ulcerant KYNA molecules were released from the destroyed

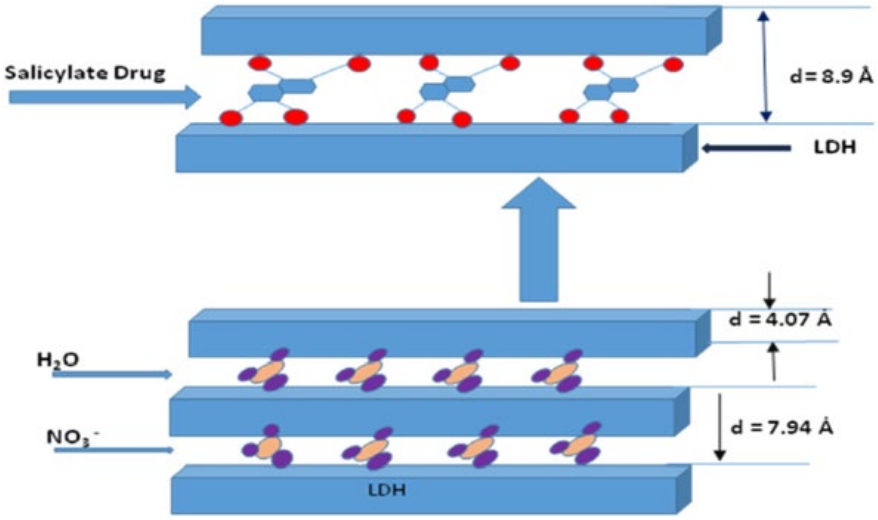

Fig. 9. Intercalation of salicylate into MgAl-LDH.

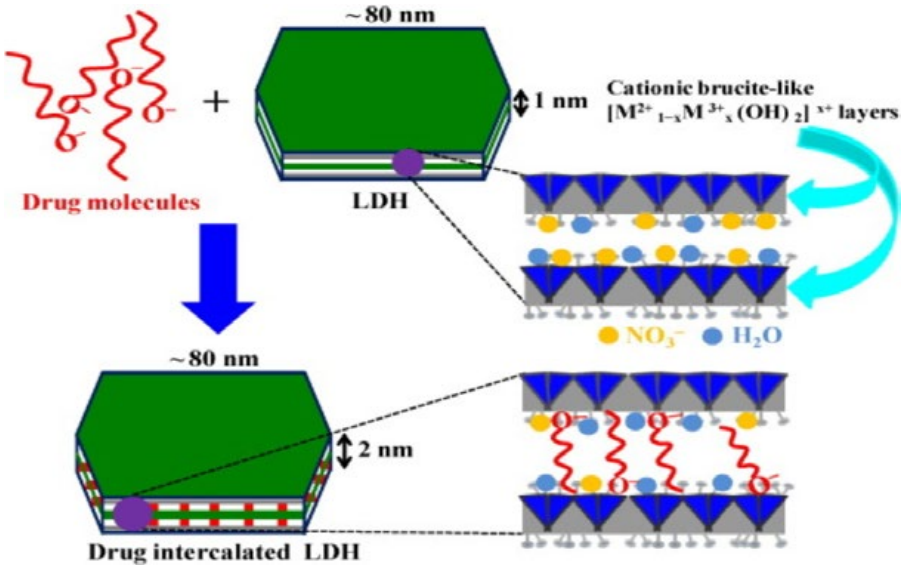

Fig. 10. Schematic model representing the structure of LDH and drug intercalation within LDH layers.

interlayers. The release properties of KYNA were studied at the pH of human saliva at a value of 6.70 and at pH of SGF (pH=1.5), as well. The release study of the KYNA/LDH has also been performed at pH=1.5. Fig. 11, presents the drug release profiles, which were carried out over a period of 240 min and at body temperature (37 °C) and in physiological saline. The released concentration of the drug was determined spectrophotometrically. The solubility and thus the release rate of anionic KYNA depend on pH [68].

In the other work, Allou, N., *et al.* (2018). Hybrid materials containing citric acid cross-linked carboxymethyl cellulose (CMC) and norfloxacin (NOR) intercalated layered double hydroxide (LDH) deposited over the surface of functionalized carbon (AC) were prepared. The synthesized CMC@AC-LDHNOR nanohybrids were characterized using different techniques and in vitro NOR release behaviors were investigated in phosphate buffer saline, pH=7.4 at 37 °C [69].

In this work, Komarala, E. P., *et al.* (2018), were reported the loading of cefotaxime sodium on MgAl layered double hydroxide (Cefo-LDH) and the formation of a nanohybrid with a fenugreek polymer (CLF nanohybrid). This nanohybrid was synthesized through the method of anion-exchange followed by sonication. The as-synthesized CLF nanohybrid was thoroughly characterized by XRD, FT-IR and zeta potential measurements, which revealed that the cefotaxime drug was bound to the LDH surface. The drug loading capacities of Cefo-LDH and the CLF nanohybrid were found to be 85.6 and 72.5 μg mg^{-1}, respectively. The drug released from the CLF nanohybrid demonstrates a controlled and sustained profile at pH=7.3 over a period of 72 h [70].

In this article, Capsoni, D., *et al.* (2018), synthesize by co-precipitation method the hybrid compound Carprofen-Zn_2Al-LDH. Carprofen, a poorly soluble anti-inflammatory drug, could also benefit of the association with a natural antacid such as LDH, to reduce the gastric irritation after its administration. The dissolution tests clearly demonstrate a significant improvement of the drug release rate when carprofen is in the form of hybrid compound [71].

The potential of the layered gadolinium hydroxide (LGdH) $[Gd_2(OH)_5]Cl.yH_2O$ (LGdH-Cl) for simultaneous drug delivery and magnetic resonance imaging was explored by Xu, Y., *et al.* (2018), in this work. Three non-steroidal anti-inflammatory drugs (diclofenac [dic], ibuprofen [ibu], and naproxen [nap]) were intercalated into LGdH-Cl for the first time, using three different routes (ion-exchange intercalation, co-precipitation, and exfoliation-self-assembly). The materials prepared by co-precipitation in general have noticeably higher drug loadings than those produced by ion-exchange or self-assembly, as a result of the incorporation of some neutral drug into the composites. The LGdH-drug intercalates are stable at neutral pH, but rapidly degrade in acidic conditions to free Gd^{3+} into solution. While LGdH-nap releases its drug loading into solution very rapidly (within *ca.* 1.5 h) at pH=7.4, LGdH-dic show sustained release over 4 h, and LGdH-ibu extends this to 24 h. The biocompatibility of selected

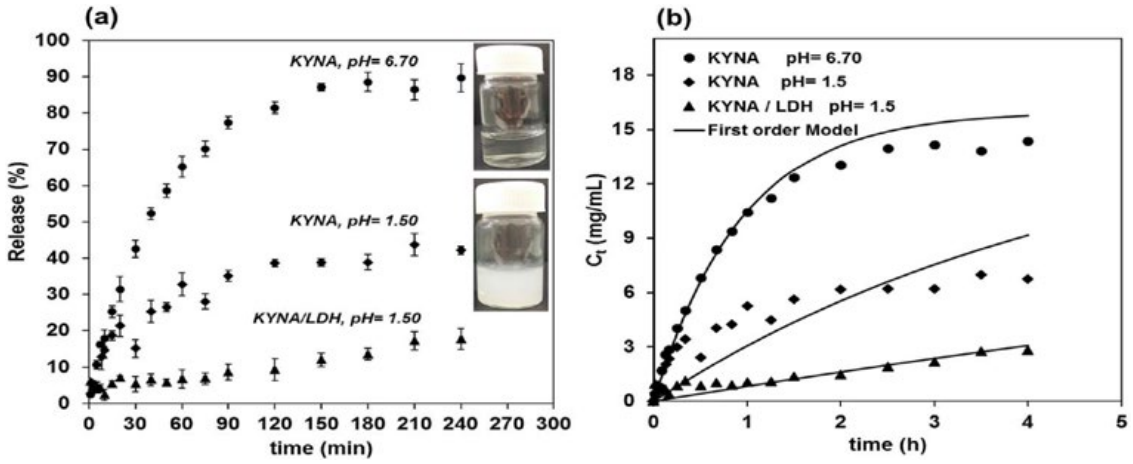

Fig. 11. The percentage release profile of anionic KYNA molecules at two different pH values (pH=6.7 and 1.5) and the KYNA release from LDH lamellae at acidic (pH=1.5) pH, as well as the measured KYNA concentration values (Ct, mg mL^{-1}) as a function of release time with the fitted curves calculated by the first-order rate model.

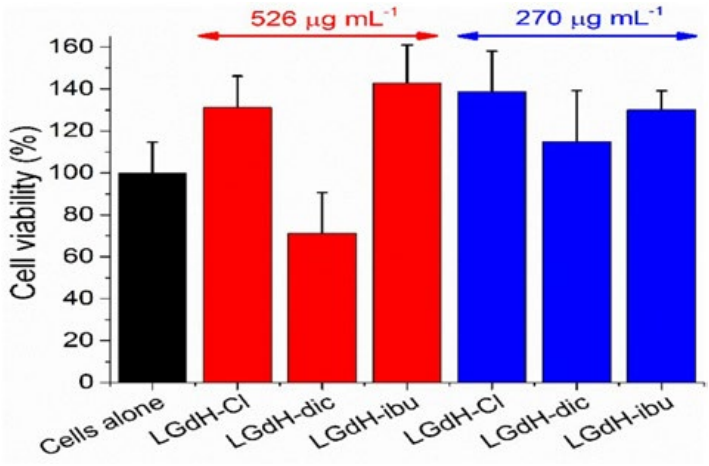

Fig. 12. The results of in vitro cell viability studies with selected LGdH materials. Experiments were performed with suspensions of the LGdHs at concentrations of 476 (red bars) or 238 (blue bars) μg mL^{-1}. Results are shown as mean ± S.D. from three independent experiments, each containing three replicates.

Table. 1. Brief summary of LDH-based DDS, reviewed in this paper.

LDH host	Synthesis method	Pharmaceutical guest	Ref
Mg, Al	Ion-exchange	Diclofenac, Gemfibrozil, Ibuprofen, Naproxen, 2-propylpentanoic acid, 4-Biphenylacetic acid and Tolfenamic acid	[45]
Mg, Al	Co-precipitation	Fenbufen	[46]
Mg, Al	Co-precipitation Ion-exchange	Adenosine triphosphate	[48]
Mg, Al	Ion-exchange, Reconstruction, Co-precipitation	Ibuprofen Copper-ibuprofen	[49]
Zn, Al	Ion-exchange	2,4-dichlorophenoxyacetate	[50]
Mg, Al	Co-precipitation	Methotrexate (MTX)	[51]
Mg, Al	Co-precipitation	Captopril	[29]
Mg, Al, Cl	Co-precipitation	Low molecular weight heparin (LMWH)	[52]
Mg, Al	Ion-exchange	Enalaprilate (Enal)	[53]
Mg, Al	Co-precipitation	Indomethacin	[54]
Mg, Al	Ion-exchange	Ibuprofen (IBU)	[44]
Mg, Al	Ion-exchange	Podophyllotoxin (PPT)	[55]
Zn, Al	Ion-exchange	5-fluorouracil (5-FU)	[56]
Mg, Al	Co-precipitation	Tetracycline, Doxorubicin (DOX), 5-fluorouracil, Vancomycin (VAN), Sodium fusidate (SF)	[57]
Zn, Al	Direct and indirect	Para-amino salicylic acid (PASA)	[58]
Mg, Al		Etoposide (VP16)	[59]
Mg, Al	Anion-exchange	5-fluorouracil (5-FU)	[60]
Mg, Al	Co-precipitation	Ibuprofen (IBU)	[61]
Mg, Al	Co-precipitation	Ibuprofen (Ibu), Naproxen (Nap) or Ketoprofen (Ket)	[62]
Mg, Al	Co-precipitation	sodium salicylate	[63]
Mg, Al	Ion-exchange	Raloxifene hydrochloride (RH)	[64]
Mg, Al		Brimonidine (Bri)	[65]
Mg, Al	Ion-exchange	Methotrexate (MTX)	[66]
Mg, Al	Co-precipitation	Doxorubicin (DOX),	[5]
Mg, Al	Ion-exchange	Kynurenic acid (KYNA)	[68]
Mg, Al	Ion-exchange	Carboxymethyl cellulose (CMC) and Norfloxacin (NOR)	[69]
Mg, Al	Anion-exchange	Cefotaxime sodium	[70]
Zn, Al	Co-precipitation	Carprofen	[71]
Gd, Cl	Ion-exchange intercalation, Co-precipitation, and exfoliation-self-assembly	Diclofenac [dic], Ibuprofen [ibu], and Naproxen [nap]	[72]
Mg, Al	Ion-exchange	5-Fluorouracil (5-FU)	[73]

LGdH-drug composites was assessed using in vitro cell viability studies. The results of performing these with the solid LGdH materials are presented in Fig. 12. At concentrations of 526 µg mL^{-1}, both LGdH-Cl and LGdH-ibu are highly biocompatible, and in fact appear to encourage cell growth. In contract, LGdH-dic causes some cell death, with a mean viability of 71 %. At a lower concentration of 270 µg mL^{-1} all three LGdH materials explored have very good biocompatibility, resulting in cell counts higher than the untreated control cells. Further experiments were undertaken with solutions made from LGdH suspensions (Fig. 12). In all cases here the cell viability was indistinguishable from the untreated cells, thereby confirming the biocompatibility of the LGdH-drug materials. [72].

The clinic application of magnesium is mainly impeded by its poor corrosion resistance and implants with localized drug delivery attract tremendous interest (Peng, F., *et al.* (2018)). Here, Mg/Al layered double hydroxide (Mg-Al LDH) film was in situ prepared on AZ31 alloy by a hydrothermal process, and further calcined to form metastable mixed oxides, also named Mg/Al layered double oxide (LDO). Finally, immersing in 5-Fluorouracil (5-FU) solution, Mg/Al LDO would revert to Mg/Al LDH via a memory effect, and be loaded with 5-FU (#LDO-5FU). This work broadens the application of calcined LDH and provides a new strategy in the field of surface modification of magnesium alloy [73].

CONCLUSION

The use of clays in various fields is well known and familiar to mankind, contributing to human health and life. In addition to their traditional applications, many types of clays, clay minerals, but also LDHs have been recently applied to diverse commercial products as simple adding or adjuvants. Increasing attention has been recently given to advanced applications, in particular based on new interdisciplinary fields developed for protective and controlled delivery of various functional compounds. The promising potential of clay minerals and LDHs offers novel perspectives for inorganic-biomaterial hybrids, and practical applications as new delivery systems are not so far. LDHs can be used in a wide range of applications in health. LDHs are being used as excipients and active principles in the pharmaceutical industry. Development of new pharmaceutical formulations is observed, based on LDHs, for cancer therapy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

[1] K. Ladewig, Z.P. Xu, G.Q. Lu, Layered double hydroxide nanoparticles in gene and drug delivery, Expert. Opin. Drug. Del., 6, 907(2009).

[2] S.-J. Choi, J.-H. Choy, Layered double hydroxide nanoparticles as target-specific delivery carriers: uptake mechanism and toxicity, Nanomedicine, 6, 803(2011).

[3] G.-F. Xiao, H.-Y. Zeng, Q.-J. Huang, W. Zhang, J.Z. Du, H. Duan, C. Chen, Facile Preparation of Modifying Layered Double Hydroxide Nanoparticles for Drug Delivery, J. Nanosci. Nanotechnol, 18, 5256(2018).

[4] G. Huang, K.-L. Zhang, S. Chen, S.-H. Li, L.-L. Wang, L.-P. Wang, R. Liu, J. Gao, H.-H. Yang, Manganese-iron layered double hydroxide: a theranostic nanoplatform with pH-responsive MRI contrast enhancement and drug release, J. Mater. Chem. B, 5, 3629(2017).

[5] X. Mei, S. Xu, T. Hu, L. Peng, R. Gao, R. Liang, M. Wei, D.G. Evans, X. Duan, Layered double hydroxide monolayers for controlled loading and targeted delivery of anticancer drugs, Nano. Res, 11, 195(2018).

[6] S.P. Newman, W. Jones, Synthesis, characterization and applications of layered double hydroxides containing organic guests, New J. Chem., 22, 105(1998).

[7] D.P. Debecker, K. Bouchmella, C. Poleunis, P. Eloy, P. Bertrand, E.M. Gaigneaux, P.H. Mutin, Design of SiO_2–Al_2O_3–MoO_3 metathesis catalysts by nonhydrolytic sol-gel, Chem. Mater., 21, 2817(2009).

[8] G. Pshinko, A. Kosorukov, L. Puzyrnaya, V. Goncharuk, Layered double hydroxides intercalated with EDTA as effective sorbents for U (VI) recovery from wastewater, Radiochem., 53, 303(2011).

[9] M.I. Carretero, M. Pozo, Clay and non-clay minerals in the pharmaceutical industry: Part I. Excipients and medical applications, Appl. Clay Sci., 46, 73(2009).

[10] P.B. Panici, S. Basile, F. Maneschi, A.A. Lissoni, M. Signorelli, G. Scambia, R. Angioli, S. Tateo, G. Mangili, D. Katsaros, Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial, JNCI: J. Natl. Cancer. Inst., 100, 1707(2008).

[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, 239(2014).

[12] V. Ambrogi, L. Perioli, C. Pagano, F. Marmottini, M. Ricci, A. Sagnella, C. Rossi, Use of SBA-15 for furosemide oral delivery enhancement, Eur. J. Pharm. Sci., 46, 43(2012).

[13] E. Conterosito, G. Croce, L. Palin, C. Pagano, L. Perioli, D. Viterbo, E. Boccaleri, G. Paul, M. Milanesio, Structural characterization and thermal and chemical stability of bioactive molecule–hydrotalcite (LDH) nanocomposites, Phys. Chem. Chem. Phys., 15, 13418(2013).

[14] L. Perioli, C. Pagano, Inorganic-organic hybrids to improve the performances of anti-inflammatory topical formulations, Int. J., 5 (2016).

[15] S. Lee, C.Y. Heo, Corporate social responsibility and

customer satisfaction among US publicly traded hotels and restaurants, Int. J. Hosp. Manag., 28, 635 (2009).
[16] M. Shamsayei, Y. Yamini, H. Asiabi, M. Safari, On-line packed magnetic in-tube solid phase microextraction of acidic drugs such as naproxen and indomethacin by using Fe_3O_4@SiO_2@ layered double hydroxide nanoparticles with high anion exchange capacity, Microchim. Acta, 185, 192 (2018).
[17] C. You, Y. Ji, Z. Liu, X. Xiong, X. Sun, Ultrathin CoFe-Borate Layer Coated CoFe-Layered Double Hydroxide Nanosheets Array: A Non-Noble-Metal 3D Catalyst Electrode for Efficient and Durable Water Oxidation in Potassium Borate, ACS Sustain. Chem. Eng., 6, 1527(2018).
[18] N. Chen, C. Long, Y. Li, D. Wang, H. Zhu, High-performance layered double hydroxide/poly (2, 6-dimethyl-1, 4-phenylene oxide) membrane with porous sandwich structure for anion exchange membrane fuel cell applications, J. Membrane Sci., 552, 51(2018).
[19] J. Yu, Q. Wang, D. O'Hare, L. Sun, Preparation of two dimensional layered double hydroxide nanosheets and their applications, Chem. Soc. Rev., 46, 5950(2017).
[20] A.U. Kura, M.Z. Hussein, S. Fakurazi, P. Arulselvan, Layered double hydroxide nanocomposite for drug delivery systems; bio-distribution, toxicity and drug activity enhancement, Chem. Cent. J., 8, 47(2014).
[21] G. Chen, I. Roy, C. Yang, P.N. Prasad, Nanochemistry and nanomedicine for nanoparticle-based diagnostics and therapy, Chem. Rev, 116, 2826(2016).
[22] S. Mondal, S. Dasgupta, K. Maji, MgAl-layered double hydroxide nanoparticles for controlled release of salicylate, Mater. Sci. Eng. C, 68, 557(2016).
[23] H. Heinz, C. Pramanik, O. Heinz, Y. Ding, R.K. Mishra, D. Marchon, R.J. Flatt, I. Estrela-Lopis, J. Llop, S. Moya, Nanoparticle decoration with surfactants: molecular interactions, assembly, and applications, Surf. Sci. Rep., 72, 1 (2017).
[24] C. Forano, F. Bruna, C. Mousty, V. Prevot, Interactions Between Biological Cells and Layered Double Hydroxides: Towards Functional Materials, Chem. Rec, (2018).
[25] R.K. Kankala, Y. Kuthati, C.-L. Liu, C.-H. Lee, Hierarchical coated metal hydroxide nanoconstructs as potential controlled release carriers of photosensitizer for skin melanoma, RSC Adv., 5, 42666(2015).
[26] L. Qiu, Y. Gao, P. Lu, D. O'hare, Q. Wang, Synthesis and properties of polypropylene/layered double hydroxide nanocomposites with different LDHs particle sizes, J. Appl. Polym. Sci., 135, 46204(2018).
[27] X. Tao, D. Liu, W. Cong, L. Huang, Controllable synthesis of starch-modified ZnMgAl-LDHs for adsorption property improvement, Appl. Surf. Sci., (2018).
[28] H.N. Tran, C.-C. Lin, H.-P. Chao, Amino acids-intercalated Mg/Al layered double hydroxides as dual-electronic adsorbent for effective removal of cationic and oxyanionic metal ions, Sep. Purif. Technol., 192, 36(2018).
[29] H. Zhang, K. Zou, S. Guo, X. Duan, Nanostructural drug-inorganic clay composites: Structure, thermal property and in vitro release of captopril-intercalated Mg-Al-layered double hydroxides, J. Solid State Chem., 179, 1792(2006).
[30] Z. Gu, J.J. Atherton, Z.P. Xu, Hierarchical layered double hydroxide nanocomposites: structure, synthesis and applications, Chem. Comm., 51, 3024(2015).
[31] J. Wang, R. Zhu, B. Gao, B. Wu, K. Li, X. Sun, H. Liu, S. Wang, The enhanced immune response of hepatitis B virus DNA vaccine using SiO_2@LDH nanoparticles as an adjuvant, Biomaterials, 35, 466(2014).
[32] S. Wu, K. Hui, K. Hui, One-dimensional core-shell architecture composed of silver nanowire@ hierarchical nickel-aluminum layered double hydroxide nanosheet as advanced electrode materials for pseudocapacitor, J. Phys. Chem. C, 119, 23358(2015).
[33] R. Soltani, A. Shahvar, M. Dinari, M. Saraji, Environmentally-friendly and ultrasonic-assisted preparation of two-dimensional ultrathin Ni/Co-NO_3 layered double hydroxide nanosheet for micro solid-phase extraction of phenolic acids from fruit juices, Ultrason. sonochem., 40, 395(2018).
[34] L. Dang, H. Liang, J. Zhuo, B.K. Lamb, H. Sheng, Y. Yang, S. Jin, Direct Synthesis and Anion Exchange of Non-Carbonate-Intercalated NiFe Layered Double Hydroxides and the Influence on Electrocatalysis, Chem. Mater., (2018).
[35] L. Valdés, I. Pérez, L.C. De Ménorval, E. Altshuler, J.O. Fossum, A. Rivera, A simple way for targeted delivery of an antibiotic: In vitro evaluation of a nanoclay-based composite, PloS one, 12, e0187879 (2017).
[36] D. Cao, Z. Xu, Y. Chen, Q. Ke, C. Zhang, Y. Guo, Ag-loaded MgSrFe-layered double hydroxide/chitosan composite scaffold with enhanced osteogenic and antibacterial property for bone engineering tissue, J. Biomed. Mater. Res. B Appl. Biomate., 106, 863(2018).
[37] M. Richetta, P. Medaglia, A. Mattoccia, A. Varone, R. Pizzoferrato, Layered Double Hydroxides: Tailoring Interlamellar Nanospace for a Vast Field of Applications, J. Mater. Sci. Eng., 6, 2169(2017).
[38] D.G. Evans, X. Duan, Preparation of layered double hydroxides and their applications as additives in polymers, as precursors to magnetic materials and in biology and medicine, Chem. Comm., 485(2006).
[39] S.-Y. Kwak, Y.-J. Jeong, J.-S. Park, J.-H. Choy, Bio-LDH nanohybrid for gene therapy, Solid State Ionics, 151, 229(2002).
[40] C.F. Bennett, M.-Y. Chiang, H. Chan, J. Shoemaker, C.K. Mirabelli, Cationic lipids enhance cellular uptake and activity of phosphorothioate antisense oligonucleotides, Mol. Pharmacol., 41, 1023(1992).
[41] J.-M. Oh, D.-H. Park, S.-J. Choi, J.-H. Choy, LDH nanocontainers as bio-reservoirs and drug delivery carriers, Recent pat. nanotech., 6, 200(2012).
[42] S.-M. Lee, S.T. Nguyen, Smart nanoscale drug delivery platforms from stimuli-responsive polymers and liposomes, Macromolecules, 46, 9169(2013).
[43] G. Mishra, B. Dash, S. Pandey, Layered double hydroxides: A brief review from fundamentals to application as evolving biomaterials, Appl. Clay Sci., 153, 172(2018).
[44] P. Aranda, M. Darder, E. Ruiz-Hitzky, Bionanocomposites based on alginate–zein/layered double hydroxide materials as drug delivery systems, J. Mater. Chem., 20, 9495(2010).
[45] A.I. Khan, L. Lei, A.J. Norquist, D. O'Hare, Intercalation and controlled release of pharmaceutically active compounds from a layered double hydroxideElectronic supplementary information (ESI) available: Fig. S1: X-ray diffraction patterns of (a)$[LiAl_2(OH)_6]Cl{\cdot}H_2O$ and (b) LDH/Ibuprofen intercalate. Chem. Comm., 2342(2001).
[46] B. Li, J. He, D. G. Evans, X. Duan, Inorganic layered double hydroxides as a drug delivery system—intercalation and in vitro release of fenbufen, Appl. Clay Sci., 27, 199(2004).
[47] H. Tamura, J. Chiba, M. Ito, T. Takeda, S. Kikkawa, Synthesis and characterization of hydrotalcite-ATP intercalates, Solid

State Ionics, 172, 607(2004).
[48] L. Mohanambe, S. Vasudevan, Anionic clays containing anti-inflammatory drug molecules: Comparison of molecular dynamics simulation and measurements, J. Phys. Chem. B, 109, 15651(2005).
[49] C.R. Gordijo, C.A. Barbosa, A.M.D.C. Ferreira, V.R. Constantino, D. de Oliveira Silva, Immobilization of ibuprofen and copper-ibuprofen drugs on layered double hydroxides, J. pharm. sci., 94, 1135(2005).
[50] M.Z. bin Hussein, A.H. Yahaya, Z. Zainal, L.H. Kian, Nanocomposite-based controlled release formulation of an herbicide, 2, 4-dichlorophenoxyacetate incapsulated in zinc-aluminium-layered double hydroxide, Sci. Tech. Adv. Mater., 6, 956(2005).
[51] J.-M. Oh, M. Park, S.-T. Kim, J.-Y. Jung, Y.-G. Kang, J.-H. Choy, Efficient delivery of anticancer drug MTX through MTX-LDH nanohybrid system, J. Phys. Chem. Solids, 67, 1024(2006).
[52] Z. Gu, A.C. Thomas, Z.P. Xu, J.H. Campbell, G.Q. Lu, In vitro sustained release of LMWH from MgAl-layered double hydroxide nanohybrids, Chem. Mater., 20, 3715(2008).
[53] C. Ribeiro, G.G.C. Arizaga, F. Wypych, M.R. Sierakowski, Nanocomposites coated with xyloglucan for drug delivery: In vitro studies, Int. J. Pharm., 367, 204(2009).
[54] F. Li, L. Jin, J. Han, M. Wei, C. Li, Synthesis and controlled release properties of prednisone intercalated Mg-Al layered double hydroxide composite, Ind. Eng. Chem. Res., 48, 5590(2009).
[55] L. Qin, M. Xue, W. Wang, R. Zhu, S. Wang, J. Sun, R. Zhang, X. Sun, The in vitro and in vivo anti-tumor effect of layered double hydroxides nanoparticles as delivery for podophyllotoxin, Int. J. Pharm., 388, 223(2010).
[56] L. Jin, Q. Liu, Z. Sun, X. Ni, M. Wei, Preparation of 5-fluorouracil/β-cyclodextrin complex intercalated in layered double hydroxide and the controlled drug release properties, Ind. Eng. Chem. Res., 49, 11176(2010).
[57] M. Chakraborti, J.K. Jackson, D. Plackett, S.E. Gilchrist, H.M. Burt, The application of layered double hydroxide clay (LDH)-poly (lactide-co-glycolic acid)(PLGA) film composites for the controlled release of antibiotics, J. Mater. Sci. Mater. Med., 23, 1705(2012).
[58] B. Saifullah, M.Z. Hussein, S.H. Hussein-Al-Ali, P. Arulselvan, S. Fakurazi, Antituberculosis nanodelivery system with controlled-release properties based on para-amino salicylate–zinc aluminum-layered double-hydroxide nanocomposites, Drug Des. Dev. Ther., 7, 1365(2013).
[59] L. Qin, M. Wang, R. Zhu, S. You, P. Zhou, S. Wang, The in vitro sustained release profile and antitumor effect of etoposide-layered double hydroxide nanohybrids, Int. J. Nanomed., 8, 2053(2013).
[60] L. Li, W. Gu, J. Chen, W. Chen, Z.P. Xu, Co-delivery of siRNAs and anti-cancer drugs using layered double hydroxide nanoparticles, Biomaterials, 35, 3331(2014).
[61] S. Barkhordari, M. Yadollahi, H. Namazi, pH sensitive nanocomposite hydrogel beads based on carboxymethyl cellulose/layered double hydroxide as drug delivery systems, J. Polym. Res., 21, 454(2014).
[62] 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., 109 119(2015).
[63] S. Mondal, S. Dasgupta, K. Maji, MgAl-Layered Double Hydroxide Nanoparticles for controlled release of Salicylate, Mater. Sci. Eng. C., 68 557(2016).
[64] S. Senapati, R. Thakur, S.P. Verma, S. Duggal, D.P. Mishra, P. Das, T. Shripathi, M. Kumar, D. Rana, P. Maiti, Layered double hydroxides as effective carrier for anticancer drugs and tailoring of release rate through interlayer anions, J. Control. Release, 224, 186(2016).
[65] J. Sun, Y. Lei, Z. Dai, X. Liu, T. Huang, J. Wu, Z.P. Xu, X. Sun, Sustained release of brimonidine from a new composite drug delivery system for treatment of glaucoma, ACS appl. mater. interfaces, 9, 7990(2017).
[66] J. Wu, A. Deng, W. Jiang, R. Tian, Y. Shen, Synthesis and in vitro evaluation of pH-sensitive magnetic nanocomposites as methotrexate delivery system for targeted cancer therapy, Mater. Sci. Eng. C., 71, 132 (2017).
[67] K. Katagiri, Y. Shishijima, K. Koumoto, K. Inumaru, Preparation of pH-Responsive hollow capsules via layer-by-layer assembly of exfoliated layered double hydroxide nanosheets and polyelectrolytes, J. Nanosci. Nanotechnol, 18, 110(2018).
[68] Á. Deák, E. Csapó, Á. Juhász, I. Dékány, L. Janovák, Anti-ulcerant kynurenic acid molecules intercalated Mg/Al-layered double hydroxide and its release study, Appl. Clay Sci., 156 (2018) 28-35.
[69] N. Allou, A. Yadav, M. Pal, R.L. Goswamee, Biocompatible nanocomposite of carboxymethyl cellulose and functionalized carbon-norfloxacin intercalated layered double hydroxides, Carbohyd. polym., 186, 282(2018).
[70] E.P. Komarala, S. Doshi, S. Thiyagarajan, M. Aslam, D. Bahadur, Studies on drug release kinetics and antibacterial activity against drug-resistant bacteria of cefotaxime sodium loaded layered double hydroxide–fenugreek nanohybrid, New J. Chem., 42, 129 (2018).
[71] D. Capsoni, I. Quinzeni, G. Bruni, V. Friuli, L. Maggi, M. Bini, Improving the Carprofen Solubility: Synthesis of the Zn_2Al-LDH Hybrid Compound, J. Pharm. Sci., 107, 267(2018).
[72] Y. Xu, A. Goyanes, Y. Wang, A. Weston, P.-W. So, C. Geraldes, A. Fogg, A. Basit, G.R. Williams, Layered gadolinium hydroxides for simultaneous drug delivery and imaging, Dalton Trans., (2018).
[73] F. Peng, D. Wang, H. Cao, X. Liu, Loading 5-Fluorouracil into calcined Mg/Al layered double hydroxide on AZ31 via memory effect, Mater. Lett., 213, 383(2018).