Indian Journal of Advances in Chemical Science

Article

Functionalized Layered Double Hydroxide (LDHs) Nanohybrids for Drug Delivery Applications

B. Adi Lakshmi[1], Chandra Sekhar Espenti, K.S.V. Krishna Rao*, B. Vijaya Kumar Naidu

[1]Polymer Biomaterial Design and Synthesis Laboratory, Department of Chemistry, Yogi Vemana University, Kadapa, Andhra Pradesh, India, [2]Department of Chemistry, Sreenidhi University, Yamnampet, Hyderabad, Telangana, India, [3]Department of Materials Science and Nanotechnology, Yogi Vemana University, Kadapa, Andhra Pradesh, India

ABSTRACT

Biomedical research involving layered double hydroxide (LDH) nanohybrid materials has received a lot of attention. These LDH nanohybrid materials have distinct properties such as biocompatibility, variable chemical compositions, anion-exchange capacity, host-guest interactions, and crystallization-dissolution properties. Drug delivery is becoming increasingly important because it enables theranostics (therapeutics and diagnostics), a concept of next-generation medicine, to combine therapy and diagnosis. Based on the unique properties of LDH-based nanohybrid materials open up new avenues for simultaneous therapy and drug release applications in almost every field of medicine. The purpose of this chapter is to investigate recent advances in multifunctional LDH nanohybrid materials, ranging from fabrication to drug molecule release applications in various bio-medical fields with therapeutic functions. Furthermore, these (LDH) nanohybrid materials have the potential to be used as both diagnostic agents and drug delivery carriers and there will be discussed in relation to advancements in bio-medical systems. Due to their exceptional physiochemical properties, two-dimensional LDHs nanohybrid materials are currently a fascinating topic of interest. LDHs have the potential to be useful in a variety of applications, such as energy, catalysis, and biomaterials; particularly in the bio-medical field as drug delivery systems. Despite the unique intrinsic properties of LDH nanohybrid materials, various functionalization strategies have been applied to LDHs, yielding even more exciting performance opportunities and providing guidelines for the design of novel functional nanomaterials.

Key words: Layered double hydroxide, Nanohybrids, Drug delivery, Bio-materials and Bio-medical applications.

1. INTRODUCTION

Polymer matrices are typically supplemented with inorganic fillers to improve their properties and expand their applications [1]. Well-known fillers include silicate, calcium carbonate, fibers, and carbon-based structures. It is evident that a high filler content is required to have a significant impact on the properties of polymer matrices. In most cases, a higher filler component increases the weight of the produced composites, restricting the applications of such devices. To overcome the weight issue, nanoparticles have recently emerged as the preferred filler for improving the properties of the resulting polymer matrix. This is due to ability of nanoparticles to change the properties of a polymer matrix with relatively modest concentrations, allowing nanocarriers to maintain the density of the polymer matrix low. The incorporation of layered inorganic fillers into polymer matrices to form polymer/layered inorganic nanocomposites has sparked a lot of attention due to its unique properties [2].

Layered double hydroxides (LDHs)/polymer nanocarriers are an important family of polymer/layered inorganic nanocomposites because they improve thermal stability, flame retardancy, and overall physical properties [3,4]. Due to the enormous pressure that could limit or prevent the use of halogen flame-retardant materials due to environmental concerns and LDHs have emerged as a viable option for halogen-free flame-retardant material [5-7]. Urea hydrolysis, hydrothermal synthesis, co-precipitation, and ion exchange are some of the methods utilized to manufacture LDH that have been widely documented in the literature [8,9]. LDH has the following structure in terms of chemistry: [Ax/m m•nH_2O] intra [MII 1x Mx III $(OH)_2$] inter [Figure 1]. The intralayer crystallographic domain and interlayer spaces are represented in the formula by the terms inter and intra. The layers of LDHs are positively charged edge-shared octahedral coordinated metal hydroxide crystal formations sandwiched by charge-compensating interlayer anions and, as an alternative, water solvation. MII (M^{2+}) is a divalent cation, MIII (M^{3+}) is a trivalent cation, and A is an anion with m-valency. When compared to well-known layered silicates, LDHs have a high charge density in the interlayer and appear to have an impermeable effect between the hydroxides, making exfoliation extremely difficult [10]. Furthermore, because polymers are hydrophobic, polymer chains are more difficult to incorporate into LDHs. To improve polymer intercalation in LDH layers, anionic materials must be utilized. The simplest and

***Corresponding author:**
K.S.V. Krishna Rao
E-mail: ksvkr@yogivemanauniversity.ac.in

ISSN NO: 2320-0898 (p); 2320-0928 (e)
DOI: 10.22607/IJACS.2023.1103006

Received: 27th April 2023;
Revised: 18th June 2023;
Accepted: 25st June 2023.

most practical way for producing polymer/LDHs with improved properties is to modify the clay with surfactant or other materials to create a stable LDHs/polymer nanocomposite system.

2. APPLICATIONS

LDHs for short are a family of materials that have a layered structure and have recently attracted a lot of attention in a variety of applications, including medication administration. When it comes to applications involving medication delivery, LDH nanohybrid, which are simply LDHs coupled with other materials or compounds, have a number of benefits. The following figure provides the important applications of LDH nanohybrids [Figure 2].

LDH nanohybrids may be used to encapsulate pharmaceuticals inside their layered structure, which allows for the controlled release of the medications. Because of this, the release of the medicine may be managed and maintained over time. The researchers were able to regulate the release rate and accomplish targeted drug distribution by altering the composition and structure of the LDH nanohybrid. This enabled them to reduce the medicine's negative effects and improve the drug's overall therapeutic effectiveness. LDH nanohybrids are sensitive to variations in pH, making them ideal for pH-responsive medication delivery. When LDHs are put in sick tissues or cellular compartments with a slightly acidic environment, the medicine inside them can be released in a controlled way. This pH-responsive behavior makes it possible to selectively administer drugs to particular locations, such as tumor tissues, where the pH is often lower than in healthy tissues. Improved drug stability LDH nanohybrids are capable of preventing the degradation of pharmaceuticals and improving the stability of medications while they are being stored or transported. LDH nanohybrids have the capacity to prolong the shelf life of pharmaceuticals and guarantee that the drug continues to be active until it reaches its intended target. This is especially beneficial for medications that have poor stability or short half-lives.

Combination treatment is possible with LDH nanohybrids because they may be functionalized concurrently with a number of different medicines or therapeutic agents. This makes combination treatment possible, in which several medications, each of which has a mechanism of action that is complementary to another, may be administered simultaneously to generate synergistic benefits, improved disease management, and a lower chance of drug resistance. For targeted drug delivery, the surface of LDH nanohybrids can be changed to make it easier for targeting ligands, antibodies, or other specific moieties to stick to them. This alteration makes active targeting of certain cells or tissues easier, which increases the amount of medicine that accumulates at the target location while reducing the number of effects that are not intended.

Biocompatibility: LDH nanohybrids have been demonstrated to have good biocompatibility and minimal toxicity, making them potential candidates for use in biomedical applications, including medication administration. They are typically well tolerated by the body and have a lower risk of causing unwanted responses. Imaging and diagnosis: LDH nanohybrids may be functionalized with imaging agents such as fluorescent dyes or contrast agents. This enables the nanohybrids to be used in imaging and diagnostics. This enables simultaneous medication administration and real-time monitoring of the therapeutic response, which supplies helpful information for diagnostics and the assessment of therapy.

LDH nanocomposites have found applications in energy, food packaging, water purification, gas detection, biomedicine, flame retardant, and agriculture [11-14]. LDHs (ZnTi-LDHs) were synthesized utilizing a hydrothermal technique, and the nanostructures were created using *in situ* chemical oxidative polymerization. A comparison was made between the LDH nanocomposites' ability to detect NH_3 and that of pure PANI and ZnTi-LDHs. With the LDHs nanocomposites, NH_3 sensing was found to be significantly better than that of clean polymer and LDHs. The increased adsorption site and ease of gas adsorption were attributable to the looser architectural structure of the nanocomposite. Because of the nanocomposite's looser architectural structure, the adsorption site is optimized and gas adsorption is facilitated. Phosphate removal was evaluated in this study by comparing the extraction efficiency of GO-LDH@SPAN nanocomposite with LDH and GO-LDH, respectively [15].

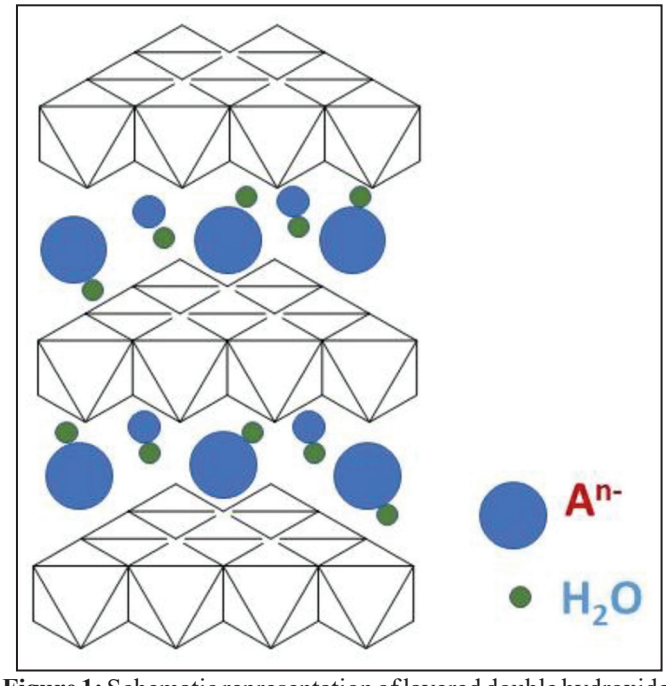

Figure 1: Schematic representation of layered double hydroxide.

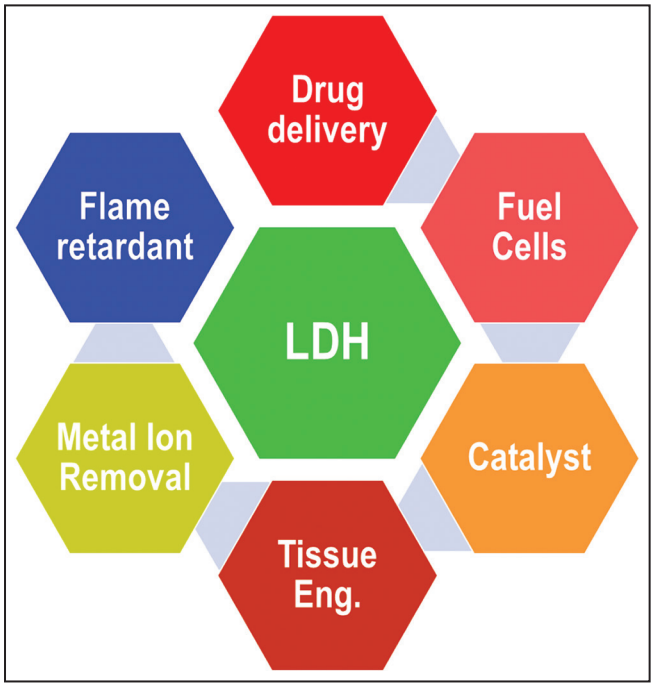

Figure 2: Various important applications of layered double hydroxide.

For phthalate extraction, the LDH@SPAN nanocomposite was superior to LDH and GO-LDH, with LDH having a lower extraction rate than GO-LDH. LDH's phthalate extraction was reduced, possibly because of a weak hydrogen link between LDH and phthalates. Due to the GO-phthalate link, GO-LDH was more efficient at extracting the phthalates than standard GO-LDH. The GO-LDH@SPAN nanocomposite displayed higher analyte extraction because SPAN can promote more direct interaction with the phthalate. As a result, SPAN's matrix comprises more active sites for analyte separation because it is composed of O=S=O bond. PMMA/Mg-Al LDH nanocomposite films for packaging purposes using *in situ* polymerization technique [11]. Results on thermal stability and gas permeability were two of the most essential factors to be considered when determining the suitability of packing material. The nanocomposites were fortified with Mg-Al LDH at a concentration of 2, 4, and 8%. There was a significant difference in the flow rate of oxygen between the nanocomposites and PMMA.

A polymer matrix, which serves as a protective barrier for oxygen permeability, was found to have flaws in its structure, which allowed oxygen to penetrate the matrix. The addition of LDH to PMMA matrix increased the thermal stability of the matrix when compared to pristine PMMA. Recently, the desire for ultra-lightweight, flexible, and robust piezoelectric nanogenerators has pushed the development of piezospun nano-fabrics using poly (vinylidene fluoride)/Ca-Al LDH composites. To create the polyvinylidene fluoride or polyvinylidene difluoride (PVDF)/Ca-Al LDH composite nano-fabrics, Ca Al-LDH nanosheets were first synthesized utilizing a modified co-precipitation technique. Electrospinning of PVDF/Ca-Al LDH composite produced nanofabrics. The electrospinning-induced synergy between the PVDF-LDH interaction and *in situ* stretching boosted the nucleation of the electroactive phase by as much as 82.79%. These composite nano-fabrics could be utilized to build piezoelectric nanogenerators. By slapping the PVDF/Ca-Al LDH composite nano-fabrics, the piezoelectric performance may reach an open circuit output voltage of 4.1 and 5.72 V, respectively, while utilizing the frequency-dependent mechanical vibration mode. The high dielectric constant and low dielectric loss of the composite nano-fabrics were also responsible for the high interfacial polarization at low frequencies with enhanced LDH loading. Thus, it was shown that these materials might be used in electrical equipment [16,17].

The development of Zn Al-LDH/PCL nano composites has made it possible to include them in drug delivery systems. Zn Al-LDH nano composites were made using the simple co-precipitation method, whereas Zn Al-LDH/PCL nano composites were made using the facile intercalation method. Weight loss and drug release were greater in the Zn Al-LDH/PCL composite nano-fabrics as compared to PCL. Using the first-order kinetic model, the dissolution kinetics of the Zn Al-LDH/PCL composites were shown to be composition dependent. In contrast, the Ritger–Peppas model accurately predicted the drug release kinetics for plain PCL, indicating that the Fikian mechanism was responsible for the release.

3. LDH-BASED DRUG DELIVERY SYSTEMS

Chakraborti *et al.*, regulated the release of antibiotics from LDH clay-poly(lactide-co-glycolic acid) (PLGA) film composites. The nanocomposites were developed via a combination of solution mixing and thin film casting. Antibacterial levels of VAN and SF were effectively given at later time points when the drug/clay complexes were disseminated in PLGA films, which resulted in a reduced burst phase of release. Double hydroxide clays layered in layers may be excellent for controlled release applications because they prevent pharmaceutical degradation and release useful levels of drug over longer period of time [18].

A new technique for reducing the flammability of LDH-based polymer composites has been developed through the production and analysis of dye-structures including LDH by Kang *et al.*, using the coprecipiation technique. LDH and PP-g-MA were combined in xylene to make a polypropylene-grafted maleic anhydride (PP-g-MA)/LDH combination, with the purpose of assessing the PP-g-MA's flammability [19].

Troutier-Thuilliez *et al.*, synthesized waterborne polyurethane and fabricated LDH nanocomposites by solution mixing and casting for coating applications [20]. The Fenton-like catalytic oxidation of phenolic compounds in chitosan/NiFe LDH (CS/NiFe-LDH) composites was developed by Yang *et al.* NiFe-LDH and CS/NiFe-LDH were made using a low-saturation coprecipitation to study their oxidation and catalytic characteristics for phenolic chemicals [21]. Phosphotungstic acid was intercalated into LDHs and used to generate flame-retardant poly(lactic acid) combinations by Zhang *et al.* The films were fabricated by melting and hot-pressing methods [22]. Jia *et al.*, established the fabrication of ternary CoNiMn LDHs/polypyrrole/reduced graphene oxide composite (CoNiMn-LDH/PPy/RGo) for oxygen reduction processes. A one-step technique in which LDH was generated by co-precipitation of metal ions (Co^{2+}, Ni^{2+}, and Mn^{2+}) and PPy was prepared by pyrrole polymerization. Developed CoNiMn-LDH/PPy/RGo composite was used for electrocatalytic applications of the oxygen reduction process [23]. Cao *et al.* fabricated conjugated LDH nanoparticles with phosphonic acid-terminated polyethylene glycol (PEG). PEGylated LDH nanoparticles had no effect on cell viability and boosted cellular absorption in an SK-MEL-28 cell culture. The findings imply that conjugating phosphonic acid ending PEG on LDH nanoparticles could be a promising strategy for increasing LDH colloidal and biological stability in the biomedical arena [24].

Ebadi *et al.* devised a drug delivery system based on Fe_3O_4 nanoparticles coated with PVA-zinc/aluminum-LDH-sorafenib. The co-precipitation method was employed by the researchers to assess the effects of coating magnetic iron oxide nanoparticles with PVA, ZLDH, and sorafenib, an anticancer drug, and the resulting nanoparticles exhibited a magnetite crystal structure with a particle size ~95 nm. According to cell viability assays, magnetic iron oxide nanoparticles coated with PVA-sorafenib-Zn/Al-LDH were more effective than sorafenib alone against HepG2 liver cancer cells but had no cytotoxicity against 3T3 fibroblast cells [25]. Malafatti *et al.*, developed electrospun PLA nanofibers coated with silver sulfadiazine/[Mg–Al]-LDH (PLA-SS-MgAl-LDH) as an antibacterial wound dressing materials. Here, PLA-SS-MgAl-LDH was used as a host matrix to develop a potential antibacterial agent to deliver silver sulfadiazine from electrospun PLA scaffolds to better heal the skin from wounds [26].

Minnelli *et al.*, found that resveratrol/LDH/BSA nanocomposites have antitumor efficacy against human lung adenocarcinoma epithelial cell line (A549) with enhanced chemotherapeutic efficiency, an inorganic host matrix, LDH-BSA might be viewed as an effective trapping and delivery system for resveratrol [27]. Xu *et al.*, developed multifunctional nanohybrids, i.e., Cu-LDH@PAMA/DMMA nanohybrids. Here, Cu-containing LDH nanoparticles demonstrate the pH-responsive magnetic resonance imaging contrast capacity (i.e., relaxivity). After intravenous injection, the charge-convertible nanohybrid accumulates 4.8% of the injected dose in the tumor for 24 h later showing their promise as a flexible delivery nanocarrier for anticancer therapy [28].

Barkhordari and Alizadeh, developed pH-responsive chitosan/LDH/Fe_3O_4 nanocomposite hydrogel beads for controlled release of diclofenac. Drug release behavior is similar to swelling behavior; however, external magnetic fields have a lesser impact than pH on drug release. Accordingly, the percentage of drug release from

nanocomposites of chitosan/LDH/Fe_3O_4 ranged from 58.3-76.4%, 20.0-26.1%, and 18.3–16.2% at pH of 1.2, 7.4, and 9.3, respectively [29]. Another pH-responsive bead was prepared from alginate/LDH by Viscusi and Gorrasi, and it was observed that diclofenac release was significantly influenced by LDH's presence, as well as by the pH and temperature of the release medium [30]. Tiwari *et al.*, developed PVP functionalized graphene oxide (PVP-GO) based nano drug delivery devices for controlled release of quercetin and gefitinib (anti-ovarian cancer drug combination). PVP-GO nano drug delivery devices loaded with several medications were shown to be far more toxic than individual drug-loaded systems or free drugs when tested against the toxicity of IOSE-364 cells. The quercetin and gefitinib loaded into PVP-GO matrix and this nano-drug delivery device is projected to be more effective than individual drug therapy because of the higher impact of the combinatorial strategy and the efficiency of chemotherapeutic administration [31].

Liu *et al.*, developed Cu-doped LDH nanomedicine with heat/pH-boosted delivery of 5-fluorouracil and albumin-bound paclitaxel (5-FU/Cu-LDH@nAb-PTX) for breast cancer synergistic chemo-phototherapy. 5-FU/Cu-LDH@nAb-PTX in combination of CD3+ and CD8+ T-cell therapy resulted in strong anti-tumor immunity. Photothermal conversion and pH/heat-triggered on-demand drug release were achieved using an LDH-based nanocarrier to deliver therapeutic drugs to the tumor site which was shown in Figure 3 [32]. Jeung *et al.*, fabricated gallium-based LDH for radio diagnostics; for this gallium ion was successfully integrated into chemically well-defined MgAl LDH complexes after hydrothermal treatment [33]. Singh *et al.*, created functionalized PVC/LDH nanocomposites and evaluated hemolysis and thrombogenicity tests, followed by cell adhesion and proliferation experiments. Results demonstrate that PVC/LDH nanocomposites could be used in a wide range of biological and related applications [34].

Wang *et al.*, designed efficient ocular medications to the posterior region of the eye by topical application. LDH-carboxy methyl chitosan hybrid nanocomposite was produced to study the drug carrier of organic-inorganic hybrid composites for the effective administration of dexamethasone disodium phosphate in the treatment of patients with inflammatory bowel disease [35]. Grazielle Emanuelle de Souza dos Santos *et al.* produced a composite based on MgAl/LDH supported on Syagrus coronata biochar for the adsorption of diclofenac. MgAl/LDH-biochar composite at 200 mg/L and 6 h of contact time showed 82% removal efficiency in the adsorption study. Results showed that composite has high DS removal performance, especially when compared to other adsorbents reported in the literature and may be used to remove this emerging contaminant from water [36]. Costard *et al.*, developed a non-viral method for delivering nucleic acids to MSCs in 2D culture and 3D tissue engineering scaffolds. LDH-nucleic acid complexes in a collagen-based delivery platform show efficient localized transfection of MSCs, which has a lot of potential for tissue regeneration applications. Through the use of mass balances, we were able to compute the synthesis of MgAl/LDH as well as the MgAl/LDH-biochar composite [Figure 4]. The findings that we got were 38.9, 68.7, and 71.8%, respectively. miRNA nanoparticles incorporated into collagen-nanohydroxyapatite scaffolds resulted in successful overexpression of miRNA in MSC, suggesting the establishment of an effective miRNA delivery platform for regenerative medicine [37].

Sharma *et al.*, developed flexible polymer-LDH material for environmental remediation, spanning from chemical pollutants to microorganisms. The antibacterial activity of LDHs-based nanomaterials has recently been proven in the field of bacteria, fungi, and viruses. LDH nanoparticles may also be useful in the production of multifunctional nanomaterials that may be used in a variety of protocalls [38]. Kuthati *et al.*, produced nanostructures from nanoparticles with hydrotalcite-like LDH to result anion exchange capacity, chemical stability, and pH-dependent solubility for drug delivery applications. The authors also reviewed the most recent advancements in the building of hybrid LDH with the goal of gaining unique properties, as well as the numerous uses of LDH in various biomedical fields [39]. Ladewig *et al.*, produced LDHs, which have been employed as catalyst and ceramic precursors, anionic pollutant traps, and polymer catalysts and additives for decades. An important field of research is the transfer of therapeutic/bioactive molecules (e.g., proteins, nucleic acids) to mammalian cells (such as peptides, proteins, and nucleic acids). The purpose of this review is to summarize recent achievements in gene and drug delivery using LDH nanoparticles. LDH nanoparticles and their cargo are examined in terms of how they enter cells and what happens to them once they are within the body [40].

Mokhtari *et al.*, developed LDH-galactose nanocarriers for delivering curcumin to hepatocellular cancer cells using SiO_2 nanodot-coating and an amine-functionalization technique. Here, galactose was

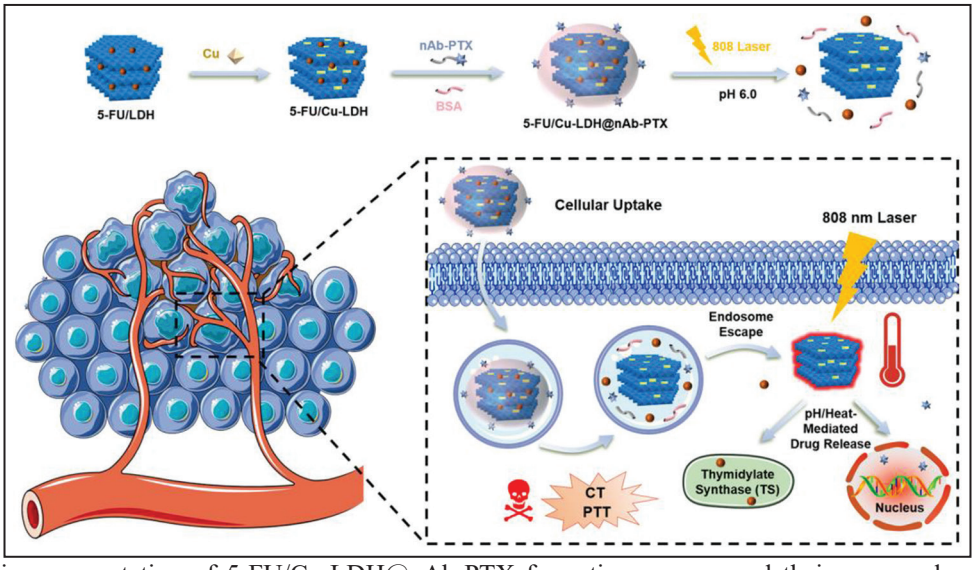

Figure 3: Schematic representation of 5-FU/Cu-LDH@nAb-PTX formation process and their proposed mechanism in cancer treatment [31] (courtesy from Elsevier).

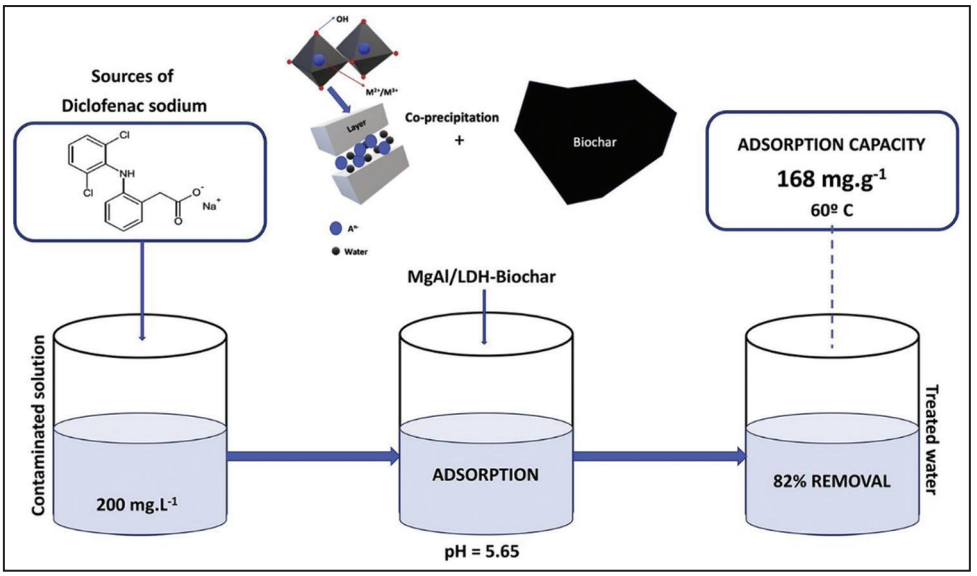

Figure 4: The fabrication of the MgAl/LDH and the MgAl/LDH-biochar composite [36] (courtesy from Elsevier).

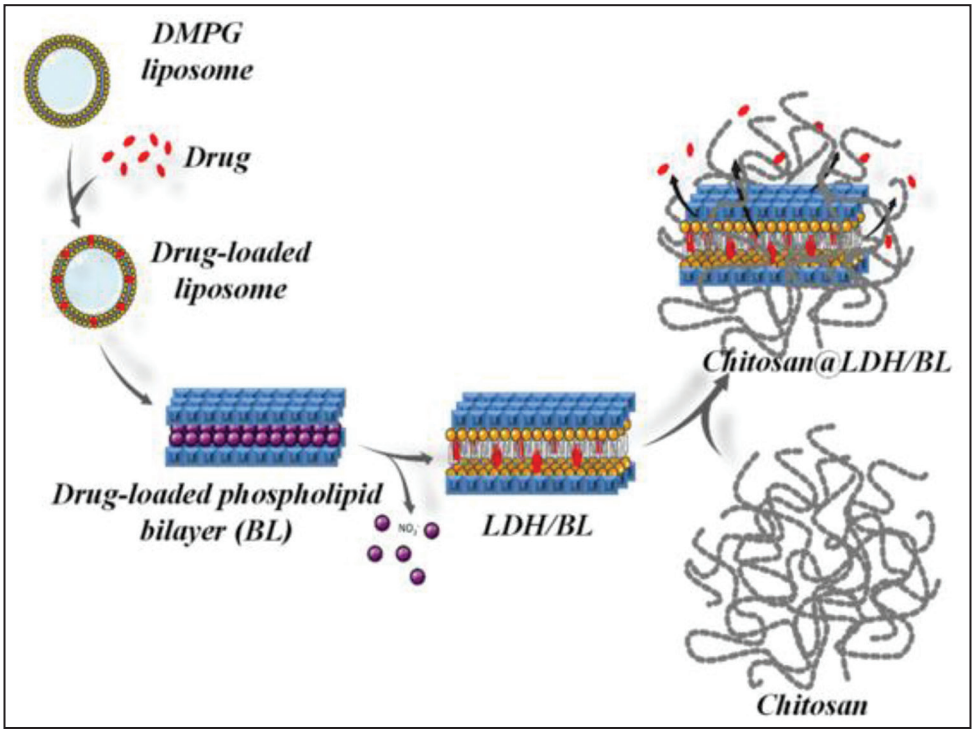

Figure 5: Bio-hybrid drug delivery system using a Mg/Al-NO_3 layered double hydroxide [60]. (Courtesy from MDPI).

attached to a curcumin/LDH nanohybrid (Gal-Cur/LDH) and used as a delivery system. Gal-Cur/LDH nanoparticles were tested for the cell viability on HepG2 cells with murine fibrosarcoma L929 cells as control cells to determine the specific targeting effectiveness of these nanoparticles for hepatoma cells. Curcumin was loaded into LDH with an efficiency of 31 % and Gal-Cur/LDH nanoparticles induced apoptosis in HepG2 cells more frequently than the other groups [41].

Brindusa *et al.*, developed MnAl-LDH nanosheets loaded with fluorouracil by co-precipitation with low supersaturation for cancer therapy. Fluorouracil loading was 6.96 and 5.28 % in MnAl-LDH nanosheets, drug relaxivities were very high when the pH was 7.4 and release of drug was followed quasi-Fickian distribution [42]. Different types of LDHs and their biomedical applications are summarized in in Table 1. Mochane *et al.* reviewed on LDHs work, preferably on nanofillers for improving polymer matrices' flame retardancy and barrier characteristics. On the other hand, enhancing the LDH/polymer system properties required dispersing the nanofiller inside the polymer matrix. The dispersion of LDHs/polymer systems was influenced by a variety of factors, including the preparation method, modifier type, and type of LDH. A wide range of polymer matrix interactions can be achieved using LDH nanofillers because of their chemical composition flexibility and variable charge density. As a result of their endothermic decomposition, LDHs are extremely important as flame retardant compounds. LDH/polymer nanocomposites are examined in this review paper for their preparation methods, morphology, flammability, and barrier properties [43].

Poly(ε-caprolactone)/LDH (PCL-LDH) microsphere nanocomposites were developed by Tina Baradaran *et al.*, for mesenchymal

Table 1: Different types of LDHs and their applications in biomedical field.

S. No.	Polymeric nanocomposites	LDHs	Method	Applications	References
1	PMMA–DPHPA–LDHs	Magnesium aluminum–LDHs	Ion exchange	Flame retardant	[2]
2	S-LDH/UP			Flame retardancy	[3]
3	Nylon 6/Mg-Al-LDH			Flame retardancy	[4]
4	Polystyrene-MgAl LDH		Bulk polymerization	Fire retardancy	[5]
5	Polyimides/Zn/Cr- LDH		Co precipitation and hydrothermal method	Tensile strength	[6]
6	poly(ethylene-co-acrylic acid)-LDH and DDA-LDH)	Clays	Thermal analysis techniques	Polymer flame retardancy	[7]
7	polyethylene, poly(ethylene-co-butyl acrylate) and poly(methyl methacrylate)	Zinc aluminum (ZnAl) and magnesium aluminum (MgAl)	Co-precipitation	Thermal applications	[8]
8	Zn/Al LDH nanosheets		Hydrothermal technique	Photoluminescence	[9]
9	Functionalized LDHs/polymethyl methacrylate	Magnesium/ aluminum–LDHs	*In situ* polymerization	Flame retardancy	[10]
10	(PMMA/LDH)	Mg–Al LDH	*In situ* polymerization technique	Packaging industry	[11]
11	ZnTi-LDHs	ZnTi-LDHs	*In-situ* chemical oxidative polymerization	Gas sensor and NH3 detection	[12]
12	(ZnAl-LDH)/polycaprolactone	ZnAl-LDH	Solution intercalation method	Drug delivery	[13]
13	Graphene oxide/LDHs[@]sulfonated polyaniline	Graphene oxide/ LDHs	Simple one-pot *in-situ* polymerization method.	Distilled herbal beverages	[12]
14	poly(vinylidene fluoride)/Ca–Al LDH nanocomposite	Ca–Al LDH	-	Electronic devices.	[14]
15	ZnAl LDH/Polycaprolactone	ZnAl LDH	Solution intercalation method.	Drug Delivery	[15]
16	LDH clay (LDH)-poly (lactide-*co*-glycolic acid) (PLGA)	Clay	-	Controlled release of antibiotics	[16]
17	Polypropylene-Grafted Maleic Anhydride/d-LDH Composites	dye		Flame retardant properties	[17]
18	LDH/waterborne polyurethane (WPU)	Mg_2Al		Coating applications	[18]
19	Chitosan/NiFe-LDHs	NiFe-LDHs	Low-saturation co-precipitation method	Catalytic Oxidation of Phenolic Compounds	[19]
20	MgAl-LDH (PWA-LDH)	MgAl-LDH	Reconstruction method	Fire resistance	[20]
21	CoNiMn-LDH/PPy/RGO	CoNiMn-LDH	One-step involving formation	Fuel cells and water splitting systems	[21]
22	LDH-Phophoric acid/PEG			Particle Stability	[22]
23	polyvinyl alcohol-zinc/aluminium-LDH	Zinc/aluminium-LDH	Co-precipitation method	Drug delivery applications	[23]
24	PLA/SDZ-[Mg–Al]-LDH	[Mg–Al]-LDH	Reconstruction method	Wound dressing	[24]
25	Resveratrol/LDH/BSA	Clay		Drug delivery	[25]
26	PAMA/DMMA-Modified Cu-LDH	Cu-LDH	Atom transfer polymerization.	Particle colloidal stability and cancer	[26]
27	Chitosan/LDH/Fe_3O_4	Mg–Al LDH	-	Controlled drug release	[27]
28	Alg/LDH-Dic	Mg–Al hydrotalcite		Drug release	[28]
29	GEF and QSR/GO-PVP			Drug delivery	[29]
30	5-FU/Cu-LDH[@]nAb-PTX	Cu-LDH	Ion exchange method	Drug release and cancer	[30] [31]
31	Ga-LDH		Post synthetic hydrothermal	Radio diagnostics	[32]

(Contd...)

Table 1: *(Continued)*.

S. No.	Polymeric nanocomposites	LDHs	Method	Applications	References
32	PVC/LDH	-	Nucleophilic substitution method	Biomedical	[33]
33	CMCS-LDHs	DEXP-LDH	Co-precipitation-hydrothermal method	Drug delivery	[34]
34	Diclofenac/MgAl/LDH	Clay	Co-precipitation method	Wastewater treatment	[35]
35	MgAl-NO3 LDH/ Nucleic acid	MgAl-NO3	Co-precipitation method.	Tissue Regeneration and drug delivery	[36]
36	Gal-Cur/LDH	Mg/Al LDH		Drug delivery	[39]
37	FU/Mn/Al LDH	Mn/Al LDH	Co-precipitation method	Medical	[40]
38	PCL/Mg/Al-LDH	Mg/Al-LDH	Freeze-drying and particulate leaching methods	Bone tissue engineering	[42]
39	LDH-MTX-DS	Mg-Al-NO3-LDH	Co-precipitation method	Drug delivery	[43]
40	Fe3O4@LDH/Ehleneglycol	Mg/Al LDH	One-step solvothermal route	Drug release	[44]
41	Gelatin/carboxymethyl cellulose dialdehyde/curcumin			Drug delivery	[45]
42	Zn/Al-LDH	Zn/Al-LDH	Co-precipitation method	Gene and drug delivery	[46]
43	DOX/PANI/N-GQD/MO/LDH	MgAl-LDH	Chemical precipitation method	Drug delivery	[47]
44	LDH-CuS NCs		Co-precipitation method	Photothermal and chemo dynamic	[48]
45	CPX-Ca-Al-LDH	Ca-Al LDH	Anion-exchange method	Drug delivery	[49]
46	Mg–Al-LDH (DE-LDH)	Mg-Al/LDH	Co-precipitation	Wastewater treatment	[50]
47.	β-glycerophosphate chitosan/LL37-modified LDH chitosan	Mg/Al LDH		Bone regeneration and vascularization	[51]
48	HA/PEG-PLG@LDH@DDC/DOX	CuAl LDH	Co-precipitation method	Drug delivery	[52]
49	PM-LDH/5ASA	Al-Ca LDH	Co-precipitation, ion exchange, reconstitution	Drug delivery	[53]
50	LDH/Bg/AZ31	AZ31 magnesium alloy	*In-situ* hydrothermal growth	Corrosion protection coatings and targeting drug delivery systems	[54]
51	Ilane-LDH	MgAl LDH		Hyperlipidemia	[55]
52	Fe_3O_4/Ag@Ca–Al LDH	Ag@Ca–Al LDH	*In situ* growth method	Reductions	[56]
53	PEG/Sorafenib–Zinc/Aluminium/MNPs	Zn/Al LDH	Co-precipitation	Drug delivery	[57]
54	MgAl-LDH@PMN	MgAl-LDH	Hydrothermal method	Drug deliver	[58]

LDH: Layered double hydroxide, PEG: Polyethylene glycol

stem cell osteogenic growth (rMSCs). Various levels of PCL-LDH nanocomposites were used in this study to create three-dimensional porous scaffolds for bone tissue engineering. PCL-LDH nanocomposites help rMSCs grow and proliferate more effectively and also PCL-LDH nanocomposites can aid rMSCs develop into osteogenic cells by increasing alkaline phosphatase activity [44]. To reduce the adverse effects of methotrexate while boosting its anti-inflammatory activity, Wang *et al.*, developed a pH-responsive drug delivery system, i.e., methotrexate-loaded LDH nanocomposites with dextran sulfate (LDH-MTX-DS). Cellular uptake tests revealed that the LDH-MTX-DS was able to specifically target scavenger receptors on the surface of activated RAW 264.7 cells when coated with dextran sulfate–modified targeting carriers [45]. To deliver anti-inflammatory drugs namely Ibuprofen and Diclofenac. Yousefi *et al.* developed core-shell type magnetic LDH (Fe_3O_4@LDH). At physiological circumstances, results show that Fe_3O_4@LDH-ibuprofen and Fe_3O_4@LDH-diclofenac are considered to be suitable drug delivery systems [46].

Biodegradable LDH-based nano carriers for the regulated release of valproate and methyldopa have been created by Yazdani *et al.* Both cooperation and ion exchange methods have been used to evaluate the performance of nanocarriers in terms of drug loading and controlled release; however, data show that the cooperation strategy has a very high efficiency [47]. Nanocarriers for doxorubicin delivery in L929 breast cancer cells were designed by combining MgAl-LDH, Mn_3O_4 nanoparticles, N-graphene quantum dot, and polyaniline (PANI/N-GQD/MO/LDH). The results of incubation with L929 cells showed that the PANI/N-GQD/MO/LDH nanocarriers exhibited no significant toxicity at dosages of up to 100 g $m.L^{-1}$. Because of this, new cancer therapies and drug delivery strategies can be developed using the created multifunctional nanocarrier [48].

CuS nanodots on LDH nanoplates (LDH-CuS NCs) were created *in situ* by Liu *et al.* Reactive oxygen species generated by LDH-CuS NCs in lysosomes are found to be a major cause of cancer cell death in

both *in vitro* and *in vivo* cancer cell investigations [49]. Ciprofloxacin (CPX) is a fluoroquinolone antibacterial drug encapsulated into calcium-aluminum LDH (CAL) by Monica Limau Jadam *et al.* The pseudo-second-order kinetic model best describes the drug release percentages into phosphate-buffered saline at pH 4.8 and 7.4, which are 67 and 60%, respectively. Antimicrobial activity of CPX, CAL, and CAC against *E. coli, Klebsiella pneumoniae,* and *Staphylococcus aureus* was examined' however, results indicate that CAL has potential as a new carrier for CPX release [50].

Sriram *et al.* employed a simple co-precipitation process to produce diatomaceous earth (DE) and Mg-Al-based LDH (DE-LDH) for the removal of toxic dyes, using Congo Red (CR) as a model dye. The maximum CR dye removal (50 mg/L) was enhanced from 15% for unmodified DE to 98 percent for modified DE-LDH, suggesting a significant improvement in efficiency. DE-LDH had the highest adsorption capacity of 305.8 mg/g compared to 23.2 mg/g of DE, demonstrating that LDH modification resulted in superior adsorption performance [51]. Liu *et al.*, fabricated a potential bilayer peptide-loaded scaffold consisting of CK2.1 coated-glycerophosphate/chitosan (CK2.1@GC) for cartilage regeneration and LL37 changed LDH/chitosan (LL37$^{@}$LC) for subchondral bone tissue regeneration in an integrated strategy involving mesenchymal stem cells recruitment and multifunctional therapeutic biomaterials of bone repair and vascularization [52]. Xu *et al.*, designed biocompatible LDH nanoparticles with poly(ethylene glycol)-g-polyglutamic acid (PEG-g-PLG) for controlled release of DOX, which intercalated into $Cu(DDC)_2$ for synergistic cancer therapy [53]. Pontes-Neto *et al.* used co-precipitation, ion exchange, and reconstitution procedures to prepare LDH-based drug delivery system using 5-aminosalicylic acid (5ASA). Changes in interplanar distances and hydrogen bonds between drug and layer hydroxyls were employed to verify the interaction between LDH and 5ASA. These findings suggest that the technique was effective for 5ASA intercalation in the LDH, lending credence to the notion that LDHs could be employed as functional medicinal excipients [54]. Ouyang *et al.* fabricated biomedical magnesium alloys using LDH/bioactive-glass coating by *in situ* hydrothermal growth to establish an LDH-container layer and then a sol-gel spin-coating approach to cover an outer bioactive-glass layer [55].

Lin *et al.* investigated the *in vitro* and *in vivo* adsorption of biocompatible surface-functionalized LDHs-G0 with enteric polymer coating. The sequential potential of a carrier with low hydrophobicity and a high positive surface charge dramatically favored successful bile acid adsorption, which has great promise for long-term hyperlipidemia treatment [56]. Using an *in-situ* growing technique, Dinari and Rajabi created a starch-based bio-nanocomposite from Fe_3O_4 and Ag nanoparticles supported on LDH (FALSNC). FALSNC was effectively used as a possible catalyst for 4-nitrophenol reduction. However, a rate kinetics comparison study of 4-nitrophenol and 2-nitrophenol revealed that the FALSNC has a higher potential in the case of the para derivative [57]. Ebadi *et al.* developed biocompatible superparamagnetic iron oxide nanoparticles (SPIONs) by coating them with PEG and sorafenib (SO)–zinc/aluminum LDH (ZLDH). Using diphenyltetrazolium bromide (MTT) assays, the drug-loaded SPIONs were examined for cytotoxicity and biocompatibility in 3T3 and HepG2 cells, revealing that the generated nanoparticles were less dangerous than the pure drug [58]. Sohrabnezhad *et al.* used a solvothermal approach to develop a biocompatible MgAl-LDH core-porous magnetic nanoparticles (PMN) shell (MgAl LDH$^{@}$PMN) as a possible pH-controlled drug delivery device. The MCF-7 cell line's reaction to the unmodified and modified carriers was utilized to assess biocompatibility. According to the kinetics of drug release, the drug-dissolving mechanism is Fickian diffusion [59]. Recently, Lerner *et al.* [60] designed a novel bio-hybrid drug delivery system using a Mg/Al-NO_3 LDH intercalated either with ibuprofenate anions (IBU) or a phospholipid bilayer (BL) containing a neutral drug, i.e., 17-estradiol, and then embedded in chitosan particles [Figure 5].

4. CONCLUSION

In the realm of drug delivery, functionalized LDHs Nanohybrids have attracted a lot of interest owing to the distinctive qualities they possess and the prospective uses they might have. LDHs are a kind of nanomaterials that have a layered structure and are made up of layers of positively charged metal hydroxide and intercalated anions. LDHs are very adaptable platforms for the administration of drugs as a result of the fact that these anions may be swapped for numerous functional molecules. Since LDHs are able to store a diverse assortment of drug molecules inside the interlayer galleries of their structures, they have a high capacity for loading drugs. Due to this, it is possible to effectively encapsulate medications that are either hydrophobic or hydrophilic. The sustained release of pharmaceuticals from LDHs may be accomplished by adjusting the interlayer spacing and surface functionalization. This allows for the regulated release of the medications. This makes it possible to have a continuous and regulated release of the encapsulated medication over a longer period of time, which results in prolonged therapeutic benefits and decreased adverse effects. LDHs are generally believed to be biocompatible, and investigations have been conducted to determine the extent of their potential for use in biological applications. Their biocompatibility may be improved by proper surface functionalization, which also helps to lessen any possible cytotoxicity. By modifying the surface of LDHs with targeting ligands (such as antibodies, peptides, or aptamers), it is possible to have precise interactions with the cells or tissues that are the focus of the treatment. This improves the selectivity of medication distribution and decreases the number of effects that are not intended. LDHs may be modified to react to changes in pH, which enables triggered drug release in certain settings. For example, the acidic conditions that are prevalent in tumor tissues can be met with this kind of release. The therapeutic effectiveness of the medicine that is administered is improved as a result of this pH-responsive behavior. To produce nanohybrids that have several functions, LDHs may be coupled with other functional materials, such as polymers, for example. These hybrid systems have the potential to give additional benefits, such as better pharmacokinetics and imaging capabilities. They also have a greater degree of stability. The capability of loading numerous medications into LDHs, each of which has unique physicochemical features, paves the way for the possibility of combination therapy. In this approach, the synergistic effects of various pharmaceuticals are combined in an effort to achieve better therapeutic results. LDHs may protect encapsulated pharmaceuticals from degradation caused by processes such as enzymatic degradation by acting as a physical barrier between the drug and the environment in which it is found.

5. REFERENCES

1. V. Mittal, (2009) Polymer layered silicate nanocomposites: A review, ***Materials***, **2**(3): 992-1057.
2. G. Huang, Z. Anan, W. Liqiang, W. Xu, (2011) Preparation and flammability properties of intumescent flame retardant-functionalized layered double hydroxides/polymethyl methacrylate nanocomposites, ***Materials Chemistry and Physics***, **130:** 714-720.
3. C. M. C. Pereira, M. Herrero, F. M. Labajos, A. T. Marques, V. Rives, (2009) Preparation and properties of new flame retardant unsaturated polyester nanocomposites based on layered double hydroxides, ***Polymer Degradation and Stability***, **94:** 939-946.

4. L. Du, B. Qu, M. Zhang, (2007) Thermal properties and combustion characterization of nylon 6/MgAl-LDH nanocomposites via organic modification and melt intercalation, ***Polymer Degradation and Stability*****, 92:** 497–502.
5. H. Benaddi, D. Benachour, Y. Grohens, (2016) Preparation and characterization of polystyrene-MgAl layered double hydroxide nanocomposites using bulk polymerization, ***Journal of Polymer Engineering***, **36:** 681-693.
6. M. Dinari, A. R. Rajabi, (2017) Structural, thermal and mechanical properties of polymer nanocomposites based on organosoluble polyimide with naphthyl pendent group and layered double hydroxide, ***High Performance Polymers***, **29:** 951-959.
7. S. Elbasuney, (2015) Surface engineering of layered double hydroxide (LDH) nanoparticles for polymer flame retardancy, ***Powder Technology***, **277:** 63-73.
8. C. Manzi-Nshuti, P. Songtipya, E. Manias, M. M. Jimenez-Gasco, J. M. Hossenlopp, C. A. Wilkie, (2009) Polymer nanocomposites using zinc aluminum and magnesium aluminum oleate layered double hydroxides: Effects of LDH divalent metals on dispersion, thermal, mechanical and fire performance in various polymers. ***Polymer***, **50:** 3564-3574.
9. D. Scarpellini, C. Falconi, P. Gaudio, A. Mattoccia, P. G. Medaglia, A. Orsini, R. Pizzoferrato, M. Richetta, (2014) Morphology of Zn/Al layered double hydroxide nanosheets grown onto aluminum thin films, ***Microelectronic Engineering***, **126:** 129-133.
10. G. Huang, A. Zhuo, L. Wang, W. Xu, (2011) Preparation and flammability properties of intumescent flame retardant-functionalized layered double hydroxides/polymethyl methacrylate nanocomposites, ***Materials Chemistry and Physics***, **130:** 714-720.
11. S. Barik, S. K. Badamali, L. Behera, P. K. Jena, (2018) Mg-Al LDH reinforced PMMA nanocomposites: A potential material for packaging industry, ***Composite Interfaces***, **25:** 369-380.
12. Y. Qin, L. Wang, X. Wang, (2019) A high performance sensor based on PANI/ZnTi-LDHs nanocomposite for trace NH3 detection, ***Organic Electronics***, **66:** 102-109.
13. H. Peng, Y. Han, T. Liu, W. C. Tjiu, C. He, (2010) Morphology and thermal degradation behavior of highly exfoliated CoAl-layered double hydroxide/polycaprolactone nanocomposites prepared by simple solution intercalation, ***Thermochimica Acta***, **502:** 1-7.
14. M. Otoukesh, Z. Es'haghi, J. Feizy, C. Nerin, (2020) Graphene oxide/layered double hydroxides@ sulfonated polyaniline: A sorbent for ultrasonic assisted dispersive solid phase extraction of phthalates in distilled herbal beverages, ***Journal of Chromatography A***, **1625:** 461307.
15. C. Shamitha, A. Mahendran, S. Anandhan, (2020) Effect of polarization switching on piezoelectric and dielectric performance of electrospun nanofabrics of poly (vinylidene fluoride)/Ca-Al LDH nanocomposite, ***Journal of Applied Polymer Science***, **137:** 48697.
16. H. Wang, J. Wu, L. Zheng, X. Cheng, (2019) Preparation and properties of ZnAl layered double hydroxide/polycaprolactone nanocomposites for use in drug delivery, ***Polymer-Plastics Technology and Materials***, **58:** 1027-1035.
17. M. Chakraborti, J. K. Jackson, D. Plackett, S. E. Gilchrist, H. M. Burt, (2012) The application of layered double hydroxide clay (LDH)-poly (lactide-co-glycolic acid)(PLGA) film composites for the controlled release of antibiotics, ***Journal of Materials Science: Materials in Medicine***, **23:** 1705-1713.
18. N. J. Kang, D. Y. Wang, B. Kutlu, P. C. Zhao, A. Leuteritz, U. Wagenknecht, G. Heinrich, (2013) A new approach to reducing the flammability of layered double hydroxide (LDH)-based polymer composites: Preparation and characterization of dye structure-intercalated LDH and its effect on the flammability of polypropylene-grafted maleic anhydride/d-LDH composites, ***ACS Applied Materials and Interfaces***, **5:** 8991-8997.
19. A. L. Troutier-Thuilliez, C. Taviot-Guého, J. Cellier, H. Hintze-Bruening, F. Leroux, (2009) Layered particle-based polymer composites for coatings: Part I. Evaluation of layered double hydroxides, ***Progress in Organic Coatings***, **64:** 182-192.
20. B. O. Yang, J. Cai, S. Wei, N. Nie, J. Liu, (2020) Preparation of chitosan/NiFe-layered double hydroxides composites and its fenton-like catalytic oxidation of phenolic compounds, ***Journal of Polymers and the Environment***, **28:** 343-353.
21. S. Zhang, Y. Yan, W. Wang, X. Gu, H. Li, J. Li, J. Sun, (2018) Intercalation of phosphotungstic acid into layered double hydroxides by reconstruction method and its application in intumescent flame retardant poly (lactic acid) composites, ***Polymer Degradation and Stability***, **147:** 142-150.
22. X. Jia, S. Gao, T. Liu, D. Li, P. Tang, Y. Feng, (2017) Fabrication and bifunctional electrocatalytic performance of ternary CoNiMn layered double hydroxides/polypyrrole/reduced graphene oxide composite for oxygen reduction and evolution reactions, ***Electrochimica Acta***, **245:** 59-68.
23. Z. Cao, N. N. M. Adnan, G. Wang, A. Rawal, R. Liu, K. Liang, L. Zhao, J. J. Gooding, C. Boyer, (2018) Conjugating layered double hydroxide nanoparticles with phosphonic acid terminated polyethylene glycol for improved particle stability, ***Journal of Colloid and Interface Science***, **521:** 242-251.
24. E. Mona, K. Buskaran, S. Bullo, M. Z. Hussein, S. Fakurazi, G. Pastorin, (2021) Drug delivery system based on magnetic iron oxide nanoparticles coated with (polyvinyl alcohol-zinc/aluminium-layered double hydroxide-sorafenib), ***Alexandria Engineering Journal***, **60:** 733-747.
25. J. O. D. Malafatti, M. P. Bernardo, F. K. V. Moreira, H. Ciol, N. M. Inada, L. H. C. Mattoso, E. C. Paris, (2020) Electrospun poly(lactic acid) nanofibers loaded with silver sulfadiazine/[Mg-Al]-layered double hydroxide as an antimicrobial wound dressing, ***Polymers for Advanced Technologies***, **31:** 1377-1387.
26. C. Minnelli, E. Laudadio, R. Galeazzi, G. Barucca, V. Notarstefano, M. Cantarini, T. Armeni, G. Mobbili, (2020) Encapsulation of a neutral molecule into a cationic clay material: Structural insight and cytotoxicity of resveratrol/layered double hydroxide/bsa nanocomposites. ***Nanomaterials***, **10:** 33.
27. T. Xu, J. Liu, L. Sun, R. Zhang, Z. P. Xu, Q. Sun, (2021) Enhancing tumor accumulation and cellular uptake of layered double hydroxide nanoparticles by coating/detaching pH-triggered charge-convertible polymers, ***ACS Omega***, **6:** 3822-3830.
28. S. Barkhordari, A. Alizadeh, (2022) Fabrication of pH-sensitive chitosan/layered double hydroxide (LDH)/Fe_3O_4 nanocomposite hydrogel beads for controlled release of diclofenac, ***Polymer Bulletin***, **79**(7): 5533-5548.
29. G. Viscusi, G. Gorrasi, (2021) Facile preparation of layered double hydroxide (LDH)-alginate beads as sustainable system for the triggered release of diclofenac: Effect of pH and temperature on release rate, ***International Journal of Biological Macromolecules***, **184:** 271-281.
30. H. Tiwari, N. Karki, M. Pal, S. Basak, R. K. Verma, R. Bal, N. D. Kandpal, G. Bisht, N. G. Sahoo, (2019) Functionalized graphene oxide as a nanocarrier for dual drug delivery applications:

The synergistic effect of quercetin and gefitinib against ovarian cancer cells, ***Colloids and Surfaces B: Biointerfaces***, **178:** 452-459.
31. J. Liu, K. Liu, L. Zhang, M. Zhong, T. Hong, R. Zhang, Y. Gao, R. Li, T. Xu, Z. P. Xu, (2021) Heat/pH-boosted release of 5-fluorouracil and albumin-bound paclitaxel from Cu-doped layered double hydroxide nanomedicine for synergistical chemo-photo-therapy of breast cancer, ***Journal of Controlled Release***, **335:** 49-58.
32. M. Shao, M. Wei, D. G. Evans, X. Duan, (2013) Hierarchical structures based on functionalized magnetic cores and layered double-hydroxide shells: Concept, controlled synthesis, and applications, ***Chemistry-A European Journal***, **19:** 4100-4108.
33. D. G. Jeung, T. H. Kim, J. M. Oh, (2021) Homogeneous incorporation of gallium into layered double hydroxide lattice for potential radiodiagnostics: Proof-of-concept, ***Nanomaterials (Basel)***, **11:** 44.
34. M. Singh, R. K. Singh, S. K. Singh, S. K. Mahto, N. Misra, (2018) *In vitro* biocompatibility analysis of functionalized poly(vinyl chloride)/layered double hydroxide nanocomposites, ***RSC Advances***, **8:** 40611-40620.
35. Y. Wang, L. Zhou, L. Fang, F. Cao, (2020) Multifunctional carboxymethyl chitosan derivatives-layered double hydroxide hybrid nanocomposites for efficient drug delivery to the posterior segment of the eye, ***Acta Biomaterialia***, **104:** 104-114.
36. G. E. De Souza dos Santos, A. H. Ide, J. L. S. Duarte, G. McKay, A. O. S. Silva, L. Meili, (2020) Adsorption of anti-inflammatory drug diclofenac by MgAl/layered double hydroxide supported on *Syagrus coronata* biochar, ***Powder Technology***, **364:** 229-240.
37. L. S. Costard, D. C. Kelly, R. N. Power, C. Hobbs, S. Jaskaniec, V. Nicolosi, F. J. O'Brien, (2020) Layered double hydroxide as a potent non-viral vector for nucleic acid delivery using gene-activated scaffolds for tissue regeneration applications, ***Pharmaceutics***, **12**(12): 1219.
38. R. Sharma, G. G. C. Arizaga, A. K. Saini, P. Shandilya, (2021) Layered double hydroxide as multifunctional materials for environmental remediation: From chemical pollutants to microorganisms, ***Sustainable Materials and Technologies***, **29**: e00319.
39. Y. Kuthati, R. K. Kankala, C. H. Lee, (2015) Layered double hydroxide nanoparticles for biomedical applications: Current status and recent prospects, ***Applied Clay Science***, **112:** 100-116.
40. S. Mokhtari, M. Solati-Hashjin, Z. Khosrowpour, M. Gholipourmalekabadi, (2021) Layered double hydroxide-galactose as an excellent nanocarrier for targeted delivery of curcumin to hepatocellular carcinoma cells, ***Applied Clay Science***, **200:** 105891.
41. C. Dragoi, M. Uritu, L. Agrigoroaie, D. Lutic, V. Hulea, G. Postole, A. Coroaba, E. Carasevici, (2021) MnAl-layered double hydroxide nanosheets infused with fluorouracil for cancer diagnosis and therapy. ***ACS Applied Nano Materials***, **4:** 2061-2075.
42. M. J. Mochane, S. I. Magagula, J. S. Sefadi, E. R. Sadiku, T. C. Mokhena, (2020) Morphology, thermal stability, and flammability properties of polymer-layered double hydroxide (LDH) nanocomposites: A review, ***Crystals***, **10:** 612.
43. S. S. Shafiei, S. Mohammadi, F. Moztarzadeh, (2020) Poly (ε-caprolactone)/layered double hydroxide microspheres-aggregated nanocomposite scaffold for osteogenic differentiation of mesenchymal stem cell, ***Materials Today Communications***, **23:** 100913.
44. X. Wang, B. Yang, X. Xu, M. Su, M. Xi, Z. Yin, (2021) Dextran sulfate-modified pH-sensitive layered double hydroxide nanocomposites for treatment of rheumatoid arthritis, ***Drug Delivery and Translational Research***, **11:** 1096-1106.
45. V. Yousefi, V. Tarhriz, S. Eyvazi, A. Dilmaghani, (2020) Synthesis and application of magnetic@ layered double hydroxide as an anti-inflammatory drugs nanocarrier, ***Journal of Nanobiotechnology***, **18:** 155.
46. Z. Kocer, B. Aru, U. A. Sezer, G. Y. Demirel, U. Beker, S. Sezer, (2019) Process optimisation, biocompatibility and anti-cancer efficacy of curcumin loaded gelatine microparticles cross-linked with dialdeyhde carboxymethyl cellulose, ***Journal of Microencapsulation***, **36:** 485-499.
47. P. Yazdani, E. Mansouri, S. Eyvazi, V. Yousefi, H. Kahroba, M. S. Hejazi, A. Mesbahi, V. Tarhriz, M. M. Abolghasemi, (2019) Layered double hydroxide nanoparticles as an appealing nanoparticle in gene/plasmid and drug delivery system in C_2C_{12} myoblast cells, ***Artificial Cells***, ***Nanomedicine***, ***and Biotechnology***, **47:** 436-442.
48. M. Ahmadi-Kashani, H. Dehghani, A. Zarrabi, (2020) A biocompatible nanoplatform formed by MgAl-layered double hydroxide modified Mn3O4/N-graphene quantum dot conjugated-polyaniline for pH-triggered release of doxorubicin, ***Materials Science and Engineering: C***, **114:** 111055.
49. C. G. Liu, H. X. Tang, X. Zheng, D. Y. Yang, Y. Zhang, J. T. Zhang, R. K. Kankala, S. B. Wang, G. Liu, A. Z. Chen, (2020) Near-infrared-activated lysosome pathway death induced by ROS generated from layered double hydroxide-copper sulfide nanocomposites, ***ACS Applied Materials and Interfaces***, **12:** 40673-40683.
50. M. L. Jadam, S. A. S. Mohamad, H. M. Zaki, Z. Jubri, S. H. Sarijo, (2021) Antibacterial activity and physicochemical characterization of calcium-aluminium-ciprofloxacin-layered double hydroxide. ***Journal of Drug Delivery Science and Technology***, **62:** 102314.
51. G. Sriram, U. T. Uthappa, D. Losic, M. Kigga, H. Y. Jung, M. D. Kurkuri, (2020) Mg-Al-layered double hydroxide (LDH) modified diatoms for highly efficient removal of Congo red from aqueous solution, ***Applied Sciences***, **10:** 2285.
52. P. Liu, M. Li, H. Yu, H. Fang, J. Yin, D. Zhu, Q. Yang, Q. Ke, Y. Huang, Y. Guo, Y. Gao, C. Zhang, (2021) Biphasic CK2. 1-coated β-glycerophosphate chitosan/LL37-modified layered double hydroxide chitosan composite scaffolds enhance coordinated hyaline cartilage and subchondral bone regeneration, ***Chemical Engineering Journal***, **418:** 129531.
53. Y. Xu, Y. Kong, J. Xu, X. Li, J. Gou, T. Yin, H. He, Y. Zhang, X. Tang, (2020) Doxorubicin intercalated copper diethyldithiocarbamate functionalized layered double hydroxide hybrid nanoparticles for targeted therapy of hepatocellular carcinoma, ***Biomaterials Science***, **8:** 897-911.
54. J. G. Pontes-Neto, T. R. F. Silva, F. O. S. Ribeiro, D. A. Silva, M. F. R. Soares, J. L. Soares-Sobrinho, (2021) Reconstitution as an alternative method for 5-aminosalicylic acid intercalation in layered double hydroxide for drug delivery, ***Journal of Thermal Analysis and Calorimetry***, **147:** 3141-3149.
55. J. Ouyang, X. Hong, Y. Gao, (2021) Retardation and self-repair of erosion pits by a two-stage barrier on bioactive-glass/layered double hydroxide coating of biomedical magnesium alloys, ***Surface and Coatings Technology***, **405:** 126562.
56. C. W. Lin, S. X. Lin, R. K. Kankala, P. Busa, J. P. Deng, S. I. Lue,

C. L. Liu, C. F. Weng, C. H. Lee, (2020) Surface-functionalized layered double hydroxide nanocontainers as bile acid sequestrants for lowering hyperlipidemia, ***International Journal of Pharmaceutics***, **590:** 119921.

57. M. Dinari, F. Dadkhah, (2020) Swift reduction of 4-nitrophenol by easy recoverable magnetite-Ag/layered double hydroxide/starch bionanocomposite, ***Carbohydrate Polymers***, **228:** 115392.
58. M. Ebadi, K. Buskaran, S. Bullo, M. Z. Hussein, S. Fakurazi, G. Pastorin, (2020) Synthesis and cytotoxicity study of magnetite nanoparticles coated with polyethylene glycol and sorafenib-zinc/aluminium layered double hydroxide, ***Polymers (Basel)***, **12:** 2716.
59. S. Sohrabnezhad, Z. Poursafar, A. Asadollahi, (2020) Synthesis of novel core@ shell of MgAl layered double hydroxide@ porous magnetic shell (MgAl-LDH@ PMN) as carrier for ciprofloxacin drug, ***Applied Clay Science***, **190:** 105586.
60. D. A. Lerner, S. Bégu, A. Aubert-Pouëssel, R. Polexe, J. M. Devoisselle, T. Azaïs, D. Tichit, (2020) Synthesis and properties of new multilayer chitosan@ layered double hydroxide/drug loaded phospholipid bilayer nanocomposite bio-hybrids, ***Materials***, **13**(16): 3565.